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Preface
Ultrasound in obstetrics

Lynn L. Simpson, MD
Guest Editor

Ultrasound has become an integral component of obstetric care, with the vast majority of patients having at least one ultrasound examination during pregnancy. From the determination of early pregnancy and gestational age to the evaluation of fetal growth and well being, ultrasound is a valuable diagnostic tool for the practicing obstetrician. Recent advances in obstetric ultrasonography have increased its importance in managing pregnancies at risk for aneuploidy, structural anomalies, preterm delivery, and blood flow abnormalities. Compiled of contributions from leading experts across the country, this issue of *Obstetrics and Gynecology Clinics of North America* demonstrates the expanding role of ultrasound in the field of obstetrics.

In the United States, ultrasound has been incorporated into prenatal screening programs aimed at identifying fetal chromosomal abnormalities. From their important work on the FASTER Trial (First and Second Trimester Evaluation of Risk), a multicenter prospective study comparing first and second trimester methods of screening for fetal aneuploidy, Karlla Brigatti and Dr. Malone provide a thorough review of first trimester screening including the ultrasonographic evaluation of nuchal translucency. The genetic sonogram, comprised of an evaluation of various sonographic markers during the second trimester, has been used to provide an individualized risk assessment for patients. An expert in both Maternal Fetal Medicine and Genetics, Dr. Stewart presents the potential benefits and obvious limitations of ultrasound in the detection of various fetal chromosomal abnormalities.

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In addition to decreasing the likelihood of fetal aneuploidy, patients want reassurance that their infants will be born without major structural abnormalities. Dr. Goldberg, who has devoted his career to prenatal diagnosis, provides an excellent overview of the routine screening ultrasound examination and the expected detection rates for fetal anomalies. My chapter on screening for congenital heart disease follows with the conclusion that the evaluation of multiple cardiac views at the time of routine prenatal ultrasound has the highest probability of detecting heart defects prior to birth. In contrast to the prenatal detection of major fetal malformations, there are many ultrasonographic findings that may or may not represent true pathology. Drs. Rochon and Eddleman present a detailed review of the most controversial ultrasound findings and provide a useful evidence-based approach to their management.

Diagnostic and therapeutic interventions are often necessary for patients at risk for aneuploidy or when an ultrasonographic abnormality is identified. Experienced clinicians, Drs. Ralston and Craigo provide a comprehensive review of the various ultrasound-guided procedures that are in use today for fetal diagnosis and therapy.

Although the fetus is often the focus during obstetric ultrasound examination, an evaluation of the cervix may be of importance in some patients. Drs. Doyle and Monga present an excellent discussion on the utility of ultrasound in women with prior second trimester pregnancy loss, previous preterm delivery, and multiple gestation. They provide logical guidelines for the ultrasonographic assessment of cervical length in patients at risk for preterm birth, emphasizing that the transvaginal approach is the optimal way to evaluate the cervix during pregnancy. In addition to an evaluation of cervical length, obstetric ultrasound plays an important role in multiple gestations. Drs. Egan and Borgida provide an extensive review of the use of ultrasound in twins, from diagnosis to delivery, demonstrating its favorable impact on the management of these high-risk pregnancies.

Ultrasound evaluations in the third trimester involve assessments of fetal growth and well-being. An expert in ultrasonography, Dr. Lerner presents an overview of fetal growth and the accuracy of ultrasound to detect abnormalities such as intrauterine growth restriction and macrosomia. In addition to fetal growth, obstetric ultrasound permits an evaluation of the intrauterine environment. In a well-illustrated review, Dr. Marino discusses the use of ultrasound to evaluate the amniotic fluid volume, fetal membranes, umbilical cord, and placenta. This issue of *Obstetrics and Gynecology Clinics of North America* is concluded with a comprehensive presentation on fetal Doppler velocimetry. All leaders in the field, Drs. Mari, Detti, Cheng, and Bahado-Singh present the major applications of Doppler velocimetry in obstetrics. Although Doppler velocimetry is a relatively new technique, it has become an integral component of fetal testing and represents a significant advance in the field of obstetric ultrasound.

I would like to extend my sincere thanks to the authors who contributed to this issue on "Ultrasound in Obstetrics". It provides a thorough update

on recent advances in the field and it is my hope that the contents will be useful to practitioners providing care to pregnant women.

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First-trimester screening for aneuploidy

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Prenatal screening for Down syndrome and other aneuploidies has expanded substantially over the past 20 years. Initially only women of advanced maternal age ($\geq$ 35 years old at delivery) or those with a previously affected pregnancy were offered the option of invasive prenatal diagnosis using amniocentesis or chorionic villus sampling (CVS). Subsequently, prenatal diagnosis of aneuploidy became possible for those in the general obstetric population identified at increased risk for Down syndrome by second-trimester multiple marker serum screening or abnormal second-trimester sonographic markers, or soft signs, for Down syndrome. At present, the most efficient multiple marker screening test in the second trimester is known as the ''quad'' screen, a biochemical marker panel comprised of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol, and inhibin-A [1]. This combination approach yields sensitivities for Down syndrome of 67% to 76% for a 5% false-positive rate, depending on whether menstrual or sonographic dating are used [2].

This common method of screening has several limitations. The earliest it can reliably be performed is 15 weeks gestation, limiting the choice of definitive diagnosis of aneuploidy to amniocentesis and pushing prenatal diagnosis into the latter second trimester. Furthermore, over 25% of Down syndrome cases are not detected with this screening approach, and the 5% false-positive rate ensures that as many as 60 amniocentesis procedures need to be performed for every single case of Down syndrome detected [3]. Given the pregnancy loss rate of 1 in 200 associated with amniocentesis, about one normal fetus is lost for every three fetuses with Down syndrome detected.

Clearly, the current approach of second-trimester screening is not ideal. A great deal of interest has been directed toward shifting prenatal screening for Down syndrome and other aneuploidies to the first trimester using the sonographic measurement of the fetal nuchal translucency (NT) alone and in com-

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bination with other sonographic and serum markers. This article focuses on the current data and status of first-trimester screening for Down syndrome and addresses the issues of implementation before it can be endorsed for widespread use in everyday clinical practice.

Fetal nuchal translucency

Nuchal translucency refers to the normal subcutaneous fluid-filled space between the back of the fetal neck and the overlying skin. In most cases, this area can be measured accurately and reproducibly on ultrasound between 10 and 14 weeks' gestation. It is commonly believed that the larger the NT measurement, the greater it's association with Down syndrome, other aneuploidy, major structural malformations, and adverse pregnancy outcome (Fig. 1) [4,5]. The etiology of increased NT may be variable, but it is commonly believed to be caused by fluid accumulation in the nuchal region because of aortic isthmic narrowing or other fetal cardiovascular defects [4], abnormalities in the extracellular matrix, or abnormal or delayed development of the lymphatic system [6].

Nuchal translucency screening for Down syndrome

Earlier studies of NT-based screening were generally performed on small numbers of subjects and retrospective in nature, drawn from select high-risk populations. They demonstrated substantial variation in Down syndrome detection rates ranging from 46% to 62%, likely caused by differing criteria and skill

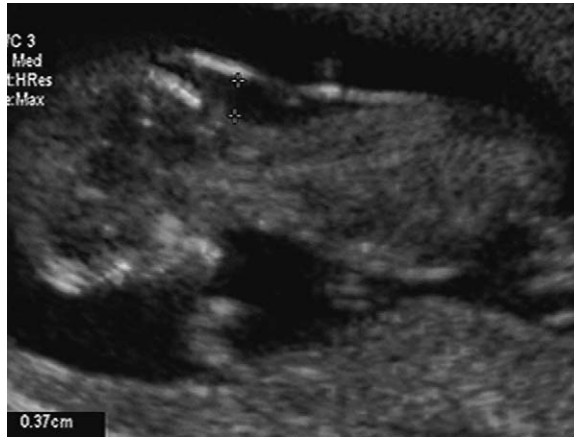

Fig. 1. Ultrasound image of a fetus with Down syndrome at 12 weeks gestation with an increased nuchal translucency of 3.7 mm.

levels at measuring NT, differences in success of obtaining measurements, variation in gestational ages included in screening, and varying definitions of normal versus abnormal NT cutoffs [3]. These studies using high-risk women could not effectively extrapolate their results to the role of NT screening in the general population, because it overestimates the true performance of the test.

Results of studies in the general obstetric population in a routine clinical setting have been mixed, with a range of detection rates for Down syndrome between 29% and 100%. Table 1 includes 30 published studies on the performance of NT-based screening for Down syndrome in the general population between 1966 and April 2003 [7–36]. Studies were included in this table if patients were reported as being unselected or from the general population, but excluded if they described less than five cases of Down syndrome or retrospective case:control series [37–40]. In total these studies include 316,311 patients screened by NT measurement in the first trimester. A total of 1177 fetuses with Down syndrome were ascertained in this population, for a prevalence of 3.7 per 1000 pregnancies. In 11 of the 30 studies included in Table 1, the prevalence of Down syndrome was 5 per 1000 or greater, suggesting that these studies were not representative of the general obstetric population [7,13–15,19,20,25,26,30,34,35]. Using data from all 30 studies, NT screening had an overall sensitivity for Down syndrome of 77% with a 6% false-positive rate. The odds of a positive screen result being a true positive for Down syndrome were approximately 5%. The data from these studies suggest that an abnormal NT measurement is 13 times more likely to be present in cases of Down syndrome, compared with when the fetus does not have this condition. Conversely, a normal NT measurement is about one quarter as likely in unaffected cases.

It should be noted that these likelihood ratios may be overestimated because of the lack of accounting for the intrauterine lethality of Down syndrome in most of these studies; as many as 40% of fetuses alive at the time of first-trimester screening result in spontaneous intrauterine demise [41]. Underascertainment of Down syndrome is a significant limitation of studies in which a fetal or neonatal karyotype is not obtained on all patients. Because Down syndrome pregnancies are more likely to result in fetal demise, a significant portion of early pregnancy losses may have Down syndrome. In one review of the topic, the mean Down syndrome detection rate for studies subject to ascertainment bias was 77%, whereas it was only 55% in studies not subject to it [42]. Only 9 of the 30 studies listed in Table 1 described efforts to maximize the ascertainment of Down syndrome cases in stillbirth or early pregnancy losses [8–10,16,17,23,28,33,36]. Ultimately, under ascertainment of Down syndrome cases can only be minimized by study methodologies that use extensive pregnancy follow-up, and eliminated altogether with complete karyotypic information on all pregnancies that were subjected to screening.

This has been a criticism of the largest study to date on NT-based screening in the general population, conducted by the Fetal Medicine Foundation in London on 96,127 unselected patients at 22 centers between 10 and 14 weeks gestation. That series reported a Down syndrome detection rate of 82% for an 8% false-

Table 1
Studies of nuchal translucency ultrasound in an unselected prenatal population

Study	Number of fetuses	Down syndrome					
		Prevalence*	Sensitivity (%)	FPR %	PPV %	LR (+)	LR (−)
Kornman et al [7]	537	13	2/7 (29)	6.4	5.6	5	0.8
Taipale et al [8]	6939	0.9	4/6 (67)	0.8	6.7	83	0.3
Hafner et al [9]	4233	1.7	3/7 (43)	1.7	4.1	25	0.6
Economides et al [10]	2256	3.5	5/8 (63)	1	17.9	63	0.4
Theodoropoulos et al [11]	3550	3.1	10/11 (91)	2.6	9.9	35	0.1
Snijders et al [12]	96,127	3.4	268/326 (82)	8	3.4	10	0.2
Pajkrt et al [13]	1473	6.1	6/9 (67)	1.8	18.2	37	0.3
De Biasio et al [14]	1467	8.9	8/13 (62)	6.7	7.5	9	0.4
Quispe et al [15]	424	16.5	7/7 (100)	1.7	50	59	—
Whitlow et al [16]	6443	3.6	13/23 (57)	0.3	37.1	188	0.4
Schwarzler et al [17]	4523	2.7	10/12 (83)	4.9	4.3	17	0.2
Thilaganathan et al [18]	9802	2.1	16/21 (76)	4.7	3.3	16	0.3
Krantz et al [19]	5809	5.7	24/33 (73)	5	7.6	15	0.3
O'Callaghan et al [20]	1000	8	6/8 (75)	6.2	8.8	12	0.3
Niemimaa et al [21]	1602	3.1	3/5 (60)	11.6	1.6	5	0.5
Schuchter et al [22]	9342	2	11/19 (58)	2.3	5	25	0.4
Audibert et al [23]	4130	2.9	9/12 (75)	4.9	4.3	15	0.3
Michailidis et al [24]	7447	3.1	19/23 (83)	4.5	5.4	18	0.2

Gasiorek-Wiens et al [25]	21,959	9.6	174/210 (83)	8.9	8.2	9	0.2
Zoppi et al [26]	10,157	6.3	58/64 (91)	9.6	5.7	9	0.1
Brizot et al [27]	2557	3.9	7/10 (70)	6.5	4	11	0.3
Wayda et al [28]	6841	2.5	17/17 (100)	4.3	5.5	23	—
Schuchter et al [29]	4939	2.8	8/14 (57)	4.9	3.2	12	0.5
Murta and Franca [30]	1152	12.2	9/14 (64)	4.2	15.8	15	0.4
Rozenberg et al [31]	6234	3.4	13/21 (62)	2.8	7	22	0.4
Crossley et al [32]	17,229	2.6	20/37 (54)	5	2.3	11	0.5
Lam et al [33]	16,237	2.2	24/35 (69)	5	2.9	14	0.3
Bindra et al [34]	14,383	5.7	64/82 (79)	5	8.3	16	0.2
Comas et al [35]	7536	5	38/38 (100)	5	9.4	20	—
Wald et al [36]	39,983	2.1	54/85 (63)	5	2.6	13	0.4
TOTAL	316,311	3.7	910/1,177 (77.3) (95% CI: 75–80)	5.9 (5.8–6)	4.7 (4.5–4.8)	13.1 (12.7–13.5)	0.24 (0.22–0.27)

Pooled 95% confidence intervals given in parentheses at bottom of table.

Abbreviations: FPR, Falsepositive rate; LR (+), likelihood ratio for Down syndrome given positive result; LR (−), likelihood ratio for Down syndrome given negative result; MoM, multiples of median; PPV, positive predictive value.

* Prevalence of Down syndrome per 1000 ascertained pregnancies.

positive rate, equivalent to a 77% detection rate for a 5% false-positive rate [12]. Investigators in that study calculated that based on the maternal age and gestational age distribution of the enrolled subjects, in the absence of any screening, 266 live Down syndrome births would have resulted in their study group. Assuming that as many as 40% of first-trimester Down syndrome cases spontaneously demise in utero, the 266 live births with Down syndrome suggest that at least 443 fetuses with Down syndrome were viable at 10 to 14 weeks gestation (40% of 443 = 177; 433 to 177 = 266 term live births). The quoted detection rate of 268 (82%) per 326 should have been stated more correctly as 268 (60%) per 443 [41]. Underascertainment of true cases of Down syndrome in this study most likely masks a true sensitivity between 60% and 77% for a 5% false-positive rate [12,41]. Indeed, this issue may be one of the reasons the Fetal Medicine Foundation group has revised the performance characteristics of NT-based screening five times over the past 6 years, with detection rates varying from 73% to 84% for a false-positive rate of 5% [12,34,43–45].

Another limitation of the current literature on NT-based screening is the lack of information on the success rate at obtaining an NT measurement [10–12,14–16,19–22,24,28,30,35]. Some studies suggest a 100% success rate at obtaining an NT measurement [17,25–27,34] but none provide any information on the

Box 1. Criteria to maximize good quality of NT ultrasound

1. NT ultrasound should only be performed by sonographers certified in the technique.
2. Transabdominal or transvaginal approach should be left to the sonographer's discretion, based on maternal body habitus, gestational age, and fetal position.
3. Gestation should be limited between 10 and 14 weeks (Crown Rump Length (CRL) 36 to 80 mm).
4. Fetus should be examined in a mid-sagittal plane.
5. Fetal neck should be in a neutral position.
6. Fetal image should occupy at least 75% of the viewable screen.
7. Fetal movement should be awaited to distinguish between amnion and overlying fetal skin.
8. Calipers should be placed on the inner borders of the nuchal fold.
9. Calipers should be placed perpendicular to the fetal body axis.
10. At least three NT measurements should be obtained, with the mean value of those used in risk assessment and patient counseling.
11. At least 20 minutes may need to be dedicated to the NT measurement before abandoning the effort as failed.

adequacy of the images once obtained. In the multicenter Scottish Trial of first-trimester screening, in which NT screening training and quality control were overseen by the Fetal Medicine Foundation, one acceptable measurement was obtained in 73% of cases, and three acceptable images were gathered in only 52% [32]. Calculating Down syndrome detection rates based on a subgroup of patients on whom the fetal NT could be measured, rather than all patients who present for screening, is inappropriate. In the Scottish Trial, the detection rate for Down syndrome was 54% for a 5% false-positive rate for patients in which an NT could be obtained, but only 44% when all patients who presented for screening were considered [32]. Special attention should be placed on quality control to ensure that the measurements obtained are consistently satisfactory. The elements of one commonly accepted NT technique, used in the recently completed FASTER Trial in the United States, are listed in Box 1.

One striking shortcoming of the current literature on NT-based screening is the lack of control group for comparison between first-trimester screening and the current standard of care of second-trimester multiple marker screening. Only one of the studies listed on Table 1 used a control group for comparison [36]. Most comparisons available to date between first- and second-trimester screenings were derived using hypothetical mathematical modeling or data from multiple studies. It is inappropriate to use data on first-trimester screening performance from one study with data on the second-trimester screening performance from a different study, because the prevalence of Down syndrome is different between those two populations.

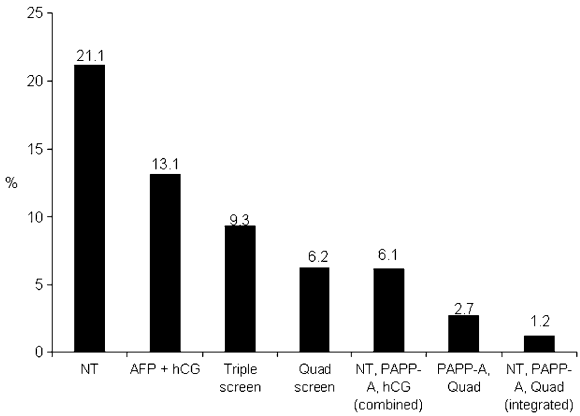

Fig. 2. Variation in false-positive rates for a fixed 85% detection rate for Down syndrome according to the method of screening. AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein-A. NT, nuchal translucency; AFP, alphafetoprotein; hCG, human chorionic gonadotropin; PAPP-A, pregnancy associated plasma protein – A. (*Data from* Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). J Med Screen 2003;10:56 – 104.)

A direct comparison between the current range of screening tests in the first and second trimesters in the general obstetric population will soon be possible through recently completed trials in the United States (the FASTER Trial) and the United Kingdom (the SURUSS Trial). The comparative performance of various screening methods from the SURUSS Trial is summarized in Fig. 2 [36].

Nuchal translucency screening for other aneuploidy

The Fetal Medicine Foundation study described previously observed that NT-based screening may identify other aneuploidies beside Down syndrome. Based on prenatal diagnosis and neonatal ascertainment, it observed detection rates of 81% for trisomy 18, 80% for Turner's syndrome, and 63% for triploidy. Cases that would be expected to spontaneously demise were not included in the analysis [12]. Because the true prevalence of these conditions in the first trimester is uncertain, and most affected fetuses spontaneously die in utero, true detection rates for these cases are difficult to calculate. Based on the frequency of these aneuploidies observed in newborns, it is estimated that approximately 80% of these cases result in spontaneous abortion in the absence of screening [46]. It is possible that NT-based screening may preferentially identify those pregnancies with the highest likelihood of intrauterine death [47]. It is a matter of debate whether a screening method that identifies such pregnancies holds any advantage for the screened population.

Nuchal translucency screening in multiple gestations

Risk assessment for Down syndrome in multiple gestation pregnancies has had several limitations until the advent of NT-based screening. Maternal serum screening has not been used widely with multiple gestations because of the potential for discordance between twins and the impact of different placentas on the various analytes. The detection rate for Down syndrome by the second-trimester serum quad test in twins has been estimated at only 47% for a 5% false-positive rate, although this varies depending on whether the pregnancy is monochorionic or dichorionic [48].

In contrast, it does not seem that NT distribution differs significantly in singleton versus twin pregnancies, such that the detection rates for single and twin gestations may be similar. The false-positive rate in monochorionic twin gestations may be higher, attributed to some complications unique to monochorionic twins that present with increased NT, such as twin-to-twin transfusion syndrome [49]. Additional research on this approach to screening multiple gestation pregnancies is still needed, although NT measurement should represent a significant improvement over serum screening for these cases. NT ultrasound is currently being used by some centers to assist in the selection of fetuses targeted for reduction in higher order multiple gestations.

Nuchal translucency measurement with maternal serum markers: combined and integrated screening

Studies of first-trimester maternal serum screening have consistently shown that increased risk of fetal Down syndrome is associated with higher levels of total hCG and the free beta component of hCG (FβhCG), and lower levels of PAPP-A. Studies of the combination of FβhCG, PAPP-A, and maternal age uniformly demonstrate a detection rate of approximately 60% with a 5% false-positive rate [50].

These first-trimester serum markers seem to be independent of NT, which implies that both serum and ultrasound approaches can be combined into a single protocol with a higher sensitivity than each alone. A total of seven published studies of the combined method of screening met the same criteria described earlier for NT-based screening alone. Detection rates for the combined test are summarized in Table 2. A total of 85,412 patients were screened in these studies, with the overall sensitivity for Down syndrome of 82% for a 5% false-positive rate [14,19,21,29,32,34,36]. Most of these studies did not provide extensive information in their methodology section describing ascertainment of pregnancy outcome, so the true estimate of Down syndrome detection is unknown. The positive predictive value for Down syndrome in the context of an abnormal combined screen was 5.4% (confidence intervals 5.1 to 5.7). Furthermore, the data from Table 2 suggest that an abnormal combined screen result is 18 times more likely when Down syndrome is present compared with euploid cases (positive likelihood ratio 17.5, 95% confidence intervals 16.6 to 18.7). A normal combined screen result is associated with a one fifth as likely chance of Down syndrome (negative likelihood ratio 0.18, 95% confidence intervals 0.14 to 0.24).

Using the NT measurement and maternal serum markers from the first trimester in combination with maternal serum analytes from the second trimester to provide one single Down syndrome risk assessment has been proposed as a superior alternative to estimating separate Down syndrome risks in each trimester alone. This two-step approach, commonly known as the ‘‘integrated test,’’ involves the combination of NT ultrasound and maternal serum PAPP-A in the first trimester followed by maternal serum AFP, hCG, unconjugated estriol, and inhibin-A in the second trimester, with a single result provided in the second trimester. The advantage of this testing seems to be its very high detection rate for Down syndrome, which models suggest may be as high as 94% for a 5% false-positive rate [51]. Such an approach could also significantly reduce the false-positive rate to as low as 1%, while maintaining a high detection rate of 85% (see Fig. 2) [36].

Integrated screening has been introduced at a few centers in the United States, but it remains controversial. The primary concern with this screening method focuses on withholding a potentially significant first-trimester NT finding from the patient until after the second-trimester component of the test has been completed [52]. One study estimated, however, that only 0.05% of women undergoing the integrated test have a risk for Down syndrome by NT measure-

Table 2
Performance characteristics of the combined test: nuchal translucency and first-trimester maternal serum

Study	Number of fetuses	Down syndrome					
		Prevalence*	Sensitivity (%)	FPR %	PPV %	LR (+)	LR (−)
DeBiasio et al [14]	1467	8.9	11/13 (85)	3.3	18.6	26	0.2
Krantz et al [19]	5809	5.7	30/33 (91)	5	9.4	18	0.1
Niemimaa et al [21]	1602	3.1	4/5 (80)	8.3	2.9	10	0.2
Schuchter et al [29]	4939	2.8	12/14 (86)	5	4.7	17	0.2
Crossley et al [32]	17,229	2.6	28/45 (62)	5	3.1	12	0.4
Bindra et al [34]	14,383	5.7	75/82 (92)	7.1	6.8	13	0.1
Wald et al [36]	39,983	2.1	68/85 (80)	3.4	4.8	24	0.2
TOTAL	85,412	3.1	228/277 (82.3) (95% CI: 77–87)	4.7 (4.6–4.8)	5.4 (5.1–5.7)	17.5 (16.6–18.7)	0.18 (0.14–0.24)

Pooled 95% confidence intervals given in parentheses at bottom of table.
Abbreviations: FPR, Falsepositive rate; LR (+), likelihood ratio for Down syndrome given positive result; LR (−), likelihood ratio for Down syndrome given negative result; PPV, positive predictive value.

* Prevalence of Down syndrome per 1000 ascertained pregnancies.

ment and maternal age alone sufficiently high that serum markers from both the first and second trimesters do not modify this risk [53].

The results of the recently completed FASTER and SURUSS trials help to evaluate the relative performances of these various approaches to Down syndrome screening and elucidate patient preference. Ultimately it is likely that national screening policy will recognize a range of possible screening options, with the decision as to which test to select individualized by the physician and genetic counselor to suit each patient's needs.

First-trimester fetal ductus venosus flow

In addition to NT measurement, first-trimester ductus venosus (DV) flow studies have been identified as useful for aneuploidy screening. Forward biphasic pulsatile DV flow is normal, whereas reversed flow at the time of atrial contraction has been associated with aneuploidy and cardiac defects (Fig. 3) [54]. Studies evaluating this association found between 59% and 93% of aneuploid fetuses had abnormal DV flow velocities, with the same finding present in only 3% to 21% of chromosomally normal fetuses [54–59]. Study of the DV flow velocity waveform following an NT ultrasound evaluation may be useful in modifying a patient's risk for aneuploidy. The use of this approach may be to improve the detection rate of NT ultrasound alone, or alternatively to reduce the false-positive rate.

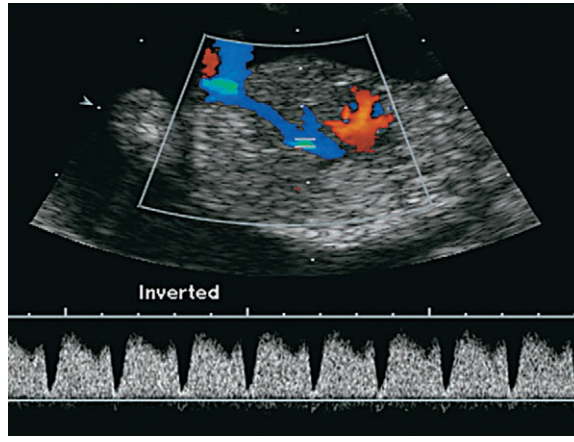

Fig. 3. Ultrasound image of ductus venous flow velocity waveform in a chromosomally normal 13-week fetus. The Doppler gate is placed in the ductus venosus between the umbilical venous sinus and the inferior vena cava. Note that there is biphasic pulsatile flow with constant forward flow. The troughs of flow during the atrial contraction also demonstrate forward flow.

Several drawbacks to DV flow studies should be considered. The DV vessel itself may be as small as 2 mm at 10 to 14 weeks and a typical Doppler gate size may vary from 0.5 to 2 mm in size. It can be difficult to obtain accurate flow velocity waveforms from such a tiny vessel without contamination of the waveform from neighboring blood vessels. For example, if the Doppler gate is placed too proximally near the umbilical sinus, normal continuous venous flow from the umbilical vein may obscure the absence of flow during the atrial contraction in the DV. Alternatively, placement of the Doppler gate too far distally, near the insertion of the DV into the inferior vena cava, may lead to the erroneous diagnosis of reversal of flow at the atrial contraction, because such reversal of flow is normal in the inferior vena cava. Furthermore, it is not sufficiently clear from published studies of NT and DV flow whether these two sonographic features are in fact completely independent of one another. If they are not then it may not be statistically valid to use one test to alter the risk assessment derived from the other. Based on these concerns, first-trimester DV Doppler flow studies may best be limited to predicting the prognosis of fetuses with normal chromosomes and increased NT [60].

First-trimester fetal nasal bone

An absent fetal nose bone on first-trimester ultrasound has been correlated with an increased risk for Down syndrome. In a study conducted by Cicero et al [61], 701 fetuses with increased NT were evaluated for the presence or absence of the nasal bone on first-trimester ultrasound. In this series, the fetal nose bone could not be visualized in 73% (43 of 59) of Down syndrome fetuses and in

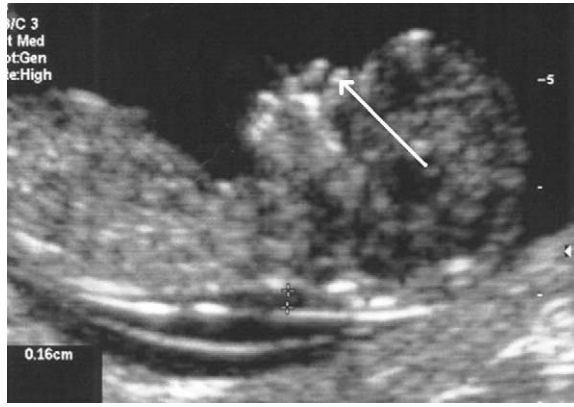

Fig. 4. Ultrasound image of fetal nasal bone evaluation in a chromosomally normal fetus at 13 weeks gestation. Various features of good nasal bone technique are evident in this image: a good mid-sagittal plane; clear fetal profile; downward-facing spine; slight neck flexion; and two echogenic lines, representing the overlying fetal skin and the nasal bone. The arrow represents the fetal nose bone, which loses its echogenicity distally.

only 0.5% (3 of 603) of unaffected ones. The authors believed that the absence of fetal nose bone to be independent of NT size and the two ultrasound screening methods could be combined into one modality, with a predicted sensitivity of 85% for a 1% false-positive rate [61]. This study was challenged by a subsequent report of five consecutive Down syndrome cases, each of which was reported to have a visible nose bone [62]. None of the five ultrasound images presented in this latter report, however, represented optimal views to evaluate the fetal nasal bone.

Adequate imaging of the fetal nose bone can be technically challenging in the first trimester. The nose bone should be visualized on ultrasound along the mid-sagittal plane of the fetus, in perfect profile and with slight neck flexion. The fetal spine should be facing downward. Two echogenic lines at the fetal nose bone profile should be evident: the superficial one of the nasal skin and a deeper echogenic line representing the nasal bone, which is also more echolucent at the distal end (Fig. 4). Furthermore, the ultrasound beam should not be parallel to the plane of the nose bone, because it may erroneously suggest an absent nose bone.

Ultimately, general population studies are needed to determine the success rate of adequately imaging the fetal nose bone, to evaluate the independence of nasal bone from NT and maternal serum markers, and to determine the feasibility of using this ultrasound marker for Down syndrome screening in mainstream clinical practice.

Implementing nuchal translucency into clinical practice

Nuchal translucency ultrasound has pushed prenatal screening for Down syndrome into the first trimester, and may lead to major advances in prenatal care. There are still several practical issues that need resolution, however, before first-trimester screening can be endorsed for implementation into routine clinical practice.

Quality control

The variability in quality control measures among earlier studies of NT screening likely accounts for the significant inconsistencies in quoted Down syndrome detection rates between them. NT ultrasound is extremely operator-dependent and is a poor technique for general obstetric screening if strict guidelines and ongoing quality control measures are not in place [63]. One multicenter study in which adequate training and quality control were not addressed had a Down syndrome detection rate of only 31% [63]. Systems must be in place at each local ultrasound practice to maintain ongoing quality control measures. Appropriate training, adherence to a standard and reproducible technique, and experience are key to the success of NT ultrasound as a reliable screening tool [64]. Box 1 lists the criteria for sustaining a reliable and high-quality NT ultrasound program.

Several pragmatic issues regarding NT quality control remain unresolved. There is no certification or credentialing system in place to ensure that those performing NT ultrasound are appropriately trained and monitored, nor are there any guidelines in place for retraining sonographers whose image quality has deteriorated over time. Consensus on the regulation and maintenance of NT ultrasound quality must be reached on a national basis before it can be applied for widespread use.

Nuchal translucency interpretation

The natural increase of NT measurement by 17% per week should be considered when calculating cutoffs for use with an increased NT [65]. It is inappropriate to choose a single millimeter cutoff to define a specific NT measurement as abnormal or select a pregnancy that warrants invasive prenatal diagnostic testing. More appropriate measures include using the 95th percentile for gestational age or multiples of the median (MoM). Unfortunately, detailed information on such cutoffs is not available in the literature and all require a computer program to integrate adequately other background data, such as maternal age, into the final risk calculation.

It is still unclear if generic population medians to interpret NT measurements are valid or whether such medians for risk calculations should be center-specific or sonographer-specific. These differences in center-specific medians were addressed in one Scottish study of 15 centers evaluating 17,229 patients with individual center NT median MoMs ranging between 0.7 and 1.4 MoMs [16]; the ideal median MoM should be 1. The dramatic consequences of such large variability in median MoMs between centers can be illustrated in the Down syndrome risk calculated for a 37-year-old patient with a 1-mm NT measurement, who would be quoted a 1:1400 risk for a fetus with Down syndrome were the 0.7 MoM used, to a 1:285 risk with a 1.4 MoM [32]. In the recently completed SURUSS study, the use of sonographer-specific medians compared with center-specific medians resulted in an improvement of 5% in overall Down syndrome detection rates [36].

Impact on second-trimester maternal serum screening

Implementing NT screening in isolation will likely have a negative impact on the current second-trimester serum screening programs, because the positive predictive value of second-trimester screening may be reduced as much as sixfold following NT screening [66]. The number of fetuses with Down syndrome entering the second trimester will be significantly reduced because many of them will have already been diagnosed in the first trimester. Sequential screening without modification of marker cutoffs may increase the overall false-positive rate substantially, resulting in an increased number of amniocenteses and procedure-related pregnancy losses [67]. It also introduces two independent risk results, creating unnecessary confusion and anxiety for the patient [53]. The only way to

eliminate this inefficiency is either to use the integrated test or modify the second-trimester risk cutoffs to account for the prior first-trimester screen result.

Eliminating second-trimester screening altogether to avoid the aforementioned confusion negatively impacts prenatal neural tube defect detection, which is performed through second-trimester maternal serum AFP evaluation. Maternal serum AFP is uninformative for neural tube defects in the first trimester, so to drop it as part of the current second-trimester serum screening program may lead to more cases of neural tube defects being missed prenatally. Furthermore, nearly 25% of pregnant women in the United States do not seek prenatal care early enough in their pregnancy to avail of first-trimester screening [68]. Second-trimester maternal serum screening will likely remain an important part of Down syndrome screening.

Impact on second-trimester genetic sonogram

First-trimester screening does not eliminate the need for second-trimester ultrasound for the detection of gross structural fetal anomalies. It does negatively impact the positive predictive value of ultrasonographic "soft markers" associated with Down syndrome (such as echogenic bowel and short femurs) because the number of fetuses with Down syndrome decreases following first-trimester screening. The manner in which patients are counseled regarding their second-trimester ultrasound findings should also be considered. The relevance of these sonographic soft markers in a population of pregnancies that has already undergone first-trimester screening is unknown. If no allowances for the reduction in second-trimester aneuploid fetuses are made when performing the second-trimester fetal anatomy ultrasound, it is likely that more unnecessary amniocenteses will be performed without a substantial increase in aneuploid detection.

Availability of early prenatal diagnosis

One of the most compelling features of first-trimester screening for Down syndrome is the shift to earlier diagnosis of aneuploidy through CVS at 10 to 13 weeks gestation. CVS is not as widely available as amniocentesis on a national basis [69]. Early amniocentesis is no longer optimal because of its higher association with fetal loss, fetal clubfoot, and procedure failure [70]. If patients identified at higher risk for Down syndrome on NT screening do not have ready access to CVS they may experience increased anxiety waiting 3 or 4 weeks for the opportunity to undergo amniocentesis at 15 weeks. A policy of first-trimester screening for Down syndrome should not be implemented unless first-trimester diagnosis by CVS is locally available. If a patient desires the benefit of first-trimester screening but does not have the option of CVS, the best approach may be to use the first-trimester screening information as part of the integrated test at 15 weeks to provide her with possibly the single most comprehensive prenatal risk assessment for Down syndrome.

Appropriate patient counseling

Informed consent regarding the variety of prenatal screening options should be an integral part of the screening process itself. The complexity of choices regarding the different screening options demands that pretest counseling be provided to patients before their deciding on these newer forms of screening. Women of advanced maternal age may use first-trimester screening to decide between CVS and amniocentesis, or whether to undergo any invasive prenatal diagnostic procedure at all. Some patients may be interested in the earliest result in pregnancy and may best be served by combined testing. Other women may be most concerned with maximizing the detection rate and may most benefit from integrated testing. There is also a subset of prenatal patients who do not present early enough in pregnancy to benefit from first-trimester screening and may need to use second-trimester multiple marker screening and second-trimester genetic sonogram for their Down syndrome risk assessment.

Cost-effectiveness

At present first-trimester ultrasound is not standard-of-care in the United States, although it offers many patient benefits, such as accurate gestational dating, determination of chorionicity in multiple gestations, and detection of major malformations like anencephaly. Because most fetal anomalies cannot be detected on ultrasound until the second trimester, the NT ultrasound presents an extra examination and additional costs. Cost-benefit analyses comparing first- and second-trimester screening have had mixed results [71]. Such analyses must also include the costs associated with prenatal diagnostic procedures, termination costs of affected pregnancies in both first and second trimesters, and costs of the aneuploid pregnancies identified in the first trimester that would normally spontaneously demise before the second trimester.

Current and future status of nuchal translucency screening in the United States

The current literature suggests that NT ultrasound screening has tremendous potential as a powerful prenatal screen for aneuploidy. Comparative data with other screening modalities are limited, however, although it indicates that the only first-trimester screening test that should be recommended at this time is the first-trimester combined test. NT screening on its own does not seem to be efficient in singleton pregnancies, because it seems to be inferior to either first-trimester combined testing or the second-trimester serum quad test.

Ultimately, before first-trimester screening can be endorsed for use in routine clinical practice, a range of troubling practical issues need resolution. The specific contribution of NT ultrasound, alone and in combination with other ultrasound and serum markers, must be assessed fully. If the performance of first-trimester screening remains as strong as predicted and it can be implemented into

mainstream practice in a consistent and organized manner, first-trimester screening will undoubtedly become a vital element of prenatal Down syndrome risk assessment to the benefit of all pregnant women.

References

[1] Wald NJ, Densem JW, George L, Muttukrishna S, Knight PG. Prenatal screening for Down's syndrome using inhibin-A as a serum marker. Prenat Diagn 1996;16:143–53.
[2] Wald NJ, Kennard A, Hackshaw AK, McGuire A. Antenatal screening for Down's syndrome. J Med Screen 1997;4:181–246.
[3] Malone FD, Berkowitz RL, Canick JA, D'Alton ME. First trimester screening for aneuploidy: research or standard of care? Am J Obstet Gynecol 2000;182:490–6.
[4] Hyett J, Perdu M, Sharland G, Snijders RS, Nicolaides KH. Using fetal nuchal translucency to screen for major congenital heart defects at 10–14 weeks of gestation: population based cohort study. BMJ 1999;318:81–5.
[5] Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. Ultrasound Obstet Gynecol 2001;18:9–17.
[6] Von Kaisenberg CS, Nicolaides KH, Brand-Saberi B. Lymphatic vessel hypoplasia in fetuses with Turner syndrome. Hum Reprod 1999;14:823–6.
[7] Kornman LH, Morssink LP, Beekhuis JR, De Wolf BT, Heringa MP, Mantingh A. Nuchal translucency cannot be used as a screening test for chromosomal abnormalities in the first trimester of pregnancy in a routine ultrasound practice. Prenat Diagn 1996;16:797–805.
[8] Taipale P, Hiilesmaa V, Salonen R, Ylostalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med 1997;337:1654–8.
[9] Hafner E, Schuchter K, Liebhart E, Philipp K. Results of routine fetal nuchal translucency measurement at weeks 10–13 in 4233 unselected pregnant women. Prenat Diagn 1998;18:29–34.
[10] Economides DL, Whitlow BJ, Kadir R, Lazanakis M, Verdin SM. First trimester sonographic detection of chromosomal abnormalities in an unselected population. BJOG 1998;105:58–62.
[11] Theodoropoulos P, Lolis D, Papageorgiou C, Papaioannou S, Plachouras N, Makrydimas G. Evaluation of first-trimester screening by fetal nuchal translucency and maternal age. Prenatal Diagnosis 1998;18:133–7.
[12] Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Lancet 1998;352:343–56.
[13] Pajkrt E, van Lith JM, Mol BW, Bilardo CM. Screening for Down's syndrome by fetal nuchal translucency measurement in a general obstetric population. Ultrasound Obstet Gynecol 1998;12:163–9.
[14] De Biasio P, Siccardi M, Volpe G, Famularo L, Santi F, Canini S. First-trimester screening for Down syndrome using nuchal translucency measurement with free β–hCG and PAPP-A between 10 and 13 weeks of pregnancy – the combined test. Prenat Diagn 1999;19:360–3.
[15] Quispe J, Almandoz A, de Quiroga M, Isabel M. Traslucencia nucal fetal, un marcador de alteraciones cromosomicas en el primer trimester. Ginecol Obstet Mex 1999;45:183–6.
[16] Whitlow BJ, Chatzipapas IK, Lazanakis ML, Kadir RA, Economides DL. The value of sonography in early pregnancy for the detection of fetal abnormalities in an unselected population. BJOG 1999;106:929–36.
[17] Schwarzler P, Carbalho JS, Senat MV, Masroor T, Campbell S, Ville Y. Screening for fetal aneuploidies and fetal cardiac abnormalities by nuchal translucency thickness measurement at 10–14 weeks of gestation as part of routine antenatal care in an unselected population. BJOG 1999;106:1029–34.

[18] Thilaganathan B, Sairam S, Michailidis G, Wathen NC. First trimester nuchal translucency: effective routine screening for Down's syndrome. Br J Radiol 1999;72:946–8.
[19] Krantz DA, Hallahan TW, Orlandi F, Buchanan P, Larsen JW, Macro JN. First-trimester Down syndrome screening using dried blood biochemistry and nuchal translucency. Obstet Gynecol 2000;96:207–13.
[20] O'Callaghan SP, Giles WB, Raymond SP, McDougall V, Morris K, Boyd J. First trimester ultrasound with nuchal translucency measurement for Down syndrome risk estimation using software developed by the Fetal Medicine Foundation, United Kingdom – the first 2000 examinations in Newcastle, New South Wales, Australia. Aust N Z J Obstet Gynaecol 2000;40:292–5.
[21] Niemimaa M, Suonpaa M, Perheentupa A, Seppala M, Heinonen S, Laitinen P, et al. Evaluation of first trimester maternal serum and ultrasound screening for Down's syndrome in Eastern and Northern Finland. Eur J Hum Genet 2001;9:404–8.
[22] Schuchter K, Hafner E, Stangl G, Ogris E, Philipp K. Sequential screening for trisomy 21 by nuchal translucency measurement in the first trimester and serum biochemistry in the second trimester in a low-risk population. Ultrasound Obstet Gynecol 2001;18:23–5.
[23] Audibert F, Dommergues M, Bennattar C, Taieb J, Thalabard JC, Frydman R. Screening for Down syndrome using first-trimester ultrasound and second-trimester maternal serum markers in a low-risk population: a prospective longitudinal study. Ultrasound Obstet Gynecol 2001;18:26–31.
[24] Michailidis GF, Spencer K, Economides DL. The use of nuchal translucency measurement and second trimester biochemical markers in screening for Down's syndrome. BJOG 2001;108: 1047–52.
[25] Gasiorek-Wiens A, Tercanli S, Kozlowski P, Kossakiewicz A, Minderer S, Meyberg H, et al. Screening for trisomy 21 by fetal nuchal translucency and maternal age: a multicenter project in Germany, Austria and Switzerland. Ultrasound Obstet Gynecol 2001;18:645–8.
[26] Zoppi MA, Ibba RM, Floris M, Monni G. Fetal nuchal translucency screening in 12,496 pregnancies in Sardinia. Ultrasound Obstet Gynecol 2001;18:649–51.
[27] Brizot ML, Carvalho MH, Liao AW, Reis NS, Armbruster-Moraes E, Zugaib M. First-trimester screening for chromosomal abnormalities by fetal nuchal translucency in a Brazilian population. Ultrasound Obstet Gynecol 2001;18:652–5.
[28] Wayda K, Kereszturi A, Orvos H, Horvath E, Pal A, Kovacs L, et al. Four years experience of first-trimester nuchal translucency screening for fetal aneuploidies with increasing regional availability. Acta Obstet Gynecol Scand 2001;80:1104–9.
[29] Schuchter K, Hafner E, Stangl G, Metzenbauer M, Hofinger D, Philipp K. The first trimester 'combined test' for the detection of Down syndrome pregnancies in 4939 unselected pregnancies. Prenat Diagn 2002;22:211–5.
[30] Murta CG, Franca LC. Medida da translucencia nucal no rastreamento de anomalies cromossomicas. Rev Bras Ginecol Obstet 2002;24:167–73.
[31] Rozenberg P, Malagrida L, Cuckle H, Durand-Zaleski I, Nisand I, Audibert F, et al. Down's syndrome screening with nuchal translucency at 12 + 0 – 14 + 0 weeks and maternal serum markers at 14 + 1 – 17 + 0 weeks: a prospective study. Hum Reprod 2002;17:1093–8.
[32] Crossley JA, Aitken DA, Cameron AD, McBride E, Connor JM. Combined ultrasound and biochemical screening for Down's syndrome in the first trimester: a Scottish multicentre study. BJOG 2002;109:667–76.
[33] Lam YH, Lee CP, Sin SY, Tang R, Wong HS, Wong SF, et al. Comparison and integration of first trimester nuchal translucency and second trimester maternal serum screening for fetal Down syndrome. Prenat Diagn 2002;22:730–5.
[34] Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One-stop clinic for assessment of risk for trisomy 21 at 11–14 weeks: a prospective study of 15,030 pregnancies. Ultrasound Obstet Gynecol 2002;20:219–25.
[35] Comas C, Torrents M, Munoz A, Antolin E, Figueras F, Echevarria M. Measurement of nuchal translucency as a single strategy in trisomy 21 screening: should we use any other marker? Obstet Gynecol 2002;100:648–54.
[36] Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second

trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). J Med Screen 2003;10:56–104.
[37] Szabo J, Gellen J, Szemere G. First-trimester ultrasound screening for fetal aneuploidies in women over 35 and under 35 years of age. Ultrasound Obstet Gynecol 1995;5:161–3.
[38] Bewley S, Roberts LJ, Mackinson AM, Rodeck CH. First trimester nuchal translucency: problems with screening the general population 2. BJOG 1995;102:386–8.
[39] Jou HJ, Shih JC, Wu SC, Li TC, Tzeng CY, Hsieh FJ. First-trimester Down's syndrome screening by fetal nuchal translucency measurement in Taiwan. J Formos Med Assoc 2001;100:257–61.
[40] Tsai MS, Huang YY, Hwa K, Cheng CC, Lee FK. Combined measurement of fetal nuchal translucency, maternal serum free β–hCG, and pregnancy-associated plasma protein A for first-trimester Down's syndrome screening. J Formos Med Assoc 2001;100:319–25.
[41] Haddow JE. Antenatal screening for Down's syndrome: where are we and where next? Lancet 1998;352:336–7.
[42] Mol BW, Lijmer JG, van der Meulen J, Pajkrt E, Billardo CM, Bossuyt PM. Effect of study design on the association between nuchal translucency measurement and Down syndrome. Obstet Gynecol 1999;94:864–9.
[43] Nicolaides KH, Sebire NJ, Snijders RJ, Johnson S. Down's syndrome screening in the UK. Lancet 1996;47:906–7.
[44] Cuckle H. Fetal nuchal translucency test for Down's syndrome. Lancet 1997;350:1629–30.
[45] Nicolaides KH, Snijders RJ, Cuckle HS. Correct estimation of parameters for ultrasound nuchal translucency screening. Prenat Diagn 1998;18:519–21.
[46] Penn PA. Advances in prenatal screening for Down syndrome: II first trimester testing, integrated testing, and future directions. Clin Chim Acta 2002;324:1–11.
[47] Pandya PP, Snijders RJ, Psara N, Hilbert L, Nicolaides KH. The prevalence of non-viable pregnancy at 10–13 weeks of gestation. Ultrasound Obstet Gynecol 1996;7:170–3.
[48] Cuckle H. Down's syndrome screening in twins. J Med Screen 1998;5:3–4.
[49] Sebire NJ, Souka A, Skentou H, Geerts L, Nicolaides KH. Early prediction of severe twin-to-twin transfusion syndrome. Hum Reprod 2000;15:2008–10.
[50] Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first-trimester screening for Down's syndrome. Prenat Diagn 1998;18:511–23.
[51] Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome based on tests performed during the first and second trimesters. N Engl J Med 1999;341:461–7.
[52] Cuckle H. Time for a total shift to first-trimester screening for Down's syndrome. Lancet 2001; 358:1658–9.
[53] Hackshaw AK, Wald NJ. Assessment of the value of reporting partial screening results in prenatal screening for Down syndrome. Prenat Diagn 2001;21:737–40.
[54] Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow. Ultrasound Obstet Gynecol 1998;12:380–4.
[55] Bilardo CM, Muller MA, Zikulnig L, Schipper M, Hecher K. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. Ultrasound Obstet Gynecol 2001;17:288–94.
[56] Zoppi MA, Putzolu M, Ibba RM, Floris M, Monni G. First-trimester ductus venosus velocimetry in relation to nuchal translucency thickness and fetal karyotype. Fetal Diagn Ther 2002; 17:52–7.
[57] Antolin E, Comas C, Torrents M, Munoz A, Figueras F, Echevarria M, et al. The role of ductus venosus blood flow assessment in screening for chromosomal abnormalities at 10–16 weeks of gestation. Ultrasound Obstet Gynecol 2001;17:295–300.
[58] Murta CG, Moron AF, Avila MA, Weiner CP. Application of ductus venosus Doppler velocimetry for the detection of fetal aneuploidy in the first trimester of pregnancy. Fetal Diagn Ther 2002; 17:308–14.
[59] Mavrides E, Sairam S, Hollis B, Thilaganathan B. Screening for aneuploidy in the first trimester by assessment of blood flow in the ductus venosus. BJOG 2002;109:1015–9.

[60] Hecher K. Assessment of ductus venosus flow during the first and early second trimesters: what can we expect? Ultrasound Obstet Gynecol 2001;17:285–7.
[61] Cicero S, Curcio P, Papageorghiou A, Soneck J, Nicolaides KH. Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks of gestation: an observational study. Lancet 2001;358:1665–7.
[62] De Biasio PD, Venturini PL. Absence of nasal bone and detection of trisomy 21. Lancet 2002; 359:1344.
[63] Haddow JE, Palomaki GE, Knight GJ, Williams J, Miller WA, Johnson A. Screening of maternal serum for fetal Down's syndrome in the first trimester. N Engl J Med 1998;338:955–61.
[64] Monni G, Zoppi MA, Ibba RM, Floris M. Results of measurement of nuchal translucency ultrasound before and after training. Lancet 1997;350:1631–2.
[65] Scott F, Boogert A, Sinosich M, Anderson J. Establishment and application of a normal range for nuchal translucency across the first trimester. Prenat Diagn 1996;16:629–34.
[66] Kadir RA, Economides DL. The effect of nuchal translucency measurement on second-trimester biochemical screening for Down's syndrome. Ultrasound Obstet Gynecol 1997;9:244–7.
[67] Hackshaw AK, Wald NJ. Inaccurate estimation of risk in second trimester serum screening for Down syndrome among women who have already had first trimester screening. Prenat Diagn 2001;21:741–6.
[68] Palomaki GE, Knight GJ, McCarthy J, Haddow JE, Donhowe JM. Maternal serum screening for Down syndrome in the United States: a 1995 survey. Am J Obstet Gynecol 1997;176:1046–51.
[69] Egan JF, Kaminsky LM, DeRoche ME, Barsoom MJ, Borgida AF, Benn PA. Antenatal Down syndrome screening in the United States in 2001: a survey of maternal-fetal medicine specialists. Am J Obstet Gynecol 2002;187:1230–4.
[70] Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT). Randomized trial to assess safety and fetal outcome of early and midtrimester amniocentesis. Lancet 1998;351:242–7.
[71] Vintzileos AM, Ananth CV, Smulian JC, Scorza WE, Knuppel RA. Cost-benefit analysis of prenatal diagnosis for Down syndrome using the British or the American Approach. Obstet Gynecol 2000;95:577–83.

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Screening for aneuploidy: the genetic sonogram

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The increase in the use of ultrasonography in the practice of obstetrics, even over the past 10 years, has been remarkable. The application of this technology in the area of prenatal diagnosis has added so much to this aspect of obstetrics that many obstetricians now devote their entire practice to this aspect of obstetrics alone. The use of ultrasound for prenatal diagnosis is appealing for many reasons. Its safety and noninvasive characteristics are certainly two of its most desirable traits. But for many patients, an ultrasound examination provides reassurance that cannot be explained by scientific facts. At least daily in our practice, a high-risk patient presents for her comprehensive ultrasound, and after being counseled at length regarding the limitations and benefits of ultrasound in the detection of aneuploidy, still asks at the end of the examination, ''Do you think the baby has Down syndrome''? Some patients seem to believe that despite the explanation of the situation, if the baby did have Down syndrome, we would know. Certainly patients are not the only people who believe this. Many obstetricians believe ultrasound to have a sensitivity and specificity that is superior to what is reported in the medical literature.

Ultrasound is an excellent tool, but it is far from perfect. Like other diagnostic tools, if its strengths and weaknesses are not understood, its use can cause harm to patients. If patients are falsely reassured by an ultrasound examination, they may decide to forego definitive testing when that is indeed what they desire. Equally worrisome is the patient who is counseled that a particular finding has more significance than it does, and she decides to have an invasive test that is not indicated and not really desired. In the current intense medicolegal environment, often medical recommendations are made more to protect the providers from possible litigation than they are based on true medical opinion. Clearly, an in-

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vasive test is unlikely to miss the diagnosis and is significantly less likely to be associated with a legal action against the providers. The application of prenatal ultrasound in aneuploidy risk assessment is a very valuable tool, and based on the exponential increase in the number of research studies being published, the value is only going to increase further. This article covers the common aneuploidies, the common findings on ultrasound, and what most of the available literature supports regarding the significance of these findings in the risk assessment of patients. Although the use of ultrasound may be complicated, most patients can understand its limitations and accept and request its use, despite its not being perfect.

Trisomy 21

Advancing maternal age causes an increase in the risk of an aneuploid fetus. The most common aneuploidy seen in women of advanced maternal age is Down syndrome, or trisomy 21. This association was recognized as early as 1909, and it is now known that there is an increased risk of nondisjunction during meiosis as the age of the oocytes increase [1]. One hundred years later, the exact mechanism responsible for this increased risk of nondisjunction is still unknown, but it is known that it also leads to an increased risk of having a pregnancy with 47, + 13; 47, + 16; 47, + 18; 47,XXX; and 47,XXY.

The classical description of children with Down syndrome was published in 1866 by Down [2]; however, it was not until 1959 that the underlying genetic etiology was discovered [3]. Trisomy 21 is now known to be one of the most common chromosomal abnormalities seen in live born children. These children all have mental retardation with most being mild to moderately mentally retarded. Although children with Down syndrome certainly have their own familial features, they also have some characteristic features that are a result of their extra 21 chromosome. Phenotypic features that are characteristic in Down syndrome children include up-slanting palpebral fissures; mid-face hypoplasia; excess skin on the back of the neck; brachycephaly; small, posteriorly rotated ears; and hypotonia. Although commonly described as having an enlarged tongue, more accurately it is their lack of muscle tone that gives them that characteristic appearance. The most common structural abnormality in these children is congenital heart disease affecting about 40% of cases. Gastrointestinal tract anomalies, such as duodenal atresia and imperforate anus, are also more common in these children.

Approximately 95% of Down syndrome is cause by simple trisomy of chromosome 21. In about 3% of cases, the extra copy of the 21st chromosome is a result of a translocation, and a small percentage of cases are mosaic [4]. In 1968, only 2 years after Steele and Breg [5] reported the first successful amniocentesis for chromosomal analysis, the first prenatal diagnosis of Down syndrome was published [6]. Since that time, there has been extensive research in improving prenatal diagnosis of Down syndrome.

Major anomalies seen with Down syndrome

Since the early use of ultrasound for the detection of Down syndrome, the focus and the approach of ultrasound screening has evolved significantly. Early attempts to diagnose Down syndrome with ultrasound were through the detection of structural anomalies during the second trimester. Recognizing that infants with Down syndrome were at increased risk for specific types of major anomalies, prenatal ultrasound was performed to detect these structural defects.

The most common congenital anomaly seen in newborns with Down syndrome is a heart defect, affecting about 40% to 45% of babies with the condition [7]. Endocardial cushion and ventricular septal defects are the two most common defects. The detection rate for congenital heart disease varies depending on the experience of the examiner and the specific defect present, but in general approximately 60% to 80% of heart defects can be detected on prenatal ultrasound when performed by an appropriately trained sonographer [8]. Unfortunately, ventricular septal defects are one of the more difficult congenital heart defects to diagnose prenatally, and most are not detected until after delivery. Although atrioventricular canal defects are the most common cardiac malformations detected on prenatal ultrasound, it is estimated that rate of detection is less than 50% on routine ultrasound examination [9].

After heart defects, abnormalities of the gastrointestinal tract are the next most common class of defects. Gastrointestinal tract abnormalities are found in up to 12% of newborns with Down syndrome [10]. The classical gastrointestinal defect is duodenal atresia or stenosis. The problem with prenatal diagnosis of this abnormality is that it is not usually apparent until later in pregnancy, usually after 20 to 24 weeks of gestation, and is not diagnosed on the 18- to 20-week anatomic survey. Duodenal atresia is the most common cause of bowel obstruction in newborns. Although it is considered one of the classic Down syndrome lesions, it is seen in only 2.5% of these newborns [11]. When duodenal atresia is diagnosed on prenatal ultrasound, however, trisomy 21 is the most frequently associated condition occurring in 27% to 34% of cases [12]. Other gastrointestinal abnormalities that can be seen in children with Down syndrome include tracheoesophageal fistula, pyloric stenosis, omphalocele, annular pancreas, Hirschsprung's disease, and imperforate anus. Each of these other gastrointestinal abnormalities is usually present in less than 1% of newborns with Down syndrome.

Another congenital malformation that is commonly described in utero is the cystic hygroma. This is a malformation of the lymphatic system that leads to enlargement and the formation of cysts. Cystic hygroma can be found in other areas, but most commonly are seen in the back of the fetal neck. These malformations characteristically are septated, and this feature helps to differentiate them from other neck masses. Cystic hygroma can vary in size and occasionally become so large that they envelop the fetus. Commonly a cystic hygroma regresses in size in utero, so that at delivery the only evidence of their previous existence is excess skin or webbing of the neonatal neck. This prenatal finding has a poor prognosis and frequently is associated with other anomalies. The

reported frequency of associated aneuploidy with cystic hygroma is 60% to 80%. Overwhelmingly, the most common chromosomal finding is Turner's syndrome, but trisomy 21 is not uncommon. Brumfield et al [13] found that the presence of septations within the cystic hygroma increased the likelihood of associated aneuploidy. They also found that fetuses with septated cystic hygroma were more likely to develop hydrops and less likely to be live born.

Multiple other structural malformations have been reported in newborns with Down syndrome, but often the abnormalities are not amenable to prenatal diagnosis. For example, abnormalities of the cervical spine are frequently present in these children, but typically cannot be diagnosed prenatally. There are other major anomalies that have been associated with Down syndrome that can be diagnosed by prenatal ultrasound, but their frequency is low and adds very little to the overall detection rate. This leaves the detection rate of Down syndrome by means of detecting major anomalies less than ideal.

Ultrasound markers and Down syndrome

Given the previous information and given the knowledge that less than 50% of newborns with Down syndrome have a major anomaly at birth, even if all the structural abnormalities present were detected using prenatal ultrasound, only a fraction of Down syndrome pregnancies would be identified prenatally. To increase the detection rate of Down syndrome fetuses, researchers have focused on detecting other Down syndrome features outside of major anomalies. Prenatal ultrasound is being primarily used to detect the variations in normal structures that are more commonly seen in fetuses with Down syndrome compared with the normal population. These variations are referred to in the literature as "soft markers" for Down syndrome. The commonly studied soft markers include increased nuchal fold, mild pyelectasis, a relative shortening of the humerus and femur, fifth finger clinodactyly, echogenic foci in the fetal heart, choroid plexus cysts (CPC), and echogenic bowel. Unfortunately, studies evaluating the significance of these markers have varied widely. Over the past 20 years, there have been hundreds of articles regarding the use of ultrasound for adjusting or estimating the risk of aneuploidy. Clearly, not all of these studies have had appropriate scientific strength definitively to guide clinical practice. As with many areas of active research, although some of the results have differed, there are some study findings that are fairly consistent. In the advanced maternal age patient, the absence of any markers seems to be associated with a decreased risk compared with their age-related empiric risk. Following a normal ultrasound, the reported reduction in aneuploidy risk has varied from approximately 60% to 83% [14–16]. In a survey of maternal-fetal medicine specialists by Egan et al [17] in 2002, 72% of maternal-fetal medicine physicians reported using second-trimester ultrasound to adjust aneuploidy risk. Of the maternal-fetal medicine specialists who reported using a normal ultrasound to decrease risk, the most frequently cited risk reduction was 50% [17]. The risk adjustment secondary to the presence of markers, and which markers are most significant, remains controversial. Of the

second-trimester markers commonly used, nuchal fold was the first to be described and hence has been studied the longest.

Children with Down syndrome are often described as having loose skin on the nape of neck; likewise, fetuses with Down syndrome frequently have the sonographic appearance of a thickened nuchal fold. The measurement is made in the transverse plane of the fetal head slightly off the biparietal diameter. This plane should include the cerebellum and the occipital bone. The measurement is from the outer edge of the occipital bone to the outer edge of the skin. Using a nuchal fold of 6 mm as a cutoff at 15 to 20 weeks, Benacerraf et al [18] reported a positive predictive value for Down syndrome of 69% with a false-positive rate of 0.1%. In their study, 42% of fetuses with Down syndrome had a nuchal fold of 6 mm or greater.

Fetal biometry has also been used as a marker for aneuploidy. It was recognized that the femur and humerus of fetuses with Down syndrome have a tendency to be slightly shorter compared with normal controls. Benacerraf et al [19–21] were one of the earliest investigators to describe this subtle difference and then apply it to fetuses referred to their unit for amniocentesis. The lengths were considered short when the ratio of the measured-to-expected femoral lengths were less than or equal to 0.91 and the ratio of the measured-to-expected humeral lengths were less than or equal to 0.90. They found that by using this definition, 44% of fetuses with Down syndrome had short femurs and 54% had a short humerus. Less than 5% of controls were defined as having short measurements. Nyberg et al [22] also studied this aspect of Down syndrome screening and reported femur and humerus cutoff ratios very similar to the previous investigators. Using measured-predicted humerus length ratio of less than or equal to 0.89 and less than or equal to 0.91 for the femur, they reported 24% of fetuses with Down syndrome had short humeri and 24% had short femurs. In a study designed to find the most diagnostically efficient of the sonographic markers in high-risk patients, Vintzileos et al [23] found 47.6% of fetuses with Down syndrome had a short humerus compared with only 24.1% with a short femur. For the purpose of decreasing the false-positive rate and simplifying the number of markers that needed to be assessed, they concluded that in their population humerus measurement was better than femur measurement. Likewise, in a study designed to improve on multiple marker screening, Owen et al [24] added measured-predicted femur length ratio as adjunct to serum screening. They found that it had very little effect on the performance of serum screening and was not beneficial. Although overall the sensitivity for these measurement ratios varies somewhat from study to study, the positive predictive value for diagnosing Down syndrome based on shortened femur or humerus has been consistently low as isolated markers. If one requires both measurements to be short to meet the criteria, the positive predictive value is slightly better at approximately 35% [22].

Another skeletal finding that has been found to be associated with Down syndrome is clinodactyly. Clinodactyly is diagnosed as either an absence or a hypoplastic appearance of the middle phalanx of the fifth digit. The diagnosis is most accurately made when the fetal fingers are extended so that the middle

phalanx can be clearly seen. This radiologic finding translates to a medial deviation of the finger on physical examination. Deren et al [25] found clinodactyly to have a sensitivity of 17% and a positive predictive value of only 5.1%. In a large multicenter study involving 176 fetuses with Down syndrome, Hobbins et al [26] reported very similar findings with clinodactyly having a sensitivity of 18%. In the orthopedic literature, this finding is seen in 1% of normal individuals depending on the definition used and population studied. Clinodactyly is observed in 60% of children with Down syndrome and is seen in a number of other genetic syndromes, such as Cornelia de Lange's syndrome, Russell-Silver dwarfism, Klinefelter's syndrome, and Turner's syndrome. Most cases of clinodactyly are isolated and inherited as an autosomal-dominant trait. Given its mode of inheritance, this finding has no value as a screening marker for Down syndrome when one of the parents is also affected.

Echogenic intracardiac focus (EIC) is another soft marker that has been studied in relation to Down syndrome. It is defined as a small bright area within the fetal ventricle on the four-chamber view of the heart. The echogenic focus is most commonly described on the left side, but it can be on the right side. Mineralization of the papillary muscle is responsible for this bright appearance on prenatal ultrasound. EIC is the most commonly found marker seen as a variant in normal fetuses. The prevalence of echogenic foci in either high- or low-risk populations is 3% to 5% [26,27]. In the detection of Down syndrome, isolated echogenic focus has a sensitivity of 21% to 28% and a positive predictive value of 7% [28]. The ultrasound setting and the ethnic background of the patient have been reported to affect the prevalence of this marker. Shipp et al [29] reported that EIC was found three times more often in Asian patients (30% prevalence) compared with whites. This needs to be considered when counseling Asian patients regarding the significance of EIC as a soft marker.

A CPC is a round discrete hypoechogenic area within the choroid plexus that has been associated with various types of aneuploidy. There have some conflicting results in the literature regarding risk of trisomy 21 when this is present on ultrasound. Bromley et al [30] reported a series of 143 fetuses with Down syndrome and found that the frequency of CPC was no greater than that found in the general population. Based on this result, they recommended that CPC in isolation not be used to increase the risk of Down syndrome. Although there has been debate regarding its association with trisomy 21, the stronger association is with trisomy 18, and is discussed in that section.

The echogenic appearance of fetal bowel is also a soft marker for aneuploidy. There has been much controversy regarding this sonographic finding, mainly stemming from the subjective nature of the diagnosis. As with intracardiac foci, the appearance of the bowel can be affected simply by altering the ultrasound machine settings. Most researchers now use the comparison of the bowel with fetal bone, and the bowel must be at least as bright as bone to be called echogenic. The sensitivity of echogenic bowel for the detection of Down syndrome is approximately 12% to 13% with a positive predictive value of 14% [26,31]. Echogenic bowel is reported in less than 1% of fetuses with a normal karyotype. Since first

reported echogenic bowel has been associated with a number of other adverse fetal outcomes including cystic fibrosis, cytomegalovirus infection, growth restriction, and bowel atresia. For this reason, a more extensive work-up needs to be considered when fetal echogenic bowel is noted on prenatal ultrasound.

Pyelectasis is another frequently used marker for Down syndrome. Most studies use a dilated renal pelvis of 4 mm in the anteroposterior dimension or greater as the definition for abnormal. Isolated pyelectasis is a frequent ultrasound finding, and its significance as a marker for Down syndrome is often debated in the literature. During the second trimester pyelectasis may be seen in approximately 2% to 3% of fetuses with a normal karyotype compared with 25% of fetuses with Down syndrome. Vintzileos et al [23] obtained the most promising results while assessing isolated pyelectasis as a soft marker for Down syndrome. Their study included over 600 high-risk patients, and they reported a sensitivity of 34.7% for the detection of Down syndrome. In a large multicentered trial that included 176 Down syndrome fetuses, however, Hobbins et al [26] reported a sensitivity of only 17.2% for isolated pyelectasis. Similarly, in another fairly large study of approximately 3838 midtrimester pregnancies, Deren et al [25] reported a sensitivity of 14%, but a positive predictive value of only 4.8% for isolated pyelectasis. Lastly, in a study designed to find the best second-trimester markers for Down syndrome, Vergani et al [32] found that although pyelectasis was significantly more common in fetuses with Down syndrome, it was not found to be an independent predictor of trisomy 21 when regression analysis was applied. Their recommendation was that when pyelectasis is diagnosed, a more thorough evaluation should be performed in search of other independent predictors of Down syndrome. The counseling given to the patient should then be based on the presence of the combination of findings, not isolated pyelectasis. In agreement with this concept, most recent investigators only use the presence of pyelectasis to adjust aneuploidy risk if it is in combination with other markers.

Not only has there been an effort to find more subtle findings for Down syndrome screening, but there has also been a major push to make the diagnosis earlier in the pregnancy. The benefits of earlier diagnosis are obvious. For most women who are at increased risk, this gives them reassurance sooner and decreases anxiety. For those women whose pregnancy is affected by aneuploidy, earlier diagnosis gives them more time to consider their options and to gather the information they need. Some of the most recent advances in the prenatal diagnosis of Down syndrome have been those tests performed in the first trimester. The reader is referred to the article elsewhere in this issue on first-trimester sonographic screening with nuchal translucency and absent nasal bone.

Trisomy 18

Trisomy 18 is the second most common autosomal trisomy that is seen in the advanced maternal age population. The incidence is about 1 per 8000 live births

[33]. Similar to Down syndrome, trisomy 18 is screened using serum screening, maternal age, and ultrasonography. Fetuses and newborns with trisomy 18 often have multiple major anomalies. Most newborns with trisomy 18 die within the first few weeks of life, but approximately 6% survive to 1 year [34]. Trisomy 18 is more commonly associated with structural anomalies and is more likely to be diagnosed with prenatal ultrasound compared with Down syndrome. The most common abnormality seen on prenatal ultrasound of trisomy 18 is not a structural abnormality or a soft marker, however, but is intrauterine growth retardation. Nyberg et al [35] reported intrauterine growth retardation in 51% of all fetuses with trisomy 18 and in 89% of fetuses who were examined after 24 weeks. Two neonatal studies on the natural history of trisomy 18 report mean birthweights of 1.8 to 2.2 kg, confirming the significant risk for intrauterine growth retardation [33,36]. As with Down syndrome ultrasound screening, trisomy 18 has been associated with specific major anomalies and the presence of soft markers. Many studies report ultrasound findings in at least 50% of fetuses, and numerous studies report 70% or more of fetuses with trisomy 18 being detected by prenatal ultrasound [15,35,37,38].

Major anomalies in trisomy 18

The most common major anomalies seen in fetuses with trisomy 18 are cardiac defects and skeletal abnormalities. Approximately 80% to 90% have a heart defect, with ventricular septal defects, patent ductus arteriosus, and atrial septal defects noted most commonly. These particular heart lesions are difficult to diagnose and most often are undetected while in utero.

The skeletal abnormalities involve the limbs and the skull. On prenatal ultrasound the fetal head in trisomy 18 is commonly brachycephalic. A finding that is fairly unique to fetuses with trisomy 18 is the so-called "strawberry-shaped" head, where there is a flattening of the occiput and a narrow bifrontal diameter. Although this finding has been strongly associated with trisomy 18, it is not a common finding. In a recent review of ultrasound findings in trisomy 18 fetuses, this was seen in only 1 out of 30 fetuses [39]. Abnormalities of the hands or feet can be seen in 73%, but these findings are rarely isolated [40]. In the classical description of fetuses with trisomy 18, the hands are fisted with the thumb and the first digit overlapping the third digit. The fetal hands are not necessarily fixed in this position, and the fingers can be seen to extend and appear normal. The lower-extremity abnormalities that can be seen in trisomy 18 are rocker-bottom foot and occasionally limb reduction abnormalities. Talipes is seen in approximately 25% to 30%, but uniformly these fetuses have other anomalies in addition to their clubfeet.

Multiple other major anomalies can be seen in trisomy 18. Omphalocele, diaphragmatic hernia, various renal anomalies, central nervous system malformations, and micrognathia have also been reported. Omphalocele has been reported in 13% to 14% [39,40] of trisomy 18 cases. The risk of aneuploidy is increased when the omphalocele does not contain liver and when other anomalies

are present. In a series of 79 fetuses with diaphragmatic hernia, Nicholaides et al [41] reported that 10 fetuses were positive for trisomy 18, and all of these fetuses had additional anomalies.

Soft markers in trisomy 18

Many of the soft markers discussed with Down syndrome are also noted in fetuses with trisomy 18 [35]. Cystic hygroma or a thickened nuchal fold is present in approximately 20%. A single umbilical artery is seen in 13% of trisomy 18 fetuses compared with 1% of all live born infants. Pyelectasis has been reported to be seen in 10% of cases with trisomy18 [39].

The most notable soft marker for trisomy 18 is the CPC. A CPC is a benign cystic structure within the lateral ventricle of the fetal brain. The prevalence is reported as 1% in the low-risk population during second-trimester ultrasound, but CPC can be documented in 3% of head ultrasounds in normal newborns [42]. There has been much controversy regarding the significance of this finding because it is often seen in normal fetuses and newborns. The reported prevalence of CPC in fetuses with trisomy 18 varies from 29% to 66% [35,39,43,44]. The wide variation in the prevalence of CPC among euploid and aneuploid fetuses has led investigators to question if there are specific characteristics of CPCs that make some of them more significant than others. Characteristics that have been studied include the significance of its size, whether it is unilateral or bilateral, whether it is persistent, its significance as an isolated finding versus being in combination with other findings, and its significance in the low-risk population. In a review of 33 articles regarding CPCs and aneuploidy, Peleg and Yankowitz [45] addressed many of the controversial issues surrounding the significance of the CPC. The size of CPC in the euploid fetuses (1 to 21 mm) tended to be slightly less than the size in the aneuploidy fetuses (3 to 20 mm). They could find no correlation between multiplicity, multilocularity, or complexity of the CPCs and aneuploidy. They confirmed the fact that most resolve later in the gestation, but resolution (or persistence) has no effect on aneuploidy risk. As with other markers, the risk of aneuploidy increases when in combination with other markers or other risk factors, such as advanced maternal age or positive serum screening, are present. In this review of the literature, of the reported abnormal karyotypes detected with CPCs, 79% were trisomy 18, 13% were trisomy 21, 1.5% were trisomy 13, 2% were triploidy, and the remainder were associated with other sporadic abnormalities.

Trisomy 13

Trisomy 13 is the third most common autosomal trisomy that has been associated with advanced maternal age. This trisomy does not have a typical pattern of serum screening and is not screened by serum analytes. The incidence of trisomy 13 is approximately 1 per 12,000 live births. These fetuses and

newborns are typical severely affected and have multiple defects. The prenatal ultrasound detection of trisomy 13 is reported to be as high as 90% to 100% [40,46].

Major anomalies in trisomy 13

Like the other trisomies, trisomy 13 fetuses have a significant risk of congenital heart defects with approximately 80% of newborns diagnosed with congenital heart defects. The most common heart lesion is a ventricular septal defect, but hypoplastic left heart and double outlet right ventricle have also been described [46,47].

Compared with the other trisomies, fetuses with trisomy 13 fetuses tend to have more severe central nervous system anomalies. The typical lesion is holoprosencephaly reported in about 39% of fetuses [46]. Other central nervous system anomalies include lateral ventricular dilation, enlarged cisterna magna, and microcephaly. Midline facial abnormalities are also frequently seen in these children, and this is most likely related to their underlying brain abnormality. The normal growth and development of the face is intimately related to the underlying brain development. Without normal underlying brain, many features of the face do not develop normally. Facial clefts, abnormal eye placement (hypotelorism), and abnormal nose development are seen with increased frequency in trisomy 13.

Renal abnormalities are also a frequent finding in fetuses with trisomy 13. Renal abnormalities may be seen in approximately one third of patients and include ureteric obstruction, multicystic kidneys, and enlarged and echogenic kidneys. The renal abnormalities may be unilateral or bilateral [46].

The limb abnormality classically described in trisomy 13 is polydactyly of the hands and feet. Polydactyly is seen in approximately 21% of fetuses with trisomy 13 and it can be seen in a number of other genetic syndromes, such as Meckel-Gruber syndrome, Bardet-Biedl syndrome, short-rib polydactyly, and Pallister-Hall syndrome [46]. Importantly, isolated polydactyly can be an autosomal-dominant trait with incomplete penetrance. In some countries in Africa the prevalence is 1% to 2%. It is seen 10 times more frequent in blacks compared with whites. Fetuses with trisomy 13 tend to have multiple anomalies, and this diagnosis is less likely in a fetus with isolated polydactyly.

Other anomalies that can be seen with trisomy 13, but are less frequent, include omphalocele and neural tube defects. Intrauterine growth retardation can be seen in up to 50% [46].

Soft markers in trisomy 13

Similar to the other trisomies, trisomy 13 has an increased prevalence of soft markers on prenatal ultrasound. Considering the fact that almost all fetuses with trisomy 13 have major anomalies that are diagnosed on prenatal ultrasound,

however, the role of soft markers is much less important with this trisomy. Soft markers that have been associated with trisomy 13 are increased nuchal fold and EIC. Nuchal thickening or cystic hygroma can be seen in approximately 20% of trisomy 13 fetuses, and EIC has been found in 30% [46].

Summary

Over the past 10 years, the use of ultrasound in aneuploidy risk estimation has improved the way obstetrics is practiced. It allows patients to obtain more personalized risk assessment and has allowed many women a reasonable alternative to invasive testing. The addition of soft markers to the sonographic screening for aneuploidy has been extremely beneficial, especially when considered in combination with other ultrasound findings. The best estimate of risk seems to be achieved through the combined use of ultrasound, maternal serum screening, and maternal age. The literature supports the use of soft markers only when applied to the high-risk population, where the prevalence of aneuploidy is increased. If this information is applied to the low-risk populations, especially in isolation, the lower prevalence of aneuploidy makes the positive predictive value too low to be of any value in counseling patients. As with many screening tests it occasionally misses the diagnosis, and every patient needs to understand this potential shortcoming. It is a personal decision regarding their willingness to accept the risk of a missed diagnosis versus the risk of fetal loss from an invasive procedure. Although it is far from perfect, in the right hands and with appropriate counseling ultrasound is an excellent tool. This is such an important decision for women and their families, and it is worth the time it takes to explain the benefits and limitations of this test.

References

[1] Shuttleworth GE. Mongolian imbecility. BMJ 1909;2:661–5.
[2] Down JLH. Observations on an ethnic classification of idiots: clinical lecture reports. London Hospital 1866;3:259.
[3] Lejeune J, Gautier M, Turpin R. Etude des chromosomes somatiques de neuf enfants mongoliens. C R Acad Sci 1959;248:1721–2.
[4] Hook EG. Epidemiology of Down syndrome. In: Pueschel SM, Rynders JE, editors. Down syndrome: advances in biomedicine and the behavioral sciences. Cambridge: Ware Press; 1982. p. 11.
[5] Steele MW, Breg WR. Chromosome analysis of human amniotic fluid cells. Lancet 1966;1: 383–5.
[6] Valenti C, Schutta EJ, Kehaty T. Prenatal diagnosis of Down's syndrome. Lancet 1968;2:220.
[7] Frid C, Drott P, Lundell B, Rasmussen F, Anneren G. Mortality in Down's syndrome in relation to congenital malformations. J Intellect Disabil Res 1999;43:234–41.
[8] Simpson LL. The four chambered view: expectations and limitations. Contemporary OB/GYN 1998;43:89–112.
[9] Allen LD. Atrioventricular septal defects in the fetus. Am J Obstet Gynecol 1999;181: 1250–3.

[10] Ranzini AC, Guzman ER, Ananth CV, Day-Salvatore D, Fisher AJ, Vintzileos AM. Sonographic identification of fetuses with Down syndrome in the third trimester: a matched control study. Obstet Gynecol 1999;93:702–6.
[11] Epstein CJ. Down syndrome, trisomy 21. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. Metabolic basis of inherited disease. New York: McGraw-Hill; 1989. p. 291–326.
[12] Bianchi DW, Crombleholme TM, D'Alton MA. Duodenal atresia. In: Fetology: diagnosis and management of the fetal patient. New York: McGraw-Hill; 2000. p. 529.
[13] Brumfield CG, Wenstrom KD, Davis RO, Owen J, Cosper P. Second trimester cystic hygroma: prognosis of septated and nonseptated lesions. Obstet Gynecol 1996;88:979–82.
[14] Nyberg AS, Bromley B, Frigoletto FD, Benacerraf BR. Can the presumed risk of autosomal trisomy be decreased in fetuses of older women following a normal sonogram? J Ultrasound Med 1995;14:297–302.
[15] Sohl BD, Scioscia AL, Budorick NE, Moore TR. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181:898–903.
[16] Vintzileos AM, Guzman ER, Smulian JC, Yeo L, William E, Knuppel RA. Down syndrome risk estimation after normal genetic sonography. Am J Obstet Gynecol 2002;187:1226–9.
[17] Egan JF, Kaminsky LM, DeRoche ME, Barsoom MJ, Borgida AF, Benn PA. Antenatal Down syndrome screening in the United States in 2001: a survey of maternal-fetal medicine specialists. Am J Obstet Gynecol 2002;187:1230–4.
[18] Benacerraf BR, Frigoletto FD, Cramer DW. Down syndrome: sonographic sign for the diagnosis in the second trimester fetus. Radiology 1987;163:811–3.
[19] Benacerraf BR, Gelman R, Frigoletto FD. Sonographic identification of second-trimester fetuses with Down syndrome. N Engl J Med 1987;317:1371–6.
[20] Benacerraf BR, Nadel A, Bromley B. Identification of second-trimester fetuses with autosomal trisomy by use of a sonographic scoring index. Radiology 1994;193:135–40.
[21] Benacerraf BR, Neuberg D, Bromley B, Frigoletto FD. Sonographic scoring index for prenatal detection of chromosomal abnormalities. J Ultrasound Med 1992;11:449–58.
[22] Nyberg DA, Resta RG, Luthy DA, Hickok DE, Williams MA. Humerus and femur length shortening in the detection of Down's syndrome. Am J Obstet Gynecol 1993;168:534–8.
[23] Vintzileos AM, Campbell WA, Guzman ER, Smulian JC, Mclean DA, Ananth CV. Second trimester ultrasound markers for detection of trisomy 21: which markers are best? Obstet Gynecol 1997;89:941–4.
[24] Owen J, Wenstrom KD, Harden MJ, Boots LR, Hsu C, Cosper PC, et al. The utility of fetal biometry as an adjunct to the multiple-marker screening test for Down syndrome. Am J Obstet Gynecol 1994;171:1041–6.
[25] Deren O, Mahoney MJ, Copel JA, Bahado-Singh RO. Subtle ultrasonographic anomalies: do they improve the Down syndrome detection rate. Am J Obstet Gynecol 1998;178:441–5.
[26] Hobbins JC, Lezotte DC, Persutte WH, DeVore GR, Benacerraf BR, Nyberg DA, et al. An 8-center study to evaluate the utility of midterm genetic sonograms among high-risk pregnancies. J Ultrasound Med 2003;22:33–8.
[27] Sepulveda W, Romero D. Significance of echogenic foci in the fetal heart. Ultrasound Obstet Gynecol 1998;12:445–9.
[28] Wax JR, Guilbert J, Mather J, Chen C, Royer D, Steinfeld JD, et al. Efficacy of community-based second trimester genetic ultrasound in detecting the chromosomally abnormal fetus. J Ultrasound Med 2000;19:689–94.
[29] Shipp TD, Bromley B, Liberman EP, Benacerraf BR. The frequency of the detection of fetal echogenic intracardiac foci with respect to maternal race. Ultrasound Obstet Gynecol 2000; 15:460–2.
[30] Bromley B, Lieberman R, Benacerraf BR. Choroid plexus cysts: not associated with Down syndrome. Ultrasound Obstet Gynecol 1996;8:232–5.
[31] Nyberg DA, Resta RG, Mahony BS, Dubinsky T, Luthy DA, Hickok DE, et al. Fetal hyperechogenic bowel and Down's syndrome. Ultrasound Obstet Gynecol 1993;3:330–3.

[32] Vergani P, Locatelli A, Piccoli MG, Ceruti P, Mariani E, Pezzullo JC, et al. Best second trimester sonographic markers for the detection of trisomy 21. J Ultrasound Med 1999;18:469–73.
[33] Embleton ND, Wyllie JP, Wright MJ, Burn J, Hunter S. Natural history of trisomy 18. Arch Dis Child 1996;75:38f–41f.
[34] Rasmussen SA, Wong LC, Yang Q, May KM, Friedman JM. Population-based analysis of mortality in trisomy 13 and trisomy 18. Pediatrics 2003;111:777–84.
[35] Nyberg DA, Kramer D, Resta RG, Kapur R, Luthy DA, Hickok DE. Prenatal sonographic findings of trisomy 18: review of 47 cases. J Ultrasound Med 1993;12:103–13.
[36] Baty BJ, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13: 1. Growth, physical assessment, medical histories, survival, and recurrence risk. Am J Med Genet 1994; 49:175–8.
[37] Devore GR. Second trimester ultrasonography may identify 77–97% of fetuses with trisomy 18. J Ultrasound Med 2000;19:565–76.
[38] Bahado-Singh RO, Choi S, Oz U, Mendilcioglu I, Rowther M, Persutte W. Early second-trimester individualized estimation of trisomy 18 risk by ultrasound. Obstet Gynecol 2003; 101:463–8.
[39] Brumfield CG, Wenstrom KD, Owen J, Davis RO. Ultrasound findings and multiple marker screening in trisomy 18. Obstet Gynecol 2000;95:51–4.
[40] Benacerraf BR, Miller WA, Frigoletto FD. Sonographic detection of fetuses with trisomies 13 and 18: accuracy and limitations. Am J Obstet Gynecol 1988;158:404–9.
[41] Nicholaides K, Shawwa L, Brizot M, Snijders R. Ultrasonographically detectable markers of fetal chromosomal defects. Ultrasound Obstet Gynecol 1993;3:56–69.
[42] Riebel T, Nasir R, Weber K. Choroid plexus cysts: a normal finding on ultrasound. Pediatr Radiol 1992;22:410–2.
[43] Benacerraf BR, Harlow B, Frigoletto FD. Are choroid plexus cysts an indication for second trimester amniocentesis? Am J Obstet Gynecol 1990;162:1001–6.
[44] Snijders R, Shawa L, Nicolaides KH. Fetal choroid plexus cysts and trisomy 18: assessment of risk based on ultrasound findings and maternal age. Prenat Diagn 1994;14:1119–27.
[45] Peleg D, Yankowitz J. Choroid plexus cysts and aneuploidy. J Med Genet 1998;35:554–7.
[46] Lehman CD, Nyberg DA, Winter TC, Kapur RP, Resta RG, Luthy DA. Trisomy 13 syndrome: prenatal US findings in a review of 33 cases. Radiology 1995;194:217–22.
[47] Wladimiroff JW, Stewart PA, Reuss A, Sachs ES. Cardiac and extra-cardiac anomalies as indicators for trisomies 13 and 18: a prenatal ultrasound study. Prenat Diagn 1989;9:515–20.

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Routine screening for fetal anomalies: expectations

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The use of ultrasound in obstetrics has become ubiquitous. Although not recommended by the American College of Obstetrics and Gynecology as a routine procedure, it is the rare fetus that escapes having at least one ultrasound. One of the most common indications for performing an ultrasound is to screen for fetal anomalies. Because of this, it is important to know what the expectations should be for both the patient who undergoes this examination and the performing sonographer. This article summarizes the literature that examines the sensitivity and specificity of ultrasound to detect fetal anomalies. In addition, it gives an overview of the routine screening ultrasound examination with emphasis on when a patient should be referred for a targeted ultrasound examination.

Epidemiology of fetal anomalies

It is important to have an understanding of the epidemiology of birth defects for several reasons. First, in examining the literature relating to the detection of birth defects by ultrasound, it is worthwhile to be aware of what the overall incidence of fetal anomalies is in the studied populations. If the incidence is lower than that expected in the population, complete ascertainment of anomalies may not have occurred. If higher, the detection rates are higher because the population may be high-risk, having already been prescreened by ultrasound or biochemical markers. Second, by knowing which fetal anomalies are most common, one can have a higher index of suspicion when screening the fetus with ultrasound. Additionally, when an anomaly is discovered, the patient can be given incidence information, which is commonly asked for in these circumstances.

Unfortunately, it is very difficult to ascertain the true incidences of various anomalies. Although many state and country birth defect registries exist, there are differences in definitions of birth defects and completeness of ascer-

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Table 1
Incidences of selected malformations (per 1000 births)

Malformation	Incidence
Heart (overall)	5.6
Central nervous system (overall)	4.3
Hydronephrosis	3.2
Cleft lip and palate	1.9
Foot deformity	1.6
Hydrocephalus	1.2
Spina bifida	1.1
Anencephaly	0.9
Ventral wall defect	0.9
Unilateral cystic renal disease	0.6
Diaphragmatic hernia	0.5
Polycystic kidney disease	0.4
Bilateral renal agenesis	0.3

Data from Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus study. Am J Obstet Gynecol 1999;181:446–54; Levi S. Ultrasound in prenatal diagnosis: polemics around routine ultrasound screening for second trimester fetal malformations. Prenat Diagn 2002;22:285–95.

tainment. In addition, many of the registries are newborn registries, underestimating the incidence at mid-gestation when a screening ultrasound is performed. One of the largest sources of data for birth defects diagnosed during pregnancy and at birth is the Eurofetus study that involved 170,800 women and 4615 malformations [1]. This was a prospective multicenter study performed at 61 centers in Europe. A listing of selected malformations by decreasing frequency is presented in Table 1. The overall incidence of malformed fetuses in this study was 2.2%.

Sensitivity of ultrasound in detecting anomalies

Significant controversy exists regarding the sensitivity of ultrasound in detecting fetal anomalies. A comprehensive review of the existing studies relating to this issue has been recently published by Levi [2]. Levi [2] compiled data from 36 studies involving over 900,000 fetuses. The overall sensitivity for detecting fetal anomalies was 40.4% (range 13.3% to 82.4%). It is useful to examine two of these studies in detail. The RADIUS trial is important because it is used as an example by many of the poor performance of ultrasound in detecting abnormalities [3]. The Eurofetus study is also significant because it is the largest prospective screening study [1]. In examining these two studies, many of the difficulties in performing this type of analysis become clear.

The first of the two studies, the RADIUS trial, was performed between 1987 and 1991 and enrolled 15,151 low-risk patients from over 100 participating practices in the United States [3]. These women were randomized into two groups, one group having two ultrasounds (15 to 22 weeks and 31 to 35 weeks) and the other control group having ultrasounds only as medically indicated. In

this control group, 60% of patients ended up having an ultrasound. The patients in the study group were seen at one of 28 ultrasound laboratories participating in the study.

Ultrasound examination detected 35% of the anomalous fetuses in the study group versus 11% in the control group. Of the detected anomalies in the study group, 17% were detected before 24 weeks of gestation. The study also separated out those abnormalities that were potentially detectable by ultrasound. Using that criteria, 47% of abnormalities were identified, 24% before 24 weeks of gestation. The authors also looked at the sensitivity of anomaly detection in tertiary versus nontertiary centers before 24 weeks gestation. The detection rate at tertiary centers was 35% versus 13% in nontertiary centers.

The Eurofetus trial included 170,800 women seen at 61 European centers between 1990 and 1993 [1]. All women were encouraged to have a scan between 18 and 22 weeks of gestation. The mean number of ultrasounds for each woman was three and the overall sensitivity for detecting malformations was 56.2%. The detection rate for major malformations was higher (73.7% versus 45.7%) than for minor abnormalities. The detection rates for selected malformations are listed in Table 2. Of the major abnormalities, 55% were detected before 24 weeks of gestation. For example, whereas 93.5% of cases of hydrocephalus were detected overall, only 35.5% were detected before 24 weeks of gestation.

Why are there such differences in the RADIUS and Eurofetus trials? Some of the differences are probably caused by different definitions of major and minor malformations in the two trials. The definition of malformations in the RADIUS trial was broader, and included a larger number of malformations that tend to decrease the detection rate. In addition, patients in the RADIUS trial were

Table 2
Detection rates for selected malformations

Malformation	% Rate
Anencephaly	99.4
Spina bifida with hydrocephalus	94.6
Hydrocephalus	93.5
Hydronephrosis	93.4
Unilateral cystic renal disease	91.7
Polycystic kidneys	91.4
Central nervous system (overall)	88.3
Bilateral renal agenesis	83.7
Ventral wall defect	81.6
Spina bifida without hydrocephalus	66.3
Diaphragmatic hernia	58
Heart (overall)	27.7
Cleft lip and palate	18
Foot deformity	17.2

Data from Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus study. Am J Obstet Gynecol 1999;181:446–54; Levi S. Ultrasound in prenatal diagnosis: polemics around routine ultrasound screening for second trimester fetal malformations. Prenat Diagn 2002;22:285–95.

all low-risk compared with women in the Eurofetus trial who were of mixed risk, again tending to reduce the detection rate in the RADIUS trial. Patients in the RADIUS trial were also scanned as early as 15 weeks of gestation when detection rates are known to be lower. Despite these differences, it is interesting to compare the detection rates of major malformations before 24 weeks of gestation in both trials. In the RADIUS trial, the detection rate was 35% in tertiary centers and 13% in nontertiary centers. In the Eurofetus trial, the detection rate before 24 weeks was 55%. All of the centers in the Eurofetus trial were tertiary centers and routinely performed a "level 2" examination on patients. It seems that the Eurofetus results should be a goal to strive for in the United States.

Timing of ultrasound

Most ultrasound laboratories recommend performing a fetal anomaly detection scan at 18 to 22 weeks of gestation. This recommendation has been based on very little data and primarily stems from subjective observations that this seems like a good time to visualize fetal anatomy at a time when termination of pregnancy is still an option. In a prospective study, Schwärzler et al [4] evaluated performing ultrasound screening for abnormalities at 18, 20, or 22 weeks. These investigators found that the anomaly detection rate was no different at each of these gestational ages. Scans performed at 18 weeks of gestation, however, had a significantly increased chance of requiring a repeat examination. In many cases, this was caused by an incomplete anatomic scan. It seems that 20 to 22 weeks of gestation is the optimal time to perform an ultrasound for detection of fetal anomalies.

With the improved resolution of ultrasound equipment, considerable interest has been directed toward earlier identification of fetal anomalies in the first trimester. Whitlow et al [5] have reported a fetal structural anomaly detection rate of 59% in a low-risk population of 6443 women screened at 11 to 14 weeks of pregnancy. Additional studies are needed to confirm this high detection rate. The embryology of the organ system being visualized must also be clearly understood. For example, it is well known that the fetal midgut is normally present in the base of the umbilical cord from approximately 8 weeks until 12 weeks of gestation [6]. It is possible to make a false-positive diagnosis of omphalocele at this gestational age. At this point, first trimester screening should only be undertaken in centers with extensive experience in this area.

Performance of the screening ultrasound

Standards

Varying standards exist for the performance of a screening ultrasound examination. One of the most widely referred to in the United States is the set

of standards published by the American Institute of Ultrasound in Medicine in 1994 [7]. In the section on fetal anatomy, these standards include examination of the following areas of fetal anatomy: cerebral ventricles; posterior fossa (including cerebellar hemispheres and cisterna magna); four-chamber view of the heart (including its position within the thorax); spine; stomach; kidneys; urinary bladder; fetal umbilical cord insertion site; and intactness of the anterior abdominal wall. In the 10 years since these standards have been published, there have been major improvements in the resolution of ultrasound machines enabling enhanced visualization of the fetus. Many experts in the field believe that additional elements should be added to the basic ultrasound examination including fetal face (lips and fetal profile); fetal heart outflow tracts; extremities including hands and feet; abdominal situs; genitalia; and number of umbilical cord vessels. It seems prudent to attempt to include these items as the current standards evolve.

Performance of the screening examination for fetal anomalies

Head and brain

Examination of the fetal head involves visualization of several key structures. The first of these structures are the lateral ventricles. The lateral ventricles are imaged in an axial view at the level of the atrium. The choroid plexus is visualized within the lateral ventricles and in cases of ventriculomegaly may be seen to be ''dangling'' (Fig. 1) [8]. Various measurements and ratios have been proposed to measure the lateral ventricle to assess for the presence of ventriculomegaly. The most commonly used method is a single measurement of the ventricular atrium at the level of the glomus of the choroid plexus [9]. Most

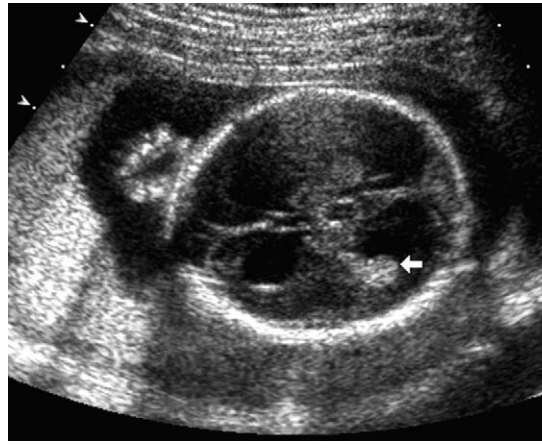

Fig. 1. Axial image of the fetal head showing the lateral ventricles. The arrow points to the ''dangling'' choroid.

investigators consider a measurement of over 10 mm to be abnormal. This upper limit seems to be stable from 14 to 40 weeks of gestation [10]. Investigators have also noted that the ventricles are normally larger in male fetuses and gender should be assessed to aid in counseling [11,12]. It is important when measuring the width of the ventricle not to include the hypoechoic margin of the cerebral hemisphere in the measurement. Also, the near hemisphere of the fetal brain cannot be well visualized in most cases because of reverberation artifact from the calvarium. It may not be possible to measure the upside ventricle.

Other structures that should be visualized in the brain include the cavum septum pellucidum (Fig. 2). This is visualized in the axial plane as a midline fluid-filled structure anterior to the thalami. Absence of the cavum septum pellucidum may indicate an abnormality in midline structures of the brain including agenesis of the corpus callosum.

The posterior fossa of the fetal brain should also be examined (see Fig. 2). The normal concave appearance of the cerebellar hemispheres should be demonstrated. The width of the cisterna magna, located posterior to the cerebellar hemispheres, should be measured. The upper limit of normal for this measurement is 10 mm [13]. Enlargement of the cisterna magna can indicate a potential Dandy-Walker malformation [14]. Effacement of the cisterna magna is seen in the Chiari II malformation, which is present in most cases of spina bifida. In the axial view that includes the cerebellar hemispheres and the cisterna magna, the width of the posterior nuchal fold should be examined. A thickened nuchal fold is one of the soft signs of Down syndrome, discussed elsewhere in this issue.

The "fruit" signs should also be sought during the fetal survey. Frontal bossing of the fetal skull seen in the axial plane is called the lemon sign (Fig. 3). This indicates an increased risk for a neural tube defect. Also associated with neural tube defects is the Chiari type II malformation, which causes a herniation

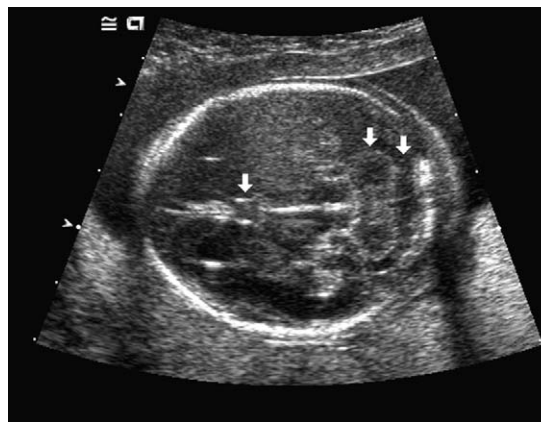

Fig. 2. Axial image of the fetal head with arrows pointing (left to right) to the cavum septum pellucidum, cerebellum, and cisterna magna.

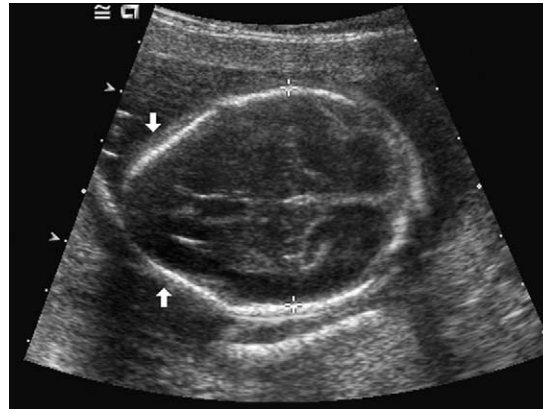

Fig. 3. Axial image of the fetal head with arrows demonstrating frontal scalloping of the calvarium typical of the "lemon" sign.

of the cerebellar vermis and downward displacement of the fourth ventricle. This causes the cerebellum to curve anteriorly forming the banana sign (Fig. 4). Almost all cases of spina bifida have one of these two cranial signs or effacement of the cisterna magna. The other fruit sign is the strawberry-shaped skull that is observed in some cases of trisomy 18.

Examination of the fetal face is becoming a routine part of the screening examination. A sagittal view of the face allows examination of the fetal profile to identify possible micrognathia or abnormalities of the fetal tongue (Fig. 5). A coronal view including the nose and upper lip allows the diagnosis of a cleft lip (Fig. 6).

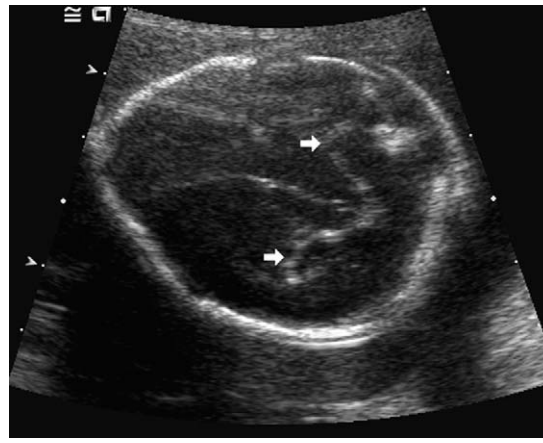

Fig. 4. Axial image of the head with arrows showing forward displacement of the cerebellum resulting in the "banana" sign.

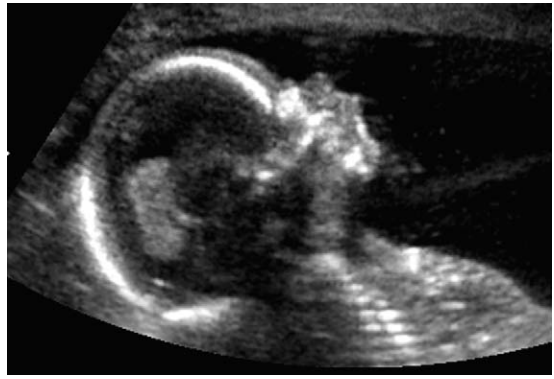

Fig. 5. Parasagittal image of the normal fetal face.

Thorax and heart

Examination of the fetal thorax primarily involves examination of the heart and its orientation within the thorax. The examination of the heart is described elsewhere in this issue. The orientation of the heart, however, is important to screen for other abnormalities in the chest. Normally the heart is situated anterior

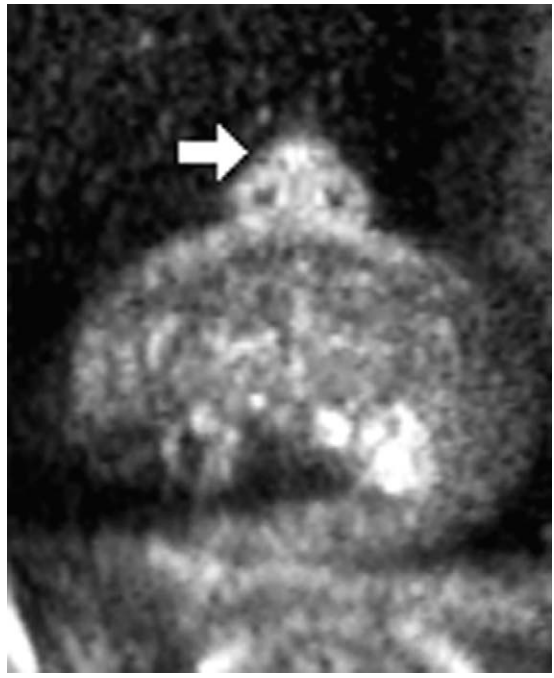

Fig. 6. Coronal image of the fetal face. The arrow is pointing at the nose with the intact upper lip below.

in the fetal chest and oriented toward the left. A line through the ventricular septum should be at approximately a 45-degree angle from the midline [15]. A shift of the fetal heart in the thorax could be indicative of a cardiac malformation or other intrathoracic mass. Any cystic structures should also be looked for in the fetal chest. These may indicate a primary lung mass or may be the stomach or bowel, which has herniated through a diaphragmatic defect.

Abdomen

Initial evaluation of the abdomen should determine situs of the abdominal organs. Bronshtein et al [16] have recently published a simple and rapid method for determining fetal situs [16]. When performing a transabdominal scan, imagine the sonographer's right hand represents the fetus with the dorsal side of the forearm representing the fetal back, the palmer side the fetal abdomen, and the fist as the fetal head. The thumb is always pointed to the fetal left side. For a transvaginal scan, the left hand of the sonographer should be used.

The fetal stomach should be visualized as a variable fluid-filled structure in the left upper quadrant. The fetal stomach should be reliably visualized after 14 weeks gestation. (Fig. 7) [17,18]. If not visualized, a repeat examination may be performed in 1 to 2 weeks. Persistent nonvisualization of the stomach may be associated with a number of abnormalities including esophageal atresia. The incidence of abnormal outcome with persistent nonvisualization of the fetal stomach ranges from 45% to 66% with the incidence of chromosomal abnormalities ranging from 3.2% to 29.6% [17–20]. The fetal diaphragm should be imaged in the sagittal plane, making sure the stomach is in the abdominal cavity. Other cystic structures should be looked for when assessing the fetal abdomen. The fetal gallbladder may be seen in the right upper quadrant adjacent to the liver.

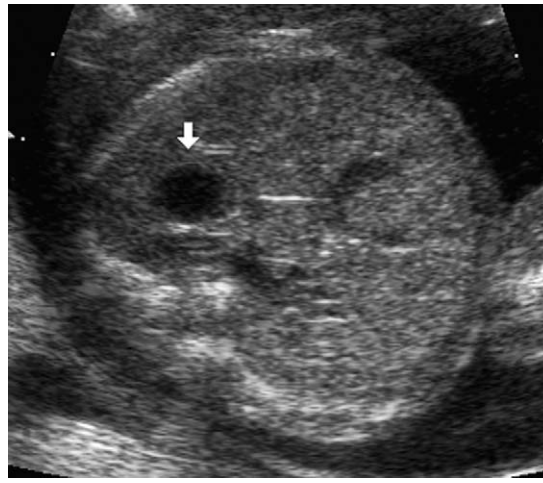

Fig. 7. Axial image of the fetal abdomen at the level of the stomach and liver. The arrow points to the fetal stomach.

Cystic structures may be seen associated with the fetal urinary system and are discussed elsewhere in this issue. Any other cystic structures seen in the abdomen should be referred for a targeted ultrasound.

The umbilical cord insertion into the anterior abdominal wall should be documented along with the integrity of the adjacent abdominal wall (Fig. 8). This should rule out all significant ventral wall abnormalities.

Echogenic bowel should be documented if present. This is usually a transient finding that occurs in the second trimester. In some cases, it may be caused by the fetus having swallowed bloody amniotic fluid in utero [21]. Various grading systems of echogenic bowel have been described [22]. The consensus of opinion seems to indicate that only bowel with echogenicity equal to that of bone is significant. Recent studies have also shown that the use of high-frequency transducers increases the bowel echogenicity [23]. Echogenic bowel may be associated with Down syndrome, cystic fibrosis, and fetal viral infection [24–26]. Also, risks for later intrauterine growth restriction and adverse fetal outcomes are increased [27–29].

Urinary tract

The fetal urinary tract is a common site of abnormality but fortunately most defects are minor. The fetal kidneys are visualized as hypoechoic, paraspinal structures that frequently have an echogenic central renal pelvis. The kidneys should be examined for any intrarenal cysts or echogenicity, which may suggest renal dysplasia. In addition, adjacent cystic structures, which might indicate a duplicated collecting system, should be noted. The most commonly seen abnormality is renal pyelectasis (Fig. 9). In a recent prospective study from Belgium, pyelectasis was seen in 4.5% of fetuses [30]. Pyelectasis was diagnosed when the anteroposterior measurement of the renal pelvis was greater than or equal to 4 mm in the second trimester or greater than or equal to 7 mm in

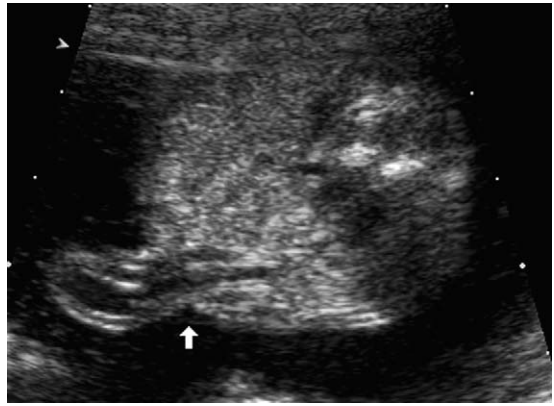

Fig. 8. Axial image of the fetal lower abdomen. The arrow indicates the umbilical cord insertion and the intact anterior abdominal wall.

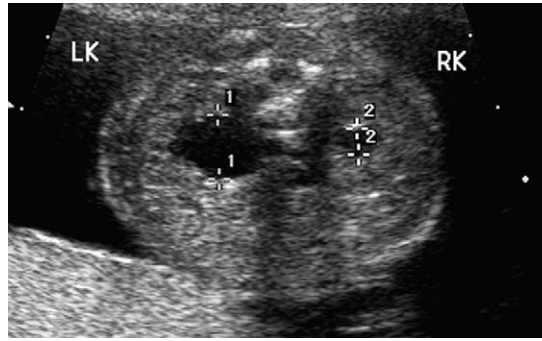

Fig. 9. Axial image at the level of the fetal kidneys. Left-sided pyelectasis is seen at the #1 cursors and a normal right kidney at the #2 cursors.

the third trimester. Controversy has existed on how to manage fetuses when pyelectasis is seen in the second trimester. A common approach has been to repeat the examination in the third trimester and only if the measurement is greater than or equal to 7 mm is postnatal follow-up recommended. The study from Belgium, however, reported that in cases of pyelectasis diagnosed in the second trimester and with values less than 7 mm in the third trimester, the incidence of significant uropathy in the newborn was 12% [30]. In infants with a renal pelvis greater than or equal to 7 mm, the positive predictive value for a renal abnormality was 69%. Complicating this situation is the observation that the finding of renal pyelectasis is highly dynamic with rapid changes in the size of the pelvis occurring over a short period of time [31]. Despite this, it seems worthwhile to suggest postnatal follow-up in those cases that have a renal pelvis greater than or equal to 4 mm in the second trimester.

The fetal bladder should also be examined. If distended, abnormalities of the kidneys and possible dilation of the ureters should be sought. Also, the volume of amniotic fluid should be evaluated. Abnormalities in the shape of the bladder may be an indicator of a cloacal abnormality.

Spine

Evaluation of the spine is an important component of the fetal survey. The spine should be imaged in parasagittal and transverse planes looking for any breaks in the symmetry of the ossification centers (Figs. 10,11). The transverse plane is usually the most sensitive for detecting a spinal defect and allows examination of each spinal segment. It is also important to demonstrate that the overlying soft tissues are intact.

Extremities

Examination of the extremities has been aided by the increased resolution of modern ultrasound equipment (Fig. 12). Although the femur is the only bone

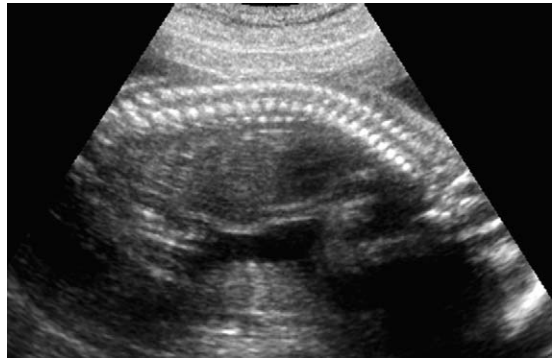

Fig. 10. Parasagittal view of the intact fetal spine.

routinely measured for biometry, all of the fetal long bones should be imaged and examined for morphology to screen for skeletal dysplasias. In addition, both hands and feet should be documented. The axis of the foot in relation to the tibula-fibula should also be imaged to rule out a clubfoot anomaly. If a clubfoot is suspected, a detailed examination of the fetus for other abnormalities should be performed. A large retrospective study showed that 48.6% of clubfeet were associated with other fetal abnormalities [32]. In addition, of the cases that were thought to be isolated at mid-trimester scan, 19% developed other abnormalities later in pregnancy. There is a high incidence of false-positive diagnoses of

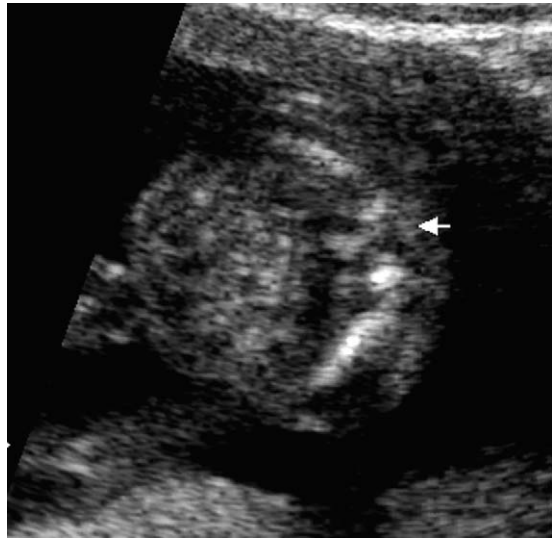

Fig. 11. Axial view of the sacral spine. Note the intact skin over the spine at the arrow.

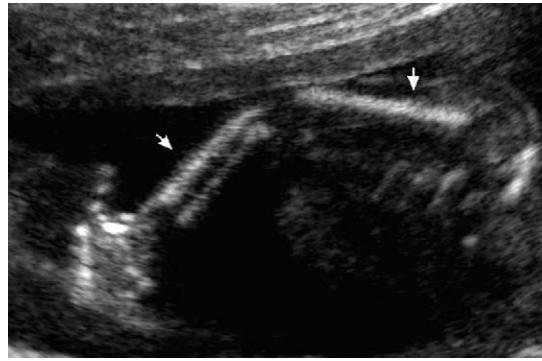

Fig. 12. Image of the upper extremity long bones and hand.

clubfeet, however, because of transient positioning artifacts of the foot. In one study, the incidence of a false-positive diagnosis was 11.2% [33].

Umbilical cord

The fetal umbilical cord should be imaged to determine the number of vessels. A single umbilical artery is seen in approximately 1% of pregnancies. The cord may be imaged in cross-section or the two arteries may be visualized as they pass around the fetal bladder (Fig. 13). Occasionally, the cord may fuse near the placental end of the cord; this area should not be used to check for the number of vessels. The finding of a two-vessel umbilical cord is an indication for a detailed ultrasound to rule out other abnormalities and for a fetal echocardiogram. The

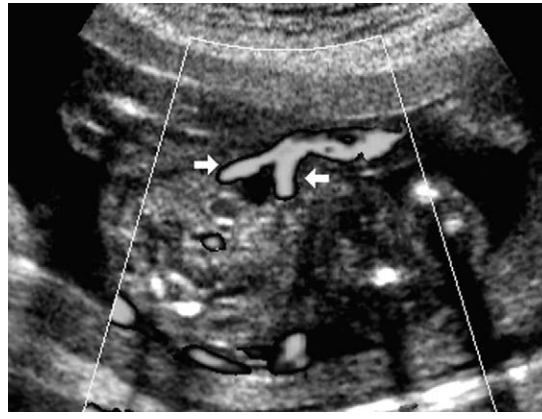

Fig. 13. Axial image at the level of the fetal bladder with arrows demonstrating the umbilical vessels on either side of the bladder.

incidence of other abnormalities is 30% to 60% [34–36]. Fetal growth restriction has also been reported with an isolated two-vessel cord [37].

Adverse effects of ultrasound screening

Ultrasound is a noninvasive screening method that has been shown to be biologically safe in long-term studies [38,39]. The adverse effects of ultrasound relate to the sensitivity and specificity of the ultrasound examination and the anxiety that this causes to the patient. It is important to make clear to the patient that ultrasound has its limitations. The patient must realize that not all malformations can be detected. The sonographer should also be aware of what is said to the patient. The statement ''everything is normal'' may have a different meaning for the patient and sonographer.

The other concern is the issue of a false-positive diagnosis or of a diagnosis that has an unclear outcome. Again, patients need to be aware of the possibility of this kind of outcome before the ultrasound procedure is performed.

Summary

Ultrasound has become a routine part of prenatal care. Despite this, the sensitivity and specificity of the procedure is unclear to many patients and health care providers. In a small study from Canada, 54.9% of women reported that they had received no information about ultrasound before their examination [40]. In addition, 37.2% of women indicated that they were unaware of any fetal problems that ultrasound could not detect [40].

Most centers that perform ultrasound do not have their own statistics regarding sensitivity and specificity; it is necessary to rely on large collaborative studies. Unfortunately, wide variations exist in these studies with detection rates for fetal anomalies between 13.3% and 82.4% [2]. The Eurofetus study is the largest prospective study performed to date and because of the time and expense involved in this type of study, a similar study is not likely to be repeated. The overall fetal detection rate for anomalous fetuses was 64.1%. It is important to note that in this study, ultrasounds were performed in tertiary centers with significant experience in detecting fetal malformations. The RADIUS study also demonstrated a significantly improved detection rate of anomalies before 24 weeks in tertiary versus community centers (35% versus 13%).

Two concepts seem to emerge from reviewing these data. First, patients must be made aware of the limitations of ultrasound in detecting fetal anomalies. This information is critical to allow them to make informed decisions whether to undergo ultrasound examination and to prepare them for potential outcomes. Second, to achieve the detection rates reported in the Eurofetus study, ultrasound examination must be performed in centers that have extensive experience in the detection of fetal anomalies.

References

[1] Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus study. Am J Obstet Gynecol 1999;181:446–54.

[2] Levi S. Ultrasound in prenatal diagnosis: polemics around routine ultrasound screening for second trimester fetal malformations. Prenat Diagn 2002;22:285–95.

[3] Ewigman BG, Crane JP, Frigoletto FD, LeFevre ML, Bain RP, McNellis D. Effect of prenatal ultrasound screening on perinatal outcome. N Engl J Med 1993;329:821–7.

[4] Schwärzler P, Senat M-V, Holden D, Bernard JP, Masroor T, Ville Y. Feasibility of the second-trimester fetal ultrasound examination in an unselected population at 18, 20, or 22 weeks of pregnancy: a randomized trial. Ultrasound Obstet Gynecol 1999;14:92–7.

[5] Whitlow BJ, Chatzipapas IK, Lazanakis ML, Kadir RA, Economides DL. The value of sonography in early pregnancy for the detection of fetal abnormalities in an unselected population. Br J Obstet Gynaecol 1999;106:929–36.

[6] Snijders RJM, Brizot ML, Faria M, Nicolaides KH. Fetal exomphalos at 11–14 weeks of gestation. J Ultrasound Med 1995;14:569–74.

[7] Guidelines for the Performance of the Antepartum Obstetrical Examination. Laurel, MD: American Institute of Ultrasound in Medicine; 1994.

[8] Cardoza JD, Filly RA, Podrasky AE. The dangling choroid plexus: a sonographic observation of value in excluding ventriculomegaly. AJR Am J Roentgenol 1988;151:767–70.

[9] Cardoza JD, Goldstein RB, Filly RA. Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology 1988;169:711–4.

[10] Filly RA, Cardoza JD, Goldstein RB, Barkovich AJ. Detection of fetal central nervous system anomalies: a practical level of effort for a routine sonogram. Radiology 1989;172:403–8.

[11] Patel MD, Goldstein RB, Tung S, Filly RA. Fetal cerebral ventricular atrium: difference in size according to sex. Radiology 1995;194:713–5.

[12] Nadel AS, Benacerraf BR. Lateral ventricular atrium: larger in male than female fetuses. Int J Gynaecol Obstet 1995;51:123–6.

[13] Mahony BS, Callen PW, Filly RA, Hoddick WK. The fetal cisterna magna. Radiology 1984; 153:773–6.

[14] Nyberg DA, Mahony BS, Hegge FN. Enlarged cisterna magna and the Dandy-Walker malformation: factors associated with chromosomal abnormalities. Obstet Gynecol 1991;77:436–42.

[15] Comstock CH. Normal fetal heart axis and position. Obstet Gynecol 1987;70:255–9.

[16] Bronshtein M, Gover A, Zimmer EZ. Sonographic definition of the fetal situs. Obstet Gynecol 2002;99:1129–30.

[17] Millener PB, Anderson NG, Chisholm RJ. Prognostic significance of non-visualization of the fetal stomach by sonography. AJR Am J Roentgenol 1993;160:827–30.

[18] McKenna KM, Goldstein RB, Stringer MD. Small or absent fetal stomach: prognostic significance. Radiology 1995;197:729–33.

[19] Brumfield CG, Davis RO, Owen J, Wenstrom K, Kynerd PM. Pregnancy outcomes following sonographic nonvisualization of the fetal stomach. Obstet Gynecol 1998;91:905–8.

[20] Pretorius DH, Gosink BB, Clautice-Engle T, Leopold GR, Minnick CM. Sonographic evaluation of the fetal stomach: significance of nonvisualization. AJR Am J Roentgenol 1988;151: 987–9.

[21] Sepulveda W, Reid R, Niicolaidis P, Prendiville O, Chapman RS, Fisk NM. Second-trimester echogenic bowel and intra-amniotic bleeding: association between fetal bowel echogenicity and amniotic fluid spectrophotometry at 410nm. Am J Obstet Gynecol 1996;174:839–42.

[22] Slotnick RN, Abuhamad AZ. Prognostic implication of fetal echogenic bowel. Lancet 1996; 347:85–7.

[23] Vincoff NS, Callen PW, Smith-Bindman R, Goldstein RB. Effect of ultrasound transducer frequency on the appearance of the fetal bowel. J Ultrasound Med 1999;18:799–803.

[24] Nyberg DA, Resta RG, Mahony BS, et al. Fetal hyperechogenci bowel and Down's syndrome. Ultrasound Obstet Gynecol 1993;3:330–3.

[25] Sepulveda W, Leung KY, Robertson ME, Kay E, Mayall ES, Fisk NM. Prevalence of cystic fibrosis mutations in pregnancies with fetal echogenic bowel. Obstet Gynecol 1996;87:103–6.
[26] Weiner Z. Congenital cytomegalovirus infection with oligohydramnios and echogenic bowel at 14 weeks' gestation. J Ultrasound Med 1995;14:617–8.
[27] Nyberg DA, Dubinsky T, Resta RG, Mahony BS, Hickok DE, Luthy DA. Echogenic fetal bowel during the second trimester: clinical importance. Radiology 1993;188:527–31.
[28] Hill LM, Fries J, Hecker J, Grzybek P. Second-trimester echogenic small bowel: an increased risk for adverse perinatal outcome. Prenat Diagn 1994;14:845–50.
[29] Simon-Bouy B, Satre V, Ferec C, et al. Hyperechogenic fetal bowel: a large French collaborative study of 682 cases. Am J Med Genet 2003;121A:209–13.
[30] Ismaili K, Hall M, Donner C, Thomas D, Vermeylen D, Avni FE. Results of systematic screening for minor degrees of fetal renal pelvis dilatation in an unselected population. Am J Obstet Gynecol 2003;188:242–6.
[31] Persutte WH, Hussey M, Chyu J, Hobbins JC. Striking findings concerning the variability in the measurement of the fetal renal collecting system. Ultrasound Obstet Gynecol 2000;15: 186–90.
[32] Bakalis S, Sairam S, Homfray T, Harrington K, Nicolaides K, Thilaganathan B. Outcome of antenatally diagnosed talipes equinovarus in an unselected obstetric population. Ultrasound Obstet Gynecol 2002;20:226–9.
[33] Shipp TD, Benacerraf BR. The significance of prenatally identified isolated clubfoot: is amniocentesis indicated? Am J Obstet Gynecol 1998;178:600–2.
[34] Chow JS, Benson CB, Doubilet PM. Frequency and nature of structural anomalies in fetuses with single umbilical arteries. J Ultrasound Med 1998;17:765–8.
[35] Jassani MN, Brennan JN, Merkatz IR. Prenatal diagnosis of single umbilical artery by ultrasound. J Clin Ultrasound 1980;8:447–8.
[36] Persutte WH, Hobbins J. Single umbilical artery: a clinical enigma in modern prenatal diagnosis. Ultrasound Obstet Gynecol 1995;6:216–29.
[37] Catanzarite VA, Hendricks SK, Maida C, Westbrook C, Cousins L, Schrimmer D. Prenatal diagnosis of the two-vessel cord: implications for patient counseling and obstetric management. Ultrasound Obstet Gynecol 1995;5:98–105.
[38] Brent RL, Jensh RP, Beckman DA. Medical sonography: reproductive effects and risks. Teratology 1991;44:123–46.
[39] Merritt CR, Kremkau FW, Hobbins JC. Diagnostic ultrasound: bioeffects and safety. Ultrasound Obstet Gynecol 1992;2:366–74.
[40] Kohut RJ, Dewey D, Love EJ. Women's knowledge of prenatal ultrasound and informed choice. J Genet Couns 2002;11:265–76.

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Screening for congenital heart disease

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Most pregnant women in the United States undergo at least one ultrasound examination before delivery. Prenatal ultrasound performed after the first trimester requires an assessment of fetal anatomy. Both the American Institute of Ultrasound in Medicine and the American College of Obstetricians and Gynecologists recommend that the four-chamber view be part of this assessment during routine prenatal ultrasonography in the second and third trimesters [1,2]. Although assessing multiple views of the heart increases the likelihood of prenatal detection of congenital heart disease, screening for cardiac defects in the fetus begins with the four-chamber view.

Basics of the four-chamber view

Although visualization of the fetal heart is possible in the first trimester, the optimal time to perform cardiac screening is between 18 and 22 weeks gestation using high-resolution real-time ultrasonography. The four-chamber view easily can be incorporated into a 30-minute screening midtrimester ultrasound with adequate visualization in over 95% of fetuses [3]. A simple approach to the four-chamber view includes an evaluation of size, position, anatomy, and function of the fetal heart [4].

The four-chamber view is obtained on a transverse image of the fetal thorax just above the diaphragm (Fig. 1). In this transverse plane, the fetal heart occupies about one third of the area of the fetal chest with an axis about 45 degrees to the left [5]. The atrial and ventricular chambers, interventricular septum, foramen ovale, and atrioventricular valves can all be assessed on the four-chamber view.

The two atria and two ventricles should be similar in size, with the left atrium closest to the spine and the right ventricle closest to the sternum. The flap of the foramen ovale should project into the left atrium through a patent foramen ovale. The internal surface of the left ventricle is smooth-looking compared with the

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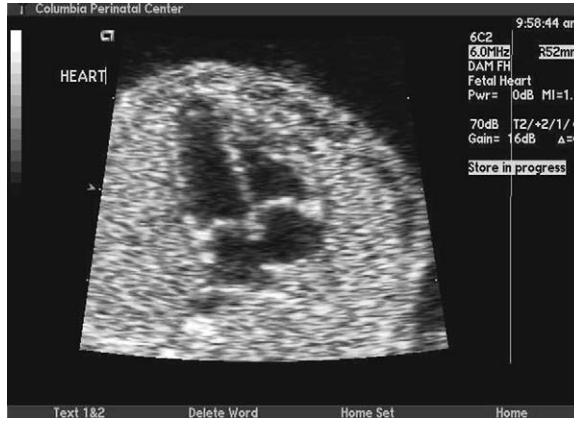

Fig. 1. A transverse view through the fetal chest demonstrating the four-chamber view. The most anterior chamber is the trabeculated right ventricle and the most posterior chamber adjacent to the spine is the left atrium.

trabeculated right ventricle containing the moderator band. The two atrioventricular valves meet at the junction of the interatrial and interventricular septa to form the crux of the heart. The mitral and tricuspid valves should move freely, with the tricuspid valve attached slightly more toward the apex than the mitral valve on the interventricular septum. Ventricular systolic function can be assessed subjectively by observing the ventricular wall movement during systole. The presence of a pericardial effusion also can be identified on the four-chamber view. Assessing the four-chamber view is more than just counting the chambers of the fetal heart. A significant amount of information easily can be obtained by incorporating a systematic evaluation of the four-chamber view into routine screening ultrasonography.

Performance of the four-chamber view

The four-chamber view was introduced as a screening tool for the prenatal detection of heart anomalies over 15 years ago [6,7]. Initial reports suggested that the four-chamber view could detect 80% to 90% of fetuses with congenital heart disease [7,8]. The sensitivity of the four-chamber view to detect cardiac anomalies varied widely, however, in subsequent studies [9–21]. For example, only 16% of fetuses with heart defects were detected using the four-chamber view in the highly publicized routine antenatal diagnostic imaging with ultrasound (RADIUS) trial of prenatal ultrasonographic screening, and no cardiac malformations were detected before 24 weeks gestation in facilities other than tertiary-level referral centers [22].

There are many possible explanations for the inconsistent performance of the four-chamber view in screening for congenital heart disease. Different ultra-

sonographers with varying levels of skill use the four-chamber view under a variety of conditions in clinical practice. Performance is also significantly influenced by such factors as a community setting versus a tertiary care center, high-risk versus low-risk patients, level of ascertainment, and availability of outcome information. Screening by skilled sonographers, experienced perinatologists, and expert pediatric cardiologists at teaching hospitals and tertiary reference centers is expected to be superior to that performed in the community. This is reflected in the poor detection rate reported in nontertiary care centers in the RADIUS study [22]. The sensitivity of any screening test also depends on the prevalence of disease in the population being studied. Tertiary care hospitals see more affected fetuses because they are the facilities to which women with abnormal serum screening, advanced maternal age, and high-risk factors for congenital heart disease are referred for evaluation. The prevalence of congenital heart disease in many tertiary care centers is twice that expected in the general population [23,24].

The ability to image the fetal heart is also influenced by gestational age, fetal position, amniotic fluid volume, and the maternal body habitus. Previous abdominal surgery also can adversely affect the image obtained [25]. Even when the four-chamber view is achieved, it is unreasonable to expect that it identifies all cases of congenital heart disease. Certain defects are easily missed on the four-chamber view, such as ventricular septal defects, atrial septal defects, coarctation, tetralogy of Fallot, transposition of the great arteries, double-outlet right ventricle, truncus arteriosus, and total anomalous pulmonary venous return [26]. Prenatal diagnosis of patent foramen ovale and patent ductus arteriosus is precluded by their normal patency in utero. The superior aspect of the interventricular septum tends to be thin, particularly in the apical view, and can be diagnosed incorrectly as a subaortic ventricular septal defect. Small muscular ventricular septal defects are the defects most commonly missed on prenatal ultrasonography. Certain cardiac malformations, such as transposition of the great vessels, double-outlet right ventricle, and tetralogy of Fallot, can be associated with a normal four-chamber view. Although most congenital heart defects occur during the period of organogenesis, some defects are known to evolve over the course of gestation and may be missed at the time of midtrimester screening. Flow abnormalities, such as valvular pulmonic stenosis, aortic stenosis, and coarctation of the aorta, are not easy to detect on the four-chamber view. Ventricular hypoplasia has been observed to develop as pregnancy advances and may not be evident on cardiac imaging in the second trimester [27]. Abnormalities of the distal pulmonary arteries and pulmonary veins are not commonly appreciated prenatally because of limited flow and filling of these vessels in utero. Even under optimal conditions, some defects are not detected at a midtrimester scan by the four-chamber view.

When used as a screening tool in the general population, the four-chamber view can be expected to detect 40% to 50% of cases of congenital heart disease [7,28]. The four-chamber view should be considered abnormal if there is ventricular or atrial disproportion, myocardial hypertrophy, dilation or hypoplasia of the chambers, septal defects apart from the foramen ovale, or abnormalities of the atrioventricular valves. Congenital heart disease may also be associated

with abnormal positioning of the heart in the fetal chest and with axis deviation [29,30].

Defects expected to be associated with an abnormal four-chamber view include hypoplasia of the right or left ventricle, atrioventricular septal defect, double-inlet ventricle, Ebstein's anomaly, single ventricle, and large ventricle septal defect. Screening with the four-chamber view may also identify dextrocardia, situs inversus, ectopia cordis, cardiomyopathies, pericardial effusion, cardiac tumors, valvular atresia, stenosis, and insufficiency. Hypoplastic ventricles and atrioventricular septal defects are the defects most often detected prenatally by the four-chamber view [26,28,31].

Ventricular outflow tract views

A limitation of cardiac screening with the four-chamber view alone is that conotruncal anomalies easily can be missed. Defects of the great vessels are associated with an abnormal four-chamber view in only 30% of cases [32]. Normal four-chamber screening can occur with transposition of the great arteries, tetralogy of Fallot, double-outlet right ventricle, pulmonary and aortic stenosis, and coarctation of the aorta [31]. Consequently, many experts recommend that views of the aortic and pulmonary outflow tracts be included with an evaluation of the four-chamber view when screening for congenital heart disease [33].

With adequate training and experience, it is possible to visualize the four-chamber view and outflow tracts in 90% of pregnant women [25]. The long-axis view of the left ventricular outflow tract and the short-axis view of the right ventricular outflow tract are the standard images used to evaluate the ventriculoarterial connections (Figs. 2 and 3). The aortic and pulmonary outflow tracts are approximately equal in size in the midtrimester and should be seen to cross as

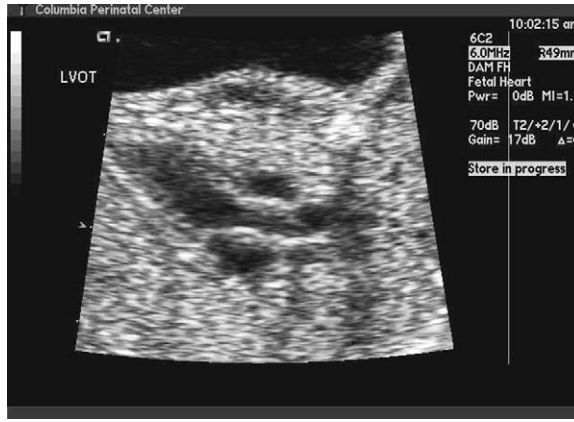

Fig. 2. A long-axis view of the left ventricular outflow tract. Note the continuity between the interventricular septum and the aorta.

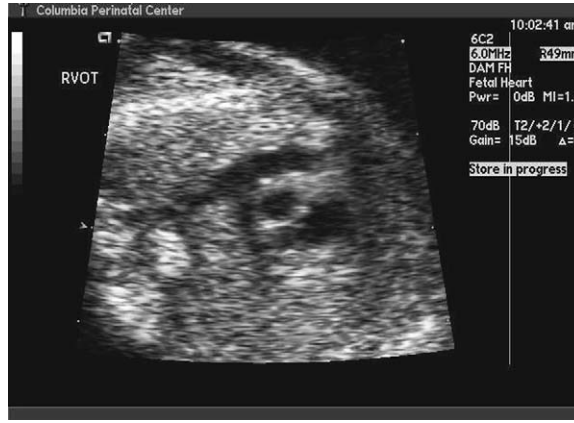

Fig. 3. A short-axis view of the right ventricular outflow tract wrapping around the aorta as it exits the heart.

they arise from their respective ventricles during real-time imaging. The aorta arises from the posterior ventricle and has branches originating from its arch that supply the head and upper extremities. The pulmonary artery arises from the anterior ventricle and branches into the ductus arteriosus and pulmonary arteries.

Performance of outflow tract views

Overall, the prenatal detection of cardiac anomalies can be increased from 40% to 50% with the four-chamber view alone to 60% to 80% when the ventricular outflow tracts are also assessed [10,34,35]. Although the highest detection rates of congenital heart disease have been reported in high-risk populations screened at referral centers, Kirk et al [28] reported a sensitivity of 66% for screening with both the four-chamber view and outflow tracts in a study of primarily low-risk patients. It is clear that multiple cardiac views are crucial for midtrimester screening for many serious congenital heart defects and that the 20% to 30% increase in detection rate that results from including the outflow tracts along with the four-chamber view can be of clinical importance [36–38]. Universal screening with the four-chamber and outflow-tract views may be optimal for midtrimester cardiac assessment.

Importance of screening

Congenital heart disease is a common condition with a prevalence of 8 per 1000 live births [39]. Heart anomalies are estimated to be responsible for most infant and childhood deaths related to congenital malformations. The prenatal diagnosis of congenital heart disease also carries a poor prognosis. Intrauterine fetal death occurs in 20% to 30% of cases; neonatal death in 40% to 60% of cases; and long-

term survival rates are low, ranging from 15% to 40% [40–44]. The presence of extracardiac anomalies and chromosomal abnormalities contributes to the poor outlook. Overall, 25% to 45% of fetuses with congenital heart disease have other malformations and 15% to 50% have abnormal karyotypes [35,45,46]. Other poor prognostic signs include hemodynamic abnormalities and the presence of hydrops. When congenital heart disease is detected prenatally, these associated findings can be important in counseling families about the likelihood of postnatal survival.

Congenital heart disease is eight times more common than trisomy 21 and four times more common than neural tube defects, two conditions for which universal screening programs are in place. Estimates indicate that 10.3 of 1000 fetuses are affected by congenital heart disease at the time of midtrimester ultrasonographic screening [47]. About 50% of cardiac defects are considered major and likely to have a significant impact on long-term morbidity and mortality. Early prenatal diagnosis of major defects is important for counseling patients about pregnancy options, therapeutic interventions, changes in obstetric care, and alternative plans for delivery.

Studies have shown that when major congenital heart disease was diagnosed in the second trimester of pregnancy, from 8% to as many as 80% of patients chose to terminate pregnancy [31,39]. In one survey of 65 women who previously had borne a child with congenital heart disease, 58% said they would elect to terminate a subsequent affected pregnancy [48]. Without universal ultrasonographic screening, the prenatal diagnosis of congenital heart disease is often made late in pregnancy when abortion is no longer available [39]. With early screening and detection of congenital heart disease, patients and their families can consider the options and make the choices that are best for them. Therapeutic interventions and improved neonatal survival are possible when congenital heart disease is detected prenatally and the timing, mode, and location of delivery can be planned. Referral to a tertiary care center where immediate therapeutic and palliative interventions are available can be lifesaving. Prompt infusion of prostaglandin E_1 or balloon atrial septostomy can significantly improve prognosis for newborns with certain cardiac defects that require postnatal maintenance of fetal flow pathways. Experienced neonatologists, pediatric cardiologists, and cardiac surgeons may have a significant impact on an infant's condition and ultimate outcome.

Population for screening

Considering its prevalence, clinical significance, and the availability of therapeutic interventions, congenital heart disease has the characteristics of a disease for which prenatal screening is appropriate. One strategy for prenatal detection is to screen patients identified to be at risk. Unfortunately, most cardiac malformations are missed if screening is done only on patients with recognized risk factors, such as a positive family history, maternal diabetes, and exposure to teratogens [49]. The traditionally accepted indications for cardiac screening are

not highly predictive of subsequent congenital heart disease. More than half of prenatally detected cardiac defects are found in patients with no predisposing risk factors [34]. Overall, 90% of such defects occur in patients who are at low risk for these problems; therefore, screening on the basis of risk factors alone is not particularly effective.

Interestingly, the factor most predictive of congenital heart disease is an abnormal cardiac examination at the time of prenatal ultrasonography. In the study by Cooper et al [49] of fetal echocardiography, only 4% of patients were referred because of an abnormal cardiac screen, yet defects were detected at a rate of 68% in this group, far in excess of the rate for all other risk factors combined. In many centers, an abnormal cardiac screen during routine ultrasonography has become the most common reason for referral for fetal echocardiography [43,50]. Universal screening makes sense because the detection of an abnormal fetal heart on prenatal ultrasonography identifies more cardiac defects than does any of the other traditional risk factors for congenital heart disease.

Summary

Congenital heart disease has the characteristics of a disease that is suited to screening, and the four-chamber view is an effective screening tool with a sensitivity of 40% to 50%. The use of multiple cardiac views can increase the prenatal detection to 60% to 80%. Given that most infants with congenital heart disease are born to low-risk women, routine screening is warranted. Early prenatal diagnosis provides an opportunity to exclude associated extracardiac and chromosomal abnormalities, discuss pregnancy options, adjust obstetric management, prepare parents for delivery of an affected baby, and plan delivery in a tertiary care center. Despite the widespread use of ultrasonography, only 15% to 30% of infants with congenital heart disease are identified prenatally [39,49]. There is a need to do better.

References

[1] American Institute of Ultrasound in Medicine. Guidelines for the performance of the antepartum obstetrical ultrasound examination. J Ultrasound Med 1991;10:576–8.
[2] American College of Obstetricians and Gynecologists. Ultrasonography in pregnancy (Technical Bulletin No. 187). Washington, DC: American College of Obstetricians and Gynecologists; 1993.
[3] Tegnander E, Eik-Nes SH, Linker DT. Incorporating the four-chamber view of the fetal heart into the second-trimester routine fetal examination. Ultrasound Obstet Gynecol 1994;4:24–8.
[4] Allan LD, Anderson RH, Cook AC. Atresia or absence of the left-sided atrioventricular connection in the fetus: echocardiographic diagnosis and outcome. Ultrasound Obstet Gynecol 1996;8:295–302.
[5] Comstock CH. Normal fetal heart axis and position. Obstet Gynecol 1987;70:255–9.
[6] Devore GR. The prenatal diagnosis of congenital heart disease: a practical approach for the fetal sonographer. J Clin Ultrasound 1985;13:229–45.
[7] Allan LD, Crawford DC, Chita SK, Tynan MJ. Prenatal screening for congenital heart disease. BMJ 1986;292:1717–9.

[8] Copel JA, Pilu G, Green J, Hobbins JG, Kleinman CS. Fetal echocardiographic screening for congenital heart disease: the importance of the four-chamber view. Am J Obstet Gynecol 1987;157:648–55.
[9] Buskens E, Grobbee DE, Frohn-Muldor IM, Stewart PA, Juttmann RE, Wladimiroff JW, et al. Efficacy of routine fetal ultrasound screening for congenital heart disease in normal pregnancy. Circulation 1996;94:67–72.
[10] Bronshtein M, Zimmer EZ, Gerlis LM, Lorber A, Drugan A. Early ultrasound diagnosis of fetal congenital heart defects in high-risk and low-risk pregnancies. Obstet Gynecol 1993;82: 225–9.
[11] Rosendahl H, Kivenen S. Antenatal detection of congenital malformations by routine ultrasonography. Obstet Gynecol 1989;73:947–51.
[12] Chitty LS, Hunt GH, Moore J, Lobb MO. Effectiveness of routine ultrasonography in detecting fetal structural abnormalities in a low-risk population. BMJ 1991;303:1165–9.
[13] Constantine G, McCormack J. Comparative audit of booking and mid-trimester ultrasound scans in the prenatal diagnosis of congenital anomalies. Prenat Diagn 1991;11:905–14.
[14] Luck CA. Value of routine ultrasound scanning at 19 weeks: a four-year study of 8,849 deliveries. BMJ 1992;304:1474–8.
[15] Shirley IM, Bottomley F, Robinson VP. Routine radiographer screening for fetal abnormalities by ultrasound in an unselected low risk population. Br J Radiol 1992;65:564–9.
[16] Wigton TR, Sabbagha RE, Tamura RK, Cohen L, Minogue JP, Strasburger JF. Sonographic diagnosis of congenital heart disease: comparison between the four-chamber view and multiple cardiac views. Obstet Gynecol 1993;82:219–24.
[17] Goncalves LF, Jeanty P, Piper JM. The accuracy of prenatal ultrasonography in detecting congenital anomalies. Am J Obstet Gynecol 1994;171:1606–12.
[18] Kirk JS, Riggs TW, Comstock CH, Lee W, Yang SS, Weinhouse E. Prenatal screening for cardiac anomalies: the value of routine addition of the aortic root to the four-chamber view. Obstet Gynecol 1994;84:427–31.
[19] Anderson N, Boswell O, Duff G. Prenatal sonography for the detection of fetal anomalies: results of a prospective study and comparison with prior series. AJR Am J Roentgenol 1995; 165:943–50.
[20] Levi S, Schaaps JP, De Havay P, Coulon R, Defoort P. End-result of routine ultrasound screening for congenital anomalies: the Belgian multicentric study 1984–92. Ultrasound Obstet Gynecol 1995;5:366–71.
[21] Tegnander E, Eik-Nes SH, Johansen OJ, Linker DT. Prenatal detection of heart defects at the routine fetal examination at 18 weeks in a non-selected population. Ultrasound Obstet Gynecol 1995;5:372–80.
[22] Crane JP, Lefevre ML, Winborn RC, Evans JK, Ewigman BG, Bain RP, et al. A randomized trial of prenatal ultrasonographic screening: impact on the detection, management, and outcome of anomalous fetuses. Am J Obstet Gynecol 1994;171:392–9.
[23] Buskens E, Stewart PA, Hess J, Grobbee DE. Efficacy of fetal echocardiography and yield by risk category. Obstet Gynecol 1996;87:423–8.
[24] Shevell T, Perez-Delboy A, Simpson L. Prenatal diagnosis of congenital heart disease and voluntary pregnancy termination: experience of a single tertiary care center. Am J Obstet Gynecol 2001;185:S254.
[25] Devore GR, Medearis AL, Bear MB, Horenstein J, Platt LD. Fetal echocardiography: factors that influence imaging of the fetal heart during the second trimester of pregnancy. J Ultrasound Med 1993;12:659–63.
[26] Allan LD, Sharland GK, Milburn A, Lockhart SM, Groves AM, Anderson RH, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 1994;23:1452–8.
[27] Hornberger LK, Need L, Benacerraf BR. Development of significant left and right ventricular hypoplasia in the second and third trimester fetus. J Ultrasound Med 1996;15:655–9.
[28] Kirk JS, Comstock CH, Lee W, Smith RS, Riggs TW, Weinhouse E. Sonographic screening

to detect fetal cardiac anomalies: a 5-year experience with 111 abnormal cases. Obstet Gynecol 1997;89:227–32.
[29] Shipp TD, Bromley B, Hornberger LK, Nadel A, Benacerraf BR. Levorotation of the fetal cardiac axis: a clue for the presence of congenital heart disease. Obstet Gynecol 1995;85:97–102.
[30] Smith RS, Comstock CH, Kirk JS, Lee W. Ultrasonographic left cardiac axis deviation: a marker for fetal anomalies. Obstet Gynecol 1995;85:187–91.
[31] Sharland GK, Allan LD. Screening for congenital heart disease prenatally. Results of a 2 1/2-year study in the South East Thames Region. Br J Obstet Gynecol 1992;9:220–5.
[32] Paladini D, Rustico M, Todros T, Palmieri S, Gaglioti P, Benettoni A, et al. Conotruncal anomalies in prenatal life. Ultrasound Obstet Gynecol 1996;8:241–6.
[33] Devore GR. The aortic and pulmonary outflow tract screening examination in the human fetus. J Ultrasound Med 1992;11:345–8.
[34] Achiron R, Glaser J, Gelernter I, Hegesh J, Yagel S. Extended fetal echocardiographic examination for detecting cardiac malformations in low risk pregnancies. BMJ 1992;304:671–4.
[35] Bromley B, Estroff JA, Sanders SP, Parad R, Roberts D, Frigoletto FD, et al. Fetal echocardiography: accuracy and limitations in a population at high and low risk for heart defects. Am J Obstet Gynecol 1992;166:1473–81.
[36] Stoll C, Alembik Y, Dott B, DeGeeter B. Evaluation of prenatal diagnosis of congenital heart disease. Prenat Diagn 1993;13:453–61.
[37] Ott WJ. The accuracy of antenatal fetal echocardiography screening in high and low risk patients. Am J Obstet Gynecol 1995;172:1741–9.
[38] Rustico MA, Benettoni A, D'Ottavio G, Maieron A, Fischer-Tamaro I, Conoscenti G, et al. Fetal heart screening in low-risk pregnancies. Ultrasound Obstet Gynecol 1995;6:313–9.
[39] Montana E, Khoury MJ, Cragan JD, Sharma S, Dhar P, Fyfe D. Trends and outcomes after prenatal diagnosis of congenital cardiac malformations by fetal echocardiography in a well defined birth population, Atlanta Georgia. 1990–1994. J Am Coll Cardiol 1996;28:1805–9.
[40] Crawford DC, Chita SK, Allan LD. Prenatal detection of congenital heart disease: factors affecting obstetric management and survival. Am J Obstet Gynecol 1988;159:352–6.
[41] Sharland GK, Lockhart SM, Chita SK, Allan LD. Factors influencing the outcome of congenital heart disease detected prenatally. Arch Dis Child 1991;66:284–7.
[42] Vergani P, Mariani S, Ghidini A, Schiavina R, Cavallone M, Locatelli A, et al. Screening for congenital heart disease with four-chamber view of the fetal heart. Am J Obstet Gynecol 1992;167:1000–3.
[43] Davis GK, Farquhar CM, Allan LD, Crawford DC, Chapman MG. Structural cardiac abnormalities in the fetus: reliability of prenatal diagnosis and outcome. Br J Obstet Gynecol 1990;97:27–31.
[44] Smythe JF, Copel JA, Kleinman CS. Outcome of prenatally detected cardiac malformations. Am J Cardiol 1992;69:1471–4.
[45] Copel JA, Pilu G, Kleinman CS. Congenital heart disease and extracardiac anomalies: associations and indications for fetal echocardiography. Am J Obstet Gynecol 1986;154:1121–32.
[46] Paladini D, Calabro R, Palmieri S, D'Andrea T. Prenatal diagnosis of congenial heart disease and fetal karyotyping. Obstet Gynecol 1993;81:679–82.
[47] Buskens E, Steyerberg EW, Hess J, Wladimiroff JW, Grobbee DE. Routine prenatal screening for congenital heart disease: what can be expected? A decision-analytic approach. Am J Public Health 1997;87:962–7.
[48] Bjorkhem G, Jorgensen C, Hanseus K. Parental reactions of fetal echocardiography. J Matern Fetal Med 1997;6:87–92.
[49] Cooper MJ, Enderlein MA, Dyson DC, Roge CL, Tarnoff H. Fetal echocardiography: retrospective review of clinical experience and an evaluation of indications. Obstet Gynecol 1995;86:577–82.
[50] Simpson LL, Marx GR, D'Alton ME. The detection of congenital heart disease in a tertiary care ultrasound practice. Am J Obstet Gynecol 1995;172:S354.

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Controversial ultrasound findings

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Ultrasound has truly revolutionized the practice of obstetrics. It is hard to imagine an era not too long ago where undiagnosed twins and term breeches were common. As amazing as it is, however, it is not a perfect technology and its ultimate usefulness is highly reliant on the person interpreting the images being obtained and acting on that information.

As ultrasound equipment becomes more and more sophisticated, the level of detail seen in the fetus improves. When new things are seen, it is sometimes difficult to know whether it is just because of improved technology or if it represents true pathology. Initial studies evaluating new ultrasound findings often are retrospective case series in patients already at a higher risk of having an abnormality because of some other reason, like advanced maternal age or elevated maternal serum screening. These initial studies are frequently followed by additional small studies that either refute or minimize their findings. Clinical care is sometimes altered as a result, before properly designed studies are undertaken. The confusion created by this apparently conflicting data makes counseling patients with these findings extremely difficult and controversial. This article takes several of the more controversial ultrasound findings (echogenic bowel, renal pyelectasis, echogenic intracardiac foci [EIF], clubfoot, single umbilical artery [SUA], and choroid plexus cyst [CPC]) and presents the best available data to come up with evidence-based approaches to their management.

Echogenic bowel

Fetal echogenic bowel refers to the presence of hyperechoic, or bright bowel, as compared with the echogenicity of adjacent bone. This finding can be diffuse or focal. Echogenic bowel is diagnosed in 0.2% to 1.4% of second-trimester ultrasounds [1]. The presence of echogenic bowel has been associated with nor-

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mal fetuses and fetuses with aneuploidy, intrauterine fetal growth restriction (IUGR), bleeding, cystic fibrosis (CF), congenital infections, and thalassemia. Its association with multiple pathologic conditions makes echogenic bowel unique among the other ultrasound findings discussed in this article. The following discussion pertains to the finding of echogenic bowel at the time of second-trimester ultrasound; echogenic bowel in the third trimester is a relatively common finding with uncertain clinical significance.

Pathophysiology

The pathophysiology of increased bowel echogenicity is likely heterogeneous in nature. In most cases the increased echogenicity is thought to be abnormal, highly viscous meconium within the small bowel caused by obstruction (meconium ileus), poor bowel motility, or abnormal pancreatic enzymatic secretion [2]. Alternatively, meconium peritonitis from a bowel perforation can cause subsequent bowel edema, which also makes the bowel appear echogenic [2]. If the meconium is confined to discrete sites of bowel perforation, the echogenicity appears as focal intra-abdominal calcifications [2]. Similar calcifications in the bowel have been associated with fetal infections, such as toxoplasmosis or cytomegalovirus (CMV), although the pathophysiology of this association is poorly understood. Focal areas of bowel echogenicity have also been attributed to areas of ischemia [2,3]. Finally, bowel may appear echogenic because of the swallowing of blood, which is extremely echogenic [4].

Diagnosis

The diagnosis of echogenic bowel is made by comparing the echogenicity of the bowel to that of the liver and adjacent bone. This is done by turning down the gain setting until other soft tissues are no longer seen and only bone or bowel is visible (Fig. 1). Although in principle this sounds straightforward, in practice the diagnosis of echogenic bowel is a subjective one, and is prone to significant interobserver and intraobserver variation [5]. Several authors have proposed a grading system to quantify the degree of echogenicity of fetal bowel to increase the accuracy of diagnosis and decrease the interobserver variation [6–9]. For example, Slotnick and Abuhamad [7] graded the degree of bowel echogenicity depending on when the echogenicity disappeared as the gain setting was decreased. Grade 0 was defined as normal, grade 1 was bowel that lost its echogenicity before that of the iliac crest, grade 2 was bowel that lost its echogenicity at the same time as the iliac crest, and grade 3 was bowel echogenicity that persisted after the loss of the iliac crest. The limitation of using a grading system is that many studies do not use one, and those that do have used a variety of different grading systems. Despite these limitations, the association of echogenic bowel with adverse pregnancy outcomes is strongest with moderate-to-severe echogenicity, when the bowel is as echogenic as or more echogenic than bone. In the series described previously, of 40 fetuses with mild (grade 1)

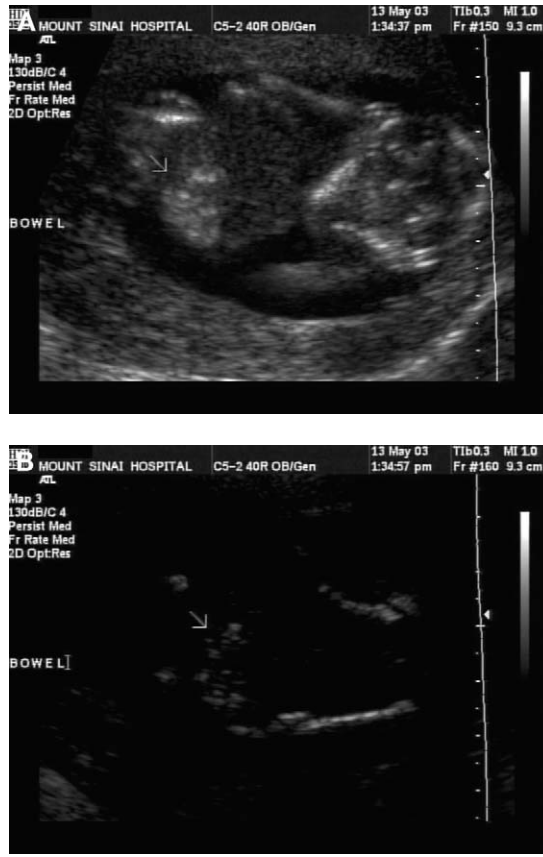

Fig. 1. (*A*) Echogenic bowel with normal gain setting (*arrow*). The bowel appears as bright as the adjacent bone. (*B*) Echogenic bowel with the gain setting turned down (*arrow*). Note that the echogenicity persists after the other soft tissues are no longer seen.

echogenicity, none had CF or aneuploidy, and of 105 fetuses with moderate-to-severe bowel echogenicity (grades 2 and 3), 7 (6.7%) had CF and 8 (7.6%) had trisomy 21 [7]. In the authors' institution, the diagnosis of echogenic bowel is made only when the bowel appears to be at least as echogenic as adjacent bone.

Further complicating the diagnosis is that the finding of echogenic bowel can vary with transducer frequency and sonographic image-processing platforms [10,11]. Because higher-frequency transducers can lead to overdiagnosis, it is recommended that the diagnosis of echogenic bowel be made with a transducer frequency of 5 MHz or less [10]. All of these factors make echogenic bowel one of the more difficult and controversial ultrasound findings used to predict the at-risk fetus. What should be clear is that criteria for the diagnosis should be strict; if less strict criteria are used, this finding is overdiagnosed and its sensitivity for detecting the fetus at risk for other abnormalities decreases.

Aneuploidy

The association of echogenic bowel with aneuploidy, particularly trisomy 21, has been demonstrated in several studies [1,12–16]. A review of 11 published series of fetuses with echogenic bowel in which information was available about aneuploidy found that 11.8% had chromosomal abnormalities [2]. The risk of aneuploidy in a fetus with echogenic bowel is highest in the presence of additional sonographic abnormalities; however, echogenic bowel may be the only sonographically detected abnormality in an aneuploid fetus [15–17]. The relative risk of Down syndrome for fetuses with hyperechoic bowel has been reported to be 5.5 times the a priori risk [18]. This association has been postulated to be caused by poor bowel motility resulting in increased water absorption and thickened meconium [6].

The largest series in the literature is a prospective collaborative series of 680 cases of fetuses with echogenic bowel referred for prenatal diagnosis, as summarized in Table 1 [16]. In this series, hyperechoic bowel was observed in 0.1% of second-trimester ultrasounds. Chromosome abnormalities were observed in 29 (4.3%) cases, of which 24 (3.5%) were severe, including 17 (2.5%) of

Table 1
Outcome of 682 cases of echogenic bowel

Outcome	N (%)	TOP (*N*)	IUFD (*N*)	Neonatal death (*N*)
Normal healthy newborn	447 (65.5)	—	—	—
Chromosomal abnormality	29 (4.3)	21	2	0
Trisomy 21	17 (2.5)	15	1	0
Other	12 (1.8)	6	1	0
Severe	7 (1)	6	1	0
Less severe[a]	5 (0.7)	0	0	0
Cystic fibrosis	21 (3.1)	16	0	0
Infectious diseases	19 (2.8)	12	1	0
Cytomegalovirus	15 (2.2)	12	1	0
Parvovirus	4 (0.6)	0	0	0
Toxoplasmosis	0 (0)	—	—	—
Rubella	0 (0)	—	—	—
IUGR	28 (4.1)	0	2	0
Intra-amniotic bleeding	21 (3.1)	NS	NS	NS
Unexplained IUFD	13 (1.9)	—	13	—
Associated structural abnormalities	47 (6.9)	17	2	3
Gastrointestinal abnormalities	20 (2.9)	3	1	0
Multiple visceral abnormalities	12 (1.8)	4	1	1
Cardiac abnormalities	5 (0.7)	2	0	1
Other	10 (1.5)	8	0	1

Abbreviations: IUFD, intrauterine fetal demise; IVGR, intrauterine growth restriction; NS, not specified; TOP, termination of pregnancy.

[a] Less severe includes Klinefelter syndrome, Robertsonian translocation, and mosaic trisomy X.

Adapted from Simon-Bouy B, Satre V, Ferec C, Malinge MC, Girodon E, Denamur E, et al. Hyperechogenic fetal bowel: a large French Collaborative Study of 682 cases. Am J Med Genet 2003; 121A(3):209–13; with permission.

which were Down syndrome. This is consistent with the findings of previous studies. In 11 (65%) of the cases with Down syndrome, echogenic bowel was the only sonographic abnormality noted. The risk of a severe chromosomal abnormality (including Down syndrome) when echogenic bowel was isolated or seen in conjunction with other abnormalities was 1.6% and 1.9%, respectively.

Cystic fibrosis

Echogenic bowel has been reported to be found on ultrasound in 50% to 78% of fetuses affected with CF [19,20]. The association of echogenic bowel with fetuses affected with CF is thought to be caused by changes in the consistency of meconium in the small intestine as a result of abnormalities in pancreatic enzyme secretion. This can result in detectible sonographic findings, such as diffuse echogenic bowel, focal echogenic bowel with calcifications, a hyperechoic mass, or bowel dilation [2,20,21]. These findings may appear as early as the second trimester [20,21]. CF has been reported to affect 0.8% to 13.3% of fetuses with echogenic bowel [1,17,22–25], markedly higher than the rate of CF expected in a white population in which the carrier frequency is 1 in 25. Simon-Bouy et al [25] found that of 682 cases of hyperechogenic bowel referred for CF testing, 21 (3.1%) were found to have CF (see Table 1).

As with any screening marker, echogenic bowel is most predictive of CF in populations at highest risk for CF. High-risk populations, however, are those that are most likely to be screened routinely for CF. There is some evidence that the detection of echogenic bowel in populations at low-risk for this disease does not increase the risk of CF when compared with the background risk [26].

Congenital infection

The association of congenital infections with echogenic bowel has been reported to be from 0% to 10% [17]. The most commonly detected infectious agent is CMV, although cases with other infections, such as toxoplasmosis, parvovirus, varicella, and herpes simplex, have also been described in case reports [2,27]. Simon-Bouy et al [25] prospectively checked maternal rubella, toxoplasmosis, and CMV serologies (IgG and IgM) in 682 cases of fetal echogenic bowel (see Table 1). When seroconversion was observed, CMV polymerase chain reaction testing was performed in amniotic fluid. Parvovirus B19 polymerase chain reaction was also performed in all cases. A total of 19 viral infections were diagnosed, which represented 2.8% of fetuses: 15 (2.2%) CMV and 4 (0.6%) parvovirus. In 11 of the fetuses with CMV, echogenic bowel was the only sonographic abnormality noted. All four of the fetuses with parvovirus had associated abnormalities. It is unclear how a viral infection results in the echogenic appearance of the bowel. It may be caused by direct intestinal damage from inflammation or meconium peritonitis or indirectly by ascites, anemia, or growth restriction [2,27].

Intrauterine growth restriction

Intrauterine fetal growth restriction has been estimated to complicate 4% to 18% of pregnancies with echogenic bowel, even in the setting of a normal karyotype [2,16,17,25]. The association of echogenic bowel with IUGR may be caused in part by ischemia from redistribution of blood flow away from the gut [3]. The presence of IUGR or elevated maternal serum alpha-fetoprotein in the second trimester in association with echogenic bowel seems to be associated with a particularly poor fetal prognosis. In one series, all six fetuses with both echogenic bowel and elevated maternal serum alpha-fetoprotein were growth restricted: four died in utero, one of two live-born infants died during the neonatal period, and the single survivor developed necrotizing enterocolitis requiring surgery [28]. This poor prognosis has been confirmed in other studies [1,15].

Intra-amniotic bleeding

Echogenic bowel has also been associated with evidence of intra-amniotic bleeding. This is thought to be caused by fetal swallowing of blood, which is very echogenic. One series found that 22% of fetuses with echogenic bowel had evidence of heme pigment in amniotic fluid [4]. In another series, 3.1% of amniotic fluid was grossly contaminated with blood [25]. Finally, Petrikovsky et al [29] examined 28 fetuses before and 12 hours after intrauterine transfusion, a procedure that commonly introduces blood into the amniotic cavity by post-puncture bleeding. Although none of the fetuses had echogenic bowel before intrauterine transfusion, 25% of these fetuses had evidence of bowel echogenicity within 12 hours of the bleeding episode and 18% still had evidence of echogenicity 2 weeks later [29]. In general, pregnancies with evidence of intra-amniotic bleeding but without additional anomalies have a good prognosis [15].

Prognosis

Although one analysis of nine studies found that 34% of fetuses with echogenic bowel have a poor perinatal outcome, the most important prognostic factor is whether or not there are associated fetal abnormalities [17]. The prognosis seems to be particularly poor in the setting of early IUGR and elevated maternal serum alpha-fetoprotein. Fetuses with echogenic bowel as an isolated finding seem to have a much better prognosis. This is because in most cases the finding of isolated echogenic bowel is associated with a normal fetus. One study, which examined 175 fetuses in 171 pregnancies complicated by isolated echogenic bowel, found that only 6.3% of fetuses were affected with CF (five fetuses), aneuploidy (five fetuses), and CMV (one fetus) [1]. In a larger series, 447 (65.5%) of 682 cases of echogenic bowel resulted in the birth of a normal healthy newborn (see Table 1) [25]. In the normal fetus, the finding of echogenic bowel usually resolves over a period of weeks with no adverse sequelae [30]. Despite this, there does seem to be an increased risk of unexplained intrauterine

fetal demise in fetuses with unexplained echogenic bowel, with a rate of 1.9% reported in one series [25].

Evaluation and management

The finding of bona fide echogenic bowel at the time of second-trimester ultrasound should prompt a work-up that targets these findings. A detailed ultrasound of the fetus should be performed, and an amniocentesis for karyotype should be recommended even when echogenic bowel is an isolated finding. A careful history should be taken to elicit any history of bleeding in the pregnancy, and there should be careful evaluation of the amniotic fluid, placenta, and membranes for any features of intra-amniotic bleeding, such as particulate debris or clot floating in the amniotic fluid or chorioamniotic separation. CF carrier testing for both parents should be recommended. Maternal serologic testing for evidence of recent CMV and toxoplasmosis should be performed (IgG and IgM). If there is evidence of recent infection, an amniocentesis can be performed and the amniotic fluid tested for evidence of CMV, toxoplasmosis, and parvovirus infection. Because these fetuses are at risk for IUGR, these fetuses should be followed with serial growth scans. If all of these studies are normal, some form of antenatal testing (nonstress test or biophysical profile) seems warranted because of the possible association between echogenic bowel and intrauterine fetal demise.

Pyelectasis

Dilation of the fetal renal pelvis is a common finding on antenatal ultrasound, with an incidence reported to be from 0.3% to 4.5%, with most reports around 1% (Fig. 2) [31–37]. Fetuses with significant pyelectasis ($\geq$ 10 mm) are clearly

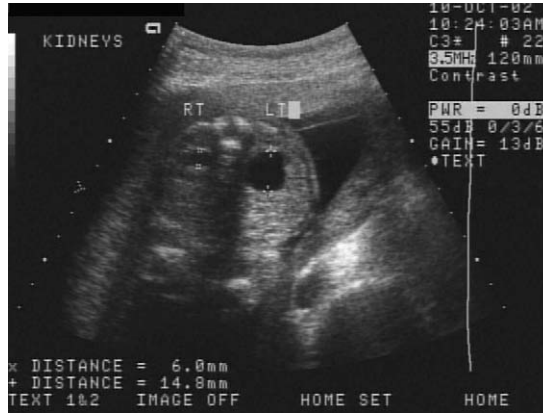

Fig. 2. Bilateral renal pyelectasis: mild on the right, moderate on the left.

at risk for having structural abnormalities that require postnatal evaluation and therapy [38]. The significance of mild pyelectasis is less clear. Mild pyelectasis refers to mild dilation of the pelvis ($\leq$ 10 mm) as measured as the anteroposterior diameter on transverse (axial) section through the fetal abdomen with minimal or no dilation of the intrarenal (calyceal) system. Mild pyelectasis has been associated with many neonatal urologic disorders and chromosomal abnormalities, most notably Down syndrome. The literature on pyelectasis is extremely heterogenous and is mostly limited to small series, making both the prenatal and postnatal management and counseling of these patients very difficult and controversial.

Diagnosis

A variety of parameters have been used in the literature to define mild pyelectasis, accounting for the wide range of reported incidences. Although mild pyelectasis was initially described as a ratio of the pelvic diameter to the renal diameter, more recent studies define mild pyelectasis using a variety of gestational age-dependent parameters of the anteroposterior diameter, some of which are described in Table 2 [39]. In general, mild pyelectasis is diagnosed when the renal pelvis anteroposterior diameter is greater than 4 or 5 mm and less than 10 mm. The fact that different ultrasound criteria are used to define pyelectasis

Table 2
Gestational age-based criteria for the diagnosis of fetal renal pyelectasis[a]

Study	Definition	N
Benacerraf 1990	$\geq$ 4 mm 16–20 wk $\geq$ 5 mm 20–30 wk $\geq$ 7 mm 30–40 wk	210
Corteville 1991	$\geq$ 4 mm < 33 wk $\geq$ 7 mm > 33 wk	63
Corteville 1992	$\geq$ 4 mm < 33 wk $\geq$ 7 mm > 33 wk	127
Adra 1995	$\geq$ 4 mm < 33 wk and $\leq$ 10 mm $\geq$ 7 mm > 33 wk and $\leq$ 10 mm	68
Langer 1996	$\geq$ 5 mm < 28 wk $\geq$ 10 mm > 28 wk	95
Wickstrom 1996a	$\geq$ 4 mm all gestational ages	82
Wickstrom 1996b	$\geq$ 4 mm < 33 wk $\geq$ 7 mm > 33 wk	121
Chudleigh 2001	$\geq$ 5 mm and $\leq$ 10 mm at 16–26 wk	737
Broadley 1999	$\geq$ 5 mm > 18 wk $\geq$ 10 mm > 30 wk	139
Ismaili 2003	$\geq$ 4 mm < 33 wk and $\leq$ 10 mm $\geq$ 7 mm > 33 wk and $\leq$ 10 mm	258
Bobrowski 1997	$\geq$ 4 mm < 32 wk $\geq$ 7 mm $\geq$ 32 wk	230

[a] Measurements are of the anteroposterior diameter of the fetal renal pelvis.

in different series, and that some of these series limit their criteria to only mild pyelectasis (anteroposterior diameter ≥ 4 mm and < 10 mm), whereas others include all fetuses with pyelectasis (≥ 4 mm), makes the literature very difficult to interpret. The optimal criteria to use depend on the condition being screened. For example, if one is screening for renal anomalies, it may be desirable to be 100% sensitive, so as to detect all fetuses that are at risk for postnatal abnormalities. Corteville et al [31] in a study evaluating the ability of six different ultrasonographic parameters to predict postnatally confirmed congenital hydronephrosis, found that an anteroposterior diameter of greater than or equal to 4 mm before 33 weeks and greater than or equal to 7 mm after 33 weeks had a sensitivity of 100%, but a false-positive rate of 21% to 55% (depending on the gestational age). If one is screening for Down syndrome, however, it is preferable to minimize the false-positive rate to less than 5% so as to avoid unintended fetal loss as a result of invasive procedures. Corteville et al [32], using the parameters of greater than or equal to 4 mm before 33 weeks and greater than or equal to 7 mm after 33 weeks, found the overall sensitivity of pyelectasis for the detection of Down syndrome to be 17%. This dropped to 4% when pyelectasis was an isolated finding. The false-positive rate in this series was 2%, with a positive predictive value of isolated pyelectasis for Downs of 1 in 340 [32].

Further complicating the diagnosis of pyelectasis is that the size of the fetal renal collecting system seems to be highly variable over time. Persutte et al [40] performed intermittent ultrasound measurements (every 15 minutes) on 20 fetuses with pyelectasis. Overall, the mean variation (minimum to maximum) for the transverse anteroposterior diameter was 3.8 ± 2.49 mm. Seventy percent of cases had both normal and abnormal values during the 2-hour study period (<4 mm and ≥ 4 mm, respectively). One should exercise significant caution when considering the implications of renal collecting system dilation based on a single anteroposterior measurement.

Characteristics

Fetal pyelectasis is more often bilateral, but when unilateral it is more likely to be on the left side [33,41]. It is more common in male fetuses both prenatally and postnatally [31,33,42–44]. Fetuses may be more likely to have pyelectasis if they have a full bladder, or if the women themselves have concomitant pyelectasis [45,46]. The effect of maternal hydration on fetal pyelectasis is unclear; aggressive maternal hydration did not increase the risk of fetal pyelectasis in some series but did in others [47–49]. Laterality does not seem to be useful for prognosis. In one study, bilateral pyelectasis was more likely to progress to hydronephrosis than unilateral pyelectasis (26% versus 3%, respectively) [50]. Another study showed that resolution was more likely to occur in fetuses with bilateral pyelectasis (39% versus 18% resolution in unilateral fetuses, $P = .046$) and that fetuses with unilateral pyelectasis had a significantly higher incidence of urinary tract pathology at birth (59% versus 34% in bilateral fetuses, $P = .03$) [43]. Gender does not seem to influence rates of progression or

resolution of pyelectasis [43,50]. The distribution of urologic abnormalities is also similar between male and female infants, although one study showed a trend toward a higher incidence of vesicoureteral reflux in male fetuses [43]. There are no data on whether unilateral or bilateral pyelectasis is more or less likely to be associated with Down syndrome.

Pyelectasis and aneuploidy

An association of pyelectasis with aneuploidy (primarily Down syndrome) was first suggested in 1990 when, in a selected high-risk population, 25% of fetuses with Down syndrome were noted to have pyelectasis compared with 2.8% of fetuses with normal karyotype [34]. Other studies, mainly in high-risk, selected populations, have supported this finding by showing that fetal pyelectasis is associated with an increased risk for both Down syndrome and other chromosomal abnormalities, although a few studies have found no association [32,33,42,43,51–54]. Pyelectasis has also been associated with an increased risk of other fetal anomalies [32]. Not surprisingly, the association of pyelectasis with Down syndrome is strongest when other anomalies are present [42,55]. The largest series of fetal pyelectasis, a multicenter, prospective, observational study of unselected fetuses examined between 16 and 26 weeks, identified 737 fetuses with mild pyelectasis in a population of 101,600 births. Of these 737 fetuses, 12 (1.7%) had chromosomal abnormalities (six trisomy 21, one trisomy 13, one trisomy 8, two Turner's syndrome, one unbalanced translocation, and one 47,XXX). Of the 12 fetuses with chromosomal abnormalities, 9 had associated sonographic abnormalities and one mother was advanced maternal age (AMA); only two chromosomal abnormalities occurred in the setting of isolated pyelectasis in low-risk women (0.3%). This study showed the risk of aneuploidy in a fetus with isolated mild pyelectasis to be 0.33% and 2.22% in women less than 36 and greater than or equal to 36 years, respectively.

The most important question is whether isolated mild pyelectasis is associated with an increased risk of aneuploidy in a low-risk population, because those who are already at a higher risk for aneuploidy are offered invasive testing whether or not mild pyelectasis is present. Unfortunately, there are little data on the ability of isolated pyelectasis to predict aneuploidy in a low-risk unselected population. A recent retrospective study reviewed the ultrasounds of 25,586 primarily low-risk, unselected women and found 320 cases of pyelectasis (defined as $\geq$ 5 mm anteroposterior diameter) for an incidence of 1.25% [33]. Nineteen of the fetuses with pyelectasis had associated sonographic anomalies, and in 301 (incidence 1.18%) pyelectasis was an isolated finding. None of the fetuses in this series had aneuploidy. Although the authors state that this study was primarily in a low-risk population, there were some women in this series who were AMA. More studies are needed to assess the predictive value of isolated mild pyelectasis in a low-risk population, particularly when taking into account the results of multiple marker screening and nuchal translucency.

Pyelectasis and postnatal renal abnormalities

In addition to its association with chromosomal abnormalities, prenatally detected pyelectasis is also useful as a marker of postnatal urinary tract abnormalities. The theoretical benefit of prenatal diagnosis is to be able to alert the pediatrician so that early intervention, if needed, can minimize postnatal morbidity. There are no data, however, to show that the prenatal detection of pyelectasis improves neonatal outcome.

Data on the natural history of pyelectasis, particularly of mild pyelectasis, are confusing because of the heterogeneous nature of this literature. A few generalizations, however, can be made. For approximately 60% to 70% of fetuses, the pyelectasis remains stable, improves, or completely resolves on subsequent examinations. The remainder, approximately one third to one quarter of fetuses, has progression of their pyelectasis [31,33,37,43,44,56]. In utero progression of pyelectasis does not necessarily predict postnatal uropathy, but it does put the fetus at increased risk for clinically significant disease. Of those kidneys showing progression, regression, or no change of isolated pyelectasis, postnatal uropathy was noted in 60%, 23%, and 32% of fetuses, respectively, in one series looking at 105 fetuses with pyelectasis [37]. When progression of pyelectasis occurred prenatally in this series, the probability of corrective surgery in the infant was 50%.

The previously mentioned cohort included fetuses with all degrees of pyelectasis. A recent series described the natural history of pyelectasis in 213 fetuses (426 kidneys) with only minor degrees of dilation (mild and moderate pyelectasis) in an unselected population [35]. In this series, fetuses were examined sonographically in both the second and third trimester. Fetuses were categorized as having had pyelectasis detected in the second trimester only, the third trimester only, or in both the second and third trimesters. In this series, 38% of fetuses with antenatal evidence of pyelectasis at any time had normal urinary tracts on postnatal examination. Sixty-two percent of fetuses (42% of all kidneys) had postnatal renal abnormalities, the distribution of which is illustrated in Table 3. Sixty-three percent of those with postnatally detected disease had significant nephrouropathies that required long-term medical care (39% of fetuses overall). Fetuses were more likely to have postnatal renal abnormalities if they had pyelectasis in the third trimester. The presence of pyelectasis in the second trimester only, however, did not completely rule out postnatal abnormalities, because 12% of those fetuses whose pyelectasis had resolved on the third-trimester scan had significant nephrouropathy.

Long-term prognosis

In the chromosomally normal fetus, the predictive value of prenatal findings for long-term postnatal genitourinary pathology remains uncertain. The best predictions can be made based on the presence of pyelectasis in the third trimester and the severity of the pyelectasis [35,38,43,57]. In one series, a cohort of

Table 3
Postnatal abnormalities found in 213 infants (426 kidneys) with prenatally diagnosed mild and moderate pyelectasis

Pathologic condition	Kidneys (%)
Pelviureteric junction stenosis	7
Primary vesicoureteric reflux	8
Transitory hydronephrosis	8
Mild idiopathic dilation	5
Megaureter	4
Complicated renal duplication	3
Noncomplicated renal duplication	3
Other pathology	3
Total kidneys with pathology	42

From Ismaili K, Hall M, Donner C, Thomas D, Vermeylen D, Avni FE. Results of systematic screening for minor degrees of fetal and renal pelvis dilation in an unselected population. Am J Obstet Gynecol 2003;188:242–6; with permission.

75 fetuses with bilateral pyelectasis were identified and followed until 4 years of age. Data from that study are summarized in Table 4 [57]. None of the fetuses with mild pyelectasis had chronic renal failure or neonatal death by age 4, although 5% of them required surgery. Of the fetuses with moderate and severe pyelectasis, 9% of the children went on to develop chronic renal failure, 15% suffered neonatal deaths, and 36% required surgery. Three of the five neonatal deaths in the moderate-severe group had severe associated anomalies; the other two children had posterior urethral valves. This study reaffirms the association between the incidence and severity of postnatal genitourinary disease with the degree of in utero pyelectasis. Overall, the prognosis for most patients with pyelectasis is good, particularly when there are no associated anomalies, and particularly when the degree of dilation is mild.

Management of a pregnancy with pyelectasis

As do any other soft markers, the detection of pyelectasis should prompt a thorough evaluation for concomitant abnormalities. A fetal echocardiogram can

Table 4
Outcome by age 4 of fetuses with prenatally diagnosed bilateral pyelectasis

Dilation	N	Chronic renal failure (%)	Neonatal death (%)	Genitourinary surgery (%)
Mild	42	0	0	5
Moderate	30	7	13	37
Severe	3	33	33	33

Mild: 5–10 mm; moderate: 10–15 mm < 30 wk; 10–20 mm > 30 wk; severe: > 15mm < 30 wk, > 20 mm > 30 wk.
From Broadley P, McHugo J, Morgan I, Whittle MJ, Kilby MD. The 4 year outcome following the demonstration of bilateral renal pelvic dilatation on pre-natal renal ultrasound. Br J Radiol 1999;72: 265–70; with permission.

be considered to evaluate the fetal heart comprehensively. In the absence of other anomalies, soft markers, or risk factors for aneuploidy (such as maternal age), amniocentesis for isolated mild pyelectasis does not seem to be warranted.

Because 30% of cases with mild pyelectasis advance to hydronephrosis, these evaluation in the third trimester (preferably after 28 weeks) is recommended to identify worsening or persistent cases. In the absence of oligohydramnios, patients can be delivered at term. Prenatal sonography does not seem to be sensitive enough to differentiate those cases with mild pyelectasis that develops postnatal uropathy from those that do not. Therefore, it is recommended that all infants with persistent mild fetal pyelectasis undergo some degree of postnatal evaluation or surveillance.

Echogenic intracardiac foci

Echogenic intracardiac foci are normally described as discrete areas of echogenicity comparable with bone in the region of the papillary muscle in either cardiac ventricle [58]. Echogenic intracardiac foci are thought to represent calcifications within the fetal papillary muscle, and may be the result of an aggregate of chordal tissues that have failed to fenestrate completely, enhancement of abnormal tissue, or a collection of fibrous tissue with increased echogenicity [59,60]. In some cases, EIF may also represent true microcalcifications within the cardiac muscle [58].

Appearing sonographically as a bright spot in one of the ventricles, EIF is a common finding seen in approximately 4% of obstetric sonograms (Fig. 3) [61]. The incidence of EIF can vary with ethnicity, with the lowest rates seen in black populations and the highest rates seen among Asian patients [62]. EIF can be single or multiple, and although they can appear in either ventricle, most (72% to 88%) are seen in the left ventricle [60,63–66]. Unlike the diagnosis of echo-

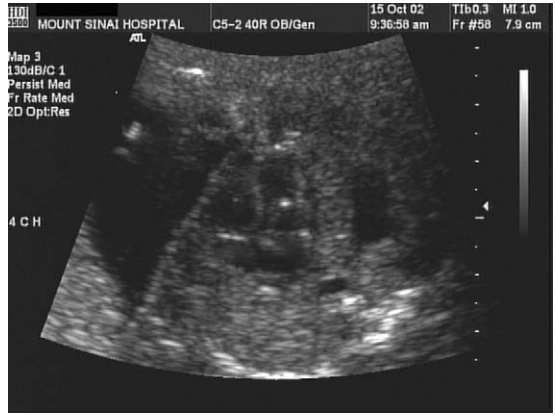

Fig. 3. Echogenic intracardiac foci.

genic bowel, which can be quite subjective, the diagnosis of EIF is relatively straightforward, although it has been suggested that technical factors, such as the experience of the sonographer, fetal position, and machine settings, may influence visualization of EIF [67].

Echogenic intracardiac foci were initially thought to represent a normal variant [68]. An association between EIF and aneuploidy was first suggested in the early 1990s when calcification of the papillary muscle was noted in 39% of abortuses with trisomy 13, 16% of abortuses with trisomy 21, and 2% of euploid abortuses [59]. Although this association has been attributed to vascular maldevelopment, the exact pathophysiologic link to aneuploidy remains uncertain [59,61]. Since that first series, there have been many studies confirming the association of EIF and aneuploidy [63,66,69–80]. For example, Bromley et al [69] prospectively evaluated 1334 patients referred for amniocentesis and found that 4 (18%) of 22 fetuses with trisomy 21 had EIF, compared with only 62 (4.7%) of 1312 fetuses without trisomy 21. Similarly, Manning et al [70] reviewed the ultrasounds of 901 high-risk women who underwent amniocentesis at the time of targeted ultrasound and found that 3 (13%) of 24 fetuses with EIF had Down syndrome, significantly more than fetuses without EIF (14 [2%] of 877 fetuses, $P = .009$). Vibhakar et al [80] confirmed these findings in a retrospective cohort study of 2412 women undergoing amniocentesis, which showed that fetuses with EIF had a relative risk of 3.3 of aneuploidy when compared with fetuses without EIF. Furthermore, in this series the presence of isolated EIF carried a relative risk of 4.1 when compared with those fetuses that sonographically had no other findings associated with aneuploidy. Finally, Winter et al [73] prospectively evaluated 3303 consecutive fetuses in a high-risk population and determined that EIF was found in 4.6% of normal fetuses and 30% of fetuses with trisomy 21. For a sonographically isolated EIF, the sensitivity, specificity, and positive predictive value were calculated to be 19%, 95%, and 3.7%, respectively, with a relative risk of 4.8.

Although these data suggest an association of EIF with Down syndrome, these studies were all performed in high-risk, selected populations (most of the patients had been referred for amniocentesis), in which amniocentesis is normally recommended even without the presence of EIF. It is more useful to evaluate the risk of aneuploidy in association with EIF in low-risk (< age 35) populations, particularly when EIF is an isolated finding, because it is in those instances that the finding of EIF can influence recommendations for invasive testing.

There are few studies evaluating EIF in a low-risk population. A recently published, large, prospective, population-based observational study of 12,373 women identified 267 cases of EIF, 72% (193 of 9167) of which were found in women under the age of 35 [81]. The overall incidence of EIF in this series was 2.2%; 2.1% in women less than 35 and 3.4% for fetuses of mothers greater than or equal to 35 years old. Isolated EIF was present in 1.6% of women less than 35 and 1.8% of women greater than or equal to 35. Of the 193 cases in low-risk women (< age 35), EIF was an isolated sonographic finding in 149 fetuses (77% of EIF cases in women < age 35). None of the cases of isolated EIF detected

on second-trimester ultrasound in women less than 35 was associated with aneuploidy. The authors concluded that EIF as an isolated finding on second-trimester ultrasound in a woman less than age 35 does not change the risk of aneuploidy and does not warrant invasive testing. Other authors have agreed with this appraisal [82].

To evaluate the clinical significance of EIF further in a low-risk patient, Caughey et al [83] created a decision analytic model that compared the standard of second-trimester triple marker screen for Down syndrome with a policy in which amniocentesis with an isolated EIF on ultrasound (in addition to the triple marker screen) is offered to all women in the United States who are less than 35 years of age. The authors calculated that using isolated EIF as a screen results in an additional 118,146 amniocenteses performed annually to diagnose 244 fetuses with Down syndrome, which results in 2.4 procedure-related losses for each additional Down syndrome fetus that was identified.

Echogenic intracardiac foci are not very useful as a marker for aneuploidy primarily because it is detected in only 11% to 30% of Down syndrome fetuses, which explains its low sensitivity [18,61,84]. A recent meta-analysis evaluating the performance of EIF for Down syndrome in 11 studies with a total of 51,831 patients found the overall sensitivity and specificity of EIF for predicting Down syndrome to be only 26% (95% CI 14%, 33%) and 95.8% (95% CI 91%, 98.2%), respectively (Table 5) [61]. The sensitivity drops even further to 22% when EIF is an isolated finding. The authors calculated that, in general, the prior risk of Down syndrome, as calculated by maternal age, history of previous affected pregnancy, and prior screening tests, is increased by a factor of 5.4 when EIF are present, and is reduced by a factor of 0.8 when no foci are detected.

In the absence of aneuploidy, EIF has not been associated with structural cardiac abnormalities [85]. One study suggested that multiple or right-sided foci may have a worse prognosis when compared with single left-sided foci, but others show no such association [60,86]. A recent study found that early ventricular filling and active atrial filling peak velocity ratios were significantly lower in fetuses with EIF, which may indicate cardiac diastolic dysfunction [87]. Despite this finding, there does not seem to be any increase in childhood myocardial dysfunction when compared with the general population, although EIF may persist into early childhood [64].

Table 5
Diagnostic performance of echogenic intracardiac foci for Down syndrome

	% Sensitivity	% Specificity	Likelihood ratio
All EIF	26	96	6.2
Isolated EIF	22	96	5.4
Combined EIF	26	96	7

Abbreviation: EIF, echogenic intracardiac foci.

Adapted from Sotiriadis A, Makrydimas G, Ioannidis PA. Diagnostic performance of intracardiac echogenic foci for Down syndrome: a meta-analysis. Obstet Gynecol 2003;101:1009–16; with permission.

Management

As with any other abnormal finding on ultrasound, the detection of an EIF should prompt a detailed sonographic examination to search for any associated anomalies. In the setting of other sonographic abnormalities, or in a high-risk population (women of advanced maternal age, women with a history of a chromosomal abnormality), EIF may carry some clinical significance, and an amniocentesis to rule out aneuploidy should be recommended. The data that are available from low-risk populations seem to indicate, however, that isolated EIF is not associated with an increased risk of Down syndrome, or if it is, that risk is much less than the procedure-related loss rates associated with invasive testing. In the authors' institution isolated EIF in a woman less than 35 is considered an incidental finding and amniocentesis is not recommended. Because there is no association of EIF with structural cardiac disease, further evaluation of EIF is not necessary either prenatally or postnatally.

Clubfoot

Clubfoot, or talipes equinovarus, is a deformity in which the foot is excessively plantar flexed, with the forefoot bent medially and the sole facing inward. This usually results in the underdevelopment of the soft tissues on the medial side of the foot and calf and to various degrees of rigidity of the foot and calf. The deformity is not passively correctable and does not resolve spontaneously. Clubfoot is a relatively common birth defect, with an incidence ranging from about 0.1% in the newborn population to 0.4% when diagnosed antenatally by ultrasound [88]. The incidence of clubfoot varies with ethnicity, with a reported incidence of 0.4 per 1000 live births in Chinese, 1 to 5 per 1000 in whites, and 6 to 8 per 1000 in Polynesians [89]. Male fetuses are more commonly affected than females, with a 2:1 predisposition [90]. Clubfoot is bilateral in approximately 50% of cases, but when unilateral is not predisposed to a particular side [91–93]. Clubfoot can be isolated, or associated with other structural abnormalities. Other abnormalities are more likely to be present if clubfoot is diagnosed antenatally. For example, clubfoot has been associated with other structural abnormalities 10% to 14% of the time in neonatal series and as high as 80% in prenatal series [92,94,95]. It can also be associated with many genetic syndromes, some of which are listed in Table 6 [90,92].

Etiology

The etiology of clubfoot remains unclear. Both environmental (extrinsic) or genetic (intrinsic) factors have been implicated. Extrinsic etiologies are related to environmental factors that cause deformations during fetal development. Several environmental etiologies have been theorized over the years, although most of the studies have been small and poorly designed [89]. It has been postulated that deformation can occur because of crowding from multiple gestations, breech

Table 6
Etiologies of clubfoot

- Intrinsic
  - Chromosomal
    - Trisomy 18
    - Deletions of chromosomes 18q, 4p, 7q, 9q, 13q
  - Connective tissue
    - Arthrogryposis
    - Collagen defects
    - Joint synostosis
  - Neurologic
    - Anencephaly
    - Anterior motor horn cell deficiency
    - Hydrancephaly
    - Holoprosencephaly
    - Meningomyelocele
    - Spina bifida
  - Muscular
    - Myopathy
    - Myotonic dystrophy
  - Skeletal dysplasia
    - Campomelic dysplasia
    - Chondrodysplasia punctata
    - Diastrophic dysplasia
    - Ellis-van Creveld syndrome
  - Syndromes
    - Escobar syndrome
    - Hecht syndrome
    - Larsen's syndrome
    - Meckel-Gruber syndrome
    - Multiple pterygium
    - Pena Shokeir
    - Smith-Lemli-Opitz
    - Zellweger's syndrome
- Extrinsic
  - Amniotic bands
  - Synechiae
  - Early amniocentesis
  - Intrauterine crowding
    - Fibroids
    - Multiple gestation
    - Oligohydramnios
      - Potter sequence
    - Increased birthweight
  - Breech
  - Nulliparity
  - Seasonal variation
    - Viral
  - Hyperthemia
  - Substance use
    - Maternal alcohol
    - Maternal and paternal smoking
    - Illicit drugs

Adapted from Magriples U. Prenatal diagnosis of clubfoot. In: UpToDate, version 11.2. Wellesley, MA: 2003; with permission. Available at www.uptodate.com.

presentation, nulliparity, increased birthweight, uterine cavity abnormalities, amniotic bands, or oligohydramnios [96]. Seasonal variation has also been reported [97,98]. It has been theorized that this may be caused by an infectious etiology, although there are no data to support this hypothesis. Hyperthermia has also been associated with clubfoot in animal studies, as have maternal alcohol consumption and maternal and paternal smoking [99–101]. Preliminary data suggest there may be an association of clubfoot with illicit drug use [96].

The strongest evidence for an environmental cause of clubfoot comes from the Canadian Early and Mid-Trimester Amniocentesis Trial, a prospective randomized study that compared the safety and accuracy of early amniocentesis with midtrimester amniocentesis [102]. In this trial, 29 (1.3%) of 2187 children of women in the early amniocentesis group compared with 2 (0.1%) of 2187 children of women in the mid-trimester amniocentesis group had talipes equinovarus; this was statistically significant ($P = .0001$). The occurrence of clubfoot increased to 15% in the setting of amniotic fluid leakage, although none of the cases with clubfoot had persistent oligohydramnios at the time of the detailed anatomic survey done at 18 to 20 weeks. This implies that it is not only the presence of oligohydramnios, but the timing of the oligohydramnios, that is important.

Intrinsic (heritable) factors have also been implicated in the disease. The genetic contribution to clubfoot is incompletely understood. Clubfoot is most commonly associated with multifactorial inheritance, although single gene transmission has been suggested [89,103]. The theory that clubfoot has a heritable component was demonstrated in one series in which the concordance for clubfoot was 32.5% in monozygotic twins and 2.9% in dizygotic twins [104]. Twins experience a similar intrauterine environment; any difference in phenotype between twin pairs must be caused by intrinsic (genetic) causes. Clubfoot has also been associated with several genetic syndromes (see Table 6) [105]. Other intrinsic causes include the development of neurologic, musculoskeletal, or connective tissue disorders, because fetuses that do not move normally in utero often develop clubfoot [105].

Further evidence for intrinsic causes of clubfoot is illustrated in the observed recurrence risk. First-degree relatives of a person with idiopathic clubfoot are at a significantly increased risk of having clubfoot when compared with the general population. The recurrence risk for siblings with normal parents varies according to the gender of the affected sibling; the recurrence risk for a sibling of an affected male is 2%, and is 5% for the sibling of an affected female [106]. If a child and another family member have clubfoot, or both parents have clubfoot, the risk of having another affected child increases to 10% to 20% [89].

Diagnosis

The prenatal diagnosis of clubfoot is made sonographically by visualization of the plantar surface of the fetal foot in the same plane as the bones of the lower leg (Fig. 4). Multiple images should be observed, preferentially with movement of the leg away from the wall of the uterus, to ensure that this is a fixed

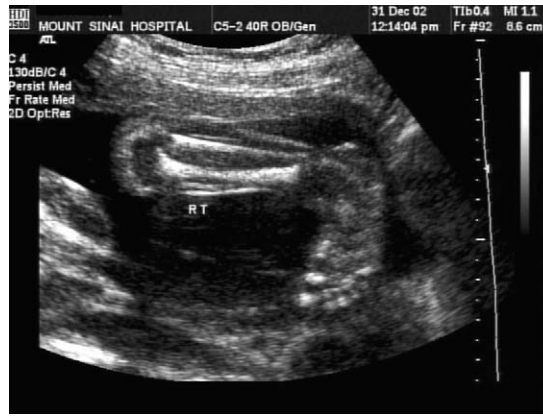

Fig. 4. Clubfoot. Note that the plantar surface of the foot is visualized in the same plane as the bones of the lower leg.

abnormality and not just a temporary positioning of a normal foot that mimics clubbing. Mild deformities may be more difficult to diagnose, because the foot may be turned inward but not entirely parallel to the lower leg. Clubfoot can be diagnosed as early as 12 or 13 weeks, although it can be diagnosed in any trimester [88]. The false-positive rate was reported in one series to be 11.8% [107].

Detection of clubfoot on prenatal ultrasound has increased during the last decade, primarily because of improvement in the quality of the ultrasound equipment, operator expertise, and increased sonographic screening during the pregnancy. Despite this, the diagnosis of clubfoot can still be difficult. In one recently published retrospective series of 281 cases, the accuracy from 1987 to 1999 was only 35% [88]. This improved to almost 70%, however, in the last year of that series. Accurate prenatal diagnosis is more likely when the condition is bilateral, or when there are associated abnormalities [88]. In one study, all cases with associated anomalies were identified prenatally [108].

Management

Sonographic detection of clubfoot warrants a detailed anatomic survey to search for any associated abnormalities. A fetal echocardiogram should be considered, and in the setting of associated structural abnormalities an amniocentesis should be recommended. There should also be a careful evaluation of the uterus looking for any evidence of uterine abnormalities, such as fibroids or a septum.

There is much controversy about whether to recommend amniocentesis after detection of an isolated clubfoot. It seems that clubfoot is associated with aneuploidy, but there are limited data adequately to quantify that risk. The data available are from small series of high-risk, selected populations (populations that

were likely to need amniocentesis anyway), as opposed to low-risk populations in which these data are the most useful. Similarly, there are no data on the sensitivity, specificity, and positive or negative predictive value of clubfoot for predicting aneuploidy. Most studies have found that fetuses with clubfoot and karyotypic abnormalities usually have additional structural abnormalities [93]. For example, in one retrospective series of 35 cases of clubfoot, all five fetuses that had karyotypic abnormalities (four with trisomy 18, one with a translocation) had associated structural abnormalities [95]. This is supported by the findings in another series of 51 fetuses with isolated clubfoot, in which there were no cases of fetal aneuploidy [93]. Other studies have suggested that clubfoot, even in the absence of associated abnormalities, confers increased risk of aneuploidy. For example, in a recently published series of 87 fetuses identified as having isolated clubfoot, 4 fetuses (4.6%) had karyotypic abnormalities (one each of trisomy 18, trisomy 21, 47 XXY, and 47 XXX) [107]. At least three of these women were considered high-risk for aneuploidy, however, and amniocentesis would have been recommended anyway: the two women with the sex chromosome abnormalities were over age 40, and the fetus with trisomy 18 had a single umbilical artery and clenched hands (diagnosed postnatally). Furthermore, the ultrasounds performed on the fetuses with the autosomal trisomies were performed at 15 and 16 weeks, and the early gestational age may account for the fact that the fetus with trisomy 18 had an undetected two-vessel cord and clenched hands. Finally, there is no mention of the results of whether multiple marker screens were performed on these fetuses and recent data indicate that integrated first- and second-trimester multiple marker screens can detect 80% to 90% of fetuses with trisomy 21 [109]. Because from these limited data the predictive value of clubfoot for aneuploidy is unknown, and amniocentesis is associated with a risk of unintended loss, many clinicians do not recommend amniocentesis when the finding of clubfoot is isolated.

An argument against this approach is the concern for the possibility of missing associated abnormalities on ultrasound. In one series three (43%) of seven fetuses thought to have isolated clubfoot were diagnosed with additional anomalies after birth [95]. None of these fetuses had karyotypic abnormalities. Based on the limited data available, in the authors' institution we do not routinely recommend amniocentesis for isolated clubfoot in a low-risk patient when the sonographic fetal anatomic survey was deemed adequate.

Once there has been a thorough evaluation of the fetus for structural and karyotypic abnormalities, the pregnancy can be allowed to continue to term. In the absence of oligohydramnios or IUGR, there is no need to do serial growth scans or antenatal testing, because isolated clubfoot has not been associated with adverse pregnancy outcomes. Antenatal referral to a pediatric orthopedic surgeon may be helpful to prepare the patient for postnatal care. Treatment depends on the severity of the clubfoot. Initial therapy consists mainly of manipulation of the foot with casting or splinting, which corrects most defects. Surgery is necessary in the minority of cases. Successful results can be obtained in 52% to 91% of cases, enabling most children to participate in normal activities [110].

Single umbilical artery

A single umbilical artery has been reported to occur in 1% of all deliveries, making it a relatively common finding [111]. The pathogenesis of a SUA is uncertain, but may result from primary aplasia of one of the two umbilical arteries, or alternatively, as consequence of the atrophy of one artery [112]. Absence of the left artery is more common than the absence of the right [113,114]. A SUA has been noted more frequently in gravidas at the extremes of reproductive ages, and is three to four times more frequent in twins (versus singletons) [115–117]. Marginal and velamentous cord insertions have been reported to occur in 18% and 9.3%, respectively, among fetuses with SUA, as compared with 6.8% and 1.1%, respectively, of the placentas in singletons [111,112].

Diagnosis

The sonographic diagnosis of SUA can be made as early as 12 weeks gestation, although the highest rates of detection are at 17 to 35 weeks [118]. Evaluation of the umbilical arteries can be done by looking at a free portion of the cord, either longitudinally or in cross-section, or by using color Doppler in the area of the fetal abdominal cord insertion site to identify the umbilical arteries as they course on either side of the fetal bladder (Fig. 5). It is by the latter method that the side of the missing umbilical artery can be determined. Some authors have suggested that visualization of the vessels around the fetal bladder may not be as accurate as looking at a free loop of cord [118,119], primarily because it seems to increase the false-positive rate. Using a transverse view of a free loop of the umbilical cord to make the diagnosis of SUA, transabdominal sonography was reported in one series to have an 85% sensitivity, a 99.7% specificity, an 85% positive predictive value, and a 99.7% negative predictive value for the detection of a two-vessel cord [118]. The false-positive rate in this series was only 0.03%; in another series that used both a cross-sectional image of the umbilical cord and visualization of the two vessels coursing around the bladder, the false-positive rate was much higher (14%) [118,120,121].

The diameter of the umbilical artery in a two-vessel cord tends to be larger than the diameter of umbilical arteries in a three-vessel cord, and the vein-to-artery ratio is decreased [122,123]. An umbilical artery greater than 4 mm or a vein-to-artery ratio less than 2 may be diagnostic of SUA, although use of these parameters does not seem to increase detection of SUA over the techniques described previously [122–124]. Umbilical cords with SUA also have less Wharton's jelly, a larger umbilical vein, and are characterized by a lower number of coils when compared with three-vessel cords [125,126].

It is important to distinguish between SUA and fusion of the two umbilical arteries. Umbilical artery fusion may occur completely or intermittently along the length of the umbilical cord [127]. Fusion of the two arteries may be mistaken for SUA if multiple portions of the cord are not examined. The frequency of fusion of the two umbilical arteries was found to be 3.1% in one study of pla-

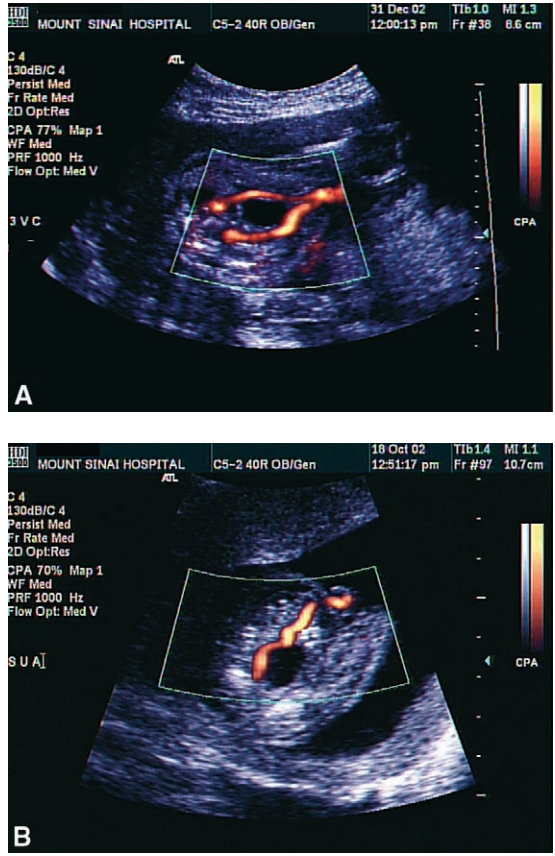

Fig. 5. Umbilical arteries as seen on color Doppler in the area of the fetal abdominal cord insertion site. (*A*) Normal appearance of two umbilical arteries as they course around the fetal bladder. (*B*) Single umbilical artery. Only one artery is seen going around the bladder.

centas from 702 consecutive deliveries [128]. The low frequency of SUA in this series (0.2%) may reflect the true incidence of SUA in the general population when fusion of the two umbilical arteries has been excluded. It is important to distinguish between fusion of the two umbilical arteries and SUA whenever possible, because there is no evidence that fusion of the two umbilical arteries is associated with adverse perinatal outcomes [111,128]. If both two- and three-vessel cords are identified, the patient should be considered to have a normal three-vessel umbilical cord [118]. Like SUA, fusion of the two umbilical arteries has been associated with increased rates of marginal (18.1%) and velamentous (4.5%) cord insertions [128] as compared with singletons.

Evaluation of the umbilical cord vessels should be part of a detailed anatomic survey. SUA can be an isolated finding, or it can be associated with other

sonographic abnormalities, such as congenital anomalies, oligohydramnios, polyhydramnios, or IUGR. The association of congenital anomalies with SUA has been well-documented [113,114,116,118,120,121,129–135]. The incidence of congenital anomalies differs depending on the population under consideration. This has been illustrated clearly in a meta-analysis of 37 studies in which the incidence of associated anomalies was 66% when the diagnosis of SUA was made using specimens obtained from early abortuses, fetal deaths, and autopsies, but only 27% when the diagnosis was made from examination of the placenta or infant after a live birth [136]. For the clinician, the most clinically relevant population is the one in which the diagnosis is made on antenatal ultrasound, because this is the population for which further evaluation and management decisions may affect outcome. Data from 10 studies of fetuses with SUA diagnosed by antenatal ultrasound are summarized in Table 7. In this population of over 900 fetuses, 37% of fetuses had sonographically detectable associated anomalies in addition to SUA.

Associated anomalies and pregnancy outcome

Although no specific pattern of anomalies has been identified, the most common anomalies associated with SUA are cardiac and genitourinary [116, 132,136]. Missing a particular umbilical artery (left or right) is not predictive of associated anomalies, although a few studies have suggested that absence of the left umbilical artery may be associated with more complex fetal anomalies [114, 121,125,137]. Associated congenital anomalies in a fetus with SUA confer increased risk of aneuploidy, estimated to be 31% (see Table 7). Surprisingly, SUA as an isolated finding is not associated with an increased risk of aneuploidy.

Single umbilical artery has been associated with a worse pregnancy outcome than fetuses with two umbilical arteries. For example, Gornall et al [135] compared 107 cases of SUA from an unselected cohort of more than 35,000 births as a comparison cohort, and found that perinatal mortality was 49 per 1000 total births for the SUA group, significantly higher than the 8.3 per 1000 total births rate for all deliveries at the same institution in the same time period. Fetuses with SUA delivered at an earlier gestational age (36.6 versus 38 weeks) weighed less (2706 versus 3017 g), were more likely to be small-for-gestational-age (defined as birthweight < 10th percentile, 27% versus 14% of fetuses), and were 1.7 times more likely to be delivered by cesarean section. These findings have been supported by some studies, whereas others have found no difference [114,130,131, 134,138–140].

In general, the increased morbidity and mortality associated with pregnancies complicated by SUA is attributable to the increased rates of associated anomalies and aneuploidy. Some studies, however, have shown a persistent increase in morbidity and mortality of fetuses with isolated SUA. In the series described previously, the perinatal mortality rate for the isolated SUA group was 24 per 1000 total births, which represented nearly a threefold increase when compared with the general rate in that institution for the same time period, although this was

Table 7
Rates of aneuploidy in fetuses with isolated and nonisolated single umbilical artery when SUA is identified by antenatal ultrasound

Study	Design	N	Incidence isolated SUA (%)	Incidence aneuploidy with ISUA (%)	Incidence aneuploidy with NISUA (%)
Nyberg 1991	Retrospective	30	50	0	40
Parilla 1995[a]	Retrospective	57	—	0	—
Catanzarite 1995	Retrospective	82	55	0	27
Abuhamad 1995	Prospective	77	74	0	30
Ulm 1997	Prospective	113	72	0	31
Chow 1998	Retrospective	167	71	—	—
Lee 1998	Retrospective	61	39	4	22
Rinehart 2000	Retrospective	27	33	0	—
Geipel 2000	Prospective	102	58	0	23
Pierce 2001	Retrospective	65	74	?	?
Budorick 2001	Retrospective	65	54	0	50
Gossett 2002	Retrospective	127	72	—	—
Total		973	64	0.4	31

Abbreviations: ISUA, isolated single umbilical artery; NISUA, nonisolated single umbilical artery (ie, with associated sonographic abnormalities; SUA, single umbilical artery.

[a] Only included fetuses with isolated SUA.

not statistically significant (OR 2.9; 95% CI 0.7,12, $P = .15$). Some studies have reported an increased rate of IUGR in fetuses with isolated SUA, although most of the data involve small numbers [131,134,141]. As an example, in a retrospective analysis of 82 fetuses with SUA, 7 (18%) of the 38 fetuses with prenatally diagnosed SUA had IUGR [131]. Increased rates of intrauterine fetal demise and preterm delivery have also been reported for fetuses with isolated SUA [121,132,141]. Other studies have not supported these findings [114,129,130].

Management of single umbilical artery

Because the finding of SUA carries with it a substantially increased risk of congenital abnormalities and aneuploidy, the finding of SUA on a second-trimester ultrasound should prompt an immediate detailed ultrasound examination to rule out any associated abnormalities. Referral to an experienced center should be done whenever necessary. Fetal echocardiography should be considered. In one series, 5% of fetuses referred for fetal echo with presumed isolated SUA had abnormal findings [121]. In another series, however, fetal echo did not add any diagnostic information in fetuses with SUA when the normal four-chamber and outflow tract views of the heart had been obtained satisfactorily [120]. The decision to refer a patient for a detailed fetal echocardiogram should be individualized and should take into account the ability to obtain adequate views of the heart and the experience of the physician and sonographer performing the screening examination.

Invasive testing for chromosome analysis should be recommended if any associated abnormalities are identified on sonogram, including structural anomalies, oligohydramnios, polyhydramnios, and IUGR. In the absence of associated anomalies, invasive testing is not warranted, because there is no increased risk of aneuploidy (see Table 7). Patients should be counseled, however, that even when SUA is apparently isolated 7% of fetuses in one series had structural anomalies diagnosed postnatally, which if diagnosed prenatally would have resulted in a recommendation for invasive testing [116].

Serial growth scans are warranted, because SUA has been associated with increased rates of IUGR. Antenatal testing is recommended in the setting of IUGR or oligohydramnios. Doppler studies should also be used to assess the status of an IUGR fetus. Despite there being only one umbilical artery, it has been shown that longitudinal changes in Doppler flow indices in normal and small-for-gestational-age fetuses with SUA have comparable, reference ranges to fetuses with three-vessel cords [142]. A large prospective series of umbilical artery Doppler velocimetry in pregnancies with a SUA found that abnormal Doppler findings were associated significantly with IUGR, presence of complex malformations, aneuploidy, preterm delivery, and perinatal mortality. Conversely, normal umbilical artery Doppler indicates a relatively good prognosis, in particular a low-risk of fetal aneuploidy or perinatal mortality [132]. Unlike umbilical artery blood flow, the ductus venosus blood flow pattern seems to be different in SUA fetuses when compared with that of fetuses with three-vessel

cords [125]. Future studies are needed to evaluate individual Doppler parameters in the fetus with SUA before they can be used routinely in these fetuses.

Choroid plexus cysts

The finding of choroid plexus cysts at the time of second-trimester ultrasound is relatively common with an incidence of approximately 1% [143]. CPCs can be single or multiple, unilateral or bilateral. Most CPCs are detected incidentally at the time of routine second-trimester anatomy scan. More than 95% disappear before 26 weeks [144]. The incidence or characteristics of CPCs does not vary with fetal gender [145].

Pathophysiology

The choroid plexus develops from the medial wall of the lateral ventricle beginning at approximately 6 weeks gestation. Followed quickly by rapid proliferation of blood vessels and formation of villi in the second trimester, cysts in the developing choroid plexus are believed to result from entrapment of cerebrospinal fluid within tangled villi. As the amount of stroma in the choroid plexus decreases with increasing gestational age, this fluid is released and the cysts resolve [146].

Diagnosis

The choroid plexus is seen in the axial plane of the head and is located in the lateral ventricle. The American Institute of Ultrasound in Medicine recommends evaluation of the lateral ventricles. The choroid plexus is typically homogeneous with an echogenicity similar to soft tissue. A CPC appears as a well-circumscribed echolucent area within the choroid plexus (Fig. 6). They can be singular or multiple, unilateral or bilateral.

Association with aneuploidy

The presence of a CPC has been associated with increased risk of aneuploidy, primarily with trisomy 18 [146–150]. Earlier studies suggested an association with trisomy 21; however, more rigorous evaluation has shown that the presence of CPCs does not increase the risk of Down syndrome above the background risk [146,151–153]. Although a significant percentage have additional abnormalities, CPC may be the only sonographic marker in a fetus with trisomy 18 [144]. This observation was confirmed by a postmortem ultrasound study, in which two out of five fetuses with CPCs had no other dysmorphic features or anomalies at autopsy [154].

It is reasonably well established that the risk of trisomy 18 is increased in the presence of an isolated CPC [144,150,152,155,156]. In a meta-analysis of more than 2000 cases of isolated CPC in selected populations, the overall risk of

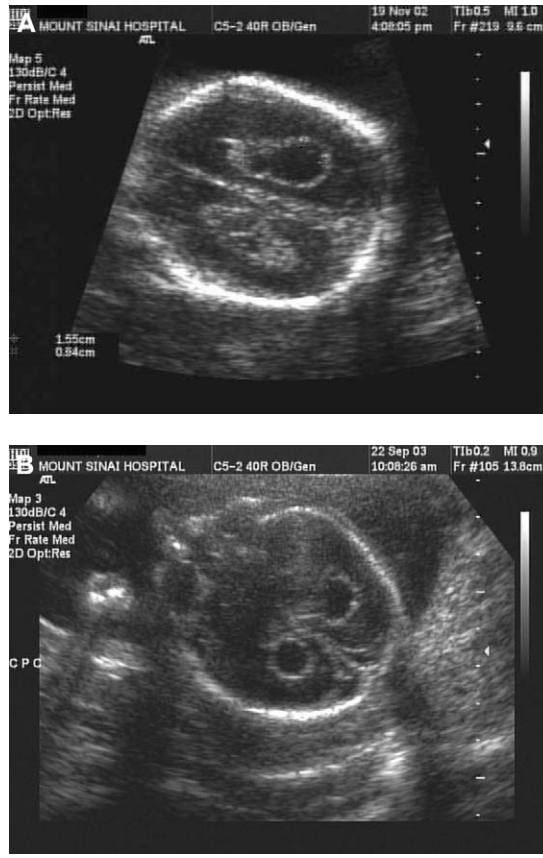

Fig. 6. (*A*) Unilateral choroid plexus cyst. (*B*) Bilateral choroid plexus cyst.

trisomy 18 was found to be 1 in 128 [146]. This risk persisted in low-risk populations in this meta-analysis, where the overall incidence of trisomy 18, as calculated by evaluation of more than 3000 cases of isolated CPC, was 1 in 189 [146].

Modifying the risk of trisomy 18

There are numerous studies that have tried to identify and quantify modifiers to individualize better a fetus' risk of trisomy 18. One obvious modifier is the presence or absence of other sonographic abnormalities. Similar to other soft markers for aneuploidy, the finding of a CPC in the presence of an additional abnormality drastically increases the risk of a chromosomal abnormality [157,158]. The characteristics of the CPC, such as laterality, number, size, complexity, and resolution, have also been examined [144]. These characteristics do not seem to affect the risk of trisomy 18 [146].

Maternal age and gestational age are both significant modifiers of the background risk of trisomy 18. Similar to Down syndrome, the risk of trisomy 18 is increased with maternal age and is inversely proportional to gestational age [159]. This effect has been calculated by Snijders et al [159] and is illustrated in Table 8. A 20-year-old woman has a background risk of trisomy 18 at 16 weeks of 1 in 3590; this risk drops to 1 in 18,013 at 40 weeks. Maternal age drastically increases this risk. For example, a 40-year-old woman has a background risk of trisomy 18 at 16 weeks of 1 in 227, almost 16 times the risk of a 20 year old at the same gestational age. Because the risk of trisomy 18 is rare, representing only 30 of every 100,000 live births, maternal age is a much better predictor of trisomy 18 than the presence of an isolated CPC [160].

Several analyses have calculated the risk of trisomy 18 in the presence of an isolated CPC using age as a modifier. For example, Gupta et al [155] analyzed nine prospective studies of more than 200,000 second-trimester examinations

Table 8
Prevalence of trisomy 18 (1 per number in table) by maternal and gestational age

	Gestational age									
Mat age	10	12	14	16	18	20	25	30	35	40
20	1993	2484	3015	3590	4215	4897	6909	9516	13028	18013
21	1968	2453	2976	3544	4160	4834	6820	9394	12860	17782
22	1934	2411	2925	3483	4090	4751	6704	9234	12641	17479
23	1891	2357	2860	3405	3998	4645	6553	9027	12357	17086
24	1835	2287	2776	3305	3880	4508	6361	8761	11994	16584
25	1765	2200	2670	3179	3732	4336	6118	8427	11536	15951
26	1679	2092	1539	3023	3549	4124	5819	8014	10972	15170
27	1575	1963	2382	2836	3330	3868	5458	7518	10292	14231
28	1453	1811	2198	2617	3073	3570	5037	6938	9498	13133
29	1316	1641	1991	2371	2783	3234	4562	6284	8603	11895
30	1168	1456	1766	2103	2469	2869	4048	5575	7633	10554
31	1014	1263	1533	1825	2143	2490	3513	4839	6625	9160
32	860	1072	1301	1549	1819	2114	2982	4107	5623	7775
33	715	891	1081	1287	1511	1755	2477	3412	4670	6458
34	582	725	880	1047	1230	1429	2016	2777	3802	5256
35	465	580	703	837	983	1142	1612	2220	3039	4202
36	366	456	553	659	774	899	1268	1747	2392	3307
37	284	354	430	512	601	698	985	1357	1858	2569
38	218	272	330	393	462	537	757	1043	1428	1974
39	167	208	252	300	352	409	577	795	1088	1505
40	126	157	191	227	267	310	437	602	824	1139
41	95	118	144	171	201	233	329	453	620	858
42	71	89	108	128	151	175	247	340	465	644
43	53	66	81	96	113	131	185	254	348	481
44	40	50	60	72	84	98	138	190	260	359

Abbreviation: Mat age, maternal age (years).
From Snijders RJM, Sebire NJ, Faria M, Patel F, Nicolaides RH. Fetal mild hydronephrosis and chromosomal defects: relation to maternal age and gestation. Fetal Diagn Ther 1995;10:349; with permission.

in an unselected population, and concluded that when the CPC is isolated, the a priori risk of trisomy 18 (determined by maternal age) should be multiplied by a likelihood ratio of 9. Based on the findings of this meta-analysis, the American College of Obstetricians and Gynecologists recommends offering amniocentesis in the presence of an isolated CPC only for women greater than or equal to 32, the age at which the risk of procedure-related loss after amniocentesis was comparable with the risk of trisomy 18, or if the serum screening results are abnormal [161].

In addition to maternal age, gestational age, and the presence of associated anomalies, another important modifier that should be considered when calculating a patient's risk for trisomy 18 is the result of a multiple marker screen. A large meta-analysis that included 13 prospective studies of 246,545 second-trimester fetuses identified 1346 fetuses with isolated CPCs, 7 of which had trisomy 18 (1 in 192). In this series, the likelihood of trisomy 18 was 13.8 times greater than the a priori age-related risk in fetuses with isolated CPC diagnosed in the second trimester, and the authors concluded that invasive testing should only be offered to women over the age of 36 or when the risk for trisomy 18 detected by a maternal serum multiple marker screen is more than 1 in 3000 [152]. Similarly, Gratton et al [148] calculated the risk of trisomy 18 in the presence of an isolated CPC taking into account maternal age, the absence of any associated abnormalities, and the results of the multiple marker screen, as illustrated in Table 9. This allows the physician to individualize each patient's risk for more precise counseling. Using these data, the risk of trisomy 18 in a patient with an isolated CPC and a normal multiple marker screen does not exceed the traditionally quoted risk of an amniocentesis until greater than 37 years of age [148].

Management

The initial management of a pregnancy in which a CPC has been detected is identical to the other soft markers discussed previously: the detection of a CPC during an examination should be followed by a detailed anatomic survey looking for any additional abnormalities. A fetal echocardiogram can be considered, depending on the quality of the anatomic survey. An amniocentesis should be recommended if any additional abnormalities are detected, and for all women over the age of 35 (for whom an amniocentesis is recommended anyway because of the age-related risk of aneuploidy). If the CPC seems to be isolated, and the patient is under the age of 35, the patient's risk of having an affected fetus should be modified with all the available information, specifically maternal age, the presence or absence of other sonographic abnormalities, and the results of the multiple marker screen. In the authors' institution, the estimates calculated by Gratton et al [148] are used to quantify more precisely an individual patient's risk and amniocentesis is recommended when the modified risk exceeds the procedure-related loss rate of amniocentesis.

In addition to counseling regarding the risk of aneuploidy, patients should be clearly counseled that it is not the presence of a CPC that puts the fetus at risk,

Table 9
Risk modification based on ultrasonographic findings and multiple-marker screening

	Age-related risk of trisomy 18			
		Modified risk		
Maternal age	Unmodified age-related risk	CPC[a]	Isolated CPC[b]	Isolated CPC and normal MMS[c]
20	1/4576	1/153	1/725	1/1804
21	1/4514	1/151	1/715	1/1779
22	1/4435	1/148	1/703	1/1749
23	1/4333	1/145	1/687	1/1708
24	1/4204	1/141	1/666	1/1658
25	1/4045	1/135	1/641	1/1595
26	1/3850	1/129	1/610	1/1518
27	1/3619	1/121	1/573	1/1427
28	1/3351	1/113	1/531	1/1362
29	1/3053	1/102	1/483	1/1203
30	1/2724	1/92	1/432	1/1074
31	1/2385	1/80	1/378	1/940
32	1/2046	1/69	1/324	1/806
33	1/1721	1/58	1/273	1/679
34	1/1420	1/48	1/225	1/560
35	1/1152	1/39	1/183	1/454
36	1/921	1/32	1/146	1/363
37	1/727	1/25	1/115	1/287
38	1/567	1/20	1/92	1/223
39	1/439	1/16	1/70	1/173
40	1/338	1/12	1/54	1/133
41	1/258	1/10	1/42	1/102
42	1/197	1/8	1/32	1/78
43	1/149	1/6	1/24	1/59
44	1/113	1/5	1/18	1/45
45	1/85	1/4	1/14	1/34

Abbreviations: CPC, choroid plexus cyst; MMS, multiple marker screen.

[a] Age-related risk of trisomy 18 in fetuses with CPC, with or without other anomalies.

[b] Age-related risk of trisomy 18 in fetuses with isolated CPC.

[c] Age-related risk of trisomy 18 in fetuses with isolated CPC and normal MMS.

From Gratton RJ, Hogge WA, Aston CE. Choroid plexus cysts and trisomy 18: risk modification based on maternal age and multiple-marker screening. Am J Obstet Gynecol 1996;175:1493–7; with permission.

but its association with aneuploidy. Patients often become very anxious when told that their fetus has a ''cyst in the brain.'' Patients should be told that most CPCs resolve by 26 to 28 weeks, and that in a karyotypically normal fetus, the presence of isolated second-trimester CPCs is not associated with any long-term effects, such as mental retardation, cerebral palsy, or delayed development [162].

Follow-up ultrasounds are not generally needed, because most CPCs resolve. A follow-up ultrasound for growth may be considered in the high-risk patient who declines invasive testing, because trisomy 18 is often associated with IUGR.

For a karyotypically normal fetus, CPCs are not associated with adverse pregnancy outcomes; ultrasounds for growth and antenatal testing are not necessary.

Summary

This article has reviewed a few of the more controversial findings in the field of obstetric ultrasound. For each one evidence-based strategies for the management of affected pregnancies have been suggested, derived from what the authors believe is the best information available. In some cases, this information is very limited, which can make counseling these patients extremely difficult. Some physicians find using specific likelihood ratios helpful in these complex discussions. An example of the relative likelihood ratios for several markers of trisomy 21 is illustrated in Table 10 [163,164].

Although the management of each of the findings discussed in this article is different, a few generalizations can be made. To begin with, the detection of any abnormal finding on ultrasound should prompt an immediate detailed ultrasound evaluation of the fetus by someone experienced in the diagnosis of fetal anomalies. If there is more than one abnormal finding on ultrasound, if the patient is over the age of 35, or if the multiple marker screen is abnormal, an amniocentesis to rule out aneuploidy should be recommended. Of the six ultrasound findings reviewed here, the authors believe that only echogenic bowel as an isolated finding confers a high enough risk of aneuploidy to recommend an amniocentesis in a low-risk patient. The other findings in isolation in a low-risk patient seem to confer only a modest increased risk of aneuploidy, if any, and this risk is certainly less than the risk of unintended loss from amniocentesis. Wherever possible, modifiers of this risk, such as maternal age, history, and first and second multiple marker screening, should be used to define more clearly the true risk of aneuploidy.

Table 10
Ultrasound criteria and likelihood ratios[a] assigned for the detection of trisomy 21

Finding	Criteria	Likelihood ratio
Structural defect	Cardiac defect, cystic hygroma, cerebral ventricular dilation	25
Nuchal thickening	>5 mm in the anteroposterior plane	18.6
Echogenic bowel	Subjectively increased, grades 2 or 3	5.5
Short humerus	Observed or predicted ration $\leq$ 0.89	2.5
Short femur	Observed or predicted ratio $\leq$ 0.91	2.2
Echogenic intracardiac focus	Present	2
Renal pyelectasis	> 3 mm in the anteroposterior plane	1.6
Normal ultrasound	None of the above abnormalities	0.4

[a] Likelihood ratio = sensitivity or false-positive rate for each as an isolated finding.
Data from references [163,164].

As obstetric ultrasound moves forward, particularly into the uncharted waters of clinical use of three- and four-dimensional ultrasound, one can expect a whole new crop of ultrasound findings with uncertain clinical significance. Clinicians are well advised to await well-designed studies to determine the clinical significance of these findings before altering clinical care.

References

[1] Al-Kouatly HB, Chasen ST, Streltzoff J, Chervenak FA. The clinical significance of fetal echogenic bowel. Am J Obstet Gynecol 2001;185:1035–8.
[2] Eddleman KA, Stone JL, Berkowitz RL. Fetal echogenic bowel: the bottom line. Contemporary Ob/Gyn 1998;43:53–69.
[3] Achiron R, Mazkereth R, Orvieto R, Kuint J, Lipitz S, Rotstein Z. Echogenic bowel in intrauterine growth restriction fetuses: does this jeopardize the gut? Obstet Gynecol 2002;100:120–5.
[4] Sepulveda W, Reid R, Nicolaidis P, Prendiville O, Chapman RS, Fisk NM. Second-trimester echogenic bowel and intraamniotic bleeding: association between fetal bowel echogenicity and amniotic fluid spectrophotometry at 410 nm. Am J Obstet Gynecol 1996;174:839–42.
[5] Harrison KL, Martinez D, Mason G. The subjective assessment of echogenic fetal bowel. Ultrasound Obstet Gynecol 2000;16:524–9.
[6] Nyberg DA, Dubinsky T, Resta RG, Mahony BS, Hickok DE, Luthy DA. Echogenic fetal bowel during the second trimester: clinical importance. Radiology 1993;188:527–31.
[7] Slotnick RN, Abuhamad AZ. Prognostic implications of fetal echogenic bowel. Lancet 1996;347:85–7.
[8] Hill LM, Fries J, Hecker J, Grzybek P. Second-trimester echogenic small bowel: an increased risk for adverse perinatal outcome. Prenat Diagn 1994;14:845–50.
[9] Scioscia AL, Pretorius DH, Budorick NE, Cahill TC, Axelrod FT, Leopold GR. Second-trimester echogenic bowel and chromosomal abnormalities. Am J Obstet Gynecol 1992;167:889–94.
[10] Vincoff NS, Callen PW, Smith-Bindman R, Goldstein RB. Effect of ultrasound transducer frequency on the appearance of the fetal bowel. J Ultrasound Med 1999;18:799–803.
[11] Lee HJ, Cho JY. Quantitative assessment of fetal bowel echogenicity: comparison of harmonic, compound, and fundamental sonographic images. J Clin Ultrasound 2003;31:302–7.
[12] Nyberg DA, Resta RG, Mahony BS, Dubinsky T, Luthy DA, Hickok DE, et al. Fetal hyperechogenic bowel and Down's syndrome. Ultrasound Obstet Gynecol 1993;3:330–3.
[13] Bahado-Singh R, Morotti R, Copel JA, Mahoney MJ. Hyperechoic fetal bowel: the perinatal consequences. Prenat Diagn 1994;14:981–7.
[14] Bromley B, Doubilet P, Frigoletto FD, Krauss C, Estroff JA, Benacerraf BR. Is fetal hyperechoic bowel on second-trimester sonogram an indication for amniocentesis? Obstet Gynecol 1994;83:647–51.
[15] Strocker AM, Snijders RJ, Carlson DE, Greene N, Gregory KD, Walla CA, et al. Fetal echogenic bowel: parameters to be considered in differential diagnosis. Ultrasound Obstet Gynecol 2000;16:519–23.
[16] Simon-Bouy B, Muller F, French Collaborative Group. Hyperechogenic fetal bowel and Down syndrome: results of a French collaborative study based on 680 prospective cases. Prenat Diagn 2002;22:189–92.
[17] Sepulveda W, Sebire NJ. Fetal echogenic bowel: a complex scenario. Ultrasound Obstet Gynecol 2000;16:510–4.
[18] Shipp TD, Benacerraf BR. Second trimester ultrasound screening for chromosomal abnormalities. Prenat Diagn 2002;22:296–307.
[19] Hill LM. Ultrasound of fetal gastrointestinal tract. In: Callen PW, editor. Ultrasonography in obstetrics and gynecology. 4th edition. Philadelphia: WB Saunders; 2000. p. 457–87.

[20] Boue A, Muller F, Nezelof C, Oury JF, Duchatel F, Dumez Y, et al. Prenatal diagnosis in 200 pregnancies with a 1-in-4 risk of cystic fibrosis. Hum Genet 1986;74:288–97.
[21] Muller F, Aubry MC, Gasser B, Duchatel F, Boue J, Boue A. Prenatal diagnosis of cystic fibrosis. II. Meconium ileus in affected fetuses. Prenat Diagn 1985;5:109–17.
[22] Berlin BM, Norton ME, Sugarman EA, Tsipis JE, Allitto BA. Cystic fibrosis and chromosome abnormalities associated with echogenic fetal bowel. Obstet Gynecol 1999;94:135–8.
[23] Muller F, Dommergues M, Simon-Buoy B, Ferec C, Oury JF, Autry MC, et al. Cystic fibrosis screening: a fetus with hyperechogenic bowel may be the index case. J Med Genet 1998;35: 657–60.
[24] Dicke JM, Crane JP. Sonographically detected hyperechoic fetal bowel: significance and implications for pregnancy management. Obstet Gynecol 1992;80:778–82.
[25] Simon-Bouy B, Satre V, Ferec C, Malinge MC, Girodon E, Denamur E, et al. Hyperechogenic fetal bowel: a large French collaborative study of 682 cases. Am J Med Genet 2003; 121A:209–13.
[26] Sepulveda W, Leung KY, Robertson ME, Kay E, Mayall ES, Fisk NM. Prevalence of cystic fibrosis mutations in pregnancies with fetal echogenic bowel. Obstet Gynecol 1996;87: 103–6.
[27] Chasen ST. Fetal echogenic bowel. In: UpToDate, version 11.2. Wellesley, MA: 2003. Available at www.uptodate.com.
[28] Achiron R, Seidman DS, Horowitz A, Mashiach S, Goldman B, Lipitz S. Hyperechogenic fetal bowel and elevated serum alpha-fetoprotein: a poor fetal prognosis. Obstet Gynecol 1996; 88:368–71.
[29] Petrikovsky B, Smith-Levitin M, Holsten N. Intra-amniotic bleeding and fetal echogenic bowel. Obstet Gynecol 1999;93:684–6.
[30] Stipoljev F, Sertic J, Kos M, Miskovic B, Obrad-Sabljak R, Stavljenic-Rukavina A, et al. Incidence of chromosomopathies and cystic fibrosis mutations in second trimester fetuses with isolated hyperechoic bowel. J Matern Fetal Neonatal Med 1999;8:44–7.
[31] Corteville JE, Gray DL, Crane JP. Congenital hydronephrosis: correlation of fetal ultrasound findings with infant outcome. Am J Obstet Gynecol 1991;165:384–8.
[32] Corteville JE, Kicke JM, Crane JP. Fetal pyelectasis and Down syndrome: is genetic amniocentesis warranted? Obstet Gynecol 1992;79:770–2.
[33] Havutcu AE, Nikolopoulos G, Adinkra P, Lamont RF. The association between fetal pyelectasis on second trimester ultrasound scan and aneuploidy among 25 586 low risk unselected women. Prenat Diagn 2002;22:1201–6.
[34] Benacerraf BR, Mandell J, Estroff JA, Harlow BL, Frigoletto F. Fetal pyelectasis: a possible association with Down syndrome. Obstet Gynecol 1990;76:58–60.
[35] Ismaili K, Hall M, Donner C, Thomas D, Vermeylen D, Avni FE. Results of systematic screening for minor degrees of fetal renal pelvis dilatation in an unselected population. Am J Obstet Gynecol 2003;188:242–6.
[36] Rosati P, Guariglia L. Transvaginal sonographic assessment of the fetal urinary tract in early pregnancy. Ultrasound Obstet Gynecol 1996;7:95–100.
[37] Wickstrom E, Maizels M, Sabbagha RE, Tamura RK, Cohen LC, Pergament E. Isolated fetal pyelectasis: assessment of risk for postnatal uropathy and Down syndrome. Ultrasound Obstet Gynecol 1996;8:236–40.
[38] Grignon A, Filion R, Filiatrault D, Robitaille P, Homsy Y, Boutin H, et al. Urinary tract dilatation in utero: classification and clinical applications. Radiology 1986;160:645–7.
[39] Jeanty P, Romero R. In: Obstetrical ultrasound. New York: McGraw-Hill; 1984. p. 143.
[40] Persutte WH, Hussey M, Chyu J, Hobbins JC. Striking findings concerning the variability in the measurement of the fetal renal collecting system. Ultrasound Obstet Gynecol 2000;15: 186–90.
[41] Chudleigh T. Mild pyelectasis. Prenat Diagn 2001;21:936–41.
[42] Chudleigh PM, Chitty LS, Pembrey M, Campbell S. The association of aneuploidy and mild

fetal pyelectasis in an unselected population: the results of a multicenter population. Ultrasound Obstet Gynecol 2001;17:197–202.
[43] Adra AM, Mejides AA, Dennaoui MS, Beydoun SN. Fetal pyelectasis: is it always "physiologic"? Am J Obstet Gynecol 1995;173:1263–6.
[44] Persutte WH, Koyle M, Lenke RR, Lkas J, Ryan C, Hobbins JC. Mild pyelectasis ascertained with prenatal ultrasonography is pediatrically significant. Ultrasound Obstet Gynecol 1997;10: 12–8.
[45] Petrikovsky BM, Cuomo MI, Schnieder IP, Wyse LJ, Cohen HL, Lesser M. Isolated fetal hydronephrosis: beware the effect of bladder filling. Prenat Diagn 1995;15:827–9.
[46] Graif M, Kessler A, Hart S, Daitzchman M, Mashiach S, Boichis H, et al. Renal pyelectasis in pregnancy: correlative evaluation of fetal and maternal collecting systems. Am J Obstet Gynecol 1992;167:1304–6.
[47] Allen KS, Arger PH, Mennuti M, Coleman BG, Mintz MC, Fishman M. Effects of maternal hydration on fetal renal pyelectasis. Radiology 1987;163:807–9.
[48] Hoddick WK, Filly RA, Mahony BS, Callen PW. Minimal fetal renal pyelectasis. J Ultrasound Med 1985;4:85–9.
[49] Robinson JN, Tice K, Kolm P, Abuhamad AZ. Effect of maternal hydration of fetal renal pyelectasis. Obstet Gynecol 1998;92:137–41.
[50] Bobrowski RA, Levin RB, Lauria MR, Treadwell MC, Gonik B, Bottom SF. In utero progression of isolated renal pelvis dilation. Am J Perinatol 1997;14:423–6.
[51] Nicolaides KH, Cheng HH, Abbas A, Snijders RJM, Gosden C. Fetal renal defects: associated malformations and chromosomal defects. Fetal Diagn Ther 1992;7:1–11.
[52] Wickstrom EA, Thangavelu M, Parilla BV, Tamura RK, Sabbagha RE. A prospective study of the association between isolated fetal pyelectasis and chromosomal abnormality. Obstet Gynecol 1996;88:379–82.
[53] Guariglia L, Rosati P. Isolated mild fetal pyelectasis detected by transvaginal sonography in advanced maternal age. Obstet Gynecol 1998;92:833–6.
[54] Snijders RJM, Sebire NJ, Faria M, Patel F, Nicolaides KH. Fetal mild hydronephrosis and chromosomal defects: relation to maternal age and gestation. Fetal Diagn Ther 1995;10: 349–55.
[55] Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002;21:1087–96.
[56] Chitty LS, Chudleigh P, Pembrey M, Campbell S. Renal pathology in fetuses with mild pyelectasis: prediction of outcome. Ultrasound Obstet Gynecol 1999;14(Suppl. 1):12.
[57] Broadley P, McHugo J, Morgan I, Whittle MJ, Kilby MD. The 4 year outcome following the demonstration of bilateral renal pelvic dilatation on pre-natal renal ultrasound. Br J Radiol 1999;72:265–70.
[58] Stone JL, Eddleman KA, Berkowitz RL. The echogenic intracardiac focus. Contemporary Ob/Gyn 1998;43:73–8.
[59] Roberts DJ, Genest D. Cardiac histologic pathology characteristic of trisomies 13 and 21. Hum Pathol 1992;23:1130–40.
[60] Bronshtein M, Jakobi P, Ofir C. Multiple fetal intracardiac echogenic foci: not always a benign sonographic finding. Prenat Diagn 1996;16:131–5.
[61] Sotiriadis A, Makrydimas G, Ioannidis PA. Diagnostic performance of intracardiac echogenic foci for Down syndrome: a meta-analysis. Obstet Gynecol 2003;101:1009–16.
[62] Shipp TD, Bromley B, Lieberman E, Benacerraf BR. The frequency of the detection of fetal echogenic intracardiac foci with respect to maternal race. Ultrasound Obstet Gynecol 2000;15: 460–2.
[63] Wax JR, Royer D, Mather J, Chen C, Aponte-Garcia A, Steinfeld JD, et al. A preliminary study of sonographic grading of fetal intracardiac echogenic foci: feasibility, reliability and association with aneuploidy. Ultrasound Obstet Gynecol 2000;16:123–7.
[64] Wax JR, Donnelly J, Carpenter M, Chard R, Pinette MG, Blackstone J, et al. Childhood cardiac

function after prenatal diagnosis of intracardiac echogenic foci. J Ultrasound Med 2003;22: 783–7.
[65] Dildy GA, Judd VE, Clark SL. Prospective evaluation of the antenatal incidence and postnatal significance of the fetal echogenic cardiac focus: a case-control study. Am J Obstet Gynecol 1996;175:1008–12.
[66] Bromley B, Lieberman E, Shipp TD, Richardson M, Benacerraf BR. Significance of an echogenic intracardiac focus in fetuses at high and low risk for aneuploidy. J Ultrasound Med 1998; 17:127–31.
[67] Levine D, Mehta TS, Min KK, Hulka CA, McArdle CR. Technical factors influencing sonographic visualization of fetal echogenic intracardiac foci. J Clin Ultrasound 2000;28:479–84.
[68] Schechter AG, Fakhry J, Shapiro LR, Gewitz MG. In utero thickening of the chordae tendinae: a cause of intracardiac echogenic foci. J Ultrasound Med 1987;6:691–5.
[69] Bromley B, Lieberman E, Laboda L, Benacerraf BR. Echogenic intracardiac focus: a sonographic sign for fetal Down syndrome. Obstet Gynecol 1995;86:998–1001.
[70] Manning JE, Ragavendra N, Sayre J, Leifer-Narin SL, Melany ML, Grant EG, et al. Significance of fetal intracardiac echogenic foci in relation to trisomy 21: a prospective sonographic study of high-risk pregnant women. AJR Am J Roentgenol 1998;170:1083–4.
[71] Sohl BD, Scioscia AL, Budorick NE, Moore TR. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181:898–903.
[72] Thilaganathan B, Olawaiye A, Sairam S, Harrington K. Isolated fetal echogenic intracardiac foci or golf balls: Is karyotyping for Down's syndrome indicated? Br J Obstet Gynaecol 1999; 106:1294–7.
[73] Winter TC, Anderson AM, Cheng EY, Komarniski CA, Souter VL, Uhrich SB, et al. Echogenic intracardiac focus in 2nd-trimester fetuses with trisomy 21: usefulness as a US marker. Radiology 2000;216:450–6.
[74] Verdin SM, Whitlow BJ, Lazanakis M, Kadir MA, Chatzipapas I, Economides DL. Ultrasonographic markers for chromosomal abnormalities in women with negative nuchal translucency and second trimester maternal serum biochemistry. Ultrasound Obstet Gynecol 2000;16: 402–6.
[75] Huggon IC, Cook AC, Simpson JM, Smeeton NC, Sharland GK. Isolated echogenic foci in the heart as a marker of chromosomal abnormality. Ultrasound Obstet Gynecol 2001;17:11–6.
[76] Nyberg DA, Souter VL, El-Bastawissi A, Young S, Luthhardt F, Luthy DA. Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. J Ultrasound Med 2001;20:1053–63.
[77] Prefumo F, Presti F, Mavrides E, Sanusi AF, Bland JM, Campbell S, et al. Isolated echogenic foci in the fetal heart: do they increase the risk of trisomy 21 in a population previously screened by nuchal translucency? Ultrasound Obstet Gynecol 2001;18:126–30.
[78] Sepulveda W, Cullen S, Nicolaides P, Hollingsworth J, Fisk NM. Echogenic foci in the fetal heart: a marker of chromosomal abnormality. Br J Obstet Gynaecol 1995;102:490–2.
[79] Sepulveda W, Romero D. Significance of echogenic foci in the fetal heart. Ultrasound Obstet Gynecol 1998;12:445–9.
[80] Vibhakar NI, Budorick NE, Scioscia AL, Harby LD, Mullen ML, Sklansky MS. Prevalence of aneuploidy with a cardiac intraventricular echogenic focus in an at-risk patient population. J Ultrasound Med 1999;18:265–8.
[81] Anderson N, Jyoti R. Relationship of isolated fetal intracardiac echogenic focus to trisomy 21 at the mid-trimester sonogram in women younger than 35 years. Ultrasound Obstet Gynecol 2003;21:354–8.
[82] Achiron R, Lipitz S, Gabbay U, Yagel S. Prenatal ultrasonographic diagnosis of fetal heart echogenic foci: no correlation with Down syndrome. Obstet Gynecol 1997;89:945–8.
[83] Caughey AB, Lyell DJ, Filly RA, Washington AE, Norton ME. The impact of the use of the isolated echogenic intracardiac focus as a screen for Down syndrome in women under the age of 35 years. Am J Obstet Gynecol 2001;185:1021–7.

[84] Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA 2001;285:1044–55.
[85] Wolman I, Jaffa A, Geva E, Diamant S, Strauss S, Lessing JB, et al. Intracardiac echogenic focus: no apparent association with structural cardiac abnormality. Fetal Diagn Ther 2000;15:216–8.
[86] Petrikovsky B, Challenger M, Gross B. Unusual appearances of echogenic foci within the fetal heart: are they benign? Ultrasound Obstet Gynecol 1996;8:229–31.
[87] Degani S, Leibovitz Z, Shapiro I, Gonen R, Ohel G. Cardiac function in fetuses with intracardiac echogenic foci. Ultrasound Obstet Gynecol 2001;18:131–4.
[88] Keret D, Ezra E, Lokiec F, Hayek S, Segev E, Wientroub S. Efficacy of prenatal ultrasonography in confirmed club foot. J Bone Joint Surg Br 2002;84:1015–9.
[89] Dietz F. The genetics of idiopathic clubfoot. Clin Orthop 2002;401:39–48.
[90] Jones KL. Genetics, genetic counselling, and prevention. In: Jones KL, editor. Smith's recognizable patterns of human malformation. Philadelphia: WB Saunders; 1997. p. 722.
[91] Carroll NC. Clubfoot. In: Staheli LT, editor. Pediatric orthopaedic secrets. Philadelphia: Hanley and Belfus; 1998. p. 230–4.
[92] Budorick NE. The fetal musculoskeletal system. In: Callen PW, editor. Ultrasonography in obstetrics and gynecology. 4th edition. Philadelphia: WB Saunders; 2000. p. 331–77.
[93] Malone FD, Marino T, Bianchi DW, Johnston K, D'Alton ME. Isolated clubfoot diagnosed prenatally: is karyotyping indicated? Obstet Gynecol 2000;95:437–40.
[94] Yamamoto H. A clinical, genetic and epidemiologic study of congenital clubfoot. Jpn J Hum Genet 1979;24:37–44.
[95] Rijhsinghani A, Yankowitz A, Kanis B, Mueller GM, Yankowitz KD, Williamson RA. Antenatal sonographic diagnosis of club foot with particular attention to the implications and outcomes of isolated club foot. Ultrasound Obstet Gynecol 1998;11:103–6.
[96] Barker S, Chesney D, Miedzybrodzka Z, Maffulli N. Genetics and epidemiology of idiopathic congenital talipes equinovarus. J Pediatr Orthop 2003;23:265–72.
[97] Pryor GA, Villar RN, Ronen A, Scott PM. Seasonal variation in the incidence of congenital talipes equinovarus. J Bone Joint Surg Br 1991;73:632–4.
[98] Robertson W, Corbett D. Congenital clubfoot: month of conception. Clin Ortho 1997;338:14–8.
[99] Edwards MJ. The experimental production of clubfoot in guinea pigs by maternal hyperthermia during gestation. J Pathol 1971;103:49–53.
[100] Halmesmaki E, Raivio K, Ylikorkala O. A possible association between maternal drinking and fetal clubfoot. N Engl J Med 1985;312:790.
[101] Honein M. Smoking during pregnancy "enormously" increases familial risk of clubfoot. Am J Epidemiol 2000;152:658–65.
[102] Farrell SA, Summers AM, Dallaire L, Singer J, Johnson JM, Wilson RD, et al. Club foot, and adverse outcome of early amniocentesis: disruption or deformation? J Med Genet 1999;36:843–6.
[103] Horton WA. Common skeletal deformities. In: Rimoin DL, Connor JM, Pyeritz RE, editors. Emery and Rimoin's practice of medical genetics. 3rd edition. New York: Churchill Livingstone; 1997. p. 2922–3.
[104] Idelberger K. Die Ergebnisse der Zwillnigsforschung beim angeborenen Klumpfuss. Brerh Dtsch Orthop Ges 1939;33:272–6.
[105] Magriples U. Prenatal diagnosis of clubfoot. In: UpToDate, version 11.2. Wellesley, MA: 2003. Available at www.uptodate.com.
[106] Wynne-Davis R. Genetic and environmental factors in the etiology of talipes equinovarus. Clin Orthop 1972;84:9–13.
[107] Shipp TD, Benacerraf BR. The significance of prenatally identified isolated clubfoot: is amniocentesis indicated? Am J Obstet Gynecol 1998;178:600–2.
[108] Treadwell MC, Stanitski CL, King M. Prenatal sonographic diagnosis of clubfoot: implications for patient counseling. J Pediatr Orthop 1999;19:8–10.

[109] Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003;7:1–77.
[110] Davidson RS. Clubfoot salvage: a review of the past decade's contributions. J Pediatr Orthop 2003;23:410–8.
[111] Heifetz SA. Single umbilical artery: a statistical analysis of 237 autopsy cases and review of the literature. Perspect Pediatr Pathos 1984;8:345–87.
[112] Benirschke K, Kaufmann P. Anatomy and pathology of umbilical cord and major fetal vessels. In: Benirschke K, Kaufman P, editors. Pathology of the human placenta. 4th edition. New York: Springer-Verlag; 2000. p. 341–2, 355, 363–6.
[113] Geipel A, Germer U, Welp T, Schwinger E, Gembruch U. Prenatal diagnosis of single umbilical artery: determination of the absent side, associated anomalies, Doppler findings and perinatal outcome. Ultrasound Obstet Gynecol 2000;15:114–7.
[114] Abuhamad A, Shaffer W, Mari G, Copel JA, Hobbins JC, Evans AT. Single umbilical artery: Does is matter which artery is missing? Am J Obstet Gynecol 1995;173:728–32.
[115] Leung AKC, Robson WLM. Single umbilical artery. Am J Dis Child 1989;143:108–11.
[116] Chow JS, Benson CB, Doubilet PM. Frequency and nature of structural anomalies in fetuses with single umbilical arteries. J Ultrasound Med 1998;17:765–8.
[117] Persutte YM, Hobbins J. Single umbilical artery: a clinical enigma in modern prenatal diagnosis. Ultrasound Obstet Gynecol 1995;6:216–29.
[118] Hill LM, Wibner D, Gonzales P, Chenevey P. Validity of transabdominal sonography in detection of a two-vessel umbilical cord. Obstet Gynecol 2001;98:837–42.
[119] Bornemeier S, Carpinito LA, Winter TC. Sonographic evaluation of the two vessel umbilical cord: a comparison between umbilical arteries adjacent to the bladder and cross-sections of the umbilical cord. J Diagn Med Sonogr 1996;12:260–5.
[120] Gossett DR, Lantz ME, Chisholm CA. Antenatal diagnosis of single umbilical artery: is fetal echocardiography warranted? Obstet Gynecol 2002;100:903–8.
[121] Budorick NE, Kelly TF, Dunn JA, Scioscia AL. The single umbilical artery in a high-risk patient population: what should be offered? J Ultrasound Med 2001;20:619–27.
[122] Persutte WH, Lenke RR. Transverse umbilical arterial diameter: technique for the prenatal diagnosis of single umbilical artery. J Ultrasound Med 1994;13:763–6.
[123] Sepulveda W, Peek MJ, Hassan J, Hollingsworth J. Umbilical vein to artery ratio in fetuses with single umbilical artery. Ultrasound Obstet Gynecol 1996;8:23–6.
[124] Wu MH, Chang FM, Shen MR, Yao BL, Chang CH, Yu CH, et al. Prenatal sonographic diagnosis of single umbilical artery. J Clin Ultrasound 1997;25:425–30.
[125] Raio L, Ghezzi F, Di Naro E, Franchi M, Bruhwiler H, Luscher KP. Prenatal assessment of Wharton's jelly in umbilical cords with single artery. Ultrasound Obstet Gynecol 1999;14:42–6.
[126] Lacro RV, Jones KL, Benirschke K. The umbilical cord twist: origin, direction, and relevance. Am J Obstet Gynecol 1987;157:833–8.
[127] Sepulveda W, Dezerega V, Carstens E, Gutierrez J. Fused umbilical arteries: prenatal sonographic diagnosis and clinical significance. J Ultrasound Med 2001;20:59–62.
[128] Fujikura T. Fused umbilical arteries near placental cord insertion. Am J Obstet Gynecol 2003;188:765–7.
[129] Nyberg DA, Mahony BS, Luthy D, Kapur R. Single umbilical artery: prenatal detection of concurrent anomalies. J Ultrasound Med 1991;10:247–53.
[130] Parilla BV, Tamura RK, MacGregor SN, Geibel LJ, Sabbagha RE. The clinical significance of a single umbilical artery as an isolated finding on prenatal ultrasound. Obstet Gynecol 1995;85:570–2.
[131] Catanzarite VA, Hendricks SK, Maida C, Westbrook C, Cousins L, Schrimmer D. Prenatal diagnosis of the two-vessel cord: implications for patient counseling and obstetric management. Ultrasound Obstet Gynecol 1995;5:75–6.

[132] Ulm B, Ulm MR, Deutinger J, Bernaschek G. Umbilical artery Doppler velocimetry in fetuses with a single umbilical artery. Obstet Gynecol 1997;90:205–9.
[133] Lee CN, Cheng WF, Lai HL, Cheng SP, Shih JC, Shyu MK, et al. Perinatal management and outcome of fetuses with single umbilical artery diagnosed prenatally. J Mat Fet Invest 1998;8:156–9.
[134] Reinhart BK, Terrone DA, Taylor CW, Isler CM, Larmon JE, Roberts WE. Single umbilical artery is associated with an increased incidence of structural and chromosomal anomalies and growth restriction. Am J Perinatol 2000;17:229–32.
[135] Gornall AS, Kurinczuk JJ, Konje JC. Antenatal detection of a single umbilical artery: does it matter? Prenat Diagn 2003;23:117–23.
[136] Thummala MR, Raju TN, Langenberg P. Isolated single umbilical artery anomaly and the risk for congenital malformations: a meta-analysis. J Pediatr Surg 1998;33:580–5.
[137] Blazer S, Sujov P, Escholi Z, Itai BH, Bronshtein M. Single umbilical artery—right or left? does it matter? Prenat Diagn 1997;17:5–8.
[138] Herrmann UJ, Sidiropoulos D. Single umbilical artery: prenatal findings. Prenat Diagn 1988;8: 275–80.
[139] Bjoro K. Vascular anomalies of the umbilical cord: obstetric implications. Early Hum Dev 1983; 8:119–27.
[140] Pierce BT, Dance VD, Wagner RK, Apodaca CC, Nielsen PE, Calhoun BC. Perinatal outcome following fetal single umbilical artery diagnosis. J Matern Fetal Med 2001;10:59–63.
[141] Sepulveda WH. Antenatal sonographic detection of single umbilical artery. J Perinat Med 1991;19:391–5.
[142] De Catte L, Burrini D, Mares C, Waterschoot T. Single umbilical artery: analysis of Doppler flow indices and arterial diameters in normal and small-for-gestational age fetuses. Ultrasound Obstet Gynecol 1996;8:27–30.
[143] Demasio K, Canterino J, Ananth C, Fernandez C, Smulian J, Vintzileos A. Isolated choroid plexus cyst in low-risk women less than 35 years old. Am J Obstet Gynecol 2002;187: 1246–9.
[144] Sepulveda W, Lopez-Tenorio J. The value of minor ultrasound markers for fetal aneuploidy. Curr Opin Obstet Gynecol 2001;13:183–91.
[145] Landy HJ, Bannon P, Zalud I, Collea JV, Lewis KM, Bartholomew ML, et al. Association of sex of the fetus in isolated choroid plexus cysts. J Ultrasound Med 1999;18:769–71.
[146] Walkinshaw SA. Fetal choroid plexus cysts: are we there yet? Prenat Diagn 2000;20:657–62.
[147] Nava S, Godmilow L, Reeser S, Ludomirsky A, Donnenfeld AE. Significance of sonographically detected second trimester choroid plexus cyst: a series of 211 cases and a review of the literature. Ultrasound Obstet Gynecol 1994;4:448–51.
[148] Gratton RJ, Hogge WA, Aston CE. Choroid plexus cysts and trisomy 18: risk modification based on maternal age and multiple-marker screening. Am J Obstet Gynecol 1996;175:1493–7.
[149] Ghidini A, Strobelt N, Locatelli A, Mariani E, Piccoli MG, Vergani P. Isolated fetal choroid plexus cysts: role of ultrasonography in establishment of the risk of trisomy 18. Am J Obstet Gynecol 2000;182:972–7.
[150] Gross SJ, Shulman LP, Tolley EA, Emerson DS, Felker RE, Simpson JL, et al. Isolated fetal choroid plexus cysts and trisomy 18: a review and meta-analysis. Am J Obstet Gynecol 1995; 172:83–7.
[151] Rotmensch S, Luo J, Nores JA, Schoenfeld D, Hobbins JC. Bilateral choroid plexus cysts in trisomy 21. Am J Obstet Gynecol 1992;166:591–2.
[152] Yoder PR, Sabbagha RE, Gross SJ, Zelop CM. The second-trimester fetus with isolated choroid plexus cysts: a meta-analysis of risk of trisomies 18 and 21. Obstet Gynecol 1999;93:869–72.
[153] Bromley B, Lieberman R, Benacerraf BR. Choroid plexus cysts: not associated with Down syndrome. Ultrasound Obstet Gynecol 1996;8:223–4.
[154] Fitzsimmons J, Wilson D, Pascoe-Mason J, Shaw CM, Cyr DR, Mack LA. Choroid plexus cysts in fetuses with trisomy 18. Obstet Gynecol 1989;73:257–60.

[155] Gupta JK, Khan KS, Thornton JG, Lilford RJ. Management of fetal choroid plexus cysts. Br J Obstet Gynecol 1997;104:881–6.
[156] Bahado-Singh RO, Choi SJ, Oz U, Mendilcioglu I, Rowther M, Persutte W. Early second-trimester individualized estimation of trisomy 18 risk by ultrasound. Obstet Gynecol 2003;101: 463–8.
[157] Leonardi MR, Wolfe HM, Lanouette JM, Landwehr JB, Hohnson MP, Evans MI. The apparently isolated choroid plexus cyst: importance of minor abnormalities in predicting the risk for aneuploidy. Fetal Diagn Ther 1998;13:49–52.
[158] Reinsch RC. Choroid plexus cysts – association with trisomy: prospective review of 16,059 patients. Am J Obstet Gynecol 1997;176:1381–3.
[159] Snijders RJM, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risk for chromosomal defects. Fetal Diagn Ther 1995;10:356–67.
[160] Benacerraf BR. Ultrasound of fetal syndromes. Philadelphia: Churchill-Livingstone; 1998.
[161] American College of Obstetricians and Gynecologists. Prenatal diagnosis of fetal chromosomal abnormalities. Practice Bulletin No. 27, May, 2001. Obstet Gynecol 2001;97(Suppl):1–12.
[162] Digiovanni LM, Quinlan MP, Verp MS. Choroid plexus cysts: infant and early childhood developmental outcome. Obstet Gynecol 1997;90:191–4.
[163] Nyberg DA, Luthy DA, Resta RG, Nyberg BC, Williams MA. Age-adjusted ultrasound risk assessment for fetal Down's syndrome during the second trimester: description of the method and analysis of 142 cases. Ultrasound Obstet Gynecol 1998;12:8–14.
[164] Snijders RJM, Nicolaides KH. Ultrasound markers for fetal chromosomal defects. Carnforth, UK: Parthenon Publishing; 1996.

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Ultrasound-guided procedures for prenatal diagnosis and therapy

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Physicians have been performing prenatal diagnostic procedures and therapies since the 1960s, but these early procedures were limited in their availability, acceptance, scope, and safety. Therapies, such as fetal intraperitoneal transfusion, were quite risky and were reserved for the most severe cases. The advent of real-time ultrasonography brought increasingly clearer visualization of the intrauterine space, and has vastly broadened the possibilities for fetal diagnosis and treatment. Being able to evaluate the fetus, cord, placenta, and vasculature in detail has allowed operators confidently to enter the amniotic cavity, chorion frondosum, and fetal circulation for diagnostic testing and fetal treatment. The ever-expanding availability of DNA molecular testing has steadily increased the number of diagnoses that can be made prenatally. This article reviews the currently available ultrasound-guided procedures for fetal diagnosis and therapy.

Diagnostic procedures

Genetic amniocentesis

History

Amniocentesis as a technique for prenatal diagnosis was first described in the 1950s as a means of sex determination by the identification of Barr bodies in noncultured amniocytes [1]. Since then, the development of tissue culturing techniques, two-dimensional ultrasonography, and modern molecular genetic testing have greatly expanded the indications and vastly improved the safety and reliability of this procedure. In the United States, there were nearly 100,000 amnio-

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centeses performed in the year 2000 (Centers for Disease Control and Prevention, unpublished data); this represents 2.4% of all births. Indications for offering amniocentesis include advanced maternal age; abnormal serum screening; family history of genetic disorders; fetal anomalies diagnosed on ultrasound; suspected fetal infections; and known carrier status in the parents of a burgeoning number of mendelian disorders including cystic fibrosis, Tay-Sachs disease, sickle cell anemia, and fragile X.

Technique

Amniocentesis is usually performed between 15 and 18 weeks gestation. Early amniocentesis (between 11 and 14 weeks), although technically feasible, is associated with an increased risk of miscarriage and fetal deformations (clubfoot) and is avoided except in cases where a fetal abnormality, such as a cystic hygroma, is diagnosed early and the benefit of early diagnosis outweighs the small added risk (see later) [2]. The technique used to perform amniocentesis has not changed dramatically over the years except for the addition of real-time ultrasonography. The pregnancy is evaluated with ultrasound to rule out any gross anomalies and to identify a good-sized pocket of amniotic fluid to access. At the same time, an assessment is made of the amniotic membrane to ensure that it has fused to the chorion; this is especially relevant for amniocentesis performed at 14 to 15 weeks when membrane fusion may be incomplete. Nonfusion of the membranes can make the procedure more difficult and may warrant postponement for a week or two.

The skin is then prepared with a surgical cleansing agent (eg, povidone-iodine, chlorhexidine, isopropyl alcohol). Sterile sonography gel is placed on the field and the ultrasound probe is covered with a sterile sleeve or sterile surgical glove. Under continuous ultrasound guidance, a 22-gauge spinal needle is inserted into a pocket of amniotic fluid (Fig. 1). Preferred pockets are located away from the fetal face or cord and do not require passage of the needle through the placenta; however, none of these is absolutely necessary to obtain amniotic fluid safely.

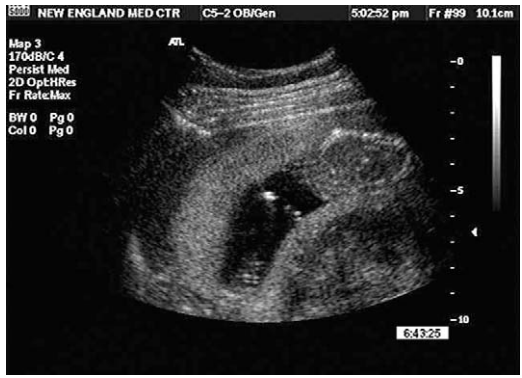

Fig. 1. Ultrasound image of amniocentesis at 16 weeks of gestation.

At least 15 to 20 mL of fluid is required for adequate culturing of amniocytes; more fluid may be necessary if additional tests are being performed, such as in situ hybridization. For early amniocentesis, 1 mL per week of gestation is withdrawn. Some advocate discarding the first 1 to 2 mL of fluid to avoid maternal cell contamination.

Safety and complications

The risk of fetal loss following midtrimester amniocentesis is generally quoted as 1 in 200 to 1 in 300. There is only one randomized trial in the literature, however, addressing this issue [3]. This study involved 4606 low-risk women in Denmark and reported a loss rate of 1.7% in those who had amniocentesis and 0.7% loss rate in the control group. Several retrospective studies have found lower loss rates [4,5]. Complication rates are increased when a larger-gauge needle is used or when more than one attempt to access the fluid is required.

Leakage of amniotic fluid following midtrimester amniocentesis occurs in 1% of patients; it is usually a small amount only and is not associated with the adverse outcomes typified by midtrimester spontaneous rupture of membranes. Over 90% of women experiencing fluid leakage after amniocentesis have a normal outcome [6]. Similarly, a small amount of vaginal bleeding has been reported in 2% to 3% of patients following genetic amniocentesis and is usually benign.

Isoimmunization following genetic amniocentesis is well described in the literature, corresponding to a small, but real risk of maternal-fetal hemorrhage with the procedure. Rh-immunoglobulin (Rhogam) should be administered to Rh-negative women after the procedure.

Despite early reports of high transmission rates in patients with HIV, the risk of transmission in patients taking multidrug antiviral regimens is probably lower. Nevertheless, the technique is probably best avoided in patients known to have HIV, hepatitis C, or active hepatitis B.

Special circumstances

Multiple gestations. Amniocentesis can be performed safely on multiple gestational sacs, the only caveat being that care must be taken adequately to map the pregnancy by ultrasound so it is absolutely clear which fetus' sac is sampled. A small amount (3 to 5 mL) of indigo carmine is injected into all but the final sac after they have been sampled to avoid inadvertently sampling the same sac more than once. Separate needles are used for each sac. There are data supporting the notion that these procedures are as safe as a singleton amniocentesis [7], but other data show slightly higher loss rates with twins [8].

Amniocentesis in the presence of bleeding. The risk of fetal loss following an amniocentesis is probably increased a small amount in women who have had antecedent bleeding during the pregnancy. One study found an excess loss rate of 0.6% in patients who experienced bleeding before their amniocentesis [9]. Patients who have had bleeding can still have an amniocentesis, but should be counseled about this increased risk.

Early amniocentesis. Amniocentesis has been described and can be performed successfully before 15 weeks gestation, but in recent years this technique has fallen out of favor because it seems to have higher risks than both midtrimester amniocentesis and chorionic villus sampling (CVS). The CEMAT trial [2] demonstrated an increased risk of fetal loss and fetal clubfoot especially when the amniocentesis was performed at less than 13 weeks gestation compared with midtrimester amniocentesis. Others have compared CVS with early amniocentesis and found similar increases in fetal loss rates or clubfoot with early amniocentesis [10,11]. Technically, an early procedure does not differ from a midtrimester procedure, although less fluid is usually removed (1 mL of fluid per week of gestation).

Chorionic villus sampling

History

Like amniocentesis, the technique of CVS was first developed in the late 1960s before the advent of real-time ultrasonography. Initially, these were transcervical procedures, and as ultrasound became more readily available, transabdominal approaches were developed in the 1980s. The major advantage of CVS is that a karyotype of the fetus can be obtained much earlier in the pregnancy than with amniocentesis; this allows for safer pregnancy termination procedures and affords the patient a greater deal of privacy than a midtrimester procedure. In the early 1990s, CVS fell out of favor in the United States because of reports of increased risks of transverse limb reduction defects associated with the procedure [12]; this trend has been changing in recent years as more data have become available about the safety of the procedure [13].

Technique

Transcervical CVS is accomplished by passing a polyethylene catheter through the cervix into the placental bed under continuous ultrasound guidance. Sterile technique is used and the cervix is initially prepared and may be stabilized with a tenaculum. Trophoblastic tissue (5 to 30 mg) is then aspirated into a syringe containing culture media. If inadequate tissue is obtained, a new catheter is used to obtain a second sample.

The transabdominal approach is similar to an amniocentesis, but a larger-gauge needle is used (18 to 20 gauge); local anesthetic may be administered in the skin and subcutaneous tissues; and the needle is directed into the placental bed instead of into the amniotic fluid. A syringe containing culture media is attached and tissue is aspirated during several passes of the needle through the placental tissue (Fig. 2).

The choice of approach is usually physician preference, although some placentas are only accessible by one approach or the other. There does not seem to be any advantage of one technique over the other in terms of safety or the ability to obtain a meaningful result [14], although in some circumstances (eg, active cervicitis, cervical myomas, and cervical stenosis) transcervical CVS is

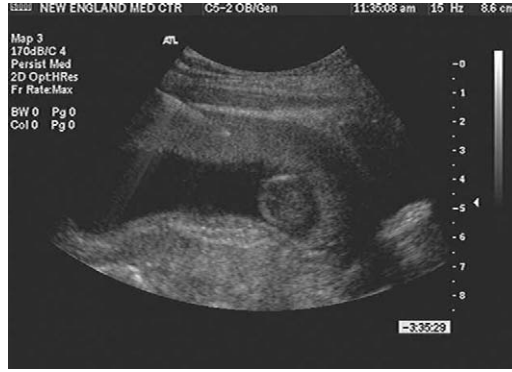

Fig. 2. Ultrasound image of transabdominal chorionic villus sampling.

contraindicated. Transabdominal CVS may not be possible with extreme retroversion of the uterus because bowel loops may be present between the maternal abdominal wall and the anterior wall of the uterus.

Safety and complications

Loss rates from CVS are greater than that for amniocentesis, and there is a large body of both prospective and retrospective data, which supports the common quotation of a 1% risk of miscarriage caused by the procedure [15,16]. Of greater concern, however, are the reports of limb-reduction defects caused by CVS, which came out in the early 1990s. Subsequently, there have been numerous reviews of tens of thousands of procedures and the association between these defects and CVS seems to be confined to those procedures performed before 10 weeks gestation or performed by inexperienced operators [16].

One disadvantage of CVS compared with amniocentesis is the approximately 1% risk of placental mosaicism. The finding of mosaicism on a CVS result can be clarified with an amniocentesis and if normal, is not associated with fetal abnormalities.

Chorionic villus sampling is also limited compared with amniocentesis in its ability to assess amniotic fluid alpha-fetoprotein. Although perfectly suited to diagnosis fetal karyotypic abnormalities and fetal conditions ranging from cystic fibrosis to hemophilia, CVS does not allow for assessment of the amniotic fluid alpha-fetoprotein and acetylcholinesterase, which are readily assessed with amniocentesis and yield much information about the status of the neural tube and ventral wall.

Special circumstances

Multiple gestations. Chorionic villus sampling has been reported in twin, triplet, and quadruplet pregnancies. Technically, these are much more complicated procedures and operator and sonographer experience are crucial to maintain

adequate safety standards. Insertion of the needle well away from the area of membrane or placental fusion is important to avoid contamination of the sample with a co-twin's tissue. Twin CVS seems to be comparable in safety with twin amniocentesis [17].

Chorionic villus sampling later in gestation: placental biopsy. Chorionic villus sampling performed after 12 weeks gestation is also referred to as "placental biopsy." Although this technique can safely obtain a karyotype in the presence of severe oligohydramnios, it is associated with higher rates of placental mosaicism than CVS and results may be more difficult to interpret. Loss rates associated with late CVS are also higher: 10% when fetal anomalies are noted and 2% in low-risk groups [18]. Sampling failure also occurs more frequently with late CVS.

Isoimmunization. As with amniocentesis, CVS can result in maternal-fetal hemorrhage and isoimmunization. Rhogam is indicated for Rh-negative women. Moreover, CVS should probably be avoided in patients who are already isoimmunized because amniocentesis is less likely to cause a further elevation in their antibody titer.

Cordocentesis

Cordocentesis, or percutaneous umbilical blood sampling (PUBS) allowing direct access to fetal circulation, was first described in 1983 by Daffos et al [19], who pioneered the procedure for use in evaluation of perinatal toxoplasmosis infection. The technique was quickly adopted and used for diagnosis of many other conditions. Notably this led to a revolutionary change in the approach to the diagnosis and management of isoimmunization. Other common indications for the procedure included rapid karyotype evaluation when fetal abnormalities were detected; evaluation of fetal growth restriction; evaluation of fetal platelet abnormalities (eg, maternal immune thrombocytopenic purpura, fetal alloimmune thrombocytopenia, TAR sequence); evaluation of fetal hydrops; evaluation of potential fetal infections; and evaluation of fetal hemoglobin in patients at genetic risk for hemoglobinopathies. Over time, the use of PUBS for evaluation of many of these indications has diminished. Other techniques were developed, which allow rapid karyotyping, and polymerase chain reaction testing from amniotic fluid is often superior for evaluation of fetal infection. Fetal growth restriction and immune thrombocytopenic purpura can be managed using noninvasive testing. The development of direct DNA testing for many genetic and infectious conditions (sickle cell disease, thalassemia, hemophilia, cytomegalovirus, and toxoplasmosis) has made PUBS unnecessary, because results can be obtained with simple amniocentesis or CVS. Still, the procedure serves a critical role in the evaluation of some fetal conditions, and by allowing access for potential fetal transfusion, it can be a lifesaving technique.

Technique

Cordocentesis has been described as early as 12 weeks of gestation [20], but is generally performed after 18 weeks gestation. The procedure is performed under continuous direct ultrasound guidance. Many centers use antibiotic prophylaxis. Color flow Doppler imaging is an important tool in evaluating the cord and placenta. The placental cord insertion is the ideal site for needle insertion, because it is fixed in place, unlike a free loop of cord. Depending on gestational age and placental position, access to the cord insertion may not be possible. After locating the placental cord insertion or other site of accessible cord, a 22-gauge spinal needle is advanced through the maternal abdomen under local anesthesia, using a free-hand technique or needle guide. The umbilical vein is targeted to decrease the risk of vasospasm. When the needle tip is thought to be within the umbilical vein the stylet is removed and a heparin-coated syringe is used to aspirate through the spinal needle (Figs. 3 and 4). If blood returns, a small amount is sent for a complete blood count to confirm its fetal source, using the higher mean corpuscular volume of fetal blood to distinguish it from maternal blood. If no blood returns, the stylet is replaced, small adjustments are made in position, and the process is repeated. After blood is obtained for the desired laboratory tests, the needle is withdrawn. The area of needle entry into the cord is inspected

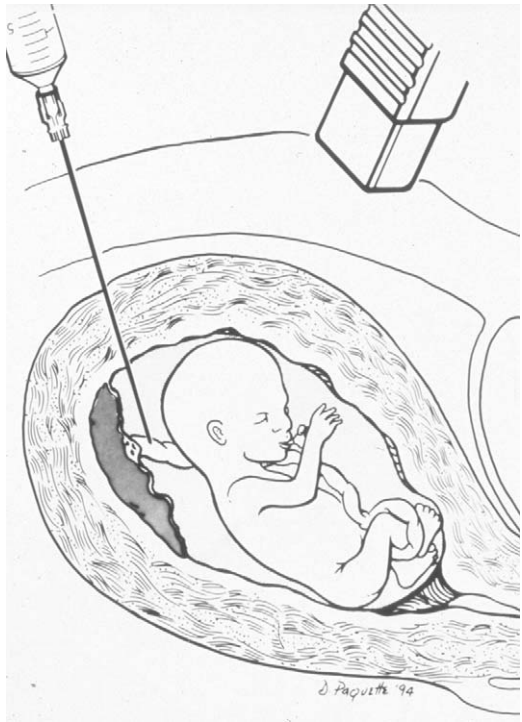

Fig. 3. Diagram of cordocentesis procedure.

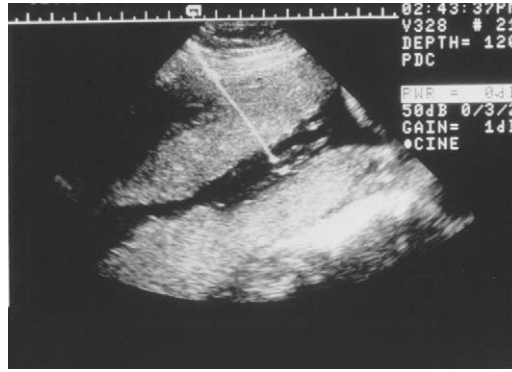

Fig. 4. Ultrasound image of cordocentesis with the needle tip located in a free loop of cord.

carefully using ultrasound to rule out bleeding or clot formation. The fetal heart rate should be assessed throughout the procedure and afterward.

Safety and complications

The risk of fetal loss associated with this procedure is 1.2% to 4.9% [21]. When hydropic and extremely growth restricted fetuses are excluded, the procedure-related loss is less than 2%. Risks include fetal loss, bleeding, cord hematoma, chorioamnionitis, preterm labor, and a risk of not being able to obtain fetal blood. Approximately 3% to 12% are complicated by transient bradycardia. In some cases bradycardia is severe and may require cesarean delivery, depending on gestational age and fetal condition.

Fetal biopsy

Some disorders require organ-specific diagnosis when diagnostic testing cannot be performed on chorionic villi, amniocytes, or fetal blood. Fetal biopsies have been performed since the 1980s, and were originally fetoscopically guided. Ultrasound-guided fetal muscle biopsy, skin biopsy, liver biopsy, and kidney biopsy have been reported and are performed in a few centers.

In 1991, Evans et al [22] reported the first solely sonographically guided muscle biopsy for diagnosis of Duchenne muscular dystrophy in a family that could not be diagnosed by fetal DNA studies alone. (Diagnosis requires evaluation of the actual muscle dystrophin protein in those families in whom DNA mutation and linkage studies are not useful.) By 1999, 17 cases had been reported from five centers, all between 18 and 25 weeks of gestation. Attempts to obtain samples were not successful in two patients (12%) and two patients had spontaneous abortions within 1 week after rupture of membranes (12%) [23]. Biopsies were obtained using different devices, including 2×2 mm biopsy forceps through a 2.2-mm trocar, a 14-gague Klear-Cut forceps gun, a 14-gauge True-Cut biopsy

needle, and an 18-gauge core biopsy system. Under local anesthesia, the sampling device is introduced with ultrasound guidance and a sample is taken from the upper outer area of the gluteal muscle. Some operators gave maternal midazolam or fetal pancuronium to reduce fetal movements. Fetoscopy was used for targeting the biopsy in a few cases, but this procedure carries its own risk, and may not be necessary at later gestational ages. Potential complications include fetal nerve or vascular injury, uteroplacental bleeding, and pregnancy loss. No surviving infant had evidence of nerve injury at birth, but small scars at the biopsy site were noted at birth.

Fetal kidney biopsy has been reported for the diagnosis of Finnish nephrosis [24], and for evaluation of renal function in cases of obstructive uropathy [25]. The latter is associated with a poor rate of adequate sampling (50%) because of thinning of the abnormal renal parenchyma, and is not widely accepted as an indication for this invasive procedure. Similar to muscle biopsy, ultrasound-guided fetal kidney biopsies are performed under direct ultrasound guidance using two to three passes of a 19-gauge spinal needle under negative pressure, or an 18-gauge Biopsy-cut spring-loaded needle gun. Care must be taken to visualize the renal blood supply to avoid vascular injury during biopsy. Despite ultrasound guidance, samples of adipose tissue, pancreatic tissue, and liver have been obtained inadvertently during attempts at kidney biopsy. Wapner et al [24] recommend having a pathologist available to evaluate immediately the sample for renal tissue.

Fetal skin biopsies may be performed for karyotype analysis in cases of mosaicism found on amniocentesis or CVS particularly when discrepant results are obtained from blood and amniocytes [26]. There have been isolated reports of fetal liver biopsy to diagnose conditions, such as ornithine transcarbamoylase deficiency, but this procedure is rarely needed and is not widely available [27].

Therapeutic procedures

Fetal transfusion

After direct access to the fetal circulation was accomplished through PUBS, fetal transfusion became possible. Although access through the fetal heart had been performed, cardiocentesis carried a higher risk of loss than cordocentesis [28]. Transfusion of blood, platelets, and medications directly to the fetus greatly expanded the options for fetal treatment. Transfusion of packed red blood cells became the standard treatment for fetal anemia caused by isoimmunization. After its introduction, the fetal mortality and morbidity associated with isoimmunization fell drastically, and survival improved to over 96% for nonhydropic fetuses and 86% for hydropic fetuses [29]. Treatment of other forms of anemia, such as that caused by parvovirus infection or anemia following a monochorionic twin demise, has also been attempted, but with varying degrees of success and controversy [30,31]. Transfusion after fetal maternal hemorrhage has been reported but is rarely an option.

Fetal platelet transfusions have played a critical role in the treatment of alloimmune thrombocytopenia. Diagnosis is often made after a history is obtained of a previous child with neonatal alloimmune thrombocytopenia. Randomized trials have shown that treatment with immune globulin is effective in most cases [32], with fetal platelet transfusion reserved for those who do not respond to medical therapy or have evidence of bleeding at PUBS. Complication rates of transfusion are higher for this indication, largely because of potential cord bleeding associated with marked thrombocytopenia [33].

Fetal transfusion of medications has been reported for a limited number of conditions. Transfusion of antiarrhythmic medications can be performed if treatment by maternal medical therapy fails. Curare-like agents can be infused into the umbilical vein to limit fetal movement to facilitate other procedures, such as a fetal blood transfusion. The authors reported a case of fetal Smith-Lemli-Opitz syndrome in which fetal transfusion of cholesterol-rich plasma was performed to improve the outcome associated with this disorder of cholesterol metabolism [34].

Technique

The team performing the procedure should be experienced, and care must be taken to make a plan for the possibility of delivery. If the procedure is performed after viability and intervention is planned should nonreassuring testing occur, access to an operating suite should be available. Plans for intervention should be clear to the patient and team in the event that prolonged fetal bradycardia or other complications occur. Cordocentesis is performed as described previously, most commonly in the placental cord insertion. Access near the fetal cord insertion can be attempted, and transfusion into the hepatic vein has been performed, but both carry increased fetal risk. Ideally, free loops of cord should be avoided for transfusion, because pushing the blood into the cord vessel can easily dislodge the needle from the intravascular position. Continuous ultrasound guidance is required, with constant evaluation of the intravascular flow. Cessation of flow may signal needle dislodgement or clot formation. If this occurs transfusion should be stopped temporarily, needle location should be reconfirmed, blood return confirmed with a syringe, and clot ruled out by careful inspection of the site and cord vessels. Color flow Doppler imaging is particularly useful while gaining access to the circulation and following the procedure. A 20- or 22-gauge spinal needle is used, reserving the smaller gauge for earlier gestations because infusing concentrated packed cells through a small-gauge needle can be difficult. Extension tubing is connected to a three-way stopcock, which in turn is connected to the unit of packed cells. A 30-mL syringe is filled from the stopcock and then used to push the blood into the fetal circulation. Formulas are used to calculate the amount of blood needed to raise the fetal hematocrit from the starting anemic level to the desired higher level. The formulas take into account the fetal weight, starting hematocrit, desired hematocrit, hematocrit of the blood unit, and a correction factor for the volume of blood contained in the placenta. The fetal heart rate should be observed intermittently during the transfusion.

For blood cells, the blood bank can prepare packed cells with a high hematocrit (80% to 90%) to limit the volume of the transfusion. Packed cells for transfusion should be type O negative (or the maternal blood type); irradiated; and cytomegalovirus negative. Similarly, platelets for fetal transfusion should be in a high-concentration, low-volume preparation. When transfusing platelets or packed cells, a posttransfusion blood count can be obtained 1 to 2 minutes after completing the transfusion to confirm the adequacy of the volume transfused.

Safety and complications

Complications of fetal transfusion include being unable to perform the procedure, fetal hemorrhage, fetal bradycardia, cord hematoma, arterial vasospasm, and fetal death. Other risks include ruptured membranes, bleeding, and preterm labor. The risk of fetal death related to the disease being treated is 8% to 16%, so procedure-related death is difficult to determine [29]. Fetal death is more likely with pre-existing hydrops or at very early gestational ages. Iron overload is a potential complication in cases requiring multiple, serial transfusions.

Amnioreduction

History

As an obstetric procedure, amnioreduction has been in existence much longer than genetic amniocentesis or amniocentesis for the assessment of erythroblastosis. Reports date back to the late nineteenth century of transabdominal amniocentesis for the treatment of massive polyhydramnios. Aside from the introduction of real-time sonography, the technique has changed little over the years.

The indications for amnioreduction include massive polyhydramnios causing maternal symptoms or preterm labor and the treatment of the twin-to-twin transfusion syndrome (TTTS). Success rates of serial amnioreduction for TTTS have been reported as high as 70% to 80% [35], although some case series have shown much poorer outcomes.

Technique

Using an 18- or 20-gauge needle (a larger needle bore is necessary to remove large volumes of fluid quickly) an amnioreduction is performed with the same technique as amniocentesis (described previously). The needle should be inserted toward the mother's head, so that as the fluid is removed and the uterus becomes smaller, the needle assumes a more upright position and does not become dislodged. Tubing is attached to the needle after removal of the stylet and either connected to a wall suction device, a vacuum bottle, or to a three-way stopcock and 50-mL syringe for manual removal of the fluid.

The volume of fluid that can be removed safely in one sitting is not clear, but several hundred milliliters to several liters have been reported in the literature [36]. Similarly, the frequency of sampling and the rapidity of withdrawal of fluid vary from study to study and there is little agreement about what these parameters should be ideally. The authors typically remove enough fluid to bring the

amniotic fluid index back to a normal range, usually no more than 2 to 3 L at a time at 15 to 20 min/L.

Safety and complications

Complication rates range from 1% to 5% in the literature. The most common complications are preterm contractions, labor, and rupture of the membranes. Abruptio placenta has also been reported following massive amnioreduction. Serial procedures are associated with higher complication rates.

Septostomy

Inadvertent disruption of the intersac membrane in twin pregnancies has been reported for many years in the amniocentesis literature, but septostomy or intentional amniotomy as a treatment for the twin-to-twin transfusion syndrome was first introduced in 1995 [37]. Various techniques have been described, but most involve the use of 20- or 22-gauge needle passes through the sac of the "stuck" twin into the twin with polyhydramnios to create a window in the membrane between the sacs. This technique is often combined with amnioreduction. Complications are similar to amniocentesis and amnioreduction, although there have also been reports of cord entanglement following this procedure because the septostomy may create an iatrogenic monoamniotic pregnancy [38].

Multifetal reduction

History

Multifetal pregnancy reduction (MFR) has become an accepted procedure, which can be performed safely with technical success. It offers an option to the large number of patients with infertility who, through assisted reproductive techniques, conceive a high-order multiple gestation. Before 1986, patients faced with this dilemma could only elect to continue or abort the entire pregnancy, both options resulting in no children in many cases. MFR offers these patients a high chance of achieving their desired outcome, to carry a pregnancy and take home a healthy newborn.

The first United States experience with MFR was reported in 1988. Berkowitz et al [39] reported a series of 12 cases using transcervical aspiration or transabdominal potassium chloride (KCl) injection, and Evans et al [40] reported four cases using fetal cardiac disruption or transabdominal KCl injection [40]. Loss rates were initially high, between 33% and 50%. Both groups moved to KCl injection into the fetal heart or thorax, with technical success and improved outcomes.

Variations on the techniques continued, with case reports or small series detailing different methods. Over time, two principle methods have become the most widely used: transabdominal or transvaginal intrathoracic KCl injection, with the transvaginal approach being performed in only a few centers.

The first-trimester procedures performed solely to reduce the number of embryos in a higher-order multiple pregnancy were initially described as another

form of selective termination. To avoid any suggestion that parents actually made choice regarding which presumably normal embryos were reduced, a plea was made to rename the procedure "multifetal pregnancy reduction" [41].

Technique

Patients identified with triplets or a higher-order multiple gestation should be referred to a center with experience in the technique of MFR. The patient should be counseled regarding the options of pregnancy management, including continuing the pregnancy versus undergoing MFR. The risks of each option should be detailed, and the patient should be given time to consider her options before scheduling the procedure. Transvaginal procedures are usually performed at 9 to 10 weeks, and transabdominal procedures are usually performed at 10 to 12 weeks. On the day of the procedure, care is taken to map sonographically the embryos and their placental positions within the uterus to eliminate any confusion regarding which fetus underwent reduction. At the same time viability of the embryos is confirmed; chorionicity is assessed; and screening for abnormalities is performed (eg, discordant size, anencephaly, increased nuchal translucency). If a particular embryo seems smaller than the others, it should be selected for reduction. In cases in which more than two embryos are being reduced, the procedure may be performed in more than one session.

Prophylactic antibiotics are given for a transabdominal procedure in most cases, although this varies among practitioners. Anesthesia may include a mild sedative or a local anesthetic. The patient's abdomen is prepared with antiseptic solution. Under continuous ultrasound guidance a needle is introduced into the thorax of an easily accessible embryo and a small amount of KCl is injected (1 to 2 mEq). The fetus overlying the cervix is usually avoided. The needle is kept in position until fetal cardiac asystole occurs and persists for 2 to 3 minutes. Using a separate needle the procedure is repeated for each embryo to be reduced. Approximately 1 hour later the fetal heart rates are checked to confirm embryonic demise of the reduced embryos, and viability of the nonreduced embryos. Resumption of fetal heat motion may occur in up to 5% of cases [42], and patients are advised that if fetal heart motion resumes, repeating the procedure is necessary because outcomes for these embryos are likely to be poor.

The transvaginal approach is similar in most respects. The vagina is prepared with antiseptic solution. Using a transvaginal ultrasound probe with a needle guide the needle is inserted into the sac and thorax of an embryo and KCl is injected. Again, care is taken to ensure complete asystole before removing the needle. Some groups use an automated puncture device. With this approach the fetus overlying the cervix is frequently reduced given the close access to the vaginal ultrasound probe.

Safety and complications

The procedure is complicated by loss of the entire pregnancy in 5% to 6% of cases [42,43]. This number varies by starting number and ending number of embryos, with high-order multiples carrying a higher risk of loss. Pregnancy losses

include those lost soon after the procedure because of infection, bleeding, or rupture of membranes, and those lost because of delivery at extremely premature gestational ages. These risks are concerning, but they are lower than the reported fetal loss rate described in twin gestations following assisted reproduction. No anatomic injury to a surviving co-sibling clearly attributable to an MFR procedure has been documented. Similarly, no case of maternal disseminated intravascular coagulation has been reported in a patient undergoing first-trimester MFR. Death of a monochorionic co-twin has been reported after intentional and unintentional reduction of a monochorionic fetus.

Benefits of MFR have been clearly demonstrated for pregnancies with four or more fetuses [44]. The mean gestational age of delivery of pregnancies originally carrying four or more fetuses but reduced to twins is significantly higher that the mean gestational ages of delivery of the nonreduced higher-order multiple pregnancies. The average birthweights are higher than those of infants in the same order multiple pregnancy not undergoing MFR. Maternal and neonatal hospital stays are shorter for reduced pregnancies than for nonreduced pregnancies, and the risk of extremely premature delivery (< 28 weeks) is reduced. Parents are more likely to take home at least one healthy baby after MFR than after carrying a higher-order multiple pregnancy.

Benefits of MFR have also been shown for triplet pregnancies including a higher mean gestational age of delivery compared with nonreduced triplets, larger birthweights, and shorter neonatal and maternal admissions [45]. No reduction in mortality or long-term morbidity has been demonstrated, so the issue is still controversial. Nevertheless, MFR for triplets is widely requested and performed.

Special considerations

Many patients considering MFR are at increased risk for aneuploidy because of maternal age. Serum screening has limited sensitivity when used in multiple gestations. Patients may choose to undergo CVS before MFR, or to undergo amniocentesis after MFR. Both options seem to be safe without carrying additional risk of pregnancy loss [12,46].

Selective termination

History

Before MFR was developed, scattered cases of selective termination were reported, in which an anomalous fetus in a twin gestation was terminated to allow continuation of the pregnancy and delivery of the normal co-twin. From 1978 to 1984, case reports described techniques in which an anomalous fetus of a twin gestation was selectively terminated using ultrasound guidance, the demised fetus was left in situ, and the co-twin was left undisturbed [47–49]. The earliest reports of selective termination described a variety of techniques, including cardiac puncture, exsanguination, injection of air into the fetal heart, air embolism through the umbilical vein, hysterotomy, calcium gluconate injection, and KCl injection.

Currently, intracardiac or intravascular KCl injection is the most widely used method for selective termination.

Technique

The technique used for selective termination is very similar to the technique used for MFR, but the procedure is usually performed later in gestation after an anomaly or chromosomal abnormality has been diagnosed. Careful mapping of the fetuses and placentas at the time of diagnostic procedure is extremely important to evaluate the chorionicity and to ensure that the correct fetus is selected in any future termination. In cases performed for major anomalies, direct visualization of the anomaly serves to confirm the correct fetus, and when twins are discordant for sex, the fetal identification is fairly straightforward. In cases of aneuploidy without major anomalies, however, the distinction can be difficult. Cordocentesis or repeat amniocentesis with rapid Fluorescent In Situ Hybridization (FISH) analysis may be used to confirm fetal diagnosis and position before selective termination.

Patients are given antibiotics and a sedative before the procedure, which is performed under continuous direct ultrasound guidance. KCl is injected into the fetal heart to cause asystole. Confirmation of the asystole is made an hour later.

Safety and complications

The procedure can be performed safely and accurately. The risk of loss of the entire pregnancy is 4% to 7.5% [50,51]. Although initial data suggested the loss rate is higher when the procedure is performed after 20 weeks gestation, a series of 200 cases from a single center did not demonstrate any additional risk for procedures performed after 20 weeks [50]. There is a risk of termination of the wrong fetus, and this unfortunate complication has been reported. Demise of a monochorionic co-twin is also possible. There have been no reports of injury to a co-twin or coagulation abnormalities following this procedure.

Special considerations

Cases of monochorionic twins discordant for an anomaly require special attention, and cannot be approached with intravascular KCl injection. Techniques have been developed and used to effect selective termination of a monochorionic anomalous twin, including cord ligation (see later) and cord coagulation. Loss rates are higher with these procedures.

Specialized procedures

Fetocentesis

Ultrasound-guided transabdominal needle aspiration of the fetal bladder (vesicocentesis) allows direct measurement of any component of fetal urine. This procedure is indicated in cases of bladder outlet obstruction. The initial tap is the most concentrated (ie, abnormal); serial taps may show improvement in urine

electrolytes. The usually hypotonic fetal urine becomes concentrated with renal damage, and elevated levels of sodium, chloride, potassium, phosphate, and osmolality have been correlated with poor renal function and outcome. Elevated levels of β_2-microglobulin suggest tubular damage and are the most sensitive and specific predictor of outcome. Abnormal urine electrolytes and β_2-microglobulin levels make further intervention unwarranted.

The vesicocentesis procedure is relatively straightforward in most cases, given the gross overdistention of the fetal bladder, which brings it forward to the fetal abdominal wall. Care should be taken to avoid fetal abdominal wall vessels and other intra-abdominal organs. Fetal risks are difficult to quantify, because the condition is lethal if left untreated.

Aspiration of other fetal cavities can be performed. Fetal hydrothorax can be evaluated by aspiration of the pleural effusion. Fluid can be tested for karyotype and a blood count can be performed to evaluate the possibility of chylothorax. In some cases of unilateral hydrothorax, the pleural effusion may not reaccumulate after one or more decompression procedures, and the aspiration can be curative.

Aspiration of a massively dilated renal pelvis or ureter is also possible and may be indicated in rare cases to evaluate renal function, and potentially to relieve pressure within the affected kidney (Fig. 5).

In cases of fetal hydrops, some practitioners advocate aspirating fetal pleural effusions immediately before delivery to assist the neonatal resuscitation team. These infants are often critically ill at birth, and the predelivery decompression may allow immediate inflation of the lungs during a complicated resuscitation effort. Case reports have described needle aspiration decompression of a large hygroma or lymphangioma to facilitate a vaginal delivery [52,53].

Shunt procedures

Vesicoamniotic shunt procedures involve placement of a double pig-tailed catheter through the fetal abdomen into the obstructed fetal bladder to allow passage of urine into the amniotic cavity. The procedure is generally reserved for

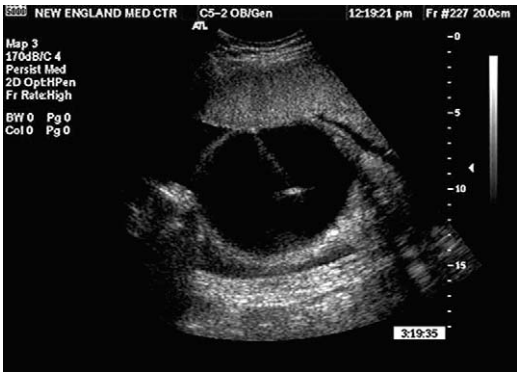

Fig. 5. Ultrasound-guided transabdominal fetocentesis.

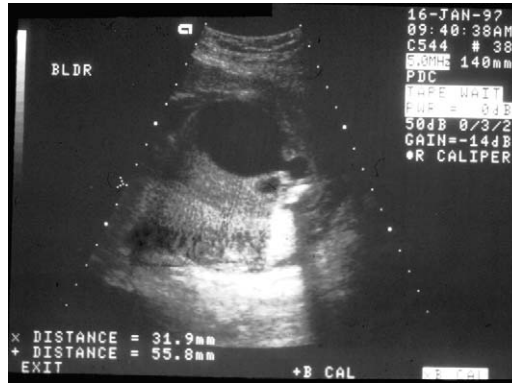

Fig. 6. Ultrasound image of bladder outlet obstruction with enlarged bladder, classic keyhole appearance seen with posterior urethral valves, and anhydramnios.

fetal bladder outlet obstruction with anhydramnios, which is an otherwise lethal fetal condition. Bladder outlet obstruction is most often caused by posterior urethral valves, but may also occur with urethral atresia, obstructing ureterocele, megacystis-microcolon, or cloacal dysgenesis (Fig. 6). Up to 20% of cases have associated chromosomal abnormalities.

The goal of shunting is to allow survival by restoring amniotic fluid volume, avoiding pulmonary hypoplasia. In some cases, shunting may also theoretically prevent worsening of the renal dysfunction. Early reports of the procedure showed limited success. Selective criteria were then developed to distinguish between groups with poor prognosis and good prognosis. Intervention in the poor prognosis group is ineffective, but intervention in the good prognosis group is associated with over 60% survival [54,55]. Surviving infants may still need renal transplantation, have severe renal insufficiency, or prune belly syndrome.

Reported complications from vesicoamniotic shunting include premature rupture of membranes, chorioamnionitis, preterm labor and delivery, procedure-related mortality, shunt occlusion or dislodgement, and iatrogenic gastroschisis; this latter complication seems to be more likely to occur if the shunt is placed above the umbilicus. Attempts to place the shunt may also fail.

When considering the procedure, care must be taken to rule out coexisting fetal anomalies and karyotype abnormalities. Vesicocentesis must be performed to evaluate renal function, and correlated with ultrasound findings. If the kidneys are hyperechoic or show cortical cysts, prognosis is poor and shunting is not recommended. Similarly, abnormal urine chemistry, coexisting chromosomal or structural anomalies, and normal amniotic fluid volume are contraindications to shunting.

Technique

The patient should receive in-depth counseling regarding the procedure, risks, and alternatives. The procedure is performed under continuous ultrasound guid-

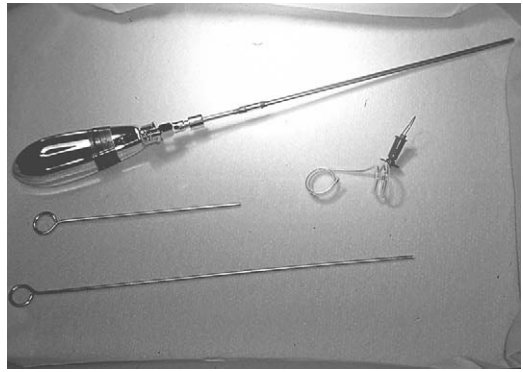

Fig. 7. Double pig-tailed Rocket catheter and trocar used for vesicoamniotic shunting.

ance. Maternal analgesia or anesthesia is required because the procedure can be prolonged and the instruments used are significantly larger than the needles used for diagnostic procedures. Prophylactic antibiotics should be considered. Fetal position is highly important when planning access to the anterior lower fetal abdomen. Avoiding a path traversing the placenta is preferable, but may not be possible depending on fetal and placental position. Several shunt catheters are available, including the Rocket catheter and Cook's Harrison catheter. Each has corresponding sized trocar, introducer, and plungers (Fig. 7). The Cook catheter comes in a disposable kit with a 13-gauge introducer. Amnioinfusion may be necessary before or during the procedure to be able to place the amniotic portion of the shunt inside the amniotic membrane correctly, which is particularly difficult in cases of complete anhydramnios. Shunts should be reassessed frequently, because blockage or dislodgement is not uncommon. Gestational age and fetal condition are factors to consider when determining whether or not to replace the shunt.

Thoracic-amniotic shunts have also been used to treat fetal hydrothorax (Fig. 8). Many cases of hydrothorax resolve after single or multiple taps, but persistent

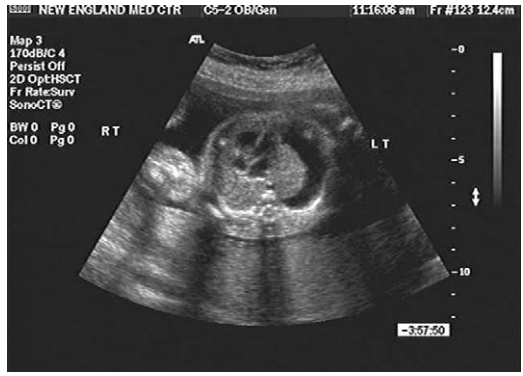

Fig. 8. Ultrasound image of unilateral hydrothorax with mild cardiac displacement.

hydrothorax can lead to pulmonary hypoplasia and cardiovascular complications. Before considering a shunt, a careful examination must be performed looking for any evidence of hydrops, and to rule out cardiac malformations. The procedure is performed similarly to the bladder shunt procedure described previously, but through the fetal chest wall between ribs. Again, fetal position is important, and because these pregnancies are not complicated by oligohydramnios, fetal curare-like medications may be given intramuscularly to maintain a desired fetal position once achieved. Contraindications to fetal chest shunt procedures include coexisting anomalies or hydrops.

Over 100 cases have been reported in the literature, with only two centers reporting more than 10 cases [56]. Success is higher when there is no evidence of systemic involvement with hydrops, and outcome is most improved when shunts are placed before 32 weeks gestation.

Cord occlusion procedures

Cord occlusion procedures have been performed in cases of monochorionic-dichorionic twins or monochorionic-monoamniotic twins discordant for an anomaly. The approach has been used to terminate selectively the abnormal fetus while attempting to prevent neurologic injury to the co-twin. It has also been used in cases of twin reverse arterial perfusion sequence and severe TTTS [57].

The procedure is performed in a few centers and can be accomplished using bipolar coagulation, intravascular coagulation, or fetoscopic cord ligation. Complications occur in approximately 40% of cases and include fetal loss, rupture of membranes, preterm labor, fetal death or neurologic injury of the co-twin, and inadvertent occlusion of the cord of the normal twin.

Balloon valvuloplasty

In utero balloon valvuloplasty has been reported (with limited success) for both right-sided and left-sided stenotic heart lesions [58,59]. The most commonly described techniques involve direct access of the affected ventricle through the fetal chest wall with subsequent passage of interventional catheters to the affected valve. Clearly, these remain experimental procedures, which require well-coordinated teams of specialists from multiple disciplines.

Summary

Ultrasonography has expanded the capabilities of perinatologists to examine, test, and treat the fetus. Amniocentesis and CVS are safe and widely available procedures, which can be used to diagnose a multitude of abnormalities through karyotype analysis and molecular studies. CVS allows earlier diagnosis, but both procedures can provide highly accurate results in the first half of pregnancy. Cordocentesis has fewer indications, but allows direct laboratory testing of fetal

blood. Fetocentesis and fetal biopsy are reserved for limited indications, but can play a crucial role in the diagnosis of some conditions, which cannot be assessed less invasively.

Fetal transfusion is an important tool in the treatment of isoimmunization, some other forms of fetal anemia, and alloimmune thrombocytopenia. Amnioreduction is a commonly used procedure for the treatment of polyhydramnios and TTTS. Multifetal reduction and selective termination offer previously unavailable options to patients carrying multiple gestations. Fetal shunts can reduce perinatal morbidity and mortality in cases of bladder outlet obstruction and hydrothorax. The limited experience with cord ligation procedures and balloon valvuloplasty suggests these relatively new procedures may serve a greater role in the future as techniques are improved.

By providing guidance for all of these procedures, real-time ultrasonography has revolutionized prenatal diagnosis and therapy; it will continue to be a crucial component in evaluating and treating complicated pregnancies.

References

[1] Fuchs F, Riis R. Antenatal sex determination. Nature 1956;177:330.
[2] CEMAT Group. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. Lancet 1998;351:242–7.
[3] Tabor A, Philip J, Madsen M, Bang J, Obel EB. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;1:1287–93.
[4] The NICHD National Registry for Amniocentesis Study Group. Midtrimester amniocentesis for prenatal diagnosis: safety and accuracy. JAMA 1976;236:1471–6.
[5] Simpson NE, Dallaire L, Miller JR, Siminovich L, Hamerton JL, Miller J, et al. Prenatal diagnosis of genetic disease in Canada: report of a collaborative study. Can Med Assoc J 1976;115:739–48.
[6] Borgida AF, Mills AA, Feldman DM, Rodis JF, Egan JF. Outcome of pregnancies complicated by ruptured membranes after genetic amniocentesis. Am J Obstet Gynecol 2000;183:937–9.
[7] Ghidini A, Lynch L, Hicks C, Alvarez M, Lockwood CJ. The risk of second-trimester amniocentesis in twin gestations: a case-control study. Am J Obstet Gynecol 1993;169:1013–6.
[8] Yukobowich E, Anteby EY, Cohen SM, Lavy Y, Granat M, Yagel S. Risk of fetal loss in twin pregnancies undergoing second trimester amniocentesis. Obstet Gynecol 2001;98:231–4.
[9] Antsaklis A, Papantoniou N, Xygakis A, Mesogitis S, Tzortzis E, Michalas S. Genetic amniocentesis in women 20–34 years old: associated risks. Prenat Diagn 2000;20:247–50.
[10] Nicolaides K, de Lourdes Brizot M, Patel F, Snijders R. Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks gestation. Lancet 1994;344:435–9.
[11] Sundberg K, Bang J, Smidt-Jensen S, Brocks V, Lundsteen C, Parrer J, et al. Ramdomised study of risk of fetal loss related to early amniocentesis versus chorionic villus sampling. Lancet 1997;350:697–703.
[12] Firth HV, Boyd PA, Chamberlain P, MacKenzie IZ, Lindenbaum RH, Huson SM. Severe limb abnormalities after chorionic villus sampling at 56–66 days' gestation. Lancet 1991;337:762–3.
[13] Kuliev A, Jackson L, Froster U, Brambati B, Simpson JL, Verlinsky Y, et al. Chorionic villus sampling safety. Report of World Health Organization/EURO meeting in association with the Seventh International Conference on Early Prenatal Diagnosis of Genetic Diseases. Tel Aviv, May 21, 1994. Am J Obstet Gynecol 1996;174:807–11.
[14] Jackson LG, Zachary JM, Fowler SE, Resnick RJ, Golbus MS, Ledbetter DH, et al. Randomized comparison of transcervical and transabdominal chorionic-villus sampling. The US

National Institute of Child Health and Human Development Chorionic-Villus Sampling and amniocentesis Study Group. N Engl J Med 1992;327:594–8.
[15] US NICHD Collaborative CVS Study Group. Transcervical and transabdominal chorionic villus sampling are comparable safe procedures for first trimester prenatal diagnosis: preliminary analysis. Am J Hum Genet 1990;47:A278.
[16] Lippman A, Tomkins DJ, Shime J, Hamerton JL. Canadian Collaborative CVS-Amniocentesis Clinical Trial Group: Canadian multicenter randomized clinical trial of chorionic villus sampling and amniocentesis: final report. Prenat Diagn 1992;12:385–408.
[17] Wapner RJ, Johnson A, Davis G, Urban A, Morgan P, Jackson L. Prenatal diagnosis in twin gestations: a comparison between second-trimester amniocentesis and first-trimester chorionic villus sampling. Obstet Gynecol 1993;82:49–56.
[18] Holzgreve W, Miny P, Schloo R. "Late CVS" international registry compilation of data from 24 centres. Prenat Diagn 1990;10:159–67.
[19] Daffos F, Capella-Pavlovsky M, Forestier F. A new procedure for fetal blood sampling in utero: preliminary results in fifty-three cases. Am J Obstet Gynecol 1983;146:985–7.
[20] Lam YH, Tang MH. Prenatal diagnosis of haemoglobin Bart's disease by cordocentesis at 12–14 weeks: experience with the first 59 cases. Prenat Diagn 2000;20:900–4.
[21] Ghidini A, Sepulveda W, Lockwood CJ, Romero R. Complications of fetal blood sampling. Am J Obstet Gynecol 1993;168:1339–44.
[22] Evans MI, Greb A, Kunkel LM, Sacks AJ, Johnson MP, Boehm C, et al. In utero fetal muscle biopsy for the diagnosis of Duchenne muscular dystrophy. Am J Obstet Gynecol 1991;165:728–32.
[23] Heckel S, Favre R, Flori J, Koenig M, Mandel J-L, Gasser B, et al. In utero fetal muscle biopsy: a precious aid for the prenatal diagnosis of Duchenne muscular dystrophy. Fetal Diagn Ther 1999;14:127–32.
[24] Wapner RJ, Jenkins TM, Silverman N, Kaufmann M, Hannau C, McCue P. Prenatal diagnosis of congenital nephrosis by in utero kidney biopsy. Prenat Diagn 2001;21:256–61.
[25] Bunduki V, Saldanha LB, Sadek L, Miguelez J, Miyadahira S, Zugaib M. Fetal renal biopsies in obstructive uropathy: feasibility and clinical correlations – preliminary results. Prenat Diagn 1998;18:101–9.
[26] Berghella V, Wapner RJ, Yang-Feng T, Mahoney MJ. Prenatal confirmation of true fetal trisomy 22 mosaicism by fetal skin biopsy following normal fetal blood sampling. Prenat Diagn 1998;18:384–9.
[27] Hogge WA, Golbus MS. Surgical management of fetal malformations. In: Evans MI, Fletcher JC, Dixler AO, Schulman JD, editors. Fetal diagnosis and therapy: science, ethics, and the law. Philadelphia: Lippincott Harper; 1989. p. 395–402.
[28] Antsaklis JI, Papantoniou NE, Mesogities SA, Koutra PT, Vintzileos AM, Aravantinos DI. Cardiocentesis: an alternative method of fetal blood sampling for the prenatal diagnosis of hemoglobinopathies. Obstet Gynecol 1992;79:630–3.
[29] Harman CR, Bowman JM, Manning FA, Menticoglou SM. Intrauterine transfusion – intraperitoneal versus intravascular approach: a case-control comparison. Am J Obstet Gynecol 1990;162:1053–9.
[30] Rodis JF, Borgida AF, Wilson M, Egan JF, Leo MV, Odibo AO, et al. Management of parvovirus infection in pregnancy and outcomes of hydrops: a survey of members of the Society of Perinatal Obstetricians. Am J Obstet Gynecol 1998;179:985–8.
[31] Tanawattanacharoen S, Taylor MJ, Letsky EA, Cox PM, Cowan FM, Fisk NM. Intrauterine rescue transfusion in monochorionic multiple pregnancies with recent single intrauterine death. Prenat Diagn 2001;21:274–8.
[32] Bussel JB, Berkowitz RL, Lynch L, Lesser ML, Paidas MJ, Huang CL, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol 1996;174:1414–23.
[33] Paidas MJ, Berkowitz RL, Lynch L, Lockwood CJ, Lapinski R, McFarland J, et al. Allo-

immune thrombocytopenia: fetal and neonatal losses related to cordocentesis. Am J Obstet Gynecol 1995;172:475–9.
[34] Irons MB, Nores J, Stewart TL, Craigo SD, Bianchi DW, D'Alton ME, et al. Antenatal therapy of Smith-Lemli-Opitz syndrome. Fetal Diagn Ther 1999;14:133–7.
[35] Mari G, Roberts A, Detti L, Kovanci E, Stefos T, Bahado-Singh RO, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. Am J Obstet Gynecol 2001;185:708–15.
[36] Elliott JP, Sawyer AT, Radin TG, Strong RE. Large-volume therapeutic amniocentesis in the treatment of hydramnios. Obstet Gynecol 1994;84:1025–7.
[37] Saade GR, Olson G, Belfort MA, Moise KJ. Amniotomy: a new approach to the "stuck twin" syndrome. Am J Obstet Gynecol 1995;172:429.
[38] Cook TL, O'Shaughnessy R. Iatrogenic creation of monoamniotic twin gestation in severe twin/twin transfusion syndrome. J Ultrasound Med 1997;16:853–5.
[39] Berkowitz RL, Lynch L, Chitkara U, Wilkins IA, Mehalek KE, Alvarez E. Selective reduction of multifetal pregnancies in the first trimester. N Engl J Med 1988;318:1043–7.
[40] Evans MI, Fletcher JC, Zador IE, Newton BW, Quigg MH, Struyk CD. Selective first trimester termination in octuplet and quadruplet pregnancies: clinical and ethical issues. Obstet Gynecol 1988;71:289–96.
[41] Berkowitz RL, Lynch L. Selective reduction; an unfortunate misnomer. Obstet Gynecol 1990;75:873–4.
[42] Lynch L, Berkowitz RL, Chitkara U, Alvarez M. First-trimester transabdominal multifetal pregnancy reduction: a report of 85 cases. Obstet Gynecol 1990;75:735–8.
[43] Stone J, Eddleman K, Lynch L, Berkowitz RL. A single center experience with 1000 consecutive cases of multifetal pregnancy reduction. Am J Obstet 2002;187:1163–7.
[44] Melgar CA, Rosenfeld DL, Rawlinson K, Greenberg M. Perinatal outcome after multifetal reduction to twins compared with nonreduced multiple gestations. Obstet Gynecol 1991;78:763–7.
[45] Stephen JA, Timor-Tritsch IE, Lerner JP, Monteagudo A, Alonso CM. Amniocentesis after multifetal pregnancy reduction: is it safe? Am J Obstet Gynecol 2000;182:962–5.
[46] Souter I, Goodwin TM. Decision making in multifetal pregnancy reduction for triplets. Am J Perinatol 1998;15:63–71.
[47] Aberg F, Mitelman F, Cantz M, Gehler J. Cardiac puncture of fetus with Hurler's disease avoiding abortion of unaffected co-twin. Lancet 1978;2:990–1.
[48] Antsaklis A, Politis J, Karagiannopoulos C, Kaskarelis D, Karababa P, Panourgias J, et al. Selective survival of only the healthy fetus following prenatal diagnosis of thalassaemia major in binovular twin gestation. Prenat Diagn 1984;4:289–96.
[49] Kerenyi TD, Chitkara U. Selective birth in twin pregnancy with discordancy for Down's syndrome. N Engl J Med 1981;304:1525–7.
[50] Eddleman KA, Stone JL, Lynch L, Berkowitz RL. Selective termination of anomalous fetuses in multifetal pregnancies: two hundred cases at a single center. Am J Obstet Gynecol 2002;187:1168–72.
[51] Evans MI, Goldberg JD, Horenstein J, Wapner RJ, Ayoub MA, Stone J, et al. Selective termination for structural, chromosomal, and mendelian anomalies: international experience. Am J Obstet Gynecol 1999;181:893–7.
[52] Kaufman GE, D'Alton ME, Crombleholme TM. Decompression of fetal axillary lymphangioma to prevent dystocia. Fetal Diagn Ther 1996;11:218–20.
[53] Chen CP, Jan SW, Lie FF, Sheu JC, Huang SH. Echo-guided lymphatic drainage by fine-needle aspiration in persistent isolated septated fetal nuchal cystic hygroma. Fetal Diagn Ther 1996;11:150–3.
[54] Johnson MP, Corsi P, Bradfield W, Hume RF, Smith C, Flake AW, et al. Sequential urinalysis improves evaluation of fetal renal function in obstructive uropathy. Am J Obstet Gynecol 1995;173:59–65.
[55] Crombleholme TM, Harrison MR, Golbus MS, Longaker MT, Langer JC, Callen PW, et al. Fetal

intervention in obstructive uropathy: prognostic indicators and efficacy of intervention. Am J Obstet Gynecol 1990;162:1239–44.
[56] Aubard Y, Derouineau I, Aubard V, Chalifour V, Preux PM. Primary fetal hydrothorax: a literature review and proposed antenatal clinical strategy. Fetal Diagn Ther 1998;13:325–33.
[57] Nicolini U, Poblete A, Boshetto C, Bonati F, Robers A. Complicated monochorionic twin pregnancies: experience with bipolar cord coagulation. Am J Obstet Gynecol 2001;185:703–7.
[58] Tulzer G, Arzt W, Franklin RC, Loughna PV, Mair R, Gardiner HM. Fetal pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. Lancet 2000;360:1567–8.
[59] Kohl T, Sharland G, Allan LD, Gembruch U, Chaoui R, Lopes LM, et al. World experience of percutaneous ultrasound-guided balloon valvuloplasty in human fetuses with severe aortic valve obstruction. Am J Cardiol 2000;85:1230–3.

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Role of ultrasound in screening patients at risk for preterm delivery

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Preterm birth is the major clinical problem associated with perinatal mortality and serious neonatal morbidity and childhood disability in developed countries [1,2]. Preterm birth is associated with 75% of perinatal morbidity and mortality in infants without congenital anomalies [3]. Despite a concerned focus on interventions aimed at reducing preterm deliveries, the preterm birth rate in the United States has increased by 28% in the last two decades and was reported to be 12% in 2002 [4]. Coinciding with the rise in preterm birth is an increase in low–birth weight infants. The low–birth weight rate in 2002 was 7.8%, the highest reported rate in more than three decades [4].

It is likely that preterm labor may result from several different pathophysiologic processes [1–3,5]. If this is true, a single intervention may not be effective in all cases of preterm labor. It has been hypothesized that interventions that failed to reduce preterm birth did so because they were universally applied without consideration of the mechanism of initiation of preterm labor [1].

Multiple factors have been examined as possible predictors of preterm birth including maternal demographics; behaviors and psychosocial factors; current pregnancy complications; maternal nutritional status; biophysical characteristics, such as cervical length; maternal infections, such as bacterial vaginosis and periodontal disease; and various biochemical markers, such as cervicovaginal fetal fibronectin and salivary estriol [1,6]. This article describes the technique of ultrasound examination of the cervix and the normal and abnormal ultrasound appearance of the cervix. Also discussed is the use of ultrasound in women with

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prior second-trimester pregnancy loss, prior preterm delivery, and multiple gestations. Finally, the pros and cons of routine assessment of the cervix in low-risk women are presented.

Ultrasound examination of the cervix: technique

In the past, transabdominal ultrasound was commonly used for cervical evaluation because second- and third-trimester obstetric ultrasounds are most often performed transabdominally. This approach, however, seems to be least accurate and least reproducible when compared with other methods [7,8]. The pitfalls of transabdominal ultrasound to evaluate the cervix in pregnancy have been well described and include the effect of maternal habitus, position of the cervix, overdistention or underdistention of the maternal bladder, and the fetal presenting part, all of which may obscure visualization of the cervix (Fig. 1) [3,7,8].

Because transvaginal ultrasound avoids these pitfalls, it has become the preferred technique [3,7,8]. Transvaginal ultrasound has been shown to produce clear, reproducible visualization of the cervix with a high degree of standardization of measurements of cervical length [7]. Transvaginal ultrasound, however, does have some limitations [9]. A poorly developed lower uterine segment, polyps, or fibroids can obscure the internal os. Rapid cervical dilatation and funneling can also affect measurements adversely. Excessive pressure on the vaginal probe and failure to empty the maternal bladder are associated with falsely long measurements and should be avoided [9].

The technique of transvaginal ultrasound has previously been described in detail [10]. The patient should be instructed to empty her bladder before the examination. She should then be place in the dorsal lithotomy position. A high resolution (> 5 MHz) endovaginal probe protected by a lubricated sterile transducer cover should be used [10]. The vaginal probe may be inserted either by the

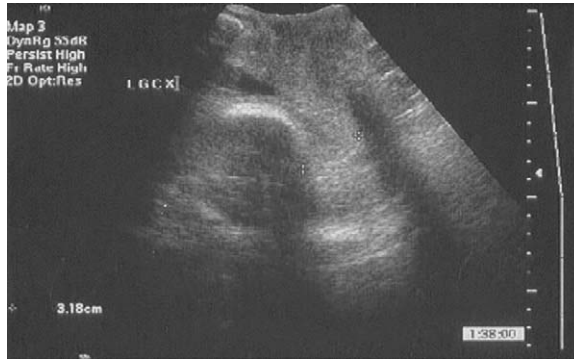

Fig. 1. Transabdominal view of the cervix. The fetal head precludes adequate visualization of the cervix. Visualization of the cervix with transabdominal ultrasound is technically more difficult than with transvaginal ultrasound.

patient with guidance, or by the ultrasonographer. Most endovaginal probes currently in use are modeled on a convex, switched array of active elements, creating a fan- or sector-shaped image [10]. Ideally, the area in view should include at least a 120-degree field of view, allowing the operator to visualize the required landmarks without excessive probe manipulation.

Identification of the bladder, amniotic fluid, and presenting part should be done first. The operator should look in the midline sagittal plane of the cervix and identify three landmarks: (1) the internal os, (2) endocervical canal, and (3) the external os. The internal os usually appears as a small notch or triangle at the interface between the amniotic cavity and the endocervical canal. It may be necessary to pull the probe back slightly and angle to get the best long axis of the cervical canal. Cervical stroma above the cervical canal should appear similar to that below the canal (Fig. 2).

Numerous components of the cervix have been measured, including the presence and size of a funnel at the internal os; the length of the closed or residual portion of the cervix; and the total (funnel length plus length of the closed portion). Researchers have recommended quantifying these cervical changes using a variety of measuring techniques, but the simplest and most reproducible measurement in sensitivity and predictive value seems to be the residual closed length of cervix [7,8,11,12]. The cervical length should be measured three times placing the calipers between the internal and external os (Fig. 3). The shortest length obtained from the best images should be recorded.

Zilianti et al [13] demonstrated effacement begins at the internal cervical os and proceeds caudad. They further described the appearance of cervical change as seen by transvaginal ultrasonography as a progression of the letters T, Y, V, and U to denote the relationship of the cervical canal to the lower uterine segment (Fig. 4). In conjunction with dilatation of the internal os, membranes and amniotic fluid invaginate into the proximal endocervical canal. This process is most commonly called funneling, although the terms ‘‘wedging’’ or ‘‘beaking’’ have

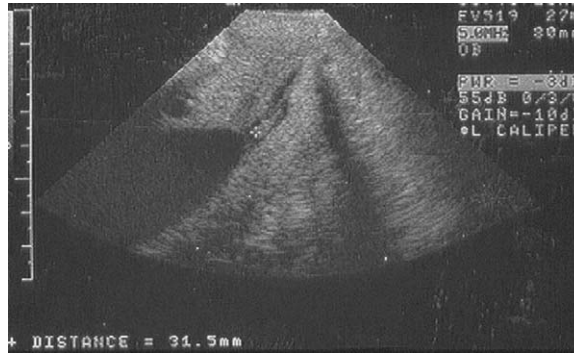

Fig. 2. Transvaginal view of the cervix. Note the normal appearance of cervical stroma above and below the cervical canal. The cervical length was 31.5 mm.

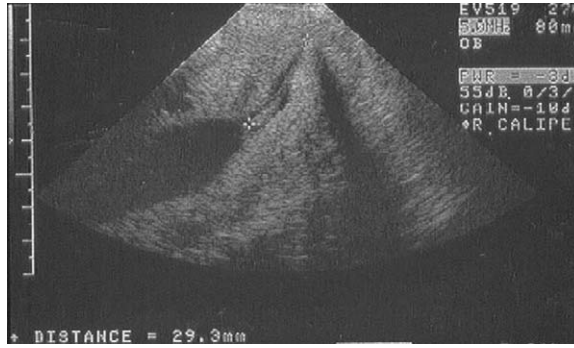

Fig. 3. Measurement of cervical length using transvaginal ultrasound. Once adequate visualization is achieved, calipers are placed at internal and external os of the cervix. Cervical length was 29.3 mm.

also been used (Fig. 5) [8]. With labor progression, in time, the entire endocervical canal becomes filled with fluid, and if the membranes remain intact, they may be visible bulging into the vagina. As part of an ultrasound examination of the cervix, any funneling or dilatation should be recorded. Funneling may appear daunting when viewed in real time; however, it should be remembered that it is a transient process. A false or pseudo funnel may occur when the lower uterine segment contracts to form a funnel above a cervix of normal length. This is of no clinical significance [3].

The use of a cervical stress test by applying transfundal pressure while scanning transvaginally or by examining the patient while she is standing has been

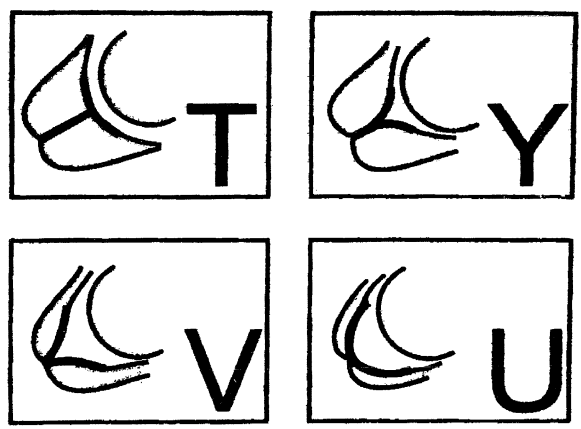

Fig. 4. Represents the progression of cervical dilatation as seen on transvaginal ultrasound and as described by Zilianti. The letters T, Y, V, and U denote the relationship of the cervical canal to the lower uterine segment. (*From* Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: a new perspective. J Ultrasound Med 1995;14:719–24; with permission.)

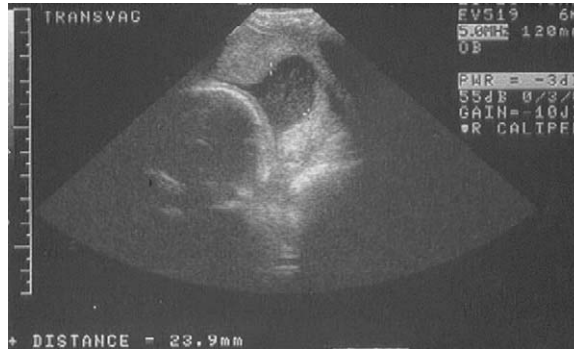

Fig. 5. Funneling or beaking of the cervix at the internal os. Beaking or funneling may be described as length of funnel, length of closed cervix remaining, or by the width of the funnel. The width of the funnel was 23.9 mm.

reported [8]. Performing such maneuvers may help identify women at risk; however, these are not recommended if the cervix can clearly be identified as dilated or short without cervical stress, because these maneuvers may aggravate the problem [8]. Otherwise, a stress test should be done by applying constant gentle fundal pressure for 15 seconds. The cervix should then be measured again and any further shortening or funneling should be recorded. It has been recommended that centers that plan to use transvaginal ultrasound should develop their own protocols because many sonographers have not been formally trained in this area [10].

Patient and examiner reticence to perform transvaginal ultrasound has led to examination using a translabial or transperineal approach. It has been shown, however, that false diagnosis of preterm cervical shortening may occur on a translabial scan if rectal gas obscures the external os [8] and transvaginal ultrasonographic examination has been shown to be superior and more reproducible than transperineal-translabial even when experienced endovaginal sonographers use contemporary ultrasonographic equipment [14,15].

Normal cervical length by ultrasound

Ultrasound measurement of the cervical canal in the second and early third trimester has been reported to range from 10 to 50 mm. Iams et al [11] measured cervical length at 24 and 28 weeks' gestation in nearly 3000 women not selected for risk of preterm delivery. At 24 weeks, mean cervical length in nulliparous women was 34 ± 7.8 mm and 36 ± 8.4 mm in parous women. At 28 weeks, the cervix shortened slightly to 32.6 ± 8.1 mm in nulliparous women and 34.5 ± 8.1 mm in parous women. The tenth percentile cervical length measurement at 24 weeks was found to be 25 mm and this increased the risk of preterm delivery

sixfold [11]. Although a cervical length measurement of 25 mm had only an 18% positive predictive value, this measurement has subsequently been used as a benchmark of short cervical length in the second trimester in many studies.

Cervical length as a predictor of cervical incompetence

The classic clinical presentation of cervical incompetence includes painless cervical dilatation resulting in second-trimester pregnancy loss. Many women, however, present with a history of second-trimester pregnancy loss preceded either by bleeding, slight cramping, or leaking of fluid that makes the diagnosis of cervical incompetence less clear. It has been suggested that cervical incompetence and preterm labor are not separate entities but part of a spectrum leading to preterm delivery and that cervical incompetence is not a categorical but rather a continuous variable [16].

Transvaginal ultrasound has been used as an adjunct to clinical examination and history to characterize women with cervical incompetence. The diagnosis of cervical incompetence with ultrasound has been challenging with differences reported by investigators [16]. Despite these differences, transvaginal ultrasound can play a useful role in detection of gross morphologic changes associated with this continuum. Three ultrasound signs have been cited as suggestive of cervical incompetence: (1) dilatation of the internal os; (2) sacculation or prolapse of the membranes into the cervix (with shortening of the functional cervical length) either spontaneously or induced by transfundal pressure; and (3) a short cervix in the absence of uterine contractions [17]. The diagnosis of cervical incompetence is rarely straightforward. In women with an atypical history (uterine cramps, abdominal pressure, bloody show, or watery discharge) of cervical incompetence, serial ultrasounds between 14 and 24 weeks have been recommended [18,19]. Criteria for diagnosis in women with atypical histories includes cervical length less than fifth to tenth percentile (20 to 25 mm) and funneling greater than 30% of total length of the cervix.

The evidence regarding cerclage placement, both the indications for and outcomes of, has been reported by many investigators and remains controversial [5,18,20–22]. Berghella et al [20] recently reported on the use of serial transvaginal sonograms in patients with a history of prior second-trimester loss. Based on their findings in 177 women with a prior history of second-trimester loss, they recommended serial transvaginal sonography of the cervix, with cerclage only if indicated by cervical length change to less than 25 mm, as a valuable alternative to a policy of uniform prophylactic cerclage. This protocol has been advocated by other authors [5,17,18,21,23–25]. In the authors' practice, they have found cervical length useful in patients with an atypical history of cervical incompetence. In these women, serial ultrasound (every 1 to 2 weeks) with cerclage placement if a short cervix is noted may be of benefit (Fig. 6).

Some authors recommend serial cervical ultrasounds for cervical length after cerclage placement (Fig. 7) [16,26,27]. Prophylactic cerclage has been associated

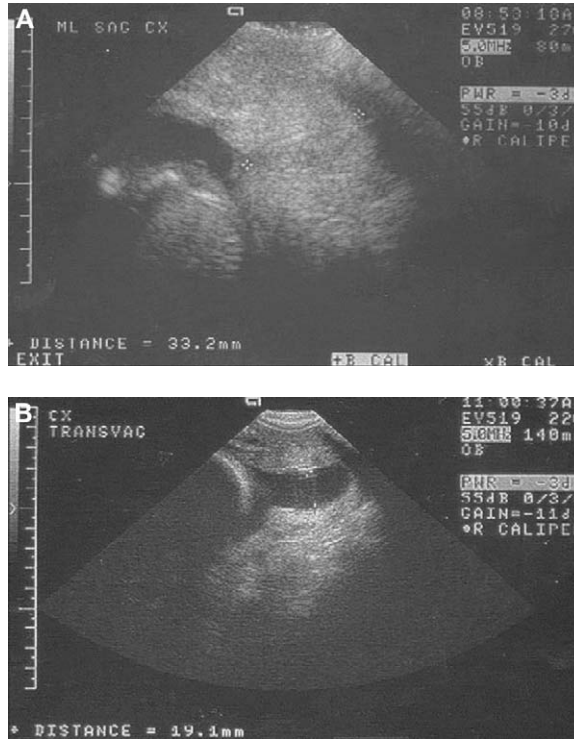

Fig. 6. This patient had an atypical history of late second trimester pregnancy loss associated with cramping. (*A*) At 16 weeks' gestation, a normal cervical length of 33.2 mm was recorded. Serial transvaginal ultrasounds were performed. (*B*) At 23 weeks' gestation, the patient experienced cramping. At that time, her cervix appeared shorter with funneling noted. The width of the funnel was 19.1 mm.

with an increase in cervical length (2.7 ± 0.9 mm to 3.6 ± 0.9 mm) [27]. This increase in cervical length is not predictive of a term delivery [26].

Cervical length as a predictor of preterm birth

Transvaginal ultrasonographic cervical measurement of less than 26 to 30 mm has been shown to be at least equivalent to Bishop scores in predicting term vaginal delivery [28,29]. It seems logical that transvaginal ultrasound cervical length may also be useful as a predictor for preterm labor. Cervical effacement in pregnancy has been demonstrated by ultrasound to begin at approximately 32 weeks for term births and as early as 16 to 24 weeks for preterm births. This process of change of the internal os often is well established before recognition of external os changes. Cervical effacement may occur slowly and often precedes clinically evident preterm labor. In symptomatic women with suspected preterm labor, a cervical length of less than 20 mm is not necessarily predictive of preterm

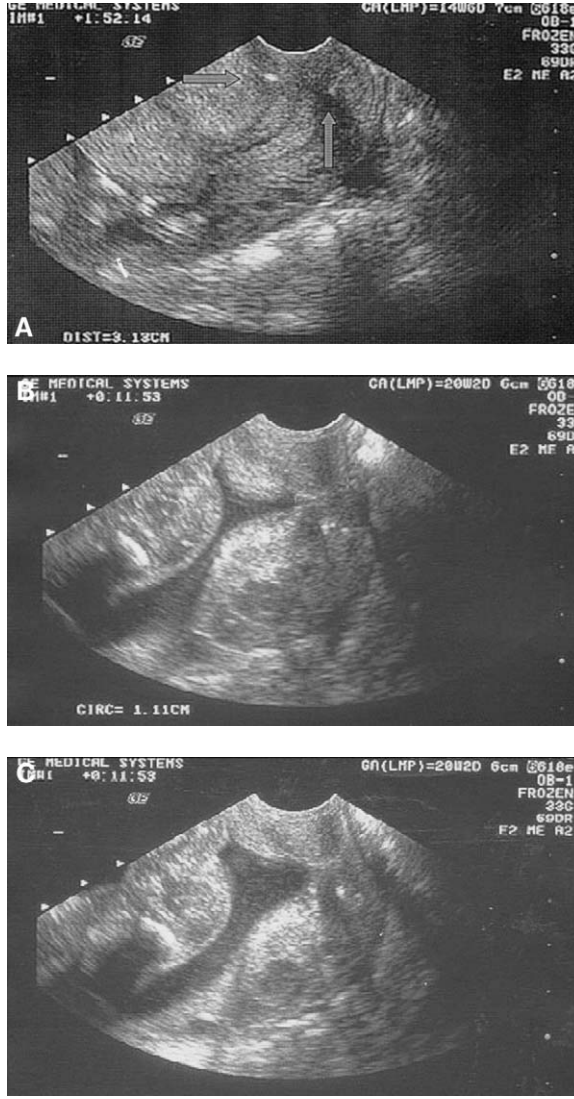

Fig. 7. This patient had a classic history of cervical incompetence in her first pregnancy. In her second pregnancy, a cerclage was placed at 14 weeks' gestation. (*A*) The cerclage is visible (*arrows*) at 15 weeks' gestation and cervix measures 31.3 mm. She had weekly ultrasounds following cerclage placement. (*B*) At 20 weeks', the cervix had shortened to 11.1 mm. (*C*) Dynamic changes were noted with funneling.

birth, but a length of more than 30 mm can reliably exclude preterm labor [3,7,10,30–32].

Several investigators have attempted to use cervical length in asymptomatic women to predict preterm delivery. Conoscenti et al [33] prospectively followed 2469 women and found that cervical length at 13 to 15 weeks' gestation was not different in women who delivered preterm versus term. Similarly, Carvalho et al [34] prospectively studied 529 women at 11 to 14 weeks and again at 22 to 24 weeks. There was no difference in mean cervical length at 11 to 14 weeks in women who delivered preterm (40.6 mm) as compared with those who delivered at term (42.7 mm). Cervical length was significantly shorter, however, at 22 to 24 weeks in the group that went on to deliver preterm (26.7 versus 39.3 mm). Most recently, Berghella et al [35] followed high-risk women with serial ultrasound starting in the first trimester and noted that cervical length less than 25 mm rarely occurred before 14 weeks' gestation even in high-risk women who delivered preterm. They noted that the average gestational age at which a short cervix is detected is 18.7 ± 2.9 weeks' gestation. These studies suggest that the cervical length seems to shorten sometime after 15 weeks' gestation in women who subsequently deliver preterm.

Many studies have evaluated second-trimester assessment of cervical length as a predictor of preterm delivery. Goldenberg et al [36] conducted the Preterm Prediction Study with the Maternal Fetal Medicine Network from 1993 through 1996. In this study, they assessed over 3000 women for risk factors, biophysical characteristics, and biochemical tests that might be predictive of preterm delivery. Using a cervical length of 25 mm as the definition of a short cervix (measured at 24 to 30 weeks' gestation), positive fetal fibronectin was the strongest predictor of preterm birth (< 35 weeks' gestation), followed by short cervical length. Moreover, over the entire range of measurements, the shorter the cervix the greater was the risk of spontaneous preterm birth. Short cervical length, however, even when combined with positive fetal fibronectin, had a low positive predictive value of preterm delivery (18%) in this population at low-risk for preterm birth.

In contrast, the same group of investigators studied 183 women at high-risk for preterm birth because of a history of prior delivery less than 32 weeks' gestation [10]. These women had transvaginal ultrasound determination of cervical length at 16 to 18 weeks and every 2 weeks' thereafter until 24 weeks' gestation. Women with a cervical length less than 25 mm had a 4.5-fold increase in rate of delivery less than 35 weeks' gestation. This threshold had a sensitivity of 69%, a specificity of 80%, and a positive predictive value of 55%.

Berghella et al [30] demonstrated in 168 women at risk for preterm delivery, a cervix of less than 25 mm had a positive predictive value of 70% when detected between 14 and 18 weeks' gestation and a positive predictive value of 40%. A patient at high-risk for preterm delivery with a cervix of greater than 35 mm between 18 and 22 weeks' gestation had a markedly decreased risk of preterm delivery of only 4%.

Shi et al [32] reported on 154 normal single nulliparous pregnant women between 16 and 35 weeks. The mean cervical length by sonography of women

who delivered at term was 32 mm (± 6 mm), whereas the group of 11 women who delivered preterm had a mean cervical length measurement of 18 mm (± 6 mm). Furthermore, they reported a cutoff of 26 mm (2 standard deviations below the mean) had 100% sensitivity and 100% negative predictive value in their population.

Multiple other studies have been performed in both low- and high-risk populations using cervical length thresholds of 15 to 30 mm as a predictor of preterm delivery [37–39]. They have found that the higher the baseline risk for preterm delivery in the study population and the shorter cervical length used, the greater the positive predictive value. Interestingly, Pardo et al [40] recently reported cervical length in nonpregnant women with a history of preterm delivery. They compared 54 women who had a history of spontaneous preterm birth before 34 weeks with 104 women who had term deliveries. They found that mean cervical length at 12 weeks' postpartum was not statistically different in women who delivered preterm (36 ± 6 mm) as compared with those who delivered at term (38 ± 4 mm). They concluded that shortening of the cervix was most probably a reversible phenomenon that occurs during pregnancy and represents failure of the competence mechanism to adapt to pregnancy.

The current debate that remains unanswered is the role of therapeutic intervention in the presence of a short cervix on ultrasound in women at risk for preterm delivery, but without evidence of preterm labor. The intervention that has been most intensely debated is the placement of cervical cerclage in such patients. Several observational and randomized studies have shown no difference in the rate of preterm delivery or the gestational age at delivery following cerclage placement in women documented short cervix in the second trimester [5,30,41]. In contrast two small studies, one observational [42] and the second randomized [23], showed that in women with significant risk for second- or early third-trimester loss, therapeutic cerclage following documentation of a short cervix (< 30 mm [27] or < 25 mm [5]) resulted in lower rate of early preterm delivery and subsequently lower rate of neonatal morbidity. The National Institute of Child Health and Human Development (NICHD) Network is currently conducting a large multicenter randomized trial of serial cervical length assessment in women at risk for preterm delivery followed by randomization to cerclage placement or observation if cervical length is noted to be less than 25 mm. This study should help to answer the question about the role of therapeutic cerclage following ultrasound documentation of short cervix in women at risk for preterm birth.

The use of transvaginal ultrasound in multiple gestations

An increase in multiple gestations accounts for some of the recent rise in preterm birth rate and low–birth weight infants. Gardner et al [42] showed that although twins account for only 2.6% of births, they represent 12.2% of premature deliveries and 15.4% of neonatal deaths. Triplets account for 0.1% to 0.3% of deliveries, have a mean gestational age at delivery of 33 weeks, and

have a perinatal mortality rate of 20% [2,43]. Transvaginal ultrasound has been used as a tool to determine normal cervical length in multiple gestations and to predict the likelihood of preterm birth in these high-risk pregnancies.

The mean cervical length in twin gestations not in labor has been reported to be 40.6 ± 9.6 mm at 22 weeks' and 34.5 ± 10.7 mm at 27 weeks' with tenth and fifth percentiles of 20 mm and 15 mm, respectively [44]. Goldenberg et al [12] reported that using a 25-mm cutoff, a short cervix was found in 9% of singletons and 18% of twins at 24 weeks and in 14% of singletons and 33% of twins at 28 weeks. In 32 triplet pregnancies, mean cervical length was reported as 42 ± 5 mm at 10 weeks, 37 ± 8 mm at 20 weeks, 26 ± 10 mm at 25 weeks, and 21 ± 7 mm at 30 weeks [43]. It has been suggested that the cervix in triplet pregnancies has a more rapid decline in length with advanced gestational age than is found in twin pregnancies [43,45].

Although there are fewer studies in multiple gestations, data suggest that spontaneous preterm birth in twins is unlikely when the cervical length measures 35 mm or more at 18 to 24 weeks' gestation [12,46–49]. Several authors have demonstrated the use of cervical length as a predictive tool for preterm birth in multiples [12,46–49]. Yang et al [49] prospectively followed 65 twin pregnancies and found that 20% had a cervical length less than 30 mm in the second trimester; of these, 62% delivered less than 35 weeks. Ten percent had cervical funneling; of these, 70% delivered less than 32 weeks. Thirty-five percent had cervical length greater than 35 mm; of these, only 4% delivered less than 35 weeks. In another prospective study of 131 twins, a cervical length of less than 20 mm between 15 and 20 weeks correlated with an 80% rate of delivery at less than 32 weeks' gestation [47]. Vayssiere et al [44] conducted a prospective trial at 13 centers that evaluated 251 women at 22 weeks, 215 at 27 weeks, and 121 at both periods. They found that a cervical length of less than 25 mm predicted preterm birth before 32 weeks with a sensitivity of 100% and specificity of 84%. They noted that the negative predictive value seems to be most useful in daily clinical practice with a risk of delivery of 3.3% at less than 32 weeks if cervical length exceeds 30 mm.

Poggi et al [50] demonstrated in a case-control study of 58 women with triplets cervical length at 16 to 20 weeks was inversely correlated with the probability of preterm delivery less than 32 weeks. Finally, in another prospective study of 43 triplets, for the primary outcome of delivery before 33 weeks gestation, cervical length less than 25 mm had 50% sensitivity. This increased to only 33% sensitivity if cervical length was less than 15 mm at 22 weeks [45]. Because of the high rate of preterm delivery in triplets, it seems that no cervical length is predictive of term delivery [43].

Summary

The ultrasound assessment of the cervix has contributed to the understanding of the pathways to preterm birth [3]. Transvaginal ultrasound measurement of the

cervix provides an objective and noninvasive tool for the evaluation of cervical status. Despite widespread use of this procedure, standardization of measurement indications, technique, and interval between examinations has not been achieved. The American College of Radiology has recently recommended that the cervix and lower uterine segment be imaged as part of every obstetric ultrasound examination in the second trimester. These guidelines specifically suggest a search for a short cervix (less than 30 mm) or funneling [8]. The expert panel on women's imaging further recommended evaluating the cervix sonographically on both the initial examination and all follow-up examinations for twin gestations [51]. The American Institute of Ultrasound in Medicine guidelines indicate that evaluation of the uterus, including cervix, should be performed, but does not indicate specifically that the cervix should be measured [52]. In contrast, the American College of Obstetricians and Gynecologists, although recognizing that cervical length assessment may be helpful in predicting the risk of preterm delivery (particularly from a negative predictive value), does not recommend routine use of cervical length measurement because of the lack of proved treatment or intervention methods [53].

A review of the literature suggests that at the time of this writing the role of routine screening of low-risk women with cervical length assessment by ultrasound is not supported. In contrast, in women at risk for preterm delivery (eg, women with a prior history of preterm birth or women with multiple gestations) cervical length assessment may be useful for its negative predictive value. At present, however, there is no therapeutic intervention that has been proved to decrease the risk of preterm delivery in women with a documented cervix on ultrasound.

References

[1] Goldenberg RL, Iams JD, Mercer BM, Meis P, Moawad A, Das A, et al. What we have learned about the predictors of preterm birth. Semin Perinatol 2003;27:185–93.
[2] Lumley J. Defining the problem: the epidemiology of preterm birth. Br J Obstet Gynaecol 2003; 110:3–7.
[3] Iams JD. Prediction and early detection of preterm labor. Obstet Gynecol 2003;101:402–12.
[4] Hamilton BE, Martin JA, Sutton PD. Births: preliminary data for 2002. Natl Vital Stat Rep 2003; 51:1–20.
[5] Rust OA, Atlas RO, Reed J, Van Gaalen J, Balducci J. Revisiting the short cervix detected by transvaginal ultrasound in the second trimester: why cerclage therapy may not help. Am J Obstet Gynecol 2001;185:1098–105.
[6] Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol 1980;55:692–5.
[7] Leitich H, Brunbauer M, Kaider A, Egarter C, Husslein P. Cervical length and dilatation of the internal cervical os detected by vaginal ultrasonography as markers for preterm delivery: a systematic review. Am J Obstet Gynecol 1999;181:1465–72.
[8] Expert Panel on Women's Imaging/ Premature cervical dilatation. Reston, VA: American College of Radiology; 1999. Available at: http://www.acr.org/dyna/?id=appropriateness_criteria. Accessed August 23, 2003.

[9] Yost NP, Bloom SL, Twickler DM, Leveno KJ. Pitfalls in ultrasonic cervical length measurement for predicting preterm birth. Obstet Gynecol 1999;93:510–6.
[10] Owen J, Iams JD. What we have learned about cervical ultrasound. Semin Perinatol 2003;27: 194–203.
[11] Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334:567–72.
[12] Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. Am J Obstet Gynecol 1996;175:1047–53.
[13] Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: a new perspective. J Ultrasound Med 1995;14: 719–24.
[14] Owen J, Neely C, Northen A. Transperineal versus endovaginal ultrasonographic examination of the cervix in the midtrimester: a blinded comparison. Am J Obstet Gynecol 1999;181: 780–3.
[15] Carr DB, Smith K, Parsons L, Chansky K, Shields LE. Ultrasonography for cervical length measurement: agreement between transvaginal and translabial techniques. Obstet Gynecol 2000; 96:554–8.
[16] Althuisius SM, Dekker GA, van Geijn HP. Cervical incompetence: a reappraisal of an obstetric controversy. Obstet Gynecol Surv 2002;57:377–87.
[17] Rozenberg P, Gillet A, Ville Y. Transvaginal sonographic examination of the cervix in asymptomatic pregnant women: review of the literature. Ultrasound Obstet Gynecol 2002;19:302–11.
[18] Guzman ER, Forster JK, Vintzileos AM, Ananth CV, Walters C, Gipson K. pregnancy outcomes in women treated with elective versus ultrasound-indicated cervical cerclage. Ultrasound Obstet Gynecol 1998;12:323–7.
[19] Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: a new perspective. J Ultrasound Med 1995;14:719–24.
[20] Berghella V, Haas S, Chervoneva I, Hyslop T. Patients with prior second-trimester loss: Prophylactic cerclage or serial transvaginal sonograms? Am J Obstet Gynecol 2002;187: 747–51.
[21] Newman RB, Krombach RS, Myers MC, McGee DL. Effect of cerclage on obstetrical outcome in twin gestations with a shortened cervical length. Am J Obstet Gynecol 2002;186:634–40.
[22] Owen J, Iams JD, Hauth JC. Vaginal sonography and cervical incompetence. Am J Obstet Gynecol 2003;188:586–96.
[23] Althuisius SM, Dekker GA, Hummel P, Bekedam DJ, van Geijn HP. Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone. Am J Obstet Gynecol 2001;185:1106–12.
[24] To MS, Palaniappan V, Skentou C, Gibb D, Nicolaides KH. Elective cerclage vs. ultrasound-indicated cerclage in high-risk pregnancies. Ultrasound Obstet Gynecol 2002;19:475–7.
[25] Odibo AO, Talucci M, Berghella V. Prediction of preterm premature rupture of membranes by transvaginal ultrasound features and risk factors in a high-risk population. Ultrasound Obstet Gynecol 2002;20:245–51.
[26] Dijkstra K, Funai EF, O'Neill L, Rebarber A, Paidas MJ, Young BK. Change in cervical length after cerclage as a predictor of preterm delivery. Obstet Gynecol 2000;96:346–50.
[27] Funai EF, Paidas MJ, Rebarber A, O'Neill L, Rosen TJ, Young BK. Change in cervical length after prophylactic cerclage. Obstet Gynecol 1999;94:117–9.
[28] Ware V, Raynor BD. Transvaginal ultrasonographic cervical measurement as a predictor of successful labor induction. Am J Obstet Gynecol 2000;182:1030–2.
[29] Rozenberg P, Goffinet F, Hessabi M. Comparison of the Bishop score, ultrasonographically measured cervical length, and fetal fibronectin assay in predicting time until delivery and type of delivery at term. Am J Obstet Gynecol 2000;182:108–13.
[30] Berghella V, Daly SF, Tolosa JE, DiVito MM, Chalmers R, Garg N, et al. Prediction of preterm delivery with transvaginal ultrasonography of the cervix in patients with high-risk pregnancies: does cerclage prevent prematurity? Am J Obstet Gynecol 1999;181:809–15.

[31] Goffinet F, Kayem G. Diagnosis and prognosis of preterm labor: physical examination and ultrasonography. J Gynecol Obstet Biol Reprod 2002;31:5S22–34.
[32] Shi CY, Zhang YY, Jin YZ, Dong Y. Study of the cervix of normal pregnancy and threatened preterm delivery using transvaginal sonography. Zhonghua Fu Chan Ke Za Zhi 2003;38:264–6.
[33] Conoscenti G, Meir YJ, D'Ottavio G, Rustico MA, Pinzano R, Fisher-Tamaro L, et al. Does cervical length at 13–15 weeks' gestation predict preterm delivery in an unselected population? Ultrasound Obstet Gynecol 2003;21:128–34.
[34] Carvalho MH, Bittar RE, Brizot ML, Maganha PP, Borges da Fonsec Zugaib M. Cervical length at 11–14 weeks' and 22–24 weeks' gestation evaluated by transvaginal sonography, and gestational age at delivery. Ultrasound Obstet Gynecol 2003;21:135–9.
[35] Berghella V, Talucci M, Desai A. Does transvaginal sonographic measurement of cervical length before 14 weeks predict preterm delivery in high-risk pregnancies? Ultrasound Obstet Gynecol 2003;21:140–4.
[36] Goldenberg RL, Iams JD, Das A, Mercer BM, Meis PJ, Moawad AH, et al. The preterm prediction study: sequential cervical length and fetal fibronectin testing for the prediction of spontaneous preterm birth. Am J Obstet Gynecol 2000;182:636–43.
[37] Hibbard JU, Tart M, Moawad AF. Cervical length at 16–22 weeks' gestation and risk for preterm delivery. Obstet Gynecol 2000;96:972–8.
[38] Andrews WW, Copper R, Hauth JC, Goldenberg RL, Neely C, Dubard M. Second-trimester cervical ultrasound: associations with increased risk for recurrent early spontaneous delivery. Obstet Gynecol 2000;95:222–6.
[39] Hassan SS, Romero R, Berry SM, Dang K, Blackwell SC, Treadwell MC, et al. Patients with an ultrasonographic cervical length $\leq$ 15mm have nearly a 50% risk of early spontaneous preterm delivery. Am J Obstet Gynecol 2000;182:1458–67.
[40] Pardo J, Yogev Y, Ben-Haroush A, Peled Y, Kaplan B, Hod M. Cervical length evaluation by transvaginal sonography in nongravid women with a history of preterm delivery. Ultrasound Obstet Gynecol 2003;21:464–6.
[41] Hassan SS, Romero R, Maymon E, Berry SM, Blackwell SC, Treadwell MC, et al. Does cervical cerclage prevent preterm delivery in patients with a short cervix? Am J Obstet Gynecol 2001;184:1325–31.
[42] Gardner MO, Goldenberg RL, Cliver SP, Tucker JM, Nelson KG, Copper RL. The origin and outcome of twin pregnancies. Obstet Gynecol 1995;85:553–7.
[43] Ramin KD, Ogburn Jr PL, Mulholland TA, Breckle RJ, Ramsey PS. Ultrasonographic assessment of cervical length in triplet pregnancies. Am J Obstet Gynecol 1999;180:1442–5.
[44] Vayssiere C, Favre R, Audibert F, Chauvet MP, Gaucherand P, Tardiff D, et al. Cervical length and funneling at 22 and 27 weeks to predict spontaneous birth before 32 weeks in twin pregnancies: a French prospective multicenter study. Am J Obstet Gynecol 2002;187:1596–604.
[45] To MS, Skentou C, Cicero S, Liao AW, Nicolaides KH. Cervical length at 23 weeks in triplets: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol 2000;16:515–8.
[46] Imseis HM, Albert TA, Iams JD. Identifying twin gestations at low risk for preterm birth with transvaginal ultrasonographic cervical measurement at 24 – 26 weeks. Am J Obstet Gynecol 1997;177:1149–55.
[47] Skentou C, Souka AP, To MS, Liao AW, Nicolaides KH. Prediction of preterm delivery in twins by cervical assessment at 23 weeks. Ultrasound Obstet Gynecol 2001;17:7–10.
[48] Kushnir O, Izquierdo LA, Smith JF, Blankstein J, Curet LB. Transvaginal sonographic measurement of cervical length: evaluation of twin pregnancies. J Reprod Med 1995;40:380–2.
[49] Yang JH, Kuhlman K, Daly S, Berghella V. Prediction of preterm birth by second trimester cervical sonography in twin pregnancies. Ultrasound Obstet Gynecol 2000;15:288–91.
[50] Poggi SH, Ghidini A, Landy HJ, Alvarez M, Pexxullo JC, Collea JV. Predictive value of transvaginal cervical length in triplet pregnancies for spontaneous preterm delivery at < or = 32 weeks. J Matern Fetal Neonatal Med 2002;12:46–9.
[51] Expert Panel on Women's Imaging/Evaluation of Multiple Gestations. Reston, VA: American

College of Radiology; 1996. Available at: http://www.acr.org/dyna/?id=appropriateness_criteria. Accessed August 23, 2003.

[52] American Institute of Ultrasound in Medicine Standard Practice Guideline. The antepartum obstetric ultrasound. 1994.

[53] American College of Obstetricians and Gynecologists Practice Bulletin. Assessment of risk factors for preterm birth, vol. 31. 2001.

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Multiple gestations: the importance of ultrasound

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On learning of a twin gestation, most parents are struck with joy and awe. The obstetrician, however, is faced with numerous management problems. Twin gestations accounted for 3% of all livebirths in the United States in 2001 and have increased rates of complications and morbidity [1]. Despite the risks, they generally result in a successful pregnancy for both the parents and physicians. This article highlights how ultrasound enhances the care of twin pregnancies. From the initial diagnosis of twins to its role in fetal therapy and in the delivery room, ultrasound has revolutionized the care of women carrying twins.

Multiple gestations have increased 1.3-fold in the United States over the past decade from 96,992 of 4,162,917 livebirths (1 of 43) in 1990 to 128,840 of 4,031,531 livebirths (1 of 31) in 2001 [1]. Fig. 1 shows the rates of twin and triplet live births in the United States from 1980 to 2001. Of interest is the decrease in the rate of triplets from 1998 to 2001 and a flattening of the increasing rate in twins over the same time frame [1]. Twins comprise 96% to 97% of all liveborn multiples. The focus here now turns to the use of ultrasound in the diagnosis of twins, its role of determining chorionicity, the management of unique twin complications, the value of cervical length determination in twins, the use of ultrasound in screening for aneuploidy in multiples, and the intrapartum role of ultrasound in twin gestations.

Etiology of twins

Twins can be classified into monozygotic and dizygotic depending on the number of fertilized eggs leading to conception. The general rate of monozygotic or identical twinning is constant across races, without considering assisted reproductive technologies, at about 1:250 pregnancies. Dizygotic twinning can

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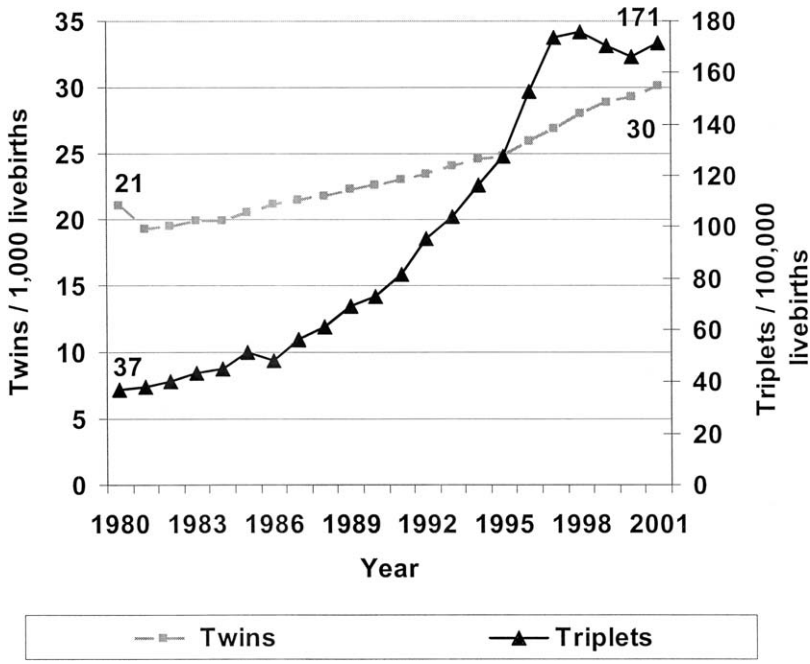

Fig. 1. Rates of twins and triplet livebirths in United States from 1980 to 2001. (*From* National Center for Health Statistics CD-ROM: 1990–1997 Natality Data Set, Series 21, Nos. 2–9, 11,12,14,15. Atlanta: Centers for Disease Control and Prevention; 1997–2001.)

vary greatly by race and has been increasing dramatically with the use of assisted reproductive technologies. With very rare exceptions, dizygotic twins are always dichorionic but monozygotic twins can have a variety of placentations depending on the timing of the twinning event [2].

Diagnosis of twins

Ultrasound is crucial for the diagnosis of twins. A clinical suspicion of multiple gestation should be raised when a patient has a larger than expected uterine size; her pregnancy-associated symptoms (eg, hyperemesis gravidarum) seem excessive; or in any patient using assisted reproductive technologies. Important sonographic details to note are the number of gestational sacs, the location of the placentas, the presence of a dividing membrane, amniotic fluid status, yolk sac, and fetal heart rate. This information is helpful at the time of diagnosis and may be crucial later in the pregnancy in counseling about potential complications.

In 1986, Landy et al [3] reported on 1000 first-trimester pregnancies with an incidence of twinning of just over 3%. They found about 20% of these twin gestations resulted in singleton livebirths with or without vaginal bleeding leading to the diagnosis of the "vanishing twin" phenomenon [3]. In a pro-

spective series of twins diagnosed with two fetal heartbeats, dichorionic twins diagnosed before 8 weeks were significantly more likely to result in a singleton pregnancy than those after 8 weeks [4]. The prognosis for singletons resulting from an early vanishing twin seems to be similar to other singletons. The sonographer may also encounter an ''appearing twin.'' Doubilet and Benson [5] have reported their experience with transvaginal ultrasound at 5 to 5.9 weeks gestation and concluded that 30 of 220 twins were thought to be singletons on initial evaluation. To describe this phenomenon, they coined the term ''appearing twin.'' They reported similar pregnancy outcomes for the ''appearing'' twin gestations. This information emphasizes the importance of a careful ultrasound examination in the early stages of pregnancy to diagnose twins correctly.

Placentation

Ultrasound is not always accurate in determining zygosity but is very useful in determining placentation, which is more important in predicting the prognosis for twin pregnancy complications [6]. The steps in determining placentation include determination of gender, visualization of placental mass, and characterization of the dividing membrane. If differing genders or two distinct placentas are noted, then a dichorionic placentation has occurred. If the same gender is present and there seems to be one placenta, the pregnancy may be dichorionic-diamniotic, monochorionic-diamniotic, monochorionic-monoamniotic, or monochorionic with conjoined twins. Several techniques can be helpful in determining chorionicity. A thin, wispy membrane, which is often difficult to visualize, may be indicative of monochorionic placentation. A thicker, more apparent, wavy membrane is more typical in dichorionic placentation. For practical purposes, the measurement of membrane thickness is not as useful for determining chorionicity as the appearance of the membrane at its insertion onto the chorionic plate or fetal surface of the placenta. If the placenta appears to fill the groove between the membranes at the insertion into the placenta, called the lambda or ''twin peak'' sign, then a fused dichorionic-diamniotic placentation is likely (Fig. 2) [7,8]. If the placentas are separate, the placenta is also dichorionic-diamniotic. Alternatively, if the insertion cleanly joins the chorionic plate of the placenta, the so-called ''T'' sign, then a monochorionic-diamniotic placentation is likely (Fig. 3). This systematic approach is very useful and accurately determines placentation about 90% of the time [9].

Monoamniotic twins

When the dividing membrane is not seen early in the ultrasound evaluation of a twin pregnancy, consideration should be given to the diagnosis of monochorionic-monoamniotic twins. They account for 1% of all monochorionic twins. The authors require that several examinations be performed to search for the

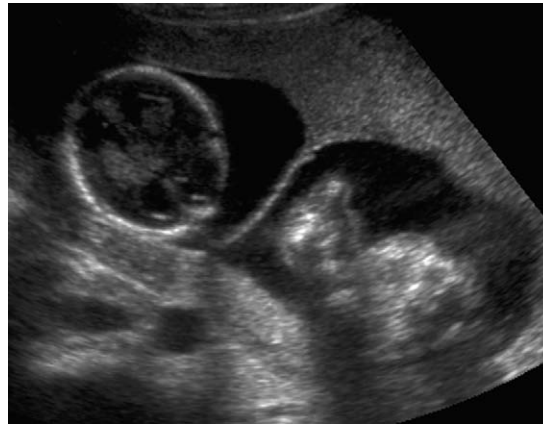

Fig. 2. Lambda sign indicates dichorionic, diamniotic placentation.

dividing membrane before making this diagnosis because the membranes may not initially be apparent by ultrasound. Distinguishing monoamniotic twins from a ''stuck'' twin can be difficult, but normal amniotic fluid volume and two free-floating twins with no visualized membrane separating them should clinch the diagnosis of monoamniotic twins. Color and two-dimensional ultrasound readily show the ever-present umbilical cord entanglement, which leads to the strikingly increased mortality for monoamniotic twins. Visualization of two cord insertions into the placenta within very close proximity to each other also is consistent with monoamniotic twins (Fig. 4). Rodis et al [10] suggested a management strategy for monoamniotic twins. This strategy includes (1) serial ultrasounds every 2 to 4 weeks to assess fetal growth, (2) corticosteroids to enhance fetal lung maturity

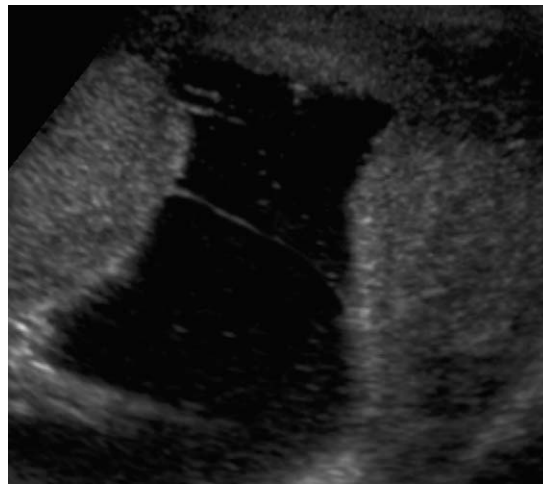

Fig. 3. T sign indicates monochorionic, diamniotic placentation.

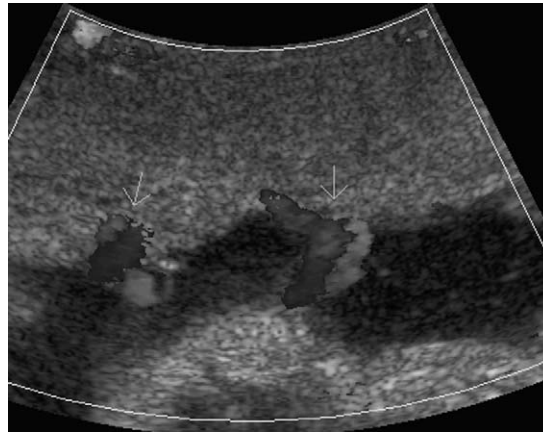

Fig. 4. Cord insertions in close proximity in a monoamniotic pregnancy using color Doppler.

at 24 to 26 weeks, (3) daily nonstress tests from 24 to 26 weeks gestation, (4) amniocentesis at 32 to 34 weeks gestation to assess fetal lung maturity, and (5) cesarean delivery when fetal lungs are mature by 35 weeks gestation. The authors have also found color-flow Doppler a useful adjunct in the care of monoamniotic twins (Fig. 5). Whenever monoamniotic twins are suspected, one should always rule out conjoined twins.

Conjoined twins

The rare phenomenon of conjoined twins occurs with monozygotic twinning when the embryo divides at 13 to 14 days from conception [11]. The two fetal poles may be attached at varying sites. The location of the sites provides the basis for the nomenclature describing conjoined twins. The most common conjoined twins are the omphalopagus or thoracopagus twins, which are joined at the abdomen or chest (Fig. 6). Ultrasound features include visualizing the twins in the same relative positions in all views, direct opposition of the twins from each other, or extreme extension of the fetal spine (Fig. 7). Numerous variations in the types of conjoined twins may occur and the prognosis for survival is gener-

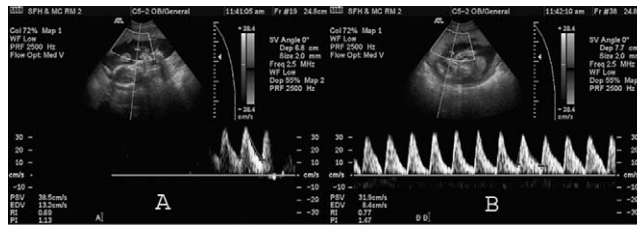

Fig. 5. Pulse-wave Doppler of the umbilical arteries in a monoamniotic twin pregnancy.

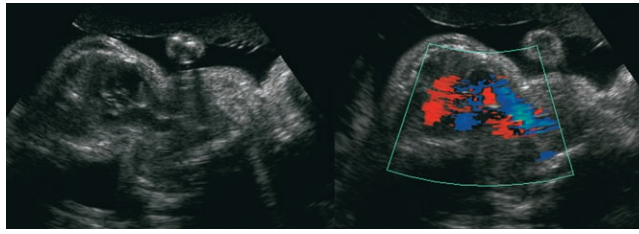

Fig. 6. Thoracopagus twins showing shared great vessels using gray-scale and color Doppler imaging.

ally poor. When conjoined twins are diagnosed there should be a systematic approach to define which major organs are present in each separate fetus, which are shared, and what vascular communications occur. These steps help determine the prognosis for postnatal separation.

Stuck twin

An ominous ultrasound finding is the "stuck" twin. This general diagnosis should not be equated with the twin-to-twin transfusion syndrome (TTTS), which is only one of the causes of a stuck twin. To make the diagnosis, careful evaluation looking for a dividing membrane is required. The fluid around the nonstuck twin may be normal, but is increased if TTTS is the etiology. The most informative areas around the fetus to look for the dividing membrane are near the fetal neck, chin, or limbs where a thin membrane may be seen bridging the

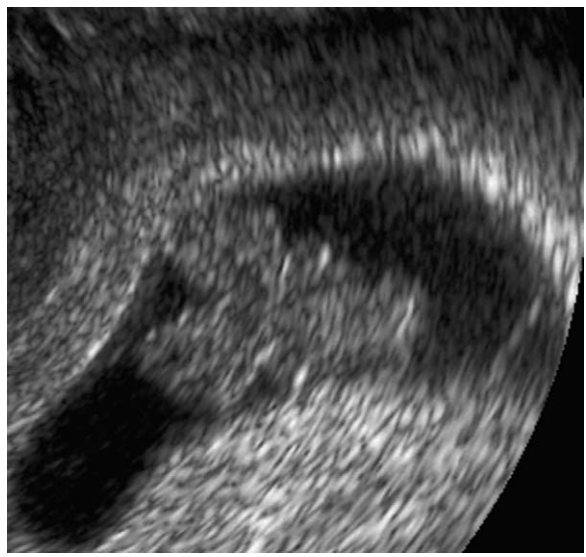

Fig. 7. Parapagus twins. Note two craniums with a single stalk.

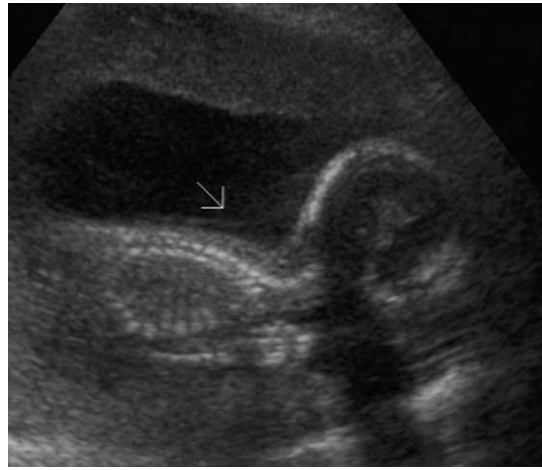

Fig. 8. Membrane reflecting off "stuck" twin.

gaps between fetal small parts (Fig. 8). The pregnant mother can be shifted from side to side to ensure that the stuck twin does not move in the amniotic cavity. When there is severe oligohydramnios around the stuck twin, an apparently adherent membrane is seen encasing the fetus, and the fetus does not move about within the uterine cavity, the diagnosis of a stuck twin is made (Fig. 9). The etiology must then be determined. A careful evaluation of the stuck twin may reveal anomalies consistent with oligohydramnios, such as renal agenesis or multicystic dysplastic kidneys. These may be difficult to determine with the oligo-

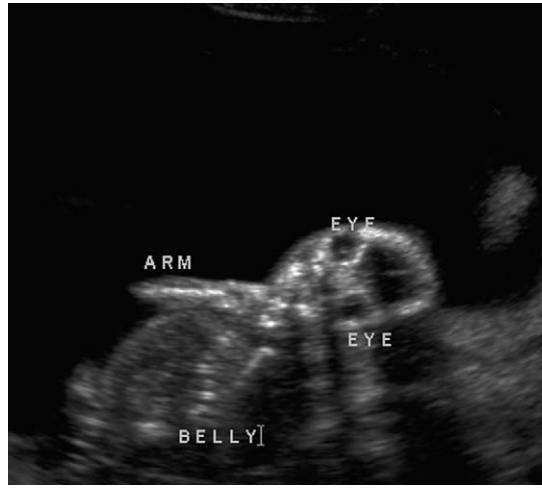

Fig. 9. "Stuck" twin. Note the position of the fetus stuck against the posterior wall of the uterus. This was present despite maternal position change.

hydramnios but a clue is normal, rather than increased, amniotic fluid around the nonstuck twin. An amnioinfusion around the stuck twin is often helpful to enable the sonographer to perform an adequate anatomic survey. The instilled fluid could also be aspirated for karyotype and infection studies.

Twin-to-twin transfusion syndrome

If the evaluation of the stuck twin has some or all of the following features, the diagnosis of TTTS must be considered: (1) monochorionic placentation, (2) same sex fetuses, (3) oligohydramnios around one twin and polyhydramnios around the other, (4) velamentous cord insertion, (5) an enlarged bladder in the recipient twin with polyhydramnios, (6) no bladder seen around the donor twin, or (7) size discrepancy with the recipient twin significantly larger than the donor. Ultrasound is uniquely helpful in establishing the diagnosis and determining the prognosis of TTTS. TTTS occurs in 10% to 20% of monochorionic pregnancies and results from an imbalance in the vascular communications, which are found in up to 80% of monochorionic placentas. The donor may be hypovolemic, anemic, growth restricted, and occasionally hypotensive. The recipient may be hypervolemic, plethoric, and polycythemic. The severity of TTTS varies, with milder forms occurring late in the second or third trimester. Quintero et al [12] defined severe TTTS as the presence of polyhydramnios (maximum vertical pocket of amniotic fluid of $\geq$ 8 cm) and oligohydramnios (maximum vertical pocket of amniotic fluid of $\leq$ 2 cm). They also used visualization of the bladder on the donor twin; the presence or absence of hydrops in either twin; and pulsed Doppler studies of the middle cerebral artery, umbilical artery, and umbilical vein. In stage I, the bladder of the donor twin is still visible, whereas in stage II, the bladder is not visualized but the Doppler studies are normal. By stage III there are Doppler abnormalities, in stage IV hydrops is present, and in stage V there is a demise of one or both twins [12]. This staging system does not seem to distinguish good from bad outcomes on initial evaluation. An increase in stage, however, carries with it a higher risk of earlier perinatal loss. Staging may be more useful in monitoring disease progression [13]. Untreated TTTS, which develops before 26 weeks, has a perinatal mortality rate of 90% [14].

A systematic approach is helpful in the management of TTTS. The authors suggest evaluating the maximum fluid pocket around the recipient twin, visualizing the fetal bladders, establishing growth curves for each, evaluating the cervical length, and performing pulse-wave Doppler of the umbilical arteries of each fetus (Fig. 10). If the amniotic fluid volume becomes excessive around the recipient, the cervical length shortens, or the Doppler interrogation reveals absent or reverse end-diastolic velocity, intervention should be considered (Fig. 11). Hydrops in either the donor or recipient fetus can occur and therapy at this point should be directed at optimizing the outcome for the nonhydropic fetus.

Several treatments exist for TTTS. These include serial amnioreductions of polyhydramnios around the recipient twin; laser ablation of the communicating

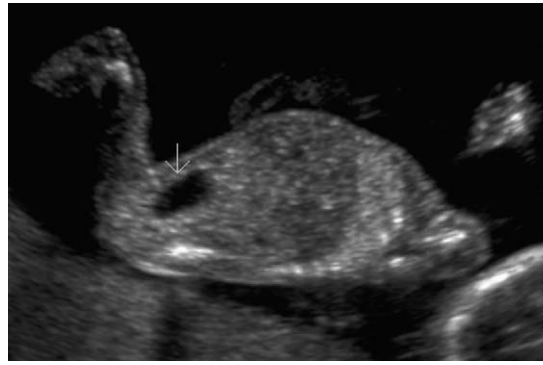

Fig. 10. Enlarged fetal bladder noted in a recipient twin in TTTS.

placental vessels; and cord ligation of one, usually the anomalous or hydropic fetus. Pregnancy termination can be considered in cases with very early onset and severe findings. If the patient is committed to full intervention, the risks and benefits of each therapy should be discussed. In cases with hydrops of one fetus, cord ligation may be considered. Sacrificing the hydropic fetus by cord ligation should prevent hypoperfusion of the surviving twin. When the blood pressure of the dying fetus collapses, the vascular communications between the twins allows the blood of the surviving twin to move down the pressure gradient to the dying twin. In this setting, a double fetal death or neurologic impairment of the survivor may occur. If one twin has a co-existing major anomaly, cord ligation has also been performed. If the goal is to maximize twin survival, the main therapies are therapeutic serial amnioreductions, amniotic membrane septostomy, or laser coagulation of the communicating placental vessels. Laser treatments require significant expertise, but may best treat the underlying pathophysiology by coagulating any communicating blood vessels between the two fetuses and thereby severing the recipient-donor relationship between the twins. Laser separation seems to have a slightly higher complica-

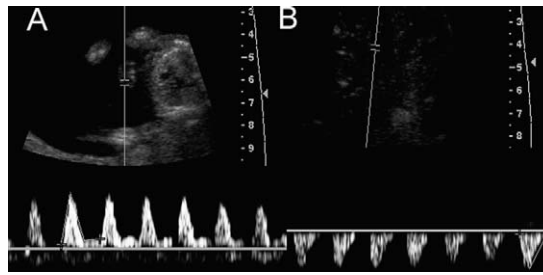

Fig. 11. Pulse-wave Doppler in a TTTS case with abnormal umbilical artery flow. (*A*) Normal umbilical artery Doppler flow in twin A. (*B*) Absent end diastolic flow in the umbilical artery of twin B.

tion rate in the short-term, but initial studies indicate there may be improved neurologic function in survivors [15].

Therapeutic amniocentesis can be performed rapidly for TTTS as a primary treatment or as a temporizing measure to allow transfer to a center for laser photocoagulation. Two useful methods have been described: the wall suction method described by Elliott et al [16] and the vacuum bottle method described by Dolinger and Donnenfeld [17]. Both are sufficient to remove the excessive amniotic fluid from the recipient twin's sac with polyhydramnios. The authors recommend using an 18- or 20-gauge spinal needle and placing the needle in the cavity away from the fundus of the uterus. By avoiding the fundus, the needle does not pull out of the amniotic cavity as the amniotic fluid volume is reduced and the size of the uterus shrinks. Removal of large quantities of amniotic fluid can be achieved safely [18]. A recommend end point is a maximum amniotic fluid depth around the recipient twin of 5 to 6 cm. Frequent assessment of fluid, fetal growth, and Doppler flow can be used to guide the timing of repeat procedures. In some cases, only one therapeutic amniocentesis is required, which led to the hypothesis of amnioseptostomy as a treatment for TTTS. By creating one or several holes in the dividing membrane, and allowing free flow of fluid between the sacs, equilibration of amniotic fluid in the two sacs may be therapeutic. Amnioinfusion of the oligohydramniotic sac may help better to identify, or tent, the dividing membrane facilitating the procedure. Randomized trials are underway to determine the best method of treatment for TTTS.

Acardiac twins

An unusual and rare form of TTTS is the acardiac twin. This probably forms from the rescue of a dying fetus by the perfusion from a healthy donor fetus. The acardiac twin may have some fetal features, such as limbs or bones, but there is no cardiac activity and major anomalies are the rule (Fig. 12). Often a vascular connection can be visualized to make the diagnosis and distinguish from an intrauterine fetal demise (Fig. 13). The acardiac twin may drain sufficient volume from the donor twin to cause hydrops. Cord ligation of the acardiac twin

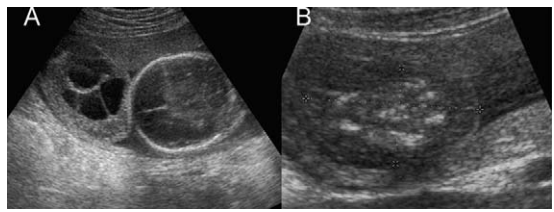

Fig. 12. Acardiac twin. (*A*) Normal-appearing cranium adjacent to the acardiac twin's cranium with the septae appearance of a cystic hygroma. (*B*) Skeletal and soft tissue components of the acardiac twin in (*A*).

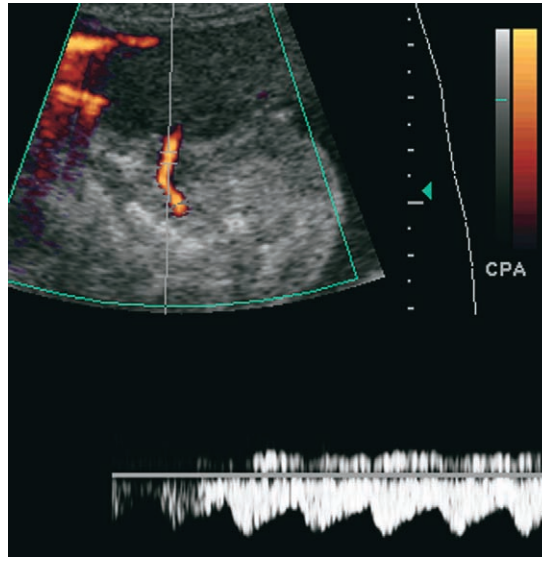

Fig. 13. Color and pulse Doppler imaging of an acardiac twin showing pulsatile flow from the donor twin.

can be considered, or expectant management, if the donor twin seems uncompromised [19].

Cervical length and spontaneous preterm birth

Twin gestations are at increased risk for preterm delivery. The mean age at delivery for liveborn twins in the United States has decreased from 35.8 weeks gestation in 1991 to 35.4 weeks gestation in 2001 [1]. The percent of twins delivering at less than 37 weeks has increased from 65% in 1991 to 74.5% in 2001 [1]. Cervical length has been used as a predictor of near-term and preterm delivery in twins. A normal cervical length generally predicts a near-term delivery. Imseis et al [20] found that a cervical length greater than 35 mm between 24 and 26 weeks gestation was associated with a low likelihood of delivery at less than 34 weeks gestation. A cervical length greater than 35 mm had 49% sensitivity, 94% specificity, and a 97% positive predictive value for a delivery greater than or equal to 34 weeks gestation. Several studies suggest that a short cervical length at 20 to 28 weeks of gestation places a twin gestation at significant risk of a preterm delivery. Souka et al [21] found that a cervical length measurement less than 25 mm at 23 weeks gestation was strongly correlated with a spontaneous preterm delivery. Goldenberg et al [22] compared cervical length with other predictors of preterm delivery. They used a cervical length of less than or equal to 25 mm at 24 weeks gestation and found that it was the better pre-

dictor of preterm delivery at less than or equal to 32, 35, and 37 weeks gestation than bacterial vaginosis, fetal fibronectin, and other risk factors. In the 147 sets of twins scanned at 24 and 28 weeks gestation, the authors found that if the cervical length was less than or equal to 25 mm at 24 weeks, 26.9% delivered at less than or equal to 32 weeks gestation. If the cervical length was less than or equal to 25 mm at 28 weeks, however, 13.2% delivered at less than 32 weeks gestation. Guzman et al [23] looked at a cervical length of less than or equal to 20 mm between 15 and 24 weeks gestation and between 25 and 28 weeks gestation. If the cervical length was less than or equal to 20 mm between 15 and 24 weeks gestation, there was a 50% delivery rate at less than 32 weeks gestation. If the cervical length between 25 and 28 weeks was less than or equal to 20 mm, the rate of delivery at less than 32 weeks gestation was 16.1%.

Newman et al [24] investigated the impact of cervical cerclage on the obstetric outcome of twin gestations with a shortened cervical length. They prospectively followed 147 consecutive twin mothers who underwent transvaginal ultrasonographic cervical length measurement between 18 and 26 weeks gestation. Those with cervical lengths less than or equal to 25 mm were offered a cervical cerclage. Twenty-one of 128 twin gestations underwent cerclage for a cervical length of less than or equal to 25 mm. The risk of preterm delivery increased with decreasing cervical length. When the twin gestations were stratified into cervical length quartiles, however, midtrimester cerclage did not alter the risks of preterm delivery in twin gestations.

Aneuploidy screening in twin gestations

Advancing maternal age is a known risk factor for autosomal trisomies, the most common of which is Down syndrome. The average age of a woman delivering twins in the United States has increased from 27.8 years old in 1991 to 29.3 in 2001 [1]. The percent of all mothers 35 or more (advanced maternal age) giving birth has increased from 8.9% in 1990 to 13.6% in 2001. Of all women delivering multiple gestations, the percentage of women 35 or more has increased from 11.4% in 1990 to 21% in 2001 [1]. Advances in reproductive technology have also played a major role in the increase in multiple gestations in the United States. Women using assisted reproductive technology are also more likely to be older and in their later reproductive years.

The risk of Down syndrome in a twin gestation is different from the age-specific risk of a singleton gestation. The precise difference, however, is difficult to determine. Rodis et al [25] calculated a theoretical maternal age-specific risk for Down syndrome in twin pregnancies. They assumed that the probability of Down syndrome was independent among the twins. They stated that a risk of one, or the other, or both twins being affected was approximately 80% higher than the singleton maternal age-specific risk. This risk was comparable with the singleton risk of a woman 2 or 3 years older. Meyers et al [26] used a similar model but corrected for maternal race and zygosity. They concluded that the twin

risk per pregnancy approximated that of the singleton risk for a mother 3 or 4 years older.

Wald [27], however, found a lower risk of Down syndrome in liveborn twins than the Rodis et al [25] or Meyers et al [26] studies. In a meta-analysis of four cohort studies of 64 Down syndrome twins, the livebirth prevalence of Down syndrome among twins was only 18% higher than singletons. They concluded that the risk for a twin pregnancy resulting in a liveborn with Down syndrome does not differ significantly from that of a singleton gestation. Doyle [28] in a study of 106 twin Down syndrome livebirths found the prevalence only 3% higher than singletons. This discrepancy between the estimated and the observed liveborn twins may be explained by the higher intrauterine lethality for Down syndrome–affected twins. The prevalence of Down syndrome is proportionately higher in the late first and second trimester than at birth.

Antenatal screening for Down syndrome in a twin gestation uses the same tools generally applied to singletons, such as maternal age, serum screening, and ultrasound. An antenatal diagnosis may be made by either chorionic villous sampling or amniocentesis. Both the screening and the diagnosis are complicated by the fact that the fetuses may be discordant for abnormal ultrasound findings, and for aneuploidy, and that an invasive test, or therapies, may place both fetuses at risk.

Using livebirth data to assess Down syndrome risk in the second trimester requires a correction for fetal loss in both affected and unaffected pregnancies. Sebire et al [6] demonstrated that the loss rate for twins from the second trimester to term varied by chorionicity. In dichorionic twins, 2.3% are lost from 16 weeks to term, whereas the loss rate for monochorionic twins from 16 weeks to term was 13.3%. Of all twin liveborns in the United States, approximately 75% are dichorionic and 25% monochorionic. Unaffected singletons have a loss rate of 1.46% from the midtrimester to term [29]. Singleton Down syndrome fetuses have an in utero loss from 16 weeks to term of 15.7%. Estimates of loss from the second trimester to term for Down syndrome twins are not available. The authors used birth certificate data to determine the ratio of reported to estimated number of Down syndrome fetuses in singleton and multiple gestations. The authors then calculated the contribution of multiples to the livebirth prevalence of Down syndrome, assuming no antenatal intervention. Using these estimates and the

Table 1
Contribution of multiple gestations to Down syndrome livebirth prevalence

Year	Total livebirths	Total Down syndrome	Down syndrome from multiple gestations	% Down syndrome from multiple gestations
1990	4,158,212	5900	152	2.6
1995	3,899,589	6292	174	2.8
1996	3,891,494	6498	231	3.6
1997	3,880,894	6629	271	4.1
1998	3,945,192	6850	294	4.3
1999	3,963,465	6955	315	4.5
2000	4,063,823	7264	334	4.6

maternal age-specific risks for singletons, the authors estimated the livebirth Down syndrome prevalence in 1990 and yearly from 1995 to 2000 (Table 1). This represents a 1.8-fold increase in the contribution of multiples to Down syndrome livebirths from 2.6% in 1990 to 4.6% by the year 2000.

The increased prevalence of Down syndrome fetuses in multiples brings with it many questions regarding Down syndrome screening. The lack of consensus on age-related risks has already been discussed. Maternal serum tests must use different norms, which factor in the contribution of both fetuses. Ultrasound screening implies that both fetuses can be imaged and that structural abnormalities in twins carry with them similar implications for Down syndrome and other aneuploidies. Testing for Down syndrome in the first trimester is performed using serum screening with pregnancy-associated plasma protein A (PAPP-A) and free beta of human chorionic gonadotropin (hCG). Spencer [30] found that the PAPP-A in twins was 1.86 multiples of the median (MoM) greater than in singletons and the free beta was 2.099 MoM. Screening is also being done using ultrasound to assess nuchal translucency. Measurements of nuchal translucency in normal and Down syndrome fetuses are approximately the same in both singletons and twins. Maymon et al [31] reported that the mean nuchal translucency in singletons was 1.5 mm ± 0.5 and in twins was also 1.5 mm ± 0.17. There was no statistically significant difference. The mean MoM (± SD) of nuchal translucency for singletons was 0.9 (± 0.5), whereas in twins it was 0.9 (± 0.4), again with no statistically significant difference. Spencer [30] developed a theoretical first-trimester twin Down syndrome detection model using a fixed 5% false-positive rate. Nuchal translucency and maternal age detected 75.2% of both discordant (one twin positive and one twin negative) and concordant Down syndrome twins. Using free beta hCG, PAPP-A, and maternal age, there was a 51.5% detection rate if the twins were discordant for Down syndrome and 55.4% detection rate if they were concordant for Down syndrome. When age, serum screening, and ultrasound are combined in the first trimester (nuchal translucency, free beta hCG, PAPP-A, and maternal age), there is a 79.7% detection rate if the twins are discordant for Down syndrome and 81.3% detection rate if they are concordant for Down syndrome.

In the United States, most Down syndrome screening is done in the second trimester. A survey of maternal fetal medicine specialists in the United States in 2001 revealed that of the time they spent on antenatal diagnosis, 87.3% was devoted to second-trimester screening and 12.7% to first-trimester screening [32]. Second-trimester screening is also based on maternal age, the serum screen, and ultrasound, or some combination of the three. The second-trimester serum screen values are approximately twice the level of singleton norms. Wald et al [33] reported that the mean MoMs for twins were 2.23 for the maternal serum alpha-fetoprotein, 1.65 MoM for estriol, 2.01 MoM for hCG, and 1.99 MoM for inhibin-A. Neveux et al [34] calculated theoretical second-trimester serum screen values for Down syndrome twins. If one twin was affected, the maternal serum alpha-fetoprotein was 1.89 MoMs and if both were affected it was 1.62 MoMs. The estriol was 1.47 MoM if one twin was affected and 1.22 MoM if both were

affected, whereas the hCG was 3.26 MoM if one was affected and 4.51 MoM when both were affected. False-positive rates for second-trimester serum screening and amniocentesis rates in twins versus singletons were estimated by Maymon et al [31]. The false-positive rate for the triple test in twins was 15% compared with 6% in singletons and the amniocentesis rate was 18.3% in twins and 7.5% in singletons. The differences in both the false-positive and amniocentesis rates were statistically significant. A summary of the efficacy of antenatal Down syndrome screening in twins can be seen in Table 2.

A survey of 543 maternal fetal medicine specialists in the United States in 2000 found that 97.6% of them used the serum screen for antenatal diagnosis and 91.5% used ultrasound [32]. Those using ultrasound focused on anomalies in 83.4%, biometry in 77.9%, and the genetic sonogram in 77.9%. Of the markers identified, the most commonly used were major anomalies, cardiac abnormalities, nuchal fold thickness, short femur or humerus, echogenic bowel, ventriculomegaly, and pyelectasis. Markers used less than 50% of the time were echogenic intracardiac focus, choroids plexus cyst, two-vessel umbilical cord, clinodactyly, sandal gap, and a wide pelvic angle. When these markers are identified, the Down syndrome risk can be modified using likelihood ratios, which are the ratio of the incidence in the exposed over the incidence in the unexposed for each marker. This risk modification can be done when these markers are found as an isolated finding or in combination. Using maternal age and the genetic sonogram in singleton pregnancies, sensitivities for Down syndrome range from 80.5% to 91.2% with false-positives ranging from 4% to 14%. The extension of this methodology to twin gestations, although intuitively attractive, has not been critically evaluated.

Ghidini et al [35] reported on 101 twins who had an amniocentesis and 108 twins with no amniocentesis. The miscarriage rate for the twin gestations that had amniocentesis was 3.5% and without the amniocentesis 3.2%, demonstrating a slightly higher incidence of miscarriage in the group with the amniocentesis. If an abnormality is found in one twin, selective reduction is possible. Evans et al [36] reported on selective reduction in 345 twin pregnancies. The loss at less than 24 weeks was 7% and after 24 weeks was 0.9%. Overall, 12.4% of the twin pregnancies delivered between 25 and 32 weeks and 79.8% delivered at greater

Table 2
The efficacy of antenatal Down syndrome screening in twins

Test	Sens %	FPR %	LR
Maternal age $\geq$ 35: United States 2000 [1] 1st trimester	50.2	13.4	3.7
Maternal age, hCG, PAPP-A [30] 1st trimester	52	5	10.4
Maternal age, hCG, PAPP-A, NT [30] 2nd trimester	80.3	5	16.0
Maternal age, triple screen [31]	53	5	10.6

FPR, false-positive rate; hCG, human chorionic gonadotropin; LR, likelihood ratio; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein A; Sens, sensitivity.

than 32 weeks. For triplets the loss rate was 12.8% before 24 weeks and for quadruplets it was 14.3% before 24 weeks.

Intrapartum use of ultrasound in twin gestations

Multiple gestations pose numerous problems in the delivery room. There is a higher incidence of prematurity, abnormal fetal lie, abnormal placentation, cord accidents, and retained placentas. Because of these potential complications, the authors believe that ultrasound is an essential component in the intrapartum management of twins. Estimation of fetal weight, fetal lie, and presentation are best accomplished by ultrasound in twin pregnancies. If the presenting fetus is in a transverse lie, ultrasound aids in the decision regarding the uterine incision. A transverse fetal lie with the back down is generally delivered through a vertical uterine incision. If the fetal lie and estimated weights support a decision for a vaginal birth, ultrasound is very helpful in visualizing the position of the second twin during the second stage. Ultrasound can ensure no cord or fetal arms are presenting. If the operator decides to perform a version of the second fetus the ultrasound is often useful during the procedure. Even when a breech extraction is planned, ultrasound can assist the clinician to identify correctly the fetal ankles aiding in the delivery process.

Summary

The use of ultrasound in the diagnosis of twins, its role of determining chorionicity, the management of unique twin complications, the value of cervical length determination in twins, the use of ultrasound in screening for aneuploidy in multiples, and the intrapartum role of ultrasound in twin gestations have been reviewed. The availability of high-resolution ultrasound has significantly improved the management of multiple gestations.

References

[1] National Center for Health Statistics CD-ROM: 1990–1997 Natality Data Set, Series 21, Nos. 2–9, 11,12,14,15. Atlanta: Centers for Disease Control and Prevention; 1997–2001.
[2] Souter VL, Kapur RP, Nyholt DR, Skoyerboe K, Myerson D, Ton CC, et al. A report of dizygous monochorionic twins. N Engl J Med 2003;349:154–8.
[3] Landy HJ, Weiner S, Corson SL, Batzer FR, Bolognese RJ. The "vanishing twin": ultrasonographic assessment of fetal disappearance in the first trimester. Am J Obstet Gynecol 1986;155: 14–9.
[4] Benson CB, Doubilet PM, Laks MP. Outcome of twin gestations following sonographic demonstration of two heart beats in the first trimester. Ultrasound Obstet Gynecol 1993;3:343–5.
[5] Doubilet PM, Benson CB. "Appearing twin": undercounting of multiple gestations on early first trimester sonograms. J Ultrasound Med 1998;17:199–203; quiz 205–6.
[6] Sebire NJ, Snijders RJ, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynaecol 1997;104:1203–7.

[7] Sepulveda W, Sebire NJ, Nicolaides KH. The lambda sign in twin pregnancies. Ultrasound Obstet Gynecol 1996;8:429.
[8] Sepulveda W, Sebire NJ, Hughes K, Odibo A, Nicolaides KH. The lambda sign at 10–14 weeks of gestation as a predictor of chorionicity in twin pregnancies. Ultrasound Obstet Gynecol 1996; 7:421–3.
[9] D'Alton ME, Dudley DK. The ultrasonographic prediction of chorionicity in twin gestation. Am J Obstet Gynecol 1989;160:557–61.
[10] Rodis JF, McIlveen PF, Egan JF, Borgida AF, Turner GW, Campbell WA. Monoamniotic twins: improved perinatal survival with accurate prenatal diagnosis and antenatal fetal surveillance. Am J Obstet Gynecol 1997;177:1046–9.
[11] Benirschke K, Kim CK. Multiple pregnancy. 2. N Engl J Med 1973;288:1329–36.
[12] Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550–5.
[13] Taylor MJ, Govender L, Jolly M, Wee L, Fisk NM. Validation of the Quintero staging system for twin-twin transfusion syndrome. Obstet Gynecol 2002;100:1257–65.
[14] Hecher K, Plath H, Bregenzer T, Hansmann M, Hackeloer BJ. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. Am J Obstet Gynecol 1999;180:717–24.
[15] Sutcliffe AG, Sebire NJ, Pigott AJ, Taylor B, Edwards PR, Nicolaides KH. Outcome for children born after in utero laser ablation therapy for severe twin-to-twin transfusion syndrome. BJOG 2001;108:1246–50.
[16] Elliott JP, Urig MA, Clewell WH. Aggressive therapeutic amniocentesis for treatment of twin-twin transfusion syndrome. Obstet Gynecol 1991;77:537–40.
[17] Dolinger MB, Donnenfeld AE. Therapeutic amniocentesis using a vacuum bottle aspiration system. Obstet Gynecol 1998;91:143–4.
[18] Elliott JP, Sawyer AT, Radin TG, Strong RE. Large-volume therapeutic amniocentesis in the treatment of hydramnios. Obstet Gynecol 1994;84:1025–7.
[19] Quintero RA, Reich H, Puder KS, Bardicef M, Evans MI, Cotton DB, et al. Brief report: umbilical-cord ligation of an acardiac twin by fetoscopy at 19 weeks of gestation. N Engl J Med 1994;330:469–71.
[20] Imseis HM, Albert TA, Iams JD. Identifying twin gestations at low risk for preterm birth with a transvaginal ultrasonographic cervical measurement at 24 to 26 weeks' gestation. Am J Obstet Gynecol 1997;177:1149–55.
[21] Souka AP, Heath V, Flint S, Sevastopoulou I, Nicolaides KH. Cervical length at 23 weeks in twins in predicting spontaneous preterm delivery. Obstet Gynecol 1999;94:450–4.
[22] Goldenberg RL, Iams JD, Miodovnik M, Van Dorsten JP, Thurnau G, Bottoms S, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1996; 175:1047–53.
[23] Guzman ER, Walters C, O'Reilly-Green C, Meirowitz NB, Gipson K, Nigam J, et al. Use of cervical ultrasonography in prediction of spontaneous preterm birth in twin gestations. Am J Obstet Gynecol 2000;183:1103–7.
[24] Newman RB, Krombach RS, Myers MC, McGee DL. Effect of cerclage on obstetrical outcome in twin gestations with a shortened cervical length. Am J Obstet Gynecol 2002;186:634–40.
[25] Rodis JF, Egan JF, Craffey A, Ciarleglio L, Greenstein RM, Scorza WE. Calculated risk of chromosomal abnormalities in twin gestations. Obstet Gynecol 1990;76:1037–41.
[26] Meyers C, Adam R, Dungan J, Prenger V. Aneuploidy in twin gestations: when is maternal age advanced? Obstet Gynecol 1997;89:248–51.
[27] Wald NJ. Recent advances in screening for neural tube defects and Down's syndrome: fetal diagnosis of genetic defects. Baillieres Clin Obstet Gynecol 1987;1:649–76.
[28] Doyle P. Twinning and Down syndrome. Ir Med J 1992;85:121.
[29] Egan JF, Benn P, Borgida AF, Rodis JF, Campbell WA, Vintzileos AM. Efficacy of screening for fetal Down syndrome in the United States from 1974 to 1997. Obstet Gynecol 2000;96:979–85.

[30] Spencer K. Screening for trisomy 21 in twin pregnancies in the first trimester: does chorionicity impact on maternal serum free beta-hCG or PAPP-A levels? Prenat Diagn 2001;21:715–7.
[31] Maymon R, Dreazen E, Rozinsky S, Bukovsky I, Weinraub Z, Herman A. Comparison of nuchal translucency measurement and second-trimester triple serum screening in twin versus singleton pregnancies. Prenat Diagn 1999;19:727–31.
[32] Egan JF, Kaminsky LM, DeRoche ME, Barsoom MJ, Borgida AF, Benn PA. Antenatal Down syndrome screening in the United States in 2001: a survey of maternal-fetal medicine specialists. Am J Obstet Gynecol 2002;187:1230–4.
[33] Wald NJ, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. J Med Screen 1997;4:181–246.
[34] Neveux LM, Palomaki GE, Knight GJ, Haddow JE. Multiple marker screening for Down syndrome in twin pregnancies. Prenat Diagn 1996;16:29–34.
[35] Ghidini A, Lynch L, Hicks C, Alvarez M, Lockwood CJ. The risk of second-trimester amniocentesis in twin gestations: a case-control study. Am J Obstet Gynecol 1993;169:1013–6.
[36] Evans MI, Goldberg JD, Horenstein J, Wapner RJ, Ayoub MA, Stone J, et al. Selective termination for structural, chromosomal, and mendelian anomalies: international experience. Am J Obstet Gynecol 1999;181:893–7.

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Fetal growth and well-being

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Accurate and effective monitoring of fetal growth is one of the key components of prenatal care. Aberrations of fetal growth at both ends of the spectrum clearly result in higher short- and long-term adverse sequelae: complications for the growth-restricted fetus include prematurity, stillbirth, and perinatal morbidity, whereas macrosomic infants have higher rates of traumatic delivery and neonatal metabolic disturbances. Growth disturbances may have long-term issues for multiple organ systems that extend well beyond the neonatal period. The current arsenal of clinical screening methods to identify better abnormally grown fetuses perform only adequately at best, and in several studies, seem to identify the small-for-gestational age (SGA) fetus in only one quarter of the cases [1].

Normal fetal growth

Fetal growth is the result of the genetic potential of the fetus that is then in turn modified by environmental factors. Growth and the maintenance of a normal growth profile have multifactorial origins. Infant birth weight patterns tend to be repeated in subsequent pregnancies. In 1979, Bakketeig et al [2] reported that mothers who gave birth to SGA infants were two to three times more likely to produce SGA infants in subsequent pregnancies compared with the total population. Several studies from the 1980s have found a strong relationship between maternal and neonatal birth weight, both before and after controlling for multiple variables [3,4]. In an interesting study of ovum donation, it was discovered that there was no correlation between ovum donor size and resulting infant birth weight, whereas the infant birth weight was significantly correlated with the recipient mother's weight [5].

In any evaluation of fetal growth, an accurately determined gestational age is of utmost importance. Determination of gestational age from ultrasound biometry

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performed in the first half of pregnancy is more accurate than menstrual dates [6]. Fundal height measurement and clinical palpation have been found to have a large range of error, although serial measurements over time may have better accuracy in identifying growth curve alterations. In a large observational study, Westin [7] found that symphysis-fundus height measurements in low-risk and uncomplicated pregnancies were superior to maternal weight gain, maternal girth measurements, and biochemical analysis for the detection of the SGA infant.

Monitoring of fetal growth is a highly inaccurate process: the estimation of fetal weight may be in error by at least 20% in over 10% of cases [8]. More than 60 formulas exist to estimate fetal weight from ultrasound measurements, which confirms that all of these estimates are subject to error [9]. It seems that ''normal fetuses'' (ie, fetuses not destined to be SGA or large-for-gestational age [LGA]) follow their own unique growth curve, which is then reflected in eventual birth weight. A 10th percentile newborn is usually symmetrically small and continues at that 10th percentile throughout pregnancy as is a 95th percentile newborn large in all measurements at each ultrasound visit. Growth-restricted and macrosomic infants, however, may divert from their expected growth curves as their growth becomes abnormal.

Historically, fetal size has been measured using standard derivations of three fetal structures or growth parameters: (1) fetal brain (biparietal diameter [BPD] and head circumference [HC]); (2) fetal nutritional status (abdominal circumference [AC]); and (3) fetal length (femur length [FL]). These three measurements have been combined in various ways to estimate fetal weight. The most commonly used equations for estimated fetal weight are the Hadlock formula and the Shephard formula, but these formulae are intended for normally grown fetuses and perform more poorly when applied to growth-restricted or macrosomic infants [10].

Maternal characteristics including weight, height, parity, and ethnic group are all strongly correlated with birth weight at term. Computer software programs within ultrasound machines can now link maternal variables with established growth curves using a multiple regression analysis to calculate individually adjusted fetal size reference curves. These specialized growth curves then improve the prediction of fetal weight gain in both low-risk and high-risk populations, and have been shown to generate birth weight estimates that are better correlated with neonatal features of growth restriction, macrosomia, and low Apgar scores [11,12].

Abnormal fetal growth

Intrauterine growth restriction (IUGR) is a relatively common condition that affects as many as 5% to 10% of all pregnancies [13]. It is a significant contributor to both perinatal morbidity and mortality. Before ultrasound surveillance, it was difficult to make an accurate diagnosis of IUGR before birth. Even with the advent of ultrasound, the definition of true IUGR is imprecise, which leads to

difficulties in the evaluation, treatment, and follow-up of these at-risk fetuses. IUGR is usually broadly defined as a fetus with an estimated fetal weight (EFW) below the 10th percentile for gestational age. There still is no definitive consensus, however, on a particular cutoff percentile. Some authors favor the fifth or the third percentile for weight based on gestational age, and others have opted for a population-based approach, such as two or more standard deviations below the mean [14–16].

Under the broadest definition, using fetal weight below the 10th percentile, approximately 70% of fetuses are constitutionally small, or SGA rather than true IUGR [17]. These healthy but SGA infants are not the result of an adverse intrauterine environment and do not experience a lack of oxygen or nutrients and are not at increased risk for perinatal morbidity or mortality. It is clear that there are multiple nonpathologic determinants of fetal size at birth including maternal ethnic and demographic factors, environmental issues, and socioeconomic conditions. The true definition of IUGR implies a pathologic process that affects normal fetal growth. As described previously, when compared with normal fetuses of the same age, IUGR fetuses have an increased risk of morbidity and mortality. This risk continues well into childhood where these previously IUGR fetuses have higher rates of neurodevelopmental delay and physical handicap, according to several long-term follow-up studies [18,19].

Weight estimation has been used as the cornerstone of identifying the IUGR fetus. A multitude of weight prediction formulae and tables have been established, typically involving measurement or ratios of various fetal body parts. These include measurement of head size (BPD or HC); AC; FL; and ratios, such as HC:AC. Unfortunately, even when based on multiple fetal part measurements, weight prediction has a wide 95% confidence range of ± 15%. Of all the ultrasound derived biometric parameters, the AC seems to be the best predictor of IUGR. When the AC measurement falls below the 2.5th percentile for gestational age, IUGR may be suspected and correctly identified in approximately 95% of the cases [20].

The etiology of IUGR has been separated into three different groups, based on timing and intrauterine environmental issues [21]. The first group is early IUGR, where there is proportional growth restriction, which begins early in gestation and is symmetric. The second group consists of growth-restricted fetuses that were subjected to poor growth factors in the intrauterine environment, and may be either symmetric or asymmetric. The third group consists of fetuses that have suffered from decreased placental supply in the last 4 to 6 weeks of pregnancy resulting in a diminution of the fetal fat stores. These infants are asymmetrically growth-restricted with an overall weight that is small for their length. Historical factors including maternal smoking and delivery of a previous growth-restricted infant also place the patient at higher risk for IUGR. In addition, an interpregnancy interval of less than 9 months increases the risk of IUGR and preterm delivery [21].

Once a small fetus is suspected, an extensive attempt should be made to determine the etiology for the IUGR. A careful sonographic examination should

be performed, at an established center with state-of-the-art equipment. This is primarily a search for associated structural anomalies and chromosomal abnormalities. Several studies have reported a 5% to 27% incidence of chromosomal abnormalities associated with IUGR, as compared with a 0.1% to 4% rate in control groups of appropriately grown neonates [22,23]. Sonographic findings that increase the likelihood of a chromosomal abnormality include fetal structural malformations, often of the head and heart. If a chromosomal abnormality is suspected, an amniocentesis or percutaneous umbilical blood sampling should be suggested to the patient and then performed to confirm the diagnosis. Fetuses with chromosomal disorders, including trisomy 13, 18, and 21, are frequently growth-restricted from early in gestation, and it has been observed that infants with other autosomal abnormalities also have smaller than expected growth. Snijders et al [24] performed fetal blood karyotyping on 458 growth-restricted fetuses between 17 and 39 weeks gestation and found that 89 (19%) of those had chromosomal defects, most commonly trisomy 18 [24].

Although less common than chromosomal abnormalities, intrauterine infection is another common cause of IUGR, perhaps accounting for 5% to 10% of cases [25]. Primary cytomegalovirus infection before the third trimester is the most common infectious cause of IUGR, and early fetal infections with parvovirus and rubella may also impair fetal growth. The association of maternal viremia with IUGR carries a poor prognosis, with up to a 50% perinatal mortality rate [26]. Maternal serum studies for viral seroconversion should be obtained, and amniotic fluid viral DNA testing performed when indicated.

The most common maternal medical complications associated with IUGR are hypertensive disorders or maternal vascular disease. The pathophysiology of vascular disease decreases uteroplacental perfusion and may be responsible for as many as 25% to 30% of all IUGR infants. Duvekot et al [27] proposed that early defective volume adaptation to pregnancy is a possible mechanism by which maternal hypertensive disease predisposes to fetal IUGR. Experimental restriction of fetal growth results in an asymmetrical pattern of fetal growth restriction whereby body weight is reduced to a greater extent than crown rump length or girth. Maternal vascular disease includes chronic hypertension, pregnancy-induced hypertension, hypertension with superimposed preeclampsia, and preeclampsia with all its variations. Maternal systolic blood pressure has been reported to be inversely proportional to infant birth weight across the full birth weight ranges of both normally grown and growth-restricted infants [28]. Experiments with sheep have proved that during hypoxemia, blood flow to the brain, heart, and adrenal glands is increased, and blood flow to the gastrointestinal, renal, and peripheral vascular beds decreases [29–31]. The redistribution of fetal cardiac output is critically important for the maintenance of general growth and optimal function of key organs, such as the brain and the heart. This redistribution of cardiac output away from peripheral and regional circulations is partly responsible for the subsequent development of IUGR. Several reports have outlined the morphologic characteristics of placentas complicated by IUGR or preeclampsia [32–34]. Macara et al [32] reported that the terminal villi in IUGR placentas were smaller

in diameter than those in normal placentas, and had thickened basal lamina and increased stromal deposition of collagens and laminin [32]. Arkwright et al [33] noted that villous trophoblasts in preeclamptic placentas were phenotypically immature, and Krebs et al [34] reported that villous capillary loops in IUGR placentas were relatively sparse in number compared with those in normal placentas. On a molecular basis, one group found that IUGR term placentas have different regulating factors regarding apoptosis of placental trophoblasts [35].

The relationship between maternal thrombophilic disorders and IUGR has been the subject of recent investigation. Certainly, the antiphospholipid syndrome has an established role in the etiology of adverse pregnancy outcome, including but not limited to IUGR. A recent review by Alfirevic et al [36] studied the association between maternal thrombophilia and adverse pregnancy outcome. These authors suggest that women with preeclampsia, stillbirth, placental abruption, and IUGR are more likely to have an abnormal thrombophilia screen than women with no significant obstetric history. Women with IUGR had a higher prevalence of heterozygosity for the G20210A prothrombin gene mutation, homozygosity for MTHFR C677T gene mutation, protein C deficiency, and anticardiolipin IgG antibodies than controls. They conclude that it is unclear which specific thrombophilias are implicated in each of the various adverse outcomes [36]. Evaluation of the congenital and acquired thrombophilic disorders should be performed in mothers with IUGR fetuses, especially if a previous pregnancy was also affected by IUGR, or early and severe preeclampsia.

Finally, one study explored the possibility of a familial pattern of transmission as a cause of IUGR. Ghezzi et al [37] investigated 70 consecutive multiparous women with IUGR fetuses and compared this group with 70 controls. They found that the proportion of women who developed preeclampsia and who had delivered an IUGR fetus in a previous pregnancy was higher in the IUGR group than in the controls [37]. After adjusting for preeclampsia, the delivery of a previous IUGR fetus remained a risk factor for having a subsequent IUGR fetus. Pedigree analysis conducted in 15 families revealed a familial cluster of IUGR infants in all families that were investigated.

Diagnosis of intrauterine growth restriction

The diagnosis of IUGR must begin with the evaluation of the at-risk patient. There are established risk factors for developing a growth-restricted fetus, which range from socioeconomic influences to chronic medical conditions. Hypertensive disorders in pregnancy, including both essential hypertension and pregnancy-induced hypertension, are established risk factors for poor fetal growth. Other risks factors include maternal smoking; poor weight gain in pregnancy; low socioeconomic status; and a previous poor obstetric history, such as IUGR, stillbirth, or neonatal death.

Ultrasound evaluation is considered the cornerstone of diagnosis and surveillance of the growth-restricted fetus. In view of the limitations of using less than

the 10th percentile for gestational age as the diagnostic criteria for IUGR, other fetal sonographic parameters have been proposed as primary tools for identification. Benson et al [38–40] have reviewed the predictive value of sonographic criteria for the antenatal diagnosis of IUGR, including such variables as placental grade, amniotic fluid volume, BPD, FL:AC ratio, HC:AC ratio, distal femoral epiphysis, and fetal weight estimation. These retrospective meta-analyses have found that most sonographic criteria have low positive predictive values for identifying affected fetuses, and that the straightforward approach of using EFW less than 10th percentile for gestational age out performs most of the other criteria. Other studies have confirmed that EFW is among the best predictors of small fetal size. Smith et al [41], however, suggests using abdominal circumference alone to predict IUGR. Parameters that provide additional information are amniotic fluid volume and maternal blood pressure status, hypertensive versus normotensive. Studies by Deter et al [42] and Hadlock et al [43] from 1982 to 1983 have suggested that serial evaluation of fetal growth is a more appropriate way to diagnose IUGR.

It is clinically important to distinguish between the two patterns of growth abnormalities: symmetric versus asymmetric. Symmetric IUGR is considered the result of an early intrinsic insult impairing fetal growth, such as a chromosome abnormality, intrauterine infection, drugs, or congenital malformations. It is theorized that the growth restriction is symmetric because the insult occurred at a time when fetal growth primarily develops by cell division. Asymmetric IUGR is believed to be the consequence of extrinsic factors, often from the inadequate availability of substrate for fetal metabolism. Small liver size and scarce subcutaneous fat are the clinical manifestations of this lack of substrate, most commonly caused by maternal vascular disease and decreased uteroplacental perfusion. Here the growth restriction is asymmetric because the insult occurred at a time when fetal growth primarily develops by cell growth, not an increase in cell number. Symmetric IUGR with a normal interval rate of growth may represent a constitutionally small but otherwise normal fetus.

Management of the growth-restricted fetus

Once a fetus is identified as growth-restricted, a heightened level of surveillance is necessary to limit the risk of hypoxia, morbidity, and even mortality. The most appropriate timing for delivery depends on the gestational age and assessment of the severity of the fetal condition. For fetuses at term or near term, delivery may be indicated when there is little interval growth over a short period of time, or if fetal lung maturity has been determined. For fetuses at earlier gestational ages, more remote from term, management of these at-risk fetuses requires close surveillance and the use of multiple testing modalities. The most common testing modalities include the biophysical profile, nonstress testing, amniotic fluid measurements, and interrogation of fetal blood vessels using Doppler velocimetry [44].

Doppler

It has been well established that the use of Doppler velocimetry can significantly reduce perinatal death and unnecessary induction of labor in the preterm IUGR fetus [45]. Doppler velocimetry evaluates the impedance of flow through selected fetal vessels in an effort to assess the fetal condition. Surveillance with Doppler is based on the premise that the fetal condition is reflected by circulatory changes. Doppler indices reflect downstream blood flow resistance, measuring afterload and preload, depending on whether the arteries or veins are interrogated, respectively. In hypoxic fetuses, preferential blood flow is distributed to the brain, heart, and adrenal glands. In Doppler studies, this is reflected in decreased resistance in these three vascular beds.

The redistribution of blood flow is the principle mechanism by which the IUGR fetus preserves adequate oxygenation in the central nervous system. The fetus first adapts to hypoxemia by instituting vasoconstriction at the level of the somatic blood vessels, whereas vasodilatation is observed at the level of the cerebral vessels. This is known as the "brain sparing" effect [46].

The two most common vessels studied in the fetal circulation are the umbilical artery and the middle cerebral artery. Angle-independent parameters are used and primarily consist of systolic-diastolic ratio, pulsatility index, and resistance index. More recent studies have looked at the fetal venous system and have found that the IUGR fetus seems to be at even greater risk of hypoxia or mortality when Doppler abnormalities are observed in the ductus venosus and the umbilical vein [47,48].

The umbilical artery has been the most extensively studied arterial vessel in the fetal circulation. Multiple retrospective and prospective studies have shown that abnormal umbilical artery waveforms are associated with adverse outcome [49]. In the usual state, the fetoplacental unit acts as a unified low-resistance system with very little impedance against blood flowing through the umbilical arteries. As the pregnancy progresses and the placenta mature, there is more development of tertiary stem villi leading to an increase in end-diastolic flow [50,51]. Goldkrand et al [52] has recently published normative data for expected blood flow in the umbilical artery from 18 weeks gestation to full term. A continuous decline in the umbilical artery resistance over the course of the pregnancy strongly correlates with normal and expected birth weight, low risk of fetal distress, or neonatal complications [53,54].

Diseases that destroy small muscular arteries in the placental tertiary stem villi result in increased impedance to flow in the umbilical artery. As the condition progresses, placental resistance increases with a progressively decreasing end-diastolic flow, until the umbilical artery has absent or even reverse end-diastolic flow. Absent or reverse end-diastolic flow in the umbilical arteries predicts poor fetal outcome and an advanced stage of placental compromise. By the time reverse end-diastolic flow is present, it is estimated that more than 70% of the placenta's arteries have been obliterated [55,56]. Several authors have suggested that the severity of the fetal compromise may be predicted by the extent of the abnormality

of the Doppler study [57,58]. Oligohydramnios, low birth weight, abnormal fetal testing, emergent cesarean section for fetal distress, and even stillbirth are all features of growth-restricted fetuses with deteriorating umbilical artery Doppler.

Fetal brain sparing is the first response to hypoxia. Doppler interrogation of the middle cerebral artery may also be used to evaluate fetal well-being. Fetal brain sparing during hypoxia is characterized by an increase in the mean blood flow velocity and systolic velocity. The middle cerebral artery, located in the circle of Willis, is perpendicular to the cerebral midline, which then allows for the Doppler signal to be easily positioned along the mid-portion of the vessel, specifically the proximal portion of the vessel, immediately after its origin at the circle of Willis. The two middle cerebral arteries (right and left) are major branches of the circle of Willis, and are supplied by the internal carotid arteries and the vertebral arteries. When a fetus is oxygen deprived, there is a central redistribution of blood flow, resulting in preferentially increased blood flow to the brain, heart, and adrenals. This redistribution of blood flow to vital organs and away from peripheral circulations is the primary fetal adaptation to oxygen deprivation and is an early response. The brain-sparing effect of this redistribution of flow may be identified by increased end-diastolic flow in the middle cerebral artery, which is reflected by a lower pulsatility index or resistance index.

In a series of IUGR fetuses with abnormal umbilical pulsatility indexes, Capponi et al [59] demonstrated that the best predictor of hypoxia at cordocentesis was the middle cerebral artery pulsatility index. One of the criticisms of using middle cerebral artery Doppler is that its prognostic utility is limited because abnormalities are often preceded by abnormalities of the umbilical artery Doppler and asymmetric abdominal circumference growth [60]. The measurement may be used in conjunction with other Doppler and non-Doppler investigations, however, to diagnose better those IUGR fetuses at greatest risk.

Doppler waveforms of the middle cerebral artery provide valuable information regarding the difficult differentiation between the growth-restricted fetus and a constitutionally small one. Normal amniotic fluid volume, normal middle cerebral artery Doppler waveforms, and normal umbilical artery parameters in a small fetus are reassuring and essentially exclude adverse perinatal outcome.

There are multiple other fetal vessels that have been studied in the evaluation of the growth-restricted fetus. The proposed pathophysiology of severe growth restriction contends that the underlying placental disease triggers compensatory hemodynamic changes which, if they worsen, lead to hemodynamic decompensation. The duration of the compensatory phase is variable and seems not to have deleterious short-term consequences if identified promptly. When the compensatory mechanisms reach their limit, hemodynamic decompensation occurs with depressed myocardial function. Abnormal fetal venous Doppler waveforms are associated with this decompensatory period. Fetal venous Doppler measurements reflect the physiologic status of the right ventricle, thereby providing important data about the fetal circulation. The umbilical vein, inferior vena cava, and ductus venosus are the vessels most commonly studied in the fetal venous circulation, although one author believes that the ductus venosus is the vein of choice

[61]. These venous vessels provide specific information regarding right ventricular preload, myocardial compliance, and right ventricular end-diastolic pressure [62–66].

The inferior vena cava can be interrogated at two locations: the inlet into the right atrium or the segment of vessel between the renal vein and the ductus venosus. The shape of the inferior vena cava waveform is triphasic: the first part correlates with ventricular systole, the second with early diastole, and the third with late diastole. The inferior vena cava has been determined to be of limited clinical value because the waveform and its indices are known to have wide variation within normal fetuses with a poor predictive value for asphyxia or stillbirth [62,63,65].

Ductus venosus waveforms may be obtained from a transverse sonographic view of the fetal abdomen at the same level that the abdominal circumference is obtained. The ductus venosus can be identified as it branches from the umbilical vein. These waveforms are biphasic in shape, the first phase corresponding to ventricular systole, the second to early diastole, and the nadir of the second phase to late diastole. The ductus venosus is a primary regulator of venous return in all fetuses, is responsive to changes in oxygenation independent of cardiac function, and is readily imaged. Chronic fetal hypoxemia raises central venous pressure that can be measured as an increased reverse flow in the Doppler waveforms of the inferior vena cava and the ductus venosus during late diastole. This is considered to be an advanced stage of fetal hypoxemia and cardiac decompensation may also be present or quickly follow. A retrograde ductus venosus atrial wave has been found to be a strong predictor of perinatal mortality and neonatal circulatory collapse [53,61]. Although it has been proposed that monitoring fetal ductus venous with Doppler may help to identify fetuses at risk of decompensation, studies by Hecher et al [67] and Baschat and Weiner [53] suggest that the benefit may be of limited value for a very short interval of time. Clearly, abnormal venous Doppler studies suggest a higher likelihood of adverse perinatal outcome, and immediate delivery may be considered.

Hecher et al [67] followed IUGR fetuses longitudinally after 24 weeks of gestation and found abnormal findings occur in the following order: umbilical artery pulsatility index, amniotic fluid index, middle cerebral artery, aorta, short-term heart rate variability, ductus venosus, and inferior vena cava. In a recent meta-analysis of 14 randomized controlled trials, perinatal mortality was significantly lower in the pregnancies monitored with Doppler, and this held true in both pregnancies with IUGR-preeclampsia and those considered to be general high-risk [68]. In the IUGR-preeclampsia studies, the number of obstetric interventions was significantly reduced in pregnancies monitored with Doppler ultrasound including antenatal admissions, inductions of labor, and cesarean sections.

Biophysical profile

The biophysical profile evaluates fetal well-being using amniotic fluid volume and three dynamic ultrasound variables: (1) fetal breathing, (2) fetal movement,

and (3) fetal tone. Nonstress tests are sometimes used as a fifth, nonsonographic parameter. Fetal behavior develops along previously established gestational periods, and also exhibits diurnal and responsive behavior. Although a complete five component biophysical profile best correlates with fetal status, each parameter might be impacted by the presence of intrauterine hypoxia. Placental dysfunction or fetal hypoxia may cause fetal oliguria and consequently oligohydramnios. Observational studies have shown that growth-restricted pregnancies complicated by oligohydramnios have a markedly increased risk of perinatal mortality [69]. Abnormal findings in any of the individual components of the biophysical profile require further investigation or follow-up. Often management is based on gestational age and the degree of abnormality of the biophysical profile in conjunction with the severity of the IUGR. Although many fetuses have been studied with biophysical profile, there is little evidence for its utility from randomized trials [70].

Cardiotocography

Antepartum cardiotocography has become widely accepted as a primary method of fetal monitoring in high-risk pregnancies. At present, however, there is not sufficient evidence from randomized controlled trials that use of cardiotocography actually leads to a reduction in perinatal morbidity and mortality, or actually improves perinatal outcome [71–73]. Although several characteristics of the fetal heart are assessed by cardiotocography, variability is considered most important. Heart rate variability involves the interaction of the sympathetic and parasympathetic innervation of the fetal heart, and is the outcome of the rhythmic and integrated activity of autonomic neurons generated by organized cardiorespiratory reflexes. One of the criticisms of cardiotocography is large interobserver and intraobserver variability in the visual interpretation of cardiotocography tracings [74,75]. Several investigators have begun using computerized analysis of cardiotocography, which improves the reliability of fetal heart rate evaluation in clinical practice [76].

Although it demonstrates a wide variety of values in the normal fetus, the most reliable single parameter of the fetal condition is variability of the baseline heart rate. Investigators have shown that the heart rate tracings of IUGR fetuses typically have higher baselines and decreased baseline variability and delayed maturation of reactivity [77,78]. A progressive reduction in baseline variability has shown to be associated with deterioration of fetal oxygenation.

There are several studies in the literature that have demonstrated that fetal heart rate patterns are closely related to fetal respiratory and metabolic status, especially in cases of IUGR [79,80]. Ribbert et al [79] performed cordocentesis immediately after obtaining a 60-minute cardiotocography record in 25 cases of IUGR. They discovered that fetal blood P_{O_2} and pH were significantly different in these IUGR cases when compared with normal values. They also found that there was a direct correlation between fetal heart rate variability, P_{O_2}, and pH

in these IUGR fetuses. Smith et al [80] evaluated the correlation between fetal heart rate and biochemical measurements from cord samples in patients delivered by cesarean section. These authors found that fetuses with abnormal fetal heart rate patterns exhibited lower umbilical artery Po_2 values than those at a matched gestational age but with normal tracings. This study demonstrated that measurements of fetal heart rate variability can help identify fetuses that may be becoming hypoxemic.

In the absence of clearly abnormal patterns, cardiotocography provides little additional insight into fetal well-being. A normal cardiotocography is associated with a stillbirth rate of 1.9 per 1000 cases within 7 days [81]. As a result, it has been suggested that other parameters must be used to evaluate more fully fetal and maternal status [44].

Macrosomia

The most commonly used definition for macrosomia is a birth weight greater than 4000 g, but as in growth-restricted infants, identification of the at-risk fetus is improved by using the definition of birth weight percentile for a given gestational age. A label of LGA is considered when an estimated fetal weight is above the 90th percentile. The rate for LGA infants in the general population should be approximately 10% by this definition, whereas the rate of macrosomia defined as an EFW greater than 4000 g is approximately 8% in the same general low-risk population [81]. Seventy percent of these LGA infants are constitutionally large and not disease related, whereas the other 30% are presumably caused by maternal diabetes and hyperglycemia during pregnancy. The prevalence of macrosomia is increased dramatically when the mother has diabetes and may affect as many as 15% to 45% of these fetuses [82]. Pedersen's [83] theory suggests that maternal hyperglycemia causes fetal hyperinsulinemia and this in turn causes fetal macrosomia [83]. This theory has been modified to include also the contributions of other metabolic components, such as lipids, amino acids, and insulin growth factor.

Most LGA infants are born to normoglycemic women and the strongest risk for having a macrosomic neonate is maternal obesity, even among diabetic women [84–86]. Fetal macrosomia resulting from maternal diabetes is considered different from LGA fetuses in nondiabetic women, and is supported by evidence that within any given birth rate percentile, the infants of diabetic mothers have a disproportionate rate of shoulder dystocia [87]. Clearly, LGA infants of nondiabetic mothers are also at risk for shoulder dystocia, with a twofold to threefold increased risk above the general population. The additional risk for shoulder dystocia in diabetic mothers seems to be the result of the different body morphometry in their infants. Estimated fetal weight curves have tried to incorporate this morphometry to identify better a macrosomic infant in a diabetic mother and several specialized growth curves have been developed to try and improve accuracy. Benson et al [88] tested several different established formulas and even

tried to devise customized formulas in diabetic pregnancies. In 160 diabetic infants, they discovered that their relative error had standard deviations of 12% to 13%, and that their best attempt at a customized formula had a standard deviation of 11%. Landon et al [89] took three separate readings of HC, AC, and FL in the third trimester and found no difference between LGA and normally grown infants in HC and FL growth, but there was a difference in AC growth between the two groups after 32 weeks [89]. Because there is not always the ability to perform serial measurements, a single AC greater than two standard deviations above the median also performed well in identifying the LGA infant [89].

Despite the clear association between macrosomia and shoulder dystocia, most infants with macrosomia do not experience shoulder dystocia. Although not a consistent finding in the literature, the only described correlation between birth weight and shoulder dystocia is in fetuses born to diabetic mothers with birth weights greater than 4500 g [90–92].

Ratios of biometric measurements may identify LGA infants with greater precision than simple EFW alone. Hadlock et al [93] and others [89,94–96] have evaluated the FL:AC ratio and established cutoffs for macrosomia: Hadlock's group [93] used a ratio of less than 20.5% as a cutoff for macrosomia, whereas Landon et al [89] preferred using 21%. Other ratios have been proposed that incorporate measurements of soft tissue thickness to evaluate better those infants most at risk for macrosomia and a traumatic delivery. Santolaya-Forgas et al [94] measured fetal subcutaneous tissue at the level of the femoral diaphysis and incorporated this measurement into a tissue:FL ratio. Other investigators have measured cheek-to-cheek diameters and BPD and chest diameter equations [95,96]. These techniques were able to identify the macrosomic infant but did not improve on the accuracy of previously described tests.

Rouse and Owen [97] reviewed 13 studies to derive an estimate of ultrasound's overall sensitivity and specificity for the detection of macrosomia at both the 4000 g and 4500 g threshold [97]. They estimated that over 8% of infants of nondiabetic mothers had birth weights between 4000 and 4500 g, and 1.5% had birth weights of 4500 g or more. In contrast, infants born to diabetic mothers had a greater proportion of LGA babies: 17% of infants weighed at least 4000 g, and 6.1% greater than 4500 g. Unfortunately it is difficult to apply these parameters to clinical practice because of the known inaccuracy of ultrasound. This same group applied their baseline sensitivity and specificity estimates to a hypothetical group of 100 term pregnant women. Although ultrasound identified 16 of those fetuses as having macrosomia, only 7 were actually macrosomic. As well, 5 of the 12 fetuses born macrosomic were incorrectly identified as being of normal weight. As a result, this group also supports the caution of others' when considering a policy of prophylactic cesarean delivery for suspected fetal macrosomia [97].

Recently, attention has turned to the evolving technology of three-dimensional ultrasound to predict fetal weight more accurately, specifically for the LGA fetus. Although two-dimensional ultrasound formulae are clearly the gold standard at the present time, research regarding the validation of new birth weight prediction

formulae based on fetal volumetric parameters is underway. Jeanty et al [98] was among the first investigators to suggest the use of limb volume to assess fetal growth, but the existing two-dimensional technology back in 1985 was limited. Standard two-dimensional technology was used to calculate limb volumes using generated circular and elliptical measurements. This process of volumetric biometry using two-dimensional ultrasound was time consuming, technically difficult, and not clinically practical.

Several formulae have been developed using three-dimensional sonography to measure fetal volumes. Measurements of upper arm and fetal thigh volumetry, limb circumference measurements, and birth weight prediction by volume of fetal thigh and abdomen have all been described. Favre et al [99] introduced three-dimensional sonography for the clinical application of fetal weight estimation in 1993. This group developed several different models of fetal weight estimation using simultaneous visualization of two perpendicular planes. A pilot study of 157 well-dated patients established normograms for volumetric formulae. This pilot study was followed by a prospective study of 213 patients where the value of the formulae was confirmed [100]. Fetal thigh circumference was found to be most useful for SGA fetuses, whereas arm circumference was used for appropriate for gestational age (AGA) and LGA fetuses. The greatest degree of accuracy was obtained among LGA fetuses where the standard deviation of mean error was 8.8%. More recent work by this group abandoned single-slice measurements and now uses a technique of serial slicing and integration to measure more accurately the volume of the fetal limb being investigated.

Investigators have measured other fetal parameters in combination. In 2001, Lee et al [101] described the prediction of fetal birth weight based on three-dimensional measurements of the upper arm, thigh, and abdomen. Estimated fetal weight determined by this technique correlated well with actual birth weight. It seems that three-dimensional sonography may play a role in the estimation of accurate birth weights, especially at the traditionally less accurate extremes of birth weight percentiles.

Prediction of macrosomia by clinical examination or sonographic technique is limited by the high false-positive and false-negative rates inherent in the performance of these tests. Clearly, continued research is necessary in this area. Sonography laboratories should try to improve their own predictive performance by establishing receiver-operator curve analysis on their own clinical data and outcomes. Separate curves then need to be derived for complicated pregnancies, such as those with diabetes or multiple gestations. It is only with this continued approach that the best prediction of clinical outcome and timing of delivery may be ensured.

Summary

Accurate monitoring of fetal growth is one of the most critically important components of prenatal care. Whether too large or too small for gestational age,

the ramifications of abnormal fetal growth have both short-term and long-term sequelae for early neonatal life and beyond. Although not perfectly accurate, ultrasound and other monitoring technologies have markedly improved the ability to follow abnormalities of fetal growth and to decide if early intervention or early delivery is necessary. Clearly, perinatal morbidity and mortality are decreased with close surveillance of these at-risk fetuses.

References

[1] Backe B, Nakling J. Effectiveness of antenatal care: a population based study. Br J Obstet Gynecol 1993;100:727–32.
[2] Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol 1979;135:1086–99.
[3] Hackman E, Emanuel I, Van Belle G, Daling J. Maternal birth weight and subsequent pregnancy outcome. JAMA 1983;250:2016–9.
[4] Klebanoff MA, Granbard BI, Kessel SS, Berendes HW. Low birth weight across generations. JAMA 1984;252:2423–7.
[5] Brooks AA, Johnson MR, Steer PJ, Parson ME, Abdalla HI. Birth weight: nature or nurture? Early Hum Dev 1995;42:29–35.
[6] Gardosi J, Geirrson RT. Routine ultrasound is the method of choice for dating pregnancy. Br J Obstet Gynecol 1998;105:933–6.
[7] Westin B. Gravidogram and fetal growth: comparison with biochemical supervision. Acta Obstet Gynecol Scand 1977;56:273–82.
[8] Jaffe R. Identification of fetal growth abnormalities in diabetes mellitus. Semin Perinatol 2002; 26:190–5.
[9] Huff RW. The use of ultrasound in the management of diabetic pregnancies. Diabetes Review 1995;3:643–51.
[10] Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology 1984;152:497–501.
[11] Gardosi J, Chang A, Kalyan B, Sahota D, Symonds E. Customized antenatal growth charts. Lancet 1992;339:283–7.
[12] Gardosi J, Mongelli M, Wilcox A, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol 1995;6:168–74.
[13] Galan HL, Ferazzi E, Hobbins JC. Intrauterine growth restriction (IUGR): biometric and Doppler assessment. Prenat Diagn 2002;22:331–7.
[14] Varma TR. Low birth weight babies: the small for gestational age. A review of current management. Obstet Gynecol Surv 1984;39:616–31.
[15] Seeds JW. Impaired fetal growth: definition and clinical diagnosis. Obstet Gynecol 1984;64: 303–30.
[16] Kierse MJNC. Epidemiology and aetiology of the growth retarded baby. Clin Obstet Gynecol 1984;11:415–22.
[17] Ott WJ. The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am 1988;15:237–63.
[18] Fattal-Valevski A, Leitner Y, Kutai M. Neurodevelopmental outcome in children with IUGR: a 3 year follow up. J Child Neurol 1999;14:724–7.
[19] Kok JH, den Ouden AL, Verlove-Vanhorick SP. Outcome of the very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynecol 1998;105:162–8.
[20] Benson CB, Doubilet PM. Fetal measurements: normal and abnormal fetal growth. In: Rumack C, Charboneau W, Wilson S, editors. Diagnostic ultrasound. 2nd edition. St. Louis: Mosby Year Book; 1998. p. 1013–31.
[21] Villar J, Belizan JM. The timing factor in the pathophysiology of the intrauterine growth retardation syndrome. Obstet Gynecol Surv 1982;137:499–510.

[22] Taylor DJ. Low birth weight and neurodevelopmental handicap. Clin Obstet Gynecol 1984; 11:525–31.
[23] Allen MC. Developmental outcome and follow-up of the small for gestational age infant. Semin Perinatol 1984;8:123–9.
[24] Snijders RJM, Sherrod C, Gosden CM, Nicolaides KH. Fetal growth retardation: associated malformations and chromosome abnormalities. Am J Obstet Gynecol 1993;168:547–55.
[25] Creasy RK, Resnik R. Intrauterine growth restriction. In: Creasy RK, Resnik R, editors. Maternal fetal medicine: principles and practice. 3rd edition. Philadelphia: WB Saunders; 1994. p. 115–27.
[26] Lin CC, Su SJ, River LP. Comparisons of associated high risk factors and perinatal outcome between symmetric and asymmetric fetal intrauterine growth retardation. Am J Obstet Gynecol 1991;164:1535–9.
[27] Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. Acta Obstet Gynecol Scand 1995;74:693–7.
[28] Huxley RR, Sheill AW, Law CM. The role of size and postnatal catch up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens 2000;18: 815–31.
[29] Jensen A, Hohmann M, Kunzel W. Dynamic changes in organ blood flow and oxygen consumption during acute asphyxia in the fetal sheep. J Dev Physiol 1987;9:325–6.
[30] Yaffe H, Parer JT, Block BS, Llanos AJ. Cardiorespiratory response to graded reductions of uterine blood flow in the sheep fetus. J Dev Physiol 1987;9:325–36.
[31] Jansen AH, Belik J, Ioffe S, Chernick V. Control of oxygen blood flow in fetal sheep during normoxia and hypoxia. Am J Physiol 1989;257:H1132–9.
[32] Macara L, Kingtom JC, Kauffmann P, Kohnen G, Hair J, More IA. Structural analysis of placental terminal villi from growth-restricted pregnancies with abnormal umbilical artery Doppler waveforms. Placenta 1996;17:37–48.
[33] Arkwright PD, Rademacher TW, Dwek RA, Redman CW. Preeclampsia is associated with an increase in trophoblast glycogen content and glycogen synthetase activity, similar to that found in hydatidiform moles. J Clin Invest 1993;91:2744–53.
[34] Krebs C, Macara LM, Leiser R, Bowman AW, Gree IA, Kingdom JC. Intrauterine growth restriction with end diastolic flow velocity in the UA is associated with maldevelopment of the placental terminal villous tree. Am J Obstet Gynecol 1996;175:1534–42.
[35] Ishihara N, Matsuo H, Murakoshi H, Laoag-Fernandez JB, Samoto T, Maruo T. Increased apoptosis in the syncytiotrophoblast in human term placentas complicated by either preeclampsia or intrauterine growth retardation. Am J Obstet Gynecol 2002;186:138–66.
[36] Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. Eur J Obstet Gynecol Reprod Biol 2002;101:6–14.
[37] Ghezzi F, Tibeletti MG, Raiol D, Inaro E, Lischetti B, Taborelli M, et al. Idiopathic IUGR: a possible inheritance pattern. Prenat Diagn 2003;23:259–64.
[38] Benson CB, Doubilet PM, Saltzman DH. Intrauterine growth retardation: predictive value of ultrasound criteria for antenatal diagnosis. Radiology 1986;160:415–26.
[39] Benson CB, Belville JA, Lentini JF, Saltzman DH, Doubilet PM. IUGR: diagnosis based on multiple parameters-a prospective study. Radiology 1990;177:499–502.
[40] Benson CB, Boswell SB, Brown DL, Saltzman DH, Doubilet PM. Improved prediction of IUGR with use of multiple parameters. Radiology 1988;168:7–12.
[41] Smith GC, Smith MFS, McNay MB, Fleming JEE. The relation between fetal AC and birthweight: findings in 3512 pregnancies. Br J Obstet Gynecol 1997;104:186–90.
[42] Deter RL, Harrist RB, Hadlock FP. The use of ultrasound in the detection of IUGR: a review. J Clin Ultrasound 1982;10:9–22.
[43] Hadlock FP, Deter RL, Harrist RB. Sonographic detection of fetal IUGR. Perinatol Neonatol 1983;7:21–32.

[44] American College of Obstetrics and Gynecology. Intrauterine growth restriction. ACOG Practice Bulletin, Number 12. Washington: ACOG; 2000.
[45] Baschat AA, Harman CR. Antenatal assessment of the growth restricted fetus. Curr Opin Obstet Gynecol 2001;13:161–8.
[46] Gaziane EP, Kno H, Ferrera B, Brandt DG, Calvin S, Knox GE. Is it time to reassess the risk for the growth retarded fetus with normal Doppler velicometry of the umbilical artery. Am J Obstet Gynecol 1994;170:1734–41.
[47] Kiserud T, Eik-Nes SH, Blaas HG, Hellerik LR. Ductus venosus blood velocity and the umbilical circulation in the seriously growth retarded fetus. Ultrasound Obstet Gynecol 1994;4: 109–14.
[48] Ferazzi E, Rigano S, Bozzo M, Bellotti M, Giovanni N, Galan H, et al. Umbilical vein blood flow in growth restricted fetuses. Ultrasound Obstet Gynecol 2000;16:432–8.
[49] Nellson JP, Alfirevic Z. Doppler ultrasound of fetal assessment in high risk pregnancy. Cochrane database of systemic reviews. Oxford: Update software; 2001.
[50] Fleischer A, Schulman H, Farmakides G, Bracero L, Blattner P, Randolph G. Umbilical artery velocity waveforms and intrauterine growth retardation. Am J Obstet Gynecol 1985; 151:502–5.
[51] Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathologic correlation. Br J Obstet Gynecol 1985;92:31–8.
[52] Goldkrand JW, Moore DH, Lentz SU, Clements SP, Turner AD, Bryant JL. Volumetric flow in the umbilical artery: normative data. J Matern Fetal Neonatal Med 2000;9:224–8.
[53] Baschat AA, Weiner CP. Umbilical artery Doppler screening for the small for gestational age fetus in need of antenatal surveillance. Am J Obstet Gynecol 2000;182:154–8.
[54] Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, et al. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol 1994;170:796–801.
[55] Kingdom JC, Burrell SJ, Kaufmann P. Pathologic and clinical implications of abnormal umbilical artery Doppler waveforms. Ultrasound Obstet Gynecol 1997;9:271–86.
[56] Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Effect of placental embolization on the umbilical artery waveform in fetal sheep. Am J Obstet Gynecol 1989;161:1055–60.
[57] Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2000;16:407–13.
[58] Muller T, Nanan R, Rehn M, Kristen P, Dietl J. Arterial and ductus venosus Doppler in fetuses with absent or reverse end diastolic flow in the umbilical artery: correlation with short-term perinatal outcome. Acta Obstet Gynecol Scand 2002;81:860–6.
[59] Capponi A, Rizzo G, Rinaldo D, Arduini D, Romanini C. Effects of cordocentesis on IVC velocity waveforms: differences between normally grown and growth retarded fetuses. Biol Neonate 1996;70:84–90.
[60] Harrington K, Thompson MO, Carpenter RG, Nguyen M, Campbell S. Doppler fetal circulation in pregnancies complicated by preeclampsia or delivery of a small for gestational age baby: longitudinal analysis. Br J Obstet Gynecol 1999;106:453–66.
[61] Kiserud T. The ductus venosus. Semin Perinatol 2001;25:11–20.
[62] Rizzo G, Capponi A, Talone PE, Arduini D, Romanini C. Doppler indices from the inferior vena cava and the ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol 1996;7:401–10.
[63] Rizzo G, Arduini D, Romanini C. Inferior vena cava flow velocity waveforms in appropriate and small for gestational age fetuses. Am J Obstet Gynecol 1992;166:1271–80.
[64] Reed KL, Appleton CP, Anderson CF, Shenker L, Sahn DJ. Doppler studies of vena cava flows in human fetuses: insights into normal and abnormal cardiac physiology. Circulation 1990;81: 498–505.
[65] Huisman TW, Stewart PA, Wladimiroff JW. Flow velocity waveforms in the fetal inferior vena cava during the second half of normal pregnancy. Ultrasound Med Biol 1991;17:679–82.

[66] Reuss ML, Rudolph AM, Dae MW. Phasic blood flow patterns in the superior and inferior venae cavae and umbilical vein of fetal sheep. Am J Obstet Gynecol 1983;145:70–8.
[67] Hecher K, Bilardo CM, Stigter RH. Monitoring of fetuses with IUGR: a longitudinal study. Ultrasound Obstet Gynecol 2001;18:564–70.
[68] Westergaard HB, Langhoff-Roos J, Lingman G. A critical appraisal of the use of umbilical artery Doppler ultrasound in high risk pregnancies: use of meta-analysis in evidence based obstetrics. Ultrasound Obstet Gynecol 2001;17:466–76.
[69] Resnik R. IUGR. Obstet Gynecol 2002;99:490–6.
[70] Alfirevic Z, Neilson JP. BPP for fetal assessment in high risk pregnancies. Cochrane database of systemic reviews. Oxford: Update software; 2000.
[71] Flynn AM, Kelly J, Mansfield H, Needham P, O'Conor M, Viegas O. A randomized trial of non stress test antepartum cardiotocography. Br J Obstet Gynecol 1982;89:427–33.
[72] Kidd LC, Patel NB, Smith R. Non stress antenatal cardiotocography- a prospective randomized clinical trial. Br J Obstet Gynecol 1985;92:1156–9.
[73] Pattison N, McCowen L. Cardiotocography for antepartum fetal assessment. Cochrane database of systemic reviews. Oxford: Update software; 1999.
[74] Lotgering FK, Wallenburg HC, Schouten HJ. Interobserver and intraobserver variation in the assessment of antepartum cardiotocograms. Am J Obstet Gynecol 1982;144:701–5.
[75] Trimbos JB, Keirse MJ. Observer variability in assessment of antepartum cardiotocograms. Br J Obstet Gynecol 1978;85:900–6.
[76] Dawes GS, Moulden M, Redman CW. System 8000: computerized antenatal FHR analysis. J Perinat Med 1991;19:47–51.
[77] Vindla S, James D, Sahota D. Computerized analysis of unstimulated and stimulated behaviour in fetuses with IUGR. Eur J Obstet Gynecol Reprod Biol 1999;83:37–45.
[78] Nijhuis IJ, Hof J, Mulder EJ. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur J Obstet Gynecol Reprod Biol 2000;89:27–33.
[79] Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relation of fetal blood gases and data from computer assisted fetal heart patterns in small for gestational age fetuses. Br J Obstet Gynecol 1991;98:820–3.
[80] Smith JH, Anand KJ, Cotes PM, Dawes GS, Harkness RA, Howletta TA, et al. Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. Br J Obstet Gynecol 1988;95:980–9.
[81] Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. JAMA 1996;276:1480–6.
[82] Langer O, Kozlowski S, Brustman L. Abnormal growth patterns in diabetes in pregnancy: a longitudinal study. Isr J Med Sci 1991;27:516–23.
[83] Pederson J. The pregnant diabetic and her newborn: problems and management. 2nd edition. Baltimore: Williams and Wilkins; 1977. p. 211–20.
[84] Spellacy WN, Miller S, Winegar A, Peterson PQ. Macrosomia: maternal characteristics and infant complications. Obstet Gynecol 1985;66:158–61.
[85] Lucas MJ, Lowe TW, Bowe L, McIntire DD. Class A1 gestational diabetes: a meaningful diagnosis? Obstet Gynecol 1993;82:260–5.
[86] Willman SP, Levano KJ, Guzick DS, Williams ML, Whalley PJ. Glucose threshold for macrosomia in pregnancy complicated by diabetes. Am J Obstet Gynecol 1986;154:470–5.
[87] Casey BM, Lucas MJ, McIntire DD. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. Obstet Gynecol 1997;90:869–73.
[88] Benson CB, Doubilet PM, Saltzman DH. Sonographic determination of fetal weights in diabetic pregnancies. Am J Obstet Gynecol 1987;156:441–4.
[89] Landon MB, Mintz MC, Gabbe SG. Sonographic evaluation of fetal abdominal growth: predictor of the large for gestational age infant in pregnancies complicated by diabetes mellitus. Am J Obstet Gynecol 1989;160:115–21.
[90] Langer O, Berkus M, Huff RW, Samueloff A. Shoulder dystocia: should the fetus weighing

greater or equal to 4000 grams be delivered by cesarean section? Am J Obstet Gynecol 1991; 165:831–7.
[91] Lipscomb KR, Gregory K, Shaw K. The outcome of macrosomic infants weighing at least 4500 grams: LA county and University of Southern California experience. Obstet Gynecol 1995;85:558–64.
[92] Keller JD, Lopez-Zeno JA, Dooley SL, Socol ML. Shoulder dystocia and birth trauma in gestational diabetes: a five year experience. Am J Obstet Gynecol 1991;165:928–30.
[93] Hadlock FP, Harris RB, Fearneyhough TC, Deter RL, Park SK, Rossavik IK. Use of FL/AC ratio in detecting the macrosomic fetus. Radiology 1985;154:503–5.
[94] Santolaya-Forgas J, Meyer WS, Gauthier DW, Kahn D. Intrapartum fetal subcutaneous tissue/FL ratio: an ultrasound clue to fetal macrosomia. Am J Obstet Gynecol 1994;171:1072–5.
[95] Abramowicz JS, Sherer DM, Woods JR. Ultrasonographic measurement of cheek-to-cheek diameter in fetal growth disturbances. Am J Obstet Gynecol 1993;169:405–8.
[96] Elliot JP, Garite TJ, Freeman RK, McQuown DS, Patel JM. Ultrasonic prediction of metal macrosomia in diabetic patients. Obstet Gynecol 1982;60:159–62.
[97] Rouse DJ, Owen J. Sonography, suspected macrosomia, and prophylactic cesarean section: a limited partnership. Clin Obstet Gynecol 2000;43:326–34.
[98] Jeanty P, Romero R, Hobbins JC. Fetal limb volume: a new parameter to assess fetal growth and nutrition. J Ultrasound Med 1985;4:273–82.
[99] Favre R, Nisaud G, Bettahar K, Grange G, Nisand I. Measurement of limb circumferences with 3 dimensional ultrasound for fetal weight estimation. Ultrasound Obstet Gynecol 1993;3: 176–9.
[100] Favre R, Bader AM, Nisand G. Prospective study on fetal weight estimation using limb circumferences obtained by 3 dimensional ultrasound. Ultrasound Obstet Gynecol 1995;6:140–4.
[101] Lee W, Deter RL, Ebersole JD, Huang R, Blanchart K, Romero R. Birth weight prediction by 3 dimensional ultrasonography: fractional limb volume. J Ultrasound Med 2001;20:1283–92.

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Ultrasound abnormalities of the amniotic fluid, membranes, umbilical cord, and placenta

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The advent of prenatal ultrasound has not only allowed clinicians to obtain more information about fetal anatomy, but also about the intrauterine environment through the evaluation of the amniotic fluid volume, fetal membranes, the umbilical cord, and the placenta. Evaluation of these entities is an integral part of every sonographic evaluation. This article reviews various conditions that can be detected by prenatal ultrasound evaluation.

Amniotic fluid

Sonographic evaluation of the amniotic fluid volume

The amniotic fluid volume is the sum of the inflows and outflows of the amniotic sac and is a reflection of the intrauterine environment. In early gestation, before the development of fetal urination and swallowing, the amniotic fluid is likely formed by active transport by the amnion into the amniotic space and water is allowed to flow passively [1]. In later gestation, when the fetal skin is keratinized, the major pathways include fetal urination, fetal swallowing, fetal lung fluid secretion, and intramembranously [1].

Ultrasound visualization of the amniotic fluid permits both subjective and objective estimates of the amniotic fluid volume. Examination of the amniotic fluid volume has become an integral part of both routine and targeted ultrasound. Subjective evaluation of the amniotic fluid volume is usually performed in pregnancies less than 20 weeks gestation; however, the use of a numerical estimate provides a more accurate assessment of fluid volume over time, allowing comparisons on follow-up. Normal amniotic fluid volumes have been defined across gestational age with a progressive increase from 8 weeks gestation to a peak of

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800 mL at 32 weeks gestation, followed by a slow decline to term and beyond [2]. Using dye dilutional studies, Didly et al [3] showed a correlation between previously reported amniotic fluid indices and term pregnancy volumes [2].

Abnormalities of the amniotic fluid volume have been associated with adverse perinatal outcome and may be a marker for other fetal abnormalities, such as congenital malformations, aneuploidy, and growth restriction. For example, oligohydramnios in the absence of premature rupture of membranes can be associated with urinary tract abnormalities, such as renal agenesis.

Several ultrasound techniques have been described to estimate the amniotic fluid volume. In 1984, Chamberlain et al [4] introduced the concept of using the depth of the maximum vertical pocket. This semiquantitative estimate measured the deepest pocket of amniotic fluid free of umbilical cord or fetal parts in the anteroposterior plane of the uterus. The amniotic fluid volume was considered normal if the maximum vertical pocket was greater than 2 cm and less than 8 cm. Oligohydramnios was defined as a pocket less than 1 cm in depth and polyhydramnios was defined as a pocket over 8 cm. In subsequent studies, the single deepest pocket technique was shown to have several shortcomings. The amniotic fluid index (AFI) was introduced as a more reliable estimate of the amniotic fluid volume [5]. This technique involves dividing the uterus into four quadrants summing the deepest vertical pockets free of umbilical cord or fetal parts. The normal range of AFI in a population of patients at increased risk for poor perinatal outcome and already undergoing antenatal testing was defined as greater than 8 and less than 18 cm [5].

Moore and Cayle [6] established normal limits of AFI per week of gestation in normal pregnancy. Oligohydramnios (5th percentile) was defined as less than 7 cm and polyhydramnios (95th percentile) greater than 21 cm. An AFI of less than or equal to 5 cm was seen in less than 1% of normal term patients and an AFI of greater than 18 cm was seen in 15% of the normal population. Magann et al [7] introduced the two-diameter semiquantitative measurement of the amniotic fluid volume where the vertical depth of the maximum vertical pocket is multiplied by the largest horizontal diameter again free of umbilical cord or fetal parts. Recently, this group performed a large-scale study comparing the AFI, single deepest pocket, and two-diameter pocket in normal pregnancies. They concluded that the AFI was the most acceptable method for assessing fluid status in a singleton gestation [8].

Disorders of the amniotic fluid volume

Oligohydramnios complicates 0.5% to 8% of pregnancies and the prognosis for pregnancies complicated by oligohydramnios is gestational age–dependent. Fetal urination is a major source of amniotic fluid in the second half of pregnancy and any condition preventing formation of urine or entry into the amniotic sac results in oligohydramnios. In a series of 128 fetuses with severe oligohydramnios in the mid-trimester (13 to 24 weeks gestation), fetal abnormalities were detected in 51%, premature rupture of membranes in 34%, abruption in 7%, and

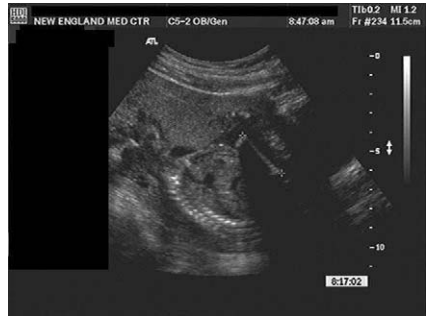

Fig. 1. Anhydramnios at 19 weeks gestation. There is no measurable pocket of fluid. The fetus is in close approximation to the placenta.

growth restriction in 5%. Aneuploidy was found in almost 1% of anomalous fetuses and in only 4% of cases no cause was detected [9].

The diagnosis of oligohydramnios is obtained by ultrasound evaluation of an AFI less than 5 cm at term (greater than 2 standard deviations below the mean); less than 8 cm before term; or a fluid pocket less than 2 cm (Figs. 1 and 2) [7]. Oligohydramnios with intact membranes warrants a comprehensive evaluation to detect possible fetal and placental abnormalities, growth restriction, or aneuploidy. Indigo carmine dye injected into the amniotic fluid cavity may facilitate the diagnosis of rupture of membranes if dye is seen on a tampon inserted into the vagina. Elevated maternal serum alpha-fetoprotein levels have also been linked to oligohydramnios, intrauterine growth restriction, preterm delivery, and fetal demise [10].

Several studies have correlated the AFI with perinatal outcome [4,11–13]. Chamberlain et al [4] reported a 13-fold increase in perinatal mortality if the amniotic fluid volume was marginally decreased and a 47-fold increase when severe oligohydramnios was present. The most common high-risk factors associated with oligohydramnios are intrauterine growth restriction and postterm pregnancy [4,12]. In a meta-analysis in 1999, an antepartum and intrapartum AFI of less than 5 cm was associated with an increased risk of cesarean section delivery for

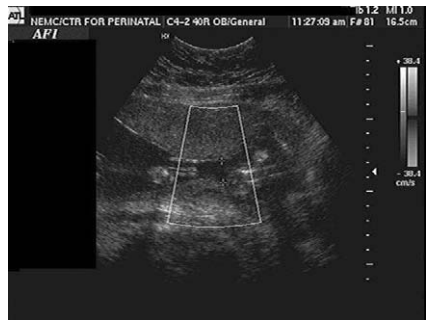

Fig. 2. Oligohydramnios. One pocket of fluid measuring less than 2 cm.

nonreassuring fetal heart rate tracings and Apgar scores of less than 7 at 5 minutes [11].

The addition of color flow Doppler has been reported to decrease significantly the measured AFI and increase the diagnosis of oligohydramnios [14,15]. The question of whether color Doppler should be used routinely remains controversial because the current normograms were obtained without the use of color Doppler.

Polyhydramnios

Polyhydramnios is defined as an AFI greater than the 95th percentile for gestational age or a maximum vertical pocket greater than 8 cm (Fig. 3) [5,6,8]. Polyhydramnios complicates approximately 1% of all pregnancies. Ultrasound evaluation of the amniotic fluid allows polyhydramnios to be classified as mild if the maximum pocket is between 8 and 11 cm, moderate if the maximum pocket is 12 to 15 cm, and severe if the maximum pocket is over 16 cm [16]. The latter occurs in less than 5% of all cases of polyhydramnios. The degree and prognosis of polyhydramnios is related to the underlying etiology. When a diagnosis of polyhydramnios is made, careful evaluation of the fetal anatomy is warranted. Fetal abnormalities of the central nervous system, gastrointestinal tract, and musculoskeletal system have been reported [16,17]. Because fetal swallowing is an important mechanism in controlling the AFI, such abnormalities as duodenal or esophageal atresia are often associated with increased fluid volume (Fig. 4). Polyhydramnios is seen in 35% of cases of anencephaly [18]. The possible pathogenesis includes transudation of the exposed meninges and lack of antidiuretic effect because of impaired arginine vasopressin secretion.

Although many cases of polyhydramnios are idiopathic, when a cause is found almost 80% have moderate or severe polyhydramnios [19]. Idiopathic polyhydramnios, usually in the mild range, although associated with macrosomia and cesarean delivery, has not been associated with adverse perinatal outcome [19]. Maternal diabetes, fetal infection, aneuploidy, and multiple gestations have also been associated with polyhydramnios [17–19]. Polyhydramnios that develops secondary to maternal diabetes is less well understood. Maternal hyperglycemia

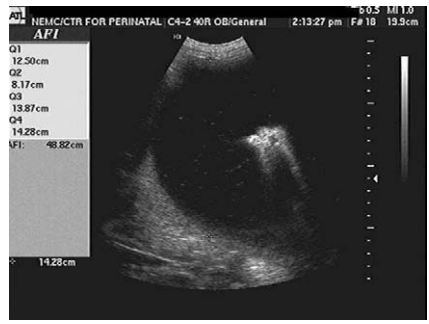

Fig. 3. Amniotic fluid pocket measuring 14.8 cm consistent with polyhydramnios.

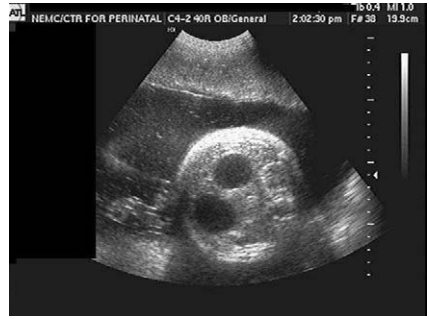

Fig. 4. Double bubble sign associated with duodenal atresia in a fetus with polyhydramnios.

causes fetal hyperglycemia, which may lead to osmotic diuresis, increased glomerular filtration rate, and urinary output [1].

Amniotic fluid volume in multiple gestations

Estimating the amniotic fluid volume in multiple gestations can be challenging because of the irregularity of the cavities occupied by each fetus and the ability to locate the separating membrane. Magann et al [20] compared the AFI, maximum vertical pocket, and two-diameter pockets in 45 dichorionic-diamniotic twin gestations where dye had been injected into each sac. When the AFI was normal, all three techniques were equivalent.

Membranes

Amnion rupture sequence or amniotic band syndrome

The amnion rupture sequence, commonly known as ''amniotic band syndrome,'' is a cause of fetal deformations involving the limbs, trunk, and craniofacial region. Most cases are sporadic with reported incidence ranges from 1 in 1200 to 15,000 live births [21]. This discrepancy in incidence rates is likely caused by misdiagnoses. The clinical manifestations of amniotic band syndrome vary from minor deformities, such as syndactyly, to severe and even lethal anomalies [22].

Several theories have been proposed to explain the occurrence of these anomalies [23–25]. The amnion and chorion normally fuse by 14 weeks; however, separation may persist into the second trimester and may be a normal finding. Persistence after 16 weeks may be associated with amnion rupture, subchorionic bleed, and early amnion rupture sequence. Rupture of the amnion without rupture of the chorion leading to transient oligohydramnios and passage of the fetus from the amniotic to the chorionic cavity is one of the most widely accepted theories [23]. The variable phenotype seen with amniotic band syndrome has been attributable to the timing of the rupture. Early rupture, within

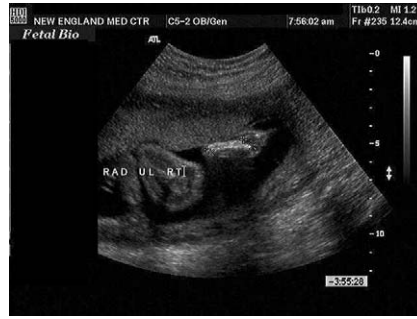

Fig. 5. Amputation of the fetal hand from suspected amniotic band syndrome.

45 days of gestation, leads to the most severe malformations, particularly of the central nervous system, face, and viscera. Amniotic bands may tear or disrupt previously normally developed structures leading to amputations and nonanatomic facial clefts (Fig. 5) [25].

Amniotic band syndrome may be detected sonographically by demonstrating fetal deformities in a nonembryologic distribution or by the visualization of bands; the latter may be extremely difficult [22,25]. The appearance of sheets or bands of amnion attached to the fetus with resultant deformity or restriction of motion allows an accurate diagnosis to be made (Fig. 6). Cranial involvement may be detected as anencephaly and facial clefts; visceral involvement may result in omphalocele or bladder exstrophy; and various limb deformities, such as constriction rings, lymphedema, amputations, and clubfoot, may occur [25]. The most common defect is constriction bands of the extremities [25]. Constriction of the umbilical cord and subsequent fetal demise has also been reported [22].

The antenatal course is dependent on the nature of the lesions and extent of the malformations [24,25]. Management may depend on the severity of the sonographic findings, and includes expectant management or termination of pregnancy. Amniocentesis should be offered if the diagnosis remains unclear. Crombleholme et al [21] reported on fetal intrauterine intervention in the lamb model with release of constrictive lesions.

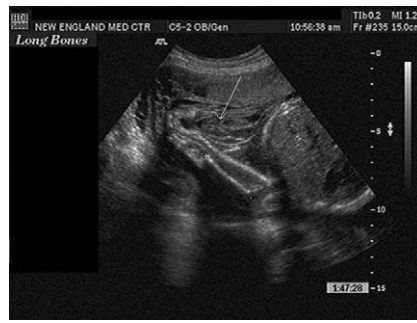

Fig. 6. Note the presence of amniotic sheets in the upper right corner (*arrow*).

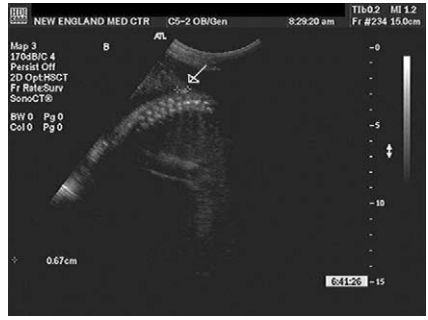

Fig. 7. Amnion nodosum. Small echogenic nodule along the membranes of a donor twin in a case of twin-to-twin transfusion syndrome (*arrow*).

Amnion nodosum

Amnion nodosum are nodules seen in the amnion that on pathologic review are often called squamous amnionic metaplasia. These nodules can vary in size from 1 to 5 mm in diameter and are composed of ectodermal debris, including vernix, hair, squames, and sebum. They are associated with oligohydramnios and are most commonly found in fetuses with renal agenesis, prolonged premature rupture of membranes, or the placenta of a donor twin in twin-to-twin transfusion syndrome (Fig. 7). The clinical significance of amnion nodosum is unknown.

Umbilical cord

The sheathing of the body stalk and omphaloenteric duct forms the umbilical cord during the embryonic period by the amniotic somatopleura. Sonographically, the umbilical cord can be seen as early at 42 days gestation and is well established by 8 to 9 weeks (Fig. 8). Transvaginal evaluation has enabled visualization of the physiologic herniation of the midgut, which occurs between

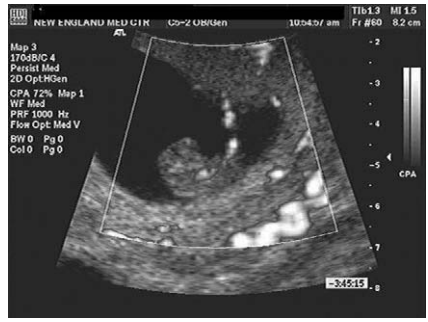

Fig. 8. Umbilical cord in the first trimester.

Table 1
Abnormalities of the umbilical cord

Abnormal length
Absence of the umbilical cord
Abnormal cord insertion
Marginal insertion
Velamentous insertion
Vasa previa
Distortional abnormalities
Loops
Knots
Coiling
Entanglement
Abnormalities of vessel number
Single umbilical artery
Persistent right umbilical vein
Umbilical cord masses and vascular malformations
Cysts
Umbilical cord hematoma
Umbilical vein or artery thrombosis
Umbilical vein varix
Umbilical artery aneurysm

Modified from Abnormalities of the umbilical cord. In: Bianchi DW, Crombleholme TM, D'Alton ME, editors. Fetology. New York: McGraw Hill; 2000; with permission.

6 and 10 to 12 weeks gestation. The umbilical cord is composed of three vessels: two arteries and one vein arranged in a spiral or helical fashion within the cord. It also contains specialized mucopolysaccharide-rich mesenchyme known as "Wharton's jelly" that protects the cord from compression. Abnormalities in the number of vessels including a two-vessel cord and persistent right umbilical vein have been reported (Table 1) [26–28].

The sonographic evaluation of the umbilical cord includes the number of vessels, the observation of coiling and looping of the cord, and Doppler velocimetry studies. The cord is evaluated at the fetal insertion site along the fetal abdominal wall, at the placental insertion site, and at a segment floating in the amniotic fluid.

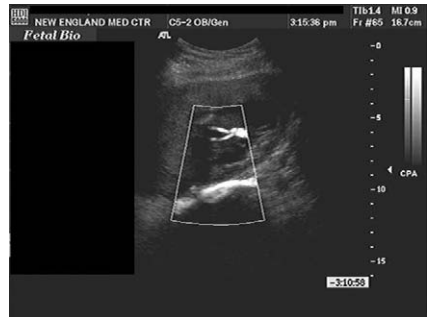

Fig. 9. Normal umbilical cord with Doppler color showing two umbilical arteries around the fetal bladder.

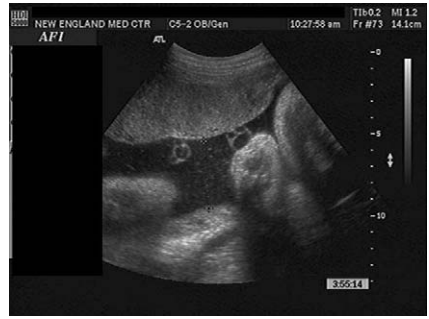

Fig. 10. Normal umbilical cord in cross-section demonstrating three vessels. The umbilical vein has the larger diameter.

A normal cord with two umbilical arteries can be confirmed on transverse section by visualizing two vessels lateral to the fetal bladder (Figs. 9 and 10).

The umbilical cord grows by tension as a result of fetal movement. The mean length of a term umbilical cord is 60 cm. A short cord is defined as less than 35 cm at term [28]. Measurement of the umbilical cord by sonographic evaluation, however, is not routinely performed.

Coiling of the umbilical cord is believed to provide protection against forces, such as tension, compression, and entanglement. Although up to 30% of umbilical cords are uncoiled at 20 weeks gestation, less than 5% lack vascular coiling at term [29]. Uncoiled umbilical cords have been associated with increased perinatal morbidity and mortality including intrauterine growth restriction, oligohydramnios, fetal anomalies, preterm delivery, and fetal demise [30].

Knots of the umbilical cord are classified as true or false knots. Prenatal diagnosis of true and false knots is extremely challenging, because there are no typical prenatal sonographic characteristics. Rarely, a vascular protuberance along the cord can be seen with false knots [31].

The umbilical cord frequently becomes coiled around fetal parts, particularly the neck, termed a ‘‘nuchal cord.’’ Sonographic detection was first reported by Jouppill and Kirkinen [32]. Nuchal cords may be present in 25% of pregnancies; however, a single nuchal loop is most likely an incidental finding not associated with fetal morbidity and mortality. The incidence of perinatal death secondary to a nuchal cord is very low. The presence of multiple nuchal cords has been associated with moderate to severe variable deceleration while monitored in labor, meconium-stained amniotic fluid, need for resuscitation, and lower umbilical artery pH [33]. Sensitivity with color Doppler to detect a nuchal cord is over 80%, which is higher than conventional gray-scale ultrasound [34].

Nyberg et al [35] reported the first case of ultrasonographic evidence of cord entanglement in a monochorionic-monoamniotic twin gestation. Ultrasound evaluation and color Doppler notes a mass-like structure between the two fetuses. Each umbilical cord should be traced to each of the twins (Fig. 11).

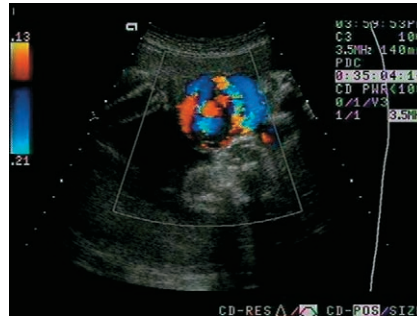

Fig. 11. Mass of entangled umbilical cords in a monochorionic-monoamniotic twin gestation.

Single umbilical artery

Single umbilical artery (SUA) is one of the most common congenital abnormalities with an incidence of about 1% of all pregnancies. Possible mechanisms giving rise to a SUA include primary agenesis of one artery, atrophy or atresia of a previously present artery, and persistence of single alloantoic artery. The left umbilical artery is more commonly absent [26]. SUA is a developmental abnormality with no known recurrence risk.

Ultrasonographic imaging has permitted the prenatal diagnosis of a SUA and a cross-section of the umbilical cord has become an integral part of every prenatal sonogram. The infrarenal portion of the umbilical arteries can be seen on transverse section lateral to the fetal bladder. Absence of one of the arteries confirms a SUA (Figs. 12 and 13). Diagnosis of a SUA has been associated with increased perinatal morbidity and mortality mostly because of an association with congenital malformations, the incidence of which may be 30% to 60% [26–28]. A SUA can be associated with malformations of almost any major organ system. The association of a single umbilical artery and other congenital abnormalities warrants a targeted sonogram and possibly a fetal echocardiogram. As an isolated finding, SUA has not been an association with aneuploidy; however, in the

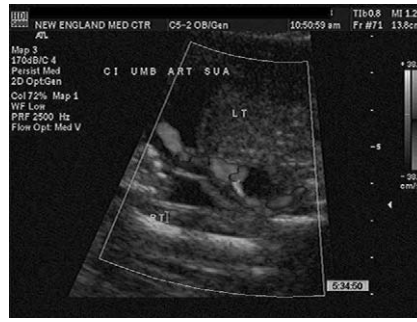

Fig. 12. Color Doppler demonstrating absence of one umbilical artery.

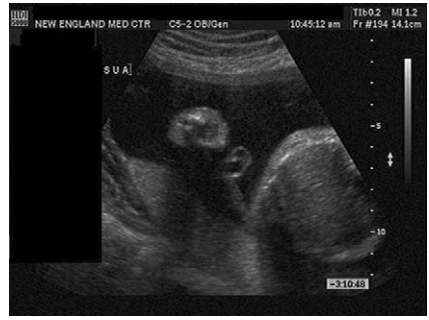

Fig. 13. Cross-section of the cord showing two vessels.

presence of other abnormalities the reported incidence of aneuploidy has been as high as 8% [26,27]. Fetal growth should be assessed in the third trimester in cases of isolated SUA because growth restriction has been reported [28].

Abnormalities of cord insertion

The umbilical cord inserts at or near the center of the placenta in over 90% of cases. Abnormalities of cord insertion can be detected sonographically and may be clinically important. Marginal insertion, also referred to as the "battledore placenta," occurs when the cord inserts at the placental margin. Marginal insertion can be seen in 5% to 7% of term pregnancies.

Velamentous insertion occurs in 1% to 2% of term singleton pregnancies and more frequently in multiple gestations. The umbilical vessels separate into the membranes at a distance from the placental margin surrounded only by a fold of amnion devoid of Wharton's jelly. Clinically, velamentous cord insertion has been associated with cord compression, poor fetal growth, thrombosis, placenta previa, and vas previa (Fig. 14).

In vasa previa, some of the fetal vessels are seen in the membranes crossing the region of the internal os ahead of the presenting part. Risk factors for vasa previa include velamentous insertion, succenturiate lobe, and low-lying placenta

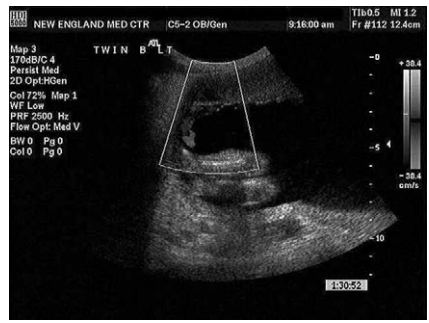

Fig. 14. Velamentous insertion of the umbilical cord.

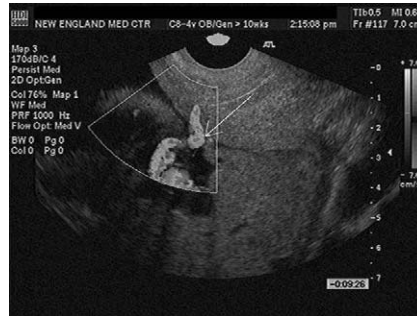

Fig. 15. Color Doppler demonstrating the presence of fetal vessels above the internal os (*arrow*).

[36]. Vasa previa can be detected by ultrasound evaluation and detection can significantly decrease fetal mortality [36]. Potential danger of exsanguination exists if rupture of membranes causes a nick in the fetal vessels. Transvaginal color Doppler imagining has increased the ability to diagnose cases of vasa previa in the mid-trimester (Fig. 15) [37].

Abdominal wall defects and the umbilical cord

Gastroschisis, omphalocele, and body stalk anomaly are abdominal wall defects that are related to the development of the umbilical cord. Gastroschisis is an abdominal wall defect likely secondary to a vascular abnormality resulting in a right paraumbilical defect. The umbilical cord is normally inserted with herniation of the gut to the right without a membranous coating. Omphalocele is distinguished from gastroschisis because the cord insertion is seen at the apex of the membrane that covers the abdominal wall defect. Body stalk anomaly is the most severe abdominal wall defect that results in the absence or shortening of the umbilical cord. The abdominal organs lie outside the abdominal cavity and appear attached to the placenta. The proposed causes of this complex abnormality include resemblance to the amnion rupture sequence or a vascular disruption and nonclosure of the abdominal wall [25,38]. The pattern of anomalies depends on the degree of abnormal development of the four embryonic folds. Sonographic evidence of body-stalk anomaly is suspected in the presence of large thoracic or abdominal wall defect; skeletal abnormalities, such as kyphosis or scoliosis; and absent or very short umbilical cord [25,38]. When the diagnosis is made, this anomaly is uniformly fatal.

Umbilical cord masses

Umbilical cord masses include cysts, tumors, aneurysms, and varices. The presence of these masses warrants careful evaluation of the umbilical vessels to evaluate complications, such as cord compression or thrombosis, and a detailed fetal survey for possible associated fetal malformations or compromise.

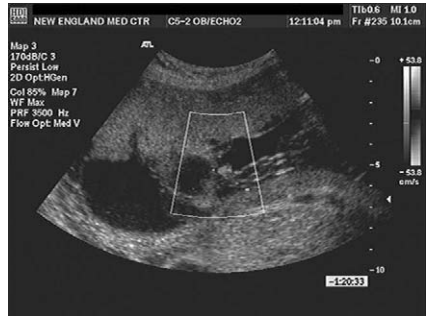

Fig. 16. Umbilical cord cyst.

Umbilical cord cysts may be true cysts or pseudocysts and this differentiation can only be established by pathologic evaluation. True cysts are derived from the embryonic remnants of either the allantoic or omphalomesenteric duct and are more common toward the fetal end of the cord (Fig. 16). A prospective screening study of 859 women noted an incidence of 3.4% in the first trimester [39]. Although many of these resolved, over 20% of these umbilical cord cysts persisted into the second and third trimester and were associated with fetal aneuploidy or fetal structural defects [39]. The detection of umbilical cord cysts in the second trimester warrants the offering of fetal karyotyping.

Prenatal sonographic diagnosis of an umbilical cord varix has been reported. Although rare, varicosity of the umbilical vein may occur in the intra-amniotic portion of the umbilical vein and the fetal intra-abdominal portion. The intra-amniotic portion is seen as an abnormal dilation of the vein at the abdominal insertion site that can lead to venous compression. The extrahepatic portion of the fetal intra-abdominal umbilical vein has been measured in normal fetuses and found to increase throughout gestation from 3 mm at 15 weeks gestation to 8 mm at term [40]. The varix of the fetal intra-abdominal umbilical vein results in an oval cystic mass between the abdominal wall and the inferior edge of the fetal liver. The detection of venous flow with color Doppler distinguishes a varix from other types of masses (Figs. 17 and 18) [40].

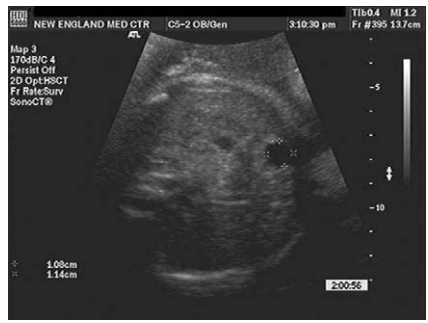

Fig. 17. Umbilical varix of the fetal intra-abdominal portion.

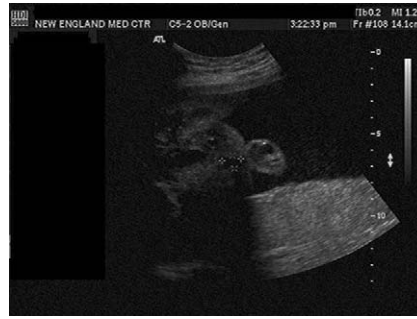

Fig. 18. Varix of the intra-amniotic portion of the umbilical cord.

The cause of the fetal intra-abdominal umbilical vein remains unknown. Possible etiology includes dilation caused by an intrinsic weakness in the wall of the extrahepatic portion of the umbilical vein, possibly of the portion where the right umbilical vein becomes obliterated during embryogenesis [28,40]. Mahoney et al [40] suggested that the detection of an umbilical cord varix is associated with an increased risk of adverse fetal outcome including fetal demise necessitating antenatal monitoring.

Spontaneous umbilical cord hematoma is a very rare condition and most cases are iatrogenic following cordocentesis or more rarely amniocentesis [31]. These usually appear as focal masses and can be associated with a 50% risk of fetal loss. Hemangiomas of the umbilical cord are the most common tumors of the umbilical cord albeit rare entities. These are most commonly seen at the placental insertion of the umbilical cord and sonographic appearance may be that of an echogenic or multicystic mass with color Doppler [31].

Placenta

The placenta can be identified as early as 6 weeks gestation by transvaginal evaluation and by 10 weeks gestation by transabdominal evaluation as an echogenic and thickened rim around the gestational sac [41]. It is distinct from the hyperechoic myometrium. The placenta increases in size throughout gestation and typically has a discoid shape. Hypoechoic areas known as ‘‘venous lakes’’ may be present in the placental parenchyma and on color Doppler blood flow are usually absent.

Although placental volume in the second trimester may be a predictor of fetal outcome, there is no accurate or acceptable method of measurement [42]. The thickness of the placenta can be assessed on sonogram and rarely exceeds 4 cm. Hyperplacentosis or placentomegaly has been associated with several entities including diabetes mellitus; immune and nonimmune hydrops; fetal infections, such as parvovirus and syphilis; molar pregnancy; and aneuploidy [41].

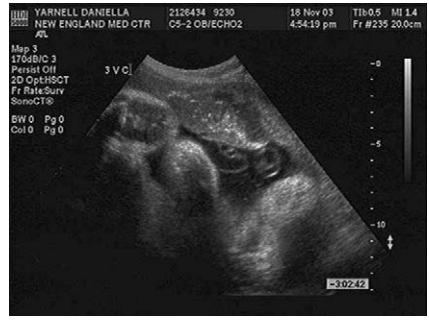

Fig. 19. Calcifications in the placenta.

Calcium deposition also occurs normally in the placenta and appears sonographically as bright intraplacental echoes. Numerical grade has been assigned from grade 0 to grade III, where grade 0 is no calcifications and grade III has extensive echogenicity. Placental grading was believed to correlate with fetal lung maturity; however, larger studies have shown this was not reliable and amniocentesis for fetal lung maturity studies remains the gold standard [43]. Placental grading has little clinical significance, although cigarette smoking has been associated with increased calcifications (Fig. 19) [44].

Placental shape abnormalities

Abnormalities of placental shape are most often secondary to disappearance of villi. The placenta normally develops where the chorionic villi interfacing the decidua basalis grow and the remaining villi undergo atrophy. Placental abnormalities can be detected by sonogram and may affect clinical management and obstetric outcome.

Placenta membranacea is an uncommon condition with an incidence of 1:3000 live births. With placenta membranacea, all the fetal membranes are covered by functioning villi. The placenta develops as an abnormally thin membranous structure. On ultrasound evaluation, the placenta is seen over the entire uterine surface. Clinically, placenta membranacea can be associated with antenatal or postpartum bleeding, the latter secondary to poor separation.

The presence of one or more small accessory lobes that develop in the membrane at a distance from the main placenta is referred to as ''succenturiate lobe.'' This can be detected sonographically and is clinically important, because retained accessory lobes can be associated with postpartum hemorrhage and infection. Succenturiate lobes are also associated with an increased incidence of velamentous insertion of the umbilical cord and vasa previa.

Bipartite placenta is a placenta that is separated in two and the lobes originate from the anterior and posterior wall of the uterus. The cord can be inserted between the two lobes. Unlike the bipartite placenta, placenta bilobate refers to a placenta where the cord inserts into either lobe but not in the chorionic ridge.

Circumvallate placenta occurs when the membranes insert away from the placental edge toward the center, but a thick chorioamniotic membrane that forms a ridge characterizes this insertion site. On sonographic evaluation, suspicion of a circumvallate placenta occurs if an irregular placental edge, uplifted margin, or placental shelf is seen. Although complete circumvallate placenta has been associated with adverse perinatal outcome, the accuracy of prenatal sonographic diagnosis remains low [45].

Abnormalities of placental location

Establishing location of the placenta in relationship to the internal cervical os is an integral part of every ultrasound evaluation. Placenta previa complicates 1 in 250 to 300 pregnancies. The concept of placental migration was introduced by King [46] and may explain why the incidence of placenta previa is gestational age–dependent. The incidence may be as high as 25% in evaluations performed at 18 weeks gestation. The resolution of a placenta previa seen early in gestation may be caused by growth of the lower uterine segment. A placenta that covers the internal os completely during the midtrimester is more likely to remain a complete placenta previa at term (Fig. 20).

Placenta previa is classified as complete or total when the placenta covers the entire internal cervical os, partial when the os is only partially covered by placenta, and marginal when the edge of the placenta is at the margin of the internal os [47]. Risk factors associated with placenta previa include advanced maternal age, previous cesarean section or uterine scar, multiple gestations, and previous elective abortions [47]. The recurrence risk may be as high as 10-fold.

The diagnostic accuracy of transvaginal sonography is superior compared with the transabdominal approach [48]. The evaluation should take place with the maternal bladder filled and again postvoid. Extensive distention of the bladder may cause apposition of the anterior and posterior uterine walls and lead to an erroneous diagnosis of placenta previa.

Abnormal placentation with myometrial invasion can be a life-threatening condition. Placenta accreta is defined as partial or total absence of the decidua

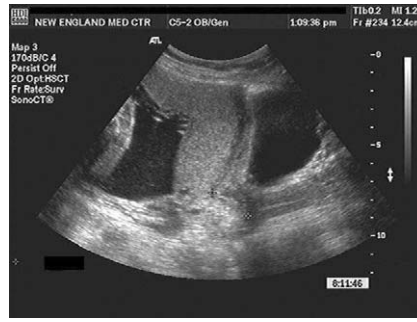

Fig. 20. Complete placenta previa over the cervical os.

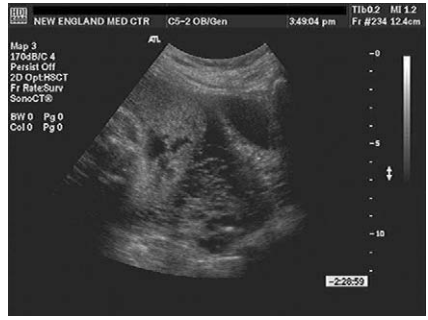

Fig. 21. Suspicion of an accreta with lacunar spaces over the cervical os.

basalis and Nutabuch layer allowing villi to attach to the myometrium. Deeper penetration into the myometrium is referred to as ''placenta increta'' and invasion through the myometrium with potential invasion of adjacent organs is known as placenta percreta [47]. The occurrence of accreta with a placenta previa may be as high as 5%. Risk factors include advanced maternal age and previous uterine surgery. The risk may be as high as 67% in women who have undergone four or more cesarean section deliveries [47].

Antenatal diagnosis caused by increased accuracy of ultrasound and MRI detection has significantly lowered postpartum hemorrhage, maternal morbidity, and mortality. Normally, the retroplacental area is composed of myometrium and uteroplacental vessels that appear hypoechoic and measure about 1 to 2 cm in thickness. Ultrasound criteria for placenta accreta involves careful evaluation of this retroplacental area where there is loss of the normally hypoechoic space and the placental myometrial interface. Markedly dilated spaces called lacunae and increased vascularity may also be present giving this area a Swiss cheese appearance [49]. Transvaginal ultrasound with color Doppler imaging improves visualization and MRI may be helpful to delineate invasion of adjacent organs (Figs. 21 and 22) [50].

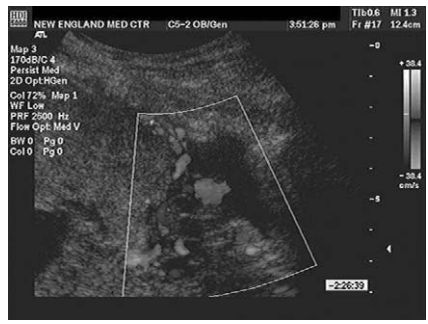

Fig. 22. Color Doppler helps demonstrate large vessels over the cervix.

Placental abruption

Placental abruption complicates approximately 1% of pregnancies and is defined as a premature separation of a normally implanted placenta. Placental abruption may present clinically with abdominal and pelvic pain, vaginal bleeding, or uterine tenderness. Numerous risk factors have been associated with placental abruption, such as maternal hypertension, smoking, cocaine use, trauma, premature rupture of membranes, and uterine anomalies [47].

The sensitivity of ultrasound to visualize a placental abruption is approximately 50% because the appearance may be variable depending on the location of the separation and timing of evaluation [51]. Acutely, the area may appear hyperechoic; however, after 1 to 2 weeks, the area of hemorrhage may become hypoechoic. Although visualization of a thickened retroplacental area may raise suspicion of a retroplacental hemorrhage, uterine contractions, subchorionic cysts, and uterine fibroids may have the same appearance [51]. Fibroids are generally more uniform and round in shape and color Doppler demonstrates increased vascular flow. Subchorionic cysts may be confused with chorioangiomas or placental abruption; however, these cysts are found most often below the chorionic plate and usually have no clinical significance. Separation of the retromembranous area may also be seen. Color Doppler studies may help differentiate these entities because placental abruption lacks vascular activity.

Prognosis depends on several factors including the amount of placental detachment and gestational age. The gravest prognosis is associated with a significant retoplacental hemorrhage involving over 30% to 40% of the placenta and may include fetal growth restriction, oligohydramnios, and preterm delivery (Fig. 23) [52].

Placental masses

Placental tumors are generally benign; however, metastatic lesions from hematogenous spread of conditions, such as metastatic melanoma, may occur. Color flow and pulsed Doppler studies can help differentiate between a vascular and nonvascular lesion.

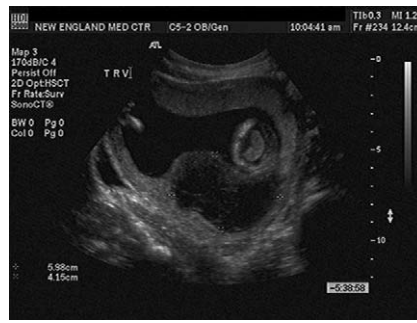

Fig. 23. Retroplacental bleed.

Chorioangioma, also referred to as ‘‘hemangioma,’’ is the most common benign placental tumor [53]. Small chorioangiomas are present in approximately 1% of all examined placentas. Large clinically significant chorioangiomas measuring over 5 cm are rare. These lesions can be associated with fetal morbidity, such as nonimmune hydrops, intrauterine growth restriction, and stillbirth. Preeclampsia, polyhydramnios, and elevated amniotic fluid and maternal serum alpha-fetoprotein have also been reported in association with large chorioangiomas [53].

On ultrasound evaluation, these lesions most commonly protrude from the fetal surface and appear as a solid well-circumscribed mass. Color Doppler evaluation denotes a very vascular lesion, differentiating chorioangiomas from avascular masses, such as fibroids, hematomas, or subchorionic fibrin. Chorioangiomas measuring greater than 5 cm in size warrant fetal evaluation and follow-up to assess for signs of fetal compromise, such as cardiac overload.

Gestational trophoblastic disease

Complete hydatidiform mole is characterized by chorionic villi that are markedly hydropic and swollen and proliferation of the trophoblastic cell resulting in very elevated human chorionic gonadotropin levels. Sonographically, hydatidiform mole has a characteristic appearance. The uterus is large and filled with multicystic hyperechoic or anechoic masses that may correlate to vesicles, the fetus is absent, and there is no amniotic fluid [54]. In the first trimester, vesicles can be detected, although these may not be delineated as easily because the uterine cavity may normally appear hyperechoic (Fig. 24) [55].

The presence of a coexisting fetus is referred to as a ‘‘partial hydatidiform mole.’’ Severe intrauterine growth restriction and fetal anomalies may be present. Karyotype notes triploidy in almost 90% of cases. Sonographic evaluation notes a thickened placenta with multiple cystic spaces (Fig. 25).

Bilateral theca lutein cysts can be seen in up to 50% of cases of gestational trophoblastic disease. These are believed to occur secondary to high circulating

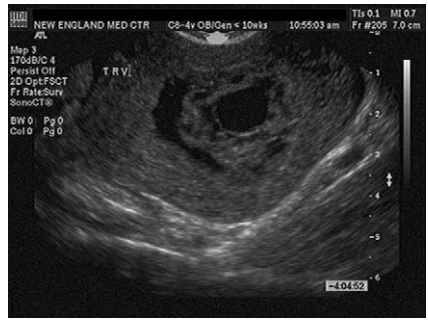

Fig. 24. Ultrasound scan of a complete mole in the first trimester.

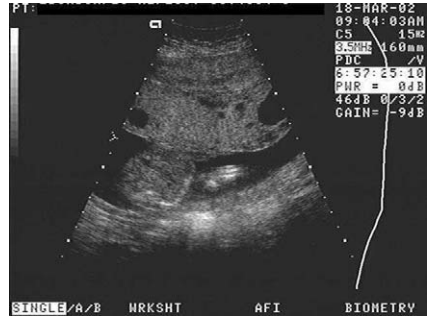

Fig. 25. Ultrasound scan of a partial mole showing multicystic masses in the placenta and presence of a fetus.

levels of stimulating β-human chorionic gonadotropin and appear as large multiloculated simple cysts, which may require months to resolve.

Doppler evaluation

The placental bed spiral arteries undergo progressive physiologic changes throughout gestation. Doppler studies of the umbilical cord are considered an evaluation of the placenta and can assess placental blood flow in pregnancy. The most commonly used measurements include the systolic over diastolic ratio and the resistance index; the latter represents the difference between the peak systolic and end-diastolic shift divided by the peak systolic shift.

In early pregnancy, placental resistance is high and absent end-diastolic velocity normally may be seen between 14 and 18 weeks gestation [56]. A continuous decline in umbilical artery resistance over gestation is normally observed. The progression of increased resistance and loss of end-diastolic velocity or eventual reversal has been associated with adverse pregnancy outcome including intrauterine growth restriction, oligohydramnios, and stillbirth. When used in high-risk pregnancies, Doppler studies can decrease perinatal mortality. Doppler studies should not be used routinely and currently no benefit other than use in the eval-

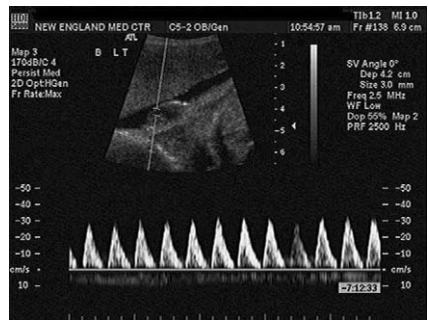

Fig. 26. Color Doppler of umbilical artery showing absent end-diastolic flow.

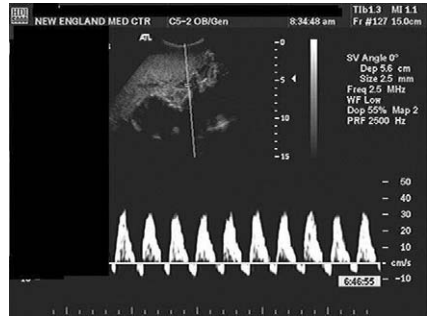

Fig. 27. Color Doppler of the umbilical artery showing reversed end-diastolic flow.

uation of intrauterine growth restriction has been established (Figs. 26 and 27) [57,58].

Summary

Prenatal ultrasound has expanded the ability to assess the umbilical cord, fetal membranes, amniotic fluid volume, and placenta. Evaluation of these structures provides information regarding the intrauterine environment. Umbilical cord abnormalities may be associated with fetal aneuploidy, structural anomalies, and fetal compromise. Estimating the amniotic fluid volume has become an integral part of a sonogram and provides immense information regarding possible fetal anomalies and perinatal outcome. Likewise, placental location or abnormalities may significantly impact obstetric management and prognosis. Early detection of several of these conditions may lead to increased vigilance that may improve perinatal outcome.

References

[1] Brace RA. Progress toward understanding the regulation of amniotic fluid volume: water and solute fluxes in and through the fetal membranes. Placenta 1995;16:1–18.
[2] Brace RA, Wolf EJ. Normal amniotic fluid volume changes throughout pregnancy. Am J Obstet Gynecol 1989;161:382–8.
[3] Dildy GA, Lira N, Moise KJ, Riddle GD, Deter RL. Amniotic fluid volume assessment comparison of ultrasound estimates vs direct measurements with dye-dilution technique in human pregnancy. Am J Obstet Gynecol 1992;167:986–94.
[4] Chamberlain PF, Manning FA, Morrison I, Harman CR, Lange IR. Ultrasound evaluation of the amniotic fluid: the relationship of marginal and decreased amniotic fluid volume to perinatal outcome. Am J Obstet Gynecol 1984;150:245–9.
[5] Phelan JP, Ahn MO, Smith CV, Rutherford SE, Anderson E. Amniotic fluid index measurement in pregnancy. J Reprod Med 1987;32:601–4.
[6] Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. Am J Obstet Gynecol 1990;162:1168–72.

[7] Magann EF, Nolan TE, Hess LW, Martin RW, Whitworth NS, Morrison JC. Measurement of the amniotic fluid volume: accuracy of ultrasonographic techniques. Am J Obstet Gynecol 1992; 167:1533–7.
[8] Magann EF, Sanderson M, Martin RW, Chauhan S. The amniotic fluid index, single deepest pocket and 2-diameter pocket in human pregnancy. Am J Obstet Gynecol 2000;182:1581–8.
[9] Shipp TD, Bromely B, Pauker S, Frigoletto FD, Benacerraf BR. Outcome of singleton pregnancies with severe oligohydramnios in the second and third trimester. Ultrasound Obstet Gynecol 1996;7:108–13.
[10] Dyer SN, Burton BK, Nelson LH. Elevated maternal serum alpha-feto-protein levels and oligohydramnios poor prognosis for pregnancy outcome. Am J Obstet Gynecol 1987;157:336–9.
[11] Chauhan S, Sanderson M, Hendrix N, Magann EF, Devoe LD. Perinatal outcome and amniotic fluid index in the antepartum and intrapartum period: a meta-analysis. Am J Obstet Gynecol 1999; 181:1473–8.
[12] Manning FA, Hill LM, Platt LQ. Qualitative amniotic fluid volume determination by ultrasound: antepartum detection of intrauterine growth restriction. Am J Obstet Gynecol 1981;139:254–8.
[13] Rutherford SE, Phelan VP, Smith CV, Jacobs N. The four-quadrant assessment of the amniotic fluid volume: an adjunct to antepartum fetal heart rate testing. Am J Obstet Gynecol 1987;70: 353–6.
[14] Bianco A, Rosen E, Kuczynski M, Tetrokalavili M, Lockwood CJ. Measurement of the amniotic fluid volume with and without color Doppler. J Perinat Med 1999;27:245–9.
[15] Magann EF, Chauhan S, Barrilleaux S, Whitworth NS, McCurley S, Martin JN. Ultrasound estimate of the amniotic fluid volume: color Doppler over diagnosis of oligohydramnios. Obstet Gynecol 2001;98:71–4.
[16] Hill LM, Breckle R, Thomas ML, Froes JK. Polyhydramnios: ultrasonographically detected prevalence and neonatal outcome. Obstet Gynecol 1987;69:21–5.
[17] Dasche JS, McIntire DD, Ramus RM, Santos-Ramos RN, Twickler DM. Hydramnios: anomaly prevalence and sonographic detection. Obstet Gynecol 2002;100:134–9.
[18] Bianchi DW, Crombleholme TM, D'Alton ME, editors. Anencephaly. In: Fetology: diagnosis and management of the fetus as a patient. New York: McGraw-Hill; 2000. p. 63–8.
[19] Panting-Kemp A, Nguyen T, Chang E, Quillan E, Castro L. Idiopathic polyhydramnios and perinatal outcome. Am J Obstet Gynecol 1999;181:1079–82.
[20] Magann EF, Chauhan S, Martin J. Ultrasound assessment of the amniotic fluid volume in diamniotic twins. J Soc Gynecol Invest 1995;2:609–13.
[21] Crombleholme TM, Dirkes K, Whitney TM, Alman B, Garmel S, Connelly RJ. Amniotic band syndrome in the fetal lambs I: Fetoscopic release and morphometric outcomes. J Pediatr Surg 1995;30:974–8.
[22] Mahoney BS, Filly RA, Callen PW, Golbus MS. The amniotic band syndrome: antenatal sonographic diagnosis and potential pitfalls. Am J Obstet Gynecol 1995;152:63–8.
[23] Torpin R. Amniochorionic mesoblastic fibrous strings and amniotic bands: associated constricting fetal anomalies or fetal death. Am J Obstet Gynecol 1965;91:65–75.
[24] Lockwood C, Ghidini A, Romero R, Hobbins J. Amniotic band syndrome: reevaluation of its pathogenesis. Am J Obstet Gynecol 1989;160:1030–3.
[25] Bianchi DW, Crombleholme TM, D'Alton ME, editors. Amniotic band syndrome. In: Fetology: diagnosis and management of the fetus as a patient. New York: McGraw-Hill; 2000. p. 761–70.
[26] Abuhamed AZ, Shaffer W, Mari G, Copel J, Hobbins J, Evans AT. Fetus-placenta-newborn: a single umbilical artery. Does it matter which artery is missing? Am J Obstet Gynecol 1995;173: 728–32.
[27] Nyberg DA, Mahoney BS, Luthy D, Kapur R. Single umbilical artery: prenatal detection of concurrent anomalies. J Ultrasound Med 1991;10:247–53.
[28] Sherer DM, Anyaegbunam A. Prenatal ultrasonographic morphologic assessment of the umbilical cord: a review. Part I. Obstet Gynecol Surv 1997;52:506–14.
[29] Strong TH, Finberg JH, Mattox JH. Antepartum diagnosis of noncoiled umbilical blood vessels. Am J Obstet Gynecol 1994;170:1729–31.

[30] Strong Jr TH, Elliott JB, Radin TG. Noncoiled umbilical blood vessels: a new marker for fetus at risk. Obstet Gynecol 1993;81:409–11.
[31] Sherer DM, Anyaegbunam A. Prenatal ultrasonographic morphologic assessment of the umbilical cord: a review. Part II. Obstet Gynecol Surv 1997;52:515–23.
[32] Jouppill P, Kirkinen P. Ultrasound diagnosis of nuchal encirclement by the umbilical cord: a case and methodological report. J Clin Ultrasound 1982;10:59–62.
[33] Jauniaux E, Ramsay B, Peellaerts C, Scholler Y. Perinatal features of pregnancies complicated by nuchal cord. Am J Perinatol 1995;12:255–8.
[34] Hanaoka U, Yanagihara T, Tanaka H, Hata T. Comparison of three-dimensional, two-dimensional and color Doppler in predicting the presence of a nuchal cord at birth. Ultrasound Obstet Gynecol 2002;19:471–5.
[35] Nyberg DA, Filly RA, Globus MS, Stephens JD. Entanglement of the umbilical cord: a sign of monoamniotic twins. J Ultrasound Med 1984;3:29–32.
[36] Fung TY, Lau TK. Poor perinatal outcome associated with vasa previa. Is it preventable? A report of three cases and review of the literature. Ultrasound Obstet Gynecol 1998;12:430–3.
[37] Nomiyama M, Toyota Y, Kawano H. Antenatal diagnosis of velamentous cord insertion and vasa previa with color Doppler imaging. Ultrasound Obstet Gynecol 1998;12:426–9.
[38] Craven C, Ward K. Placental causes of fetal malformations. Clin Obstet Gynecol 1996;39: 588–606.
[39] Ross JA, Jurlovic D, Zosmer N, Jauniaux E, Hacket E, Nicolaides KH. Umbilical cord cysts early in pregnancy. Obstet Gynecol 1997;89:442–5.
[40] Mahoney BS, McGahan JP, Nyberg DA, Reisner DP. Varix of the fetal intra-abdominal umbilical vein: comparison with normal. J Ultrasound Med 1992;11:73–6.
[41] Kuhlmann RS, Warsof S. Ultrasound of the placenta. Clin Obstet Gynecol 1996;39:519–34.
[42] Wolf H, Oosting H, Treffers PE. Second trimester placental volume measurement by ultrasound: prediction of fetal outcome. Am J Obstet Gynecol 1989;160:121–6.
[43] Spirt BA, Gordon LP. The placenta as an indicator of fetal maturity: fact and fancy. Semin Ultrasound CT MR 1984;5:290–7.
[44] Pinette MG, Loftus-Brault K, Nard DA. Maternal smoking and accelerated placental maturation. Obstet Gynecol 1989;73:379–82.
[45] Harris RD, Wells WA, Black WC, Chertoff JT, Poplack SP, Sargent SK, et al. Accuracy of prenatal sonography for detection of circumvallate placenta. AJR Am J Roentgenol 1997;168: 1603–8.
[46] King DL. Placenta migration demonstrated by ultrasonography: a hypothesis of dynamic placentation. Radiology 1973;109:167–70.
[47] Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GV, et al. Obstetrical hemorrhage. In: Williams obstetrics. 21st edition. New York: Appleton and Lange; 2001. p. 619–69.
[48] Farine D, Peisner DB, Timor-Trisch IE. Placenta previa: is the traditional diagnostic approach satisfactory? J Clin Ultrasound 1990;18:328–30.
[49] Cox SM, Carpenter RJ, Cotton DB. Placenta percreta: ultrasound diagnosis and conservative surgical management. Obstet Gynecol 1988;71:454–6.
[50] Levine D, Hulka C, Ludmir J. Placenta accreta: evaluation with color Doppler, power color Doppler and MR imaging. Radiology 1997;205:773–6.
[51] Nyberg DA, Cyr DR, Mack LA, Wilson DA, Schuman WP. Sonographic spectrum of placental abruption. AJR Am J Roentgenol 1987;148:161–4.
[52] Nyberg DA, Mack LA, Benedetti TJ, Cyr DR, Schuman WP. Placental abruption and placental hemorrhage: correlation of sonographic findings with fetal outcome. Radiology 1987;164: 357–61.
[53] Shalev E. Prenatal diagnosis of placental hemangioma and clinical implications; a case report. Int J Gynecol Obstet 1984;22:291–3.
[54] Wagner BJ, Woodward PJ, Dickey GE. From the archives of the AFIP. Gestational trophoblastic disease: radiologic-pathologic correlation. Radiographics 1996;16:131–48.

[55] Lazarus E, Hulka C, Siewert B, Levine D. Sonographic appearance of early complete molar pregnancies. J Ultrasound Med 1999;18:589–94.
[56] Harman CR, Baschat AA. Comprehensive assessment of fetal well being: which Doppler tests should be performed? Curr Opin Obstet Gynecol 2003;15:147–57.
[57] American College of Obstetrics and Gynecology. Intrauterine growth restriction. Washington DC: The American College of Obstetricians and Gynecologists; Practice Bulletin. No. 12. January 2000.
[58] American College of Obstetrics and Gynecology. Antepartum fetal surveillance. Washington DC: The American College of Obstetricians and Gynecologists; Practice Bulletin No. 9. October 1999.

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Fetal Doppler velocimetry

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Doppler velocimetry is now widely used in diagnostic medicine. The physical principle behind the Doppler effect is well established. A brief summary of these principles is appropriate at this point.

A sound wave that is transmitted from a source (incident beam) is propagated at a particular frequency. On hitting a moving target, a percentage of these waves is reflected back (reflected waves) to the original source of the incident waves. The frequency of the reflected waves is altered compared with that of the incident wave. The difference in frequency between incident and reflected value, called the "frequency shift," is determined by the velocity at which the target is moving. If the angle between the direction of the incident sound wave and direction of movement of the target is known, then the velocity of the latter can be determined based on the frequency shift. In the case of vascular Doppler, the moving target is a column of blood in a vessel. The velocity of blood flowing in a given vessel reflects the impedance or resistance to flow in the vessels that are downstream to the one being insonated. For example, umbilical artery Doppler provides information on the impedance to flow in the placental vasculature. The impedance is a metaphor for the state of dilation, vasospasm, or indeed whether or not some of these downstream vessels have been obliterated.

Obstetric Doppler has been used most gainfully in the evaluation of fetal growth restriction caused by placental dysfunction [1]. Other exciting applications have been more recently reported. Doppler velocimetry is now being used to detect fetal anemia caused by Rh sensitization and other etiologies, such as parvovirus infection. Among the most exciting vascular territory to be investigated is the fetal ductus venosus. Preliminary data suggest that ductus venosus Doppler is a strong predictor of severe morbidity and mortality in the growth-restricted fetus. In addition, in the first trimester it may also predict karyotypic

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abnormalities and congenital heart defects. This article covers the major applications in obstetrics and also the most commonly insonated fetal vessels. In addition we have discussed the preliminary data related to the potential significance of ductus venosus Doppler velocimetry. The authors believe these represent the most important recent advances in obstetric Doppler. Briefer mention is also made of the other fetal vessels that have been studied.

Doppler indices

Knowledge of the angle between the ultrasound beam and the blood flow allows an estimation of the blood flow velocity. When the angle is not known, angle-independent indices are used to derive approximate information regarding vascular impedance [2]. These indices are (1) systolic-diastolic ratio [3], (2) resistance index [4], and (3) pulsatility index (PI) [5]. All of these indices can be calculated easily by determining the velocity at the peak systolic and the end-diastolic phase of the cardiac cycle. None of the angle-independent indices seems clearly superior in assessing the fetal status.

Flow velocity waveforms (FVW) of the umbilical artery change with advancing gestation [3,6]. End-diastolic velocity is often absent in the first trimester and the diastolic component increases with advancing gestation [7]. The PI, resistance index, and systolic-diastolic ratio decrease with advancing gestation, most likely because of a decrease in placental vascular resistance [7–9]. As a result, the gestational age becomes a critical factor in interpreting Doppler velocimetry.

The arteries of the circle of Willis have different FVWs, and it is important to know which artery is being studied at a particular time [10]. The middle cerebral artery (MCA) is the vessel of choice for evaluating the fetal cerebral circulation because it is easy to identify, Doppler velocimetry has reproducibility, and MCA Doppler provides information on the brain-sparing effect [11]. Additionally, it can be studied easily with an angle of zero degrees between the ultrasound beam and the direction of blood flow. The smaller the angle of insonation, the more precise is the estimation of flow velocity. Information on the true velocity of the blood flow may be obtained from the MCA [12]. The PI of the MCA during gestation has a parabolic shape indicating a lowering of the vascular resistance in the cranial vessels in the third trimester [13].

Doppler velocimetry in the growth-restricted fetus

The growth-restricted fetus is one that does not reach his or her growth potential for pathologic reasons. Doppler ultrasound can help to identify those fetuses that are small because of uteroplacental insufficiency in distinction to the constitutionally small and normal fetus. Currently, the two vessels yielding the best information in the fetus with intrauterine growth restriction (IUGR) appear to be the umbilical artery and MCA.

Umbilical blood flow velocity waveforms

In placental insufficiency, there is an elevated placental vascular resistance, which is reflected as a decreased diastolic component of the umbilical artery Doppler waveforms [14–18]. An abnormal umbilical artery waveform has a PI, resistance index, or systolic-diastolic ratio value above the normal range. As the placental insufficiency worsens over time, the diastolic velocity decreases because of greater resistance to blood flow, with reduced forward velocity when the ventricles are not actively contracting. In this progression the end diastolic forward velocity can eventually disappear altogether. At the extreme, there is reversal of the direction of flow in the umbilical artery during cardiac diastole (Fig. 1).

Cerebral blood flow velocity waveforms

Animal and human experiments have shown that in the IUGR fetus, there is increased blood flow to the brain [19–21]. This increase of blood flow is manifested by increased diastolic velocity and lower PI Doppler values of the MCA [11] (Fig. 2). In IUGR fetuses with MCA PIs below the normal range, there is a greater incidence of adverse perinatal outcome [11]. The brain-sparing effect may be transient as reported during prolonged hypoxemia in animal experiments [22].

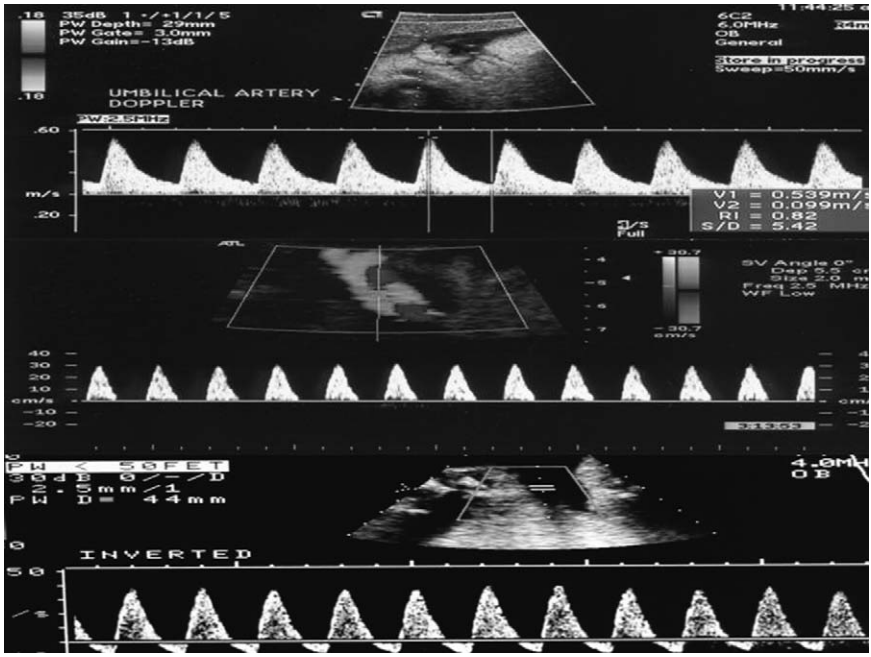

Fig. 1. Flow velocity waveforms of the umbilical artery in an appropriate-for-gestational-age fetus (*top*) and in two intrauterine growth restriction fetuses with absent (*middle*) and reversed (*bottom*) flow in the umbilical artery.

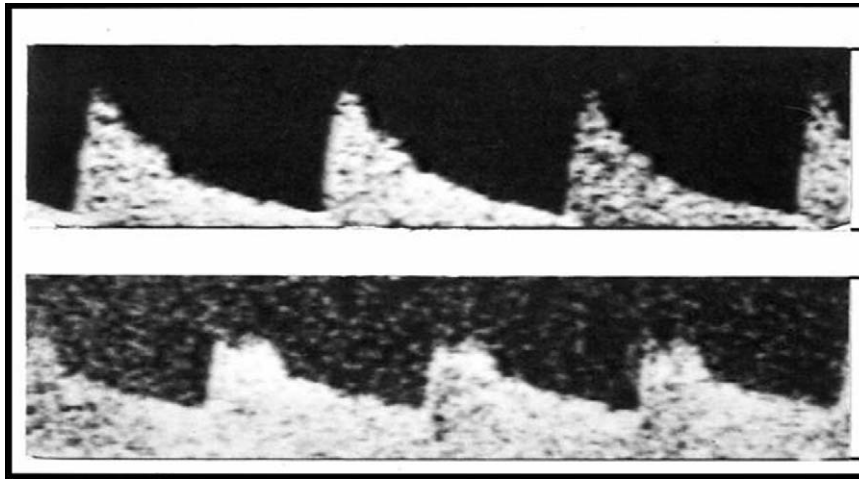

Fig. 2. Flow velocity waveforms of the middle cerebral artery in an appropriate-for-gestational-age fetus and severe intrauterine growth restriction fetus.

The overstressed human fetus can also lose the brain-sparing effect [23]. It has been reported that the MCA PI is below the normal range when the fetal P_{O_2} is reduced [24]. Maximum reduction in PI is reached when the P_{O_2} is two to four standard deviations below normal for gestation. When the oxygen deficit is greater than these levels, there is a tendency for the PI to rise again, presumably reflecting the development of brain edema. In IUGR fetuses, the disappearance of the brain-sparing effect seems to precede fetal death [23,25–27].

Cerebral-umbilical ratios

Mathematically, the preferential shunting of blood to the fetal brain can be represented as the ratio between cranial and umbilical Doppler indices. It has been reported that the internal carotid-umbilical artery PI ratio has a sensitivity of 70% in identifying growth-restricted fetuses, as opposed to 60% sensitivity for the internal carotid artery and 48% for the umbilical artery by themselves [28]. Others have selected the MCA-umbilical artery ratio and have reported that in appropriate-for-gestational-age fetuses, this ratio remains constant after 30 weeks' gestation. The cerebral-placental ratio seems to be a better prognostic indicator than the umbilical artery Doppler alone in the IUGR fetus [29].

Other blood flow velocity waveforms of the cardiovascular system

Many other fetal arteries and veins have been studied in appropriate-for-gestational-age and IUGR fetuses. Their study has increased the understanding of fetal physiology and pathophysiology in normally grown and abnormally small fetuses. In the authors' experience, however, the study of these vessels as cur-

rently performed does not add any new information to umbilical artery and MCA Doppler in the management of IUGR fetuses. The ductus venosus could be an exception to this conclusion. A brief overview of these fetal vessels, including Doppler of the fetal heart, is presented next.

Descending aorta

Flow velocity waveforms from the fetal descending aorta are usually recorded at the level of the diaphragm. The PI of the fetal descending aorta remains relatively constant through gestation [30]. In severe IUGR fetuses, there is reversed diastolic flow of the descending aorta Doppler waveform.

Celiac trunk

The celiac trunk arises from the aorta between the crura of the diaphragm at the level of the 12th thoracic vertebra. It has three main branches: (1) splenic, (2) common hepatic, and (3) left gastric arteries. The splenic artery supplies the spleen, a great part of the stomach, and the pancreas. The superior mesenteric artery arises anteriorly from the abdominal aorta just below the celiac artery at the level of the two renal arteries. It supplies the distal part of the duodenum, jejunum, cecum, appendix, ascending colon, and most of the transverse colon.

Splenic artery

Mari et al [31] have found that IUGR fetuses have a lower splenic artery PI value. This suggests that in cases of chronic hypoxia, there is an increased blood flow to the spleen because of the increased erythropoiesis [32,33].

Superior mesenteric artery

Superior mesenteric artery FVWs Doppler indices increase with advancing gestation [34]. This may reflect an increased bowel resistance because of increased bowel length with advancing gestation. The superior mesenteric artery FVWs does not seem useful in assessing IUGR fetuses [35].

Adrenal artery

In IUGR fetuses, there is a lower adrenal artery PI that suggests an ‘‘adrenal stress response’’ and increased perfusion of this organ as reported in animal studies [36].

Renal artery

The renal artery can be studied by a coronal section of the abdominal aorta with the sampling site after its origin from the descending aorta. Along with decrease in the values of the angle independent Doppler indices that have been reported, the renal artery peak systolic velocities (PSV) are decreased in fetuses with severe IUGR [37]. This indicates reduced kidney perfusion.

Femoral artery and external iliac artery

The femoral artery FVWs are obtained soon after its origin. There are no differences between the femoral artery PI and the external iliac artery PI related to IUGR [30].

Superior cerebellar artery

The superior cerebellar artery arises from the basilar artery before it divides into the two posterior cerebral arteries. The superior cerebellar artery PI is similar to the PI of the MCA. Uerpairojkit et al [38] have found that the PI of the superior cerebellar artery is lower than normal in IUGR fetuses, whereas it is in the normal range in small-for-gestational-age fetuses with no pathologic etiology.

Coronary sinus

Visualization of coronary blood flow by color Doppler imaging is possible in the human fetus. Pulsed wave Doppler measurements are infrequently obtained, making this study for routine assessment of myocardial blood flow unfeasible [39].

Fetal venous system in intrauterine growth restriction

The umbilical vein velocities become pulsatile in the severely IUGR fetus [40,41]. Fetuses with pulsation in the umbilical vein in the second and third trimester have a higher morbidity and mortality, even in the setting of normal umbilical arterial blood flow.

In IUGR fetuses, the inferior vena cava is characterized by increased reverse flow during atrial contractions [42]. The mechanism of this increase is attributed to abnormal ventricular filling characteristics, abnormal ventricular chamber or wall compliance, or abnormal end-diastolic pressure.

Ductus venosus

The ductus venosus is a vein that connects the umbilical sinus in the liver to the inferior vena cava. Most commonly, it opens separately into the left side of the inferior vena cava. The umbilical vein carries oxygenated blood from the placenta to the liver. A portion of this flow is transported by the ductus venosus through the inferior vena cava across the foramen ovale and into the left atrium. Ultimately, this oxygenated blood is distributed by the left ventricle to vital organs, such as the fetal brain. The significance of the ductus venosus rests largely on the important role it plays in regulating the flow of highly oxygenated blood to the left heart. Normally, about 20% to 30% of oxygenated blood from the placenta goes through the ductus venosus [43,44]. During fetal hypoxia, the

percentage of umbilical venous blood through the ductus increases up to 70%, ensuring preferential oxygenation of the vital organs [45].

The high velocity in the proximal or isthmic portion of the ductus venosus, near the connection with the umbilical vein, results in aliasing and a spectral appearance on color flow imaging. The ductus venosus Doppler waveform has a triphasic profile. The first peak corresponds to ventricular systole. There is a second and smaller peak noted during ventricular filling. Finally, there is a nadir corresponding to atrial contraction. During significant hypoxia, reduced oxygenation of the heart with stiffening of the myocardium occurs. As a consequence, there is decreased compliance and increased end-diastolic pressures, which are transmitted to the central venous system. From the perspective of the ductus venosus Doppler waveform, this manifests principally as reduced forward blood velocity during atrial contraction. There is a deeper trough at the atrial nadir on waveform analysis. In its most severe manifestation there is reversal of the velocity in the atrial contraction phase (Fig. 3). These findings likely represent the effect of high intracardiac pressure causing greater resistance to flow, going from the ductus venosus to the inferior vena cava. Other Doppler changes in the ductus venosus associated with hypoxia include reduced peak velocities during the ventricular systolic and diastolic phases of the cardiac cycle. Various Doppler indices have been developed to quantitate these changes. They include the ratio of the ventricular systolic to ventricular diastolic peak, ventricular systole to atrial

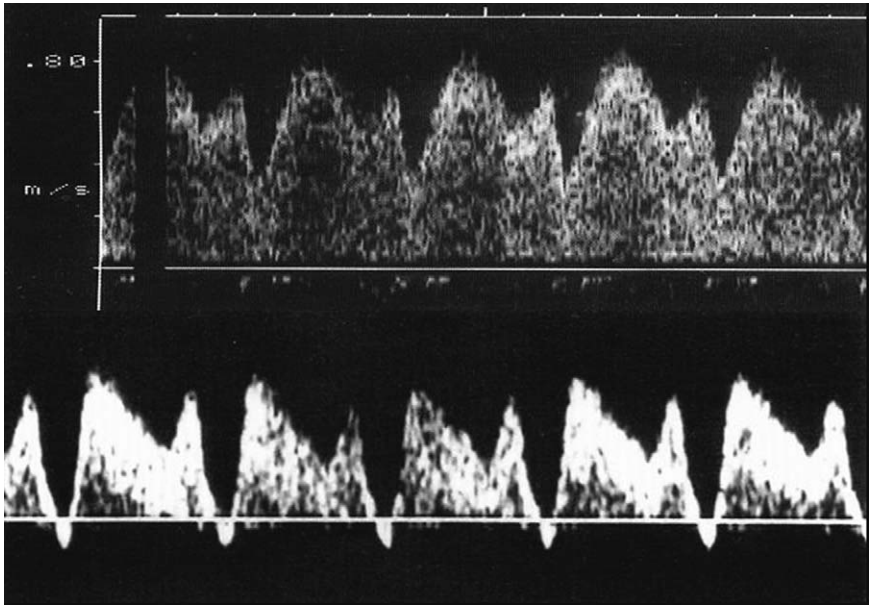

Fig. 3. Flow velocity waveforms of the ductus venosus in an appropriate-for-gestational-age fetus and intrauterine growth restriction fetus.

contraction, or the time averaged mean velocity during the cardiac cycle. Absence or reversal of the flow velocity in the atrial contraction phase represents the most extreme Doppler abnormality in this vessel.

Ductus venosus Doppler velocimetry has been used most extensively in the evaluation of the growth-restricted fetus. Based on the putative mechanism by which hypoxia results in ductus venosus Doppler changes (ie, myocardial hypoxia and stiffness), it is reasonable to expect that severe Doppler changes in the ductus venosus occur late in the natural history of fetal growth restriction. Additionally, it is likely that the development of such changes is a harbinger of poor perinatal outcome. Both of these expectations have been substantiated in human studies. Hecher et al [46] studied 100 growth-restricted fetuses greater than or equal to 24 weeks in a longitudinal fashion. The timing of onset and correlation with adverse outcome of the following biophysical indices was evaluated: fetal arterial and venous (including ductus venosus) Doppler indices; short-term heart rate variability; and amniotic fluid volume. In severely growth-restricted fetuses delivered less than 32 weeks (60 cases), reduction of amniotic fluid volume was the earliest abnormality to manifest followed by Doppler abnormalities in the umbilical artery and then the MCA. Doppler abnormalities of the ductus venosus appeared relatively late in the natural history of hypoxic progression. For the fetuses delivered after 32 weeks (which constituted a less severe group), a similar pattern was seen with all the biophysical abnormalities, although they occurred less frequently. For the overall study group, when both short-term variability and ductus venosus Doppler were abnormal, the perinatal mortality was 39%. In a smaller study of 26 growth-restricted pregnancies that were followed longitudinally, ductus venosus changes also developed late [47].There were 9 (34.6%) of 26 perinatal deaths and both gestational age and birth weight were significant independent predictors of death. The most significant Doppler predictors of poor perinatal outcome were the late changes, which included the ductus venosus, reversed umbilical artery velocity, and aortic and pulmonary artery Doppler changes [47].

Hofstaetter et al [48] prospectively and serially evaluated various Doppler velocities in 154 growth-restricted fetuses, 37 of which had reversed umbilical artery Doppler wave profile. In the latter subgroup there were 15 perinatal deaths. There was a strong correlation noted between increasing placental resistance and ductus venosus Doppler changes. When surviving fetuses were compared with nonsurvivors, among those with reversed umbilical artery velocimetry, significant worsening of the ductus venosus velocimetry was noted. Ductus venosus velocity during atrial contraction had 79% sensitivity and 68% specificity for predicting perinatal mortality, which was statistically significant. Cross-sectional studies of growth-restricted fetuses have documented a correlation between fetal acidemia documented by cordocentesis and ductus venosus Doppler changes [49]. The clinical question that naturally arises is how ductus venosus velocimetry data should influence management. The study of Ferrazzi et al [47] provides some insights into this question. Among their cases delivered after 28 weeks there was a sharp differential in perinatal mortality rate based on ductus

Doppler. In such cases, late Doppler changes included ductus venosus alterations. The perinatal mortality was 57% in cases with late changes compared with 10% in cases with early Doppler changes, such as umbilical artery and MCA indices. There is strong empirical support for expeditious delivery of cases with significant changes in ductus waveforms. On this basis, it also seems that a good case could even be made for delivering fetuses before development of ductus venosus abnormalities. Timing of delivery is also influenced by the chances of postnatal survival based on gestational age, birth weight, and the prior use of antenatal steroids. At the very least, the identification of severe ductus venosus Doppler abnormalities should be considered an unambiguous indication for immediate admission, continuous intensive fetal surveillance, antenatal steroids, and delivery before discharge from the hospital in cases where the fetus is considered viable, particularly in the third trimester.

Other intriguing applications of fetal ductus venosus Doppler velocimetry have been reported and are currently being investigated. One such application is the use of ductus venosus velocimetry to predict congenital heart defects in the first trimester. Montenegro et al [50] reported that five first-trimester fetuses with increased nuchal translucency had chromosomal abnormalities. All five had reduced or reversal of atrial contraction phase of the ductus Doppler velocity. The authors hypothesized that this might reflect cardiac failure or heart defects known to be common in trisomy 21 and 18 fetuses. This seems to be consistent with second-trimester studies reported by Kiserud et al [51]. In 28 cases of structural heart defects, these authors found that 64% had reduced Doppler velocity in the atrial contraction phase of the ductus venosus waveform. In major malformations involving the ventricular inlet and outlet, 81% of cases had reduced atrial contraction velocity on ductus venosus Doppler. First-trimester ductus venosus Doppler has been shown to have 58.7% sensitivity for detection of Down syndrome fetuses [52]. Although exciting, further studies are necessary to validate these findings and to establish their usefulness in the prenatal detection of congenital heart defect and chromosome abnormalities.

Fetal cardiac flow velocity waveforms in appropriate-for-gestational-age and intrauterine growth restriction fetuses

Atrioventricular valves

Atrioventricular valve Doppler flow velocities can be obtained from a four-chamber view by placing the sample volume just distal (within the ventricles) to the valve leaflets. Usually, two peaks are observed in the atrioventricular valve signal: the first peak reflects passive ventricular filling in early diastole (E), and the second peak reflects the atrial contraction in late diastole (A). Early in gestation, A is much higher than E, indicating that the atrial contraction is important in filling the fetal ventricles at this stage. With advancing gestation, E increases and equals A, suggesting that the atrial systole becomes less im-

portant with maturation and increased compliance of the ventricular myocardium [53–57]. At birth and thereafter, E becomes higher than A.

The most commonly used index to quantify these waveforms is the E:A ratio. When the atrioventricular valve velocity waveforms are studied with a low incident angle, the blood velocity obtained is close to the true velocity. The increase of E:A ratio with advancing gestation has been considered a sign of progressive improvement in myocardial compliance. In IUGR fetuses, the E:A ratio is higher than that of normal controls for gestational age. These changes are attributed to preload changes without impairment in fetal myocardial diastolic function.

Aortic and pulmonary valve flow velocity waveforms

Aortic and pulmonary valve velocities are studied at the level of the respective outflow tracts. Various indices have been used to quantify these waveforms including PSV, acceleration time, ejection time, and time velocity integral. Peak velocity across both valves increases with advancing gestation [58]. In IUGR fetuses, the aortic and pulmonary velocities have been noted to decrease, which may be secondary to increased placental resistance [59].

Doppler velocimetry in the prediction of fetal hematocrit

The fetal hematocrit increases with advancing gestation. Fetal anemia is said to exist when the hematocrit is below two standard deviations of the mean for gestational age. The PI of several fetal vessels and estimation of the fetal cardiac output has been evaluated as predictors of fetal anemia. These have not been found to be very useful, however, for the diagnosis of fetal anemia [60–62].

In contrast, the peak velocity of the MCA has been shown to be related to fetal anemia. During anemia, the blood viscosity decreases and the blood velocity increases [63]. A correction of the fetal anemia decreases the fetal blood velocity. The MCA can be studied with an angle of zero degree between the ultrasound beam and the direction of blood flow. This allows the calculation of the true blood velocity at level of the MCA. The MCA-PSV detects moderate and severe anemia with a sensitivity of 100% (CI: 0.86 to 1). The MCA-PSV can also estimate the actual value of hematocrit in moderate and severe anemia [64]. Additionally, serial values of the MCA-PSV measurements can be regressed and used to predict whether a fetus will become anemic [65]. Furthermore, a prospective study with intention to treat showed the MCA-PSV was an excellent tool to diagnose anemia. In this study, an invasive procedure (amniocentesis and cordocentesis) was avoided in 90 of 125 patients at risk of developing severe anemia [66].

Similar results could be obtained while studying other vessels of the fetal circulation (ie, splenic artery) [67]. The authors, however, have selected the MCA-PSV because of the ease of measurement and reproducibility of the results. MCA-PSV has also been useful in the diagnosis of fetal anemia caused by parvovirus infection [68].

Summary

The introduction of new techniques for evaluating fetal status, particularly fetuses at theoretical risk for hypoxic ischemic encephalopathy, requires the most rigorous evaluation before widespread clinical deployment. The considerations extend beyond clinical value to the significant medicolegal implications of a failure to predict or ascertain compromise. The attitudes to clinical Doppler velocimetry have been shaped to a large extent by these practical concerns and the initial skepticism, which is a necessary component of scientific rigor. Available data strongly indicate, however, that in competent hands umbilical artery Doppler improves the clinical management of IUGR pregnancies [1]. Failure to use Doppler may have the undesirable effect of increasing the risk of adverse outcome in the growth-restricted fetus. There is also strong evidence of benefit in the management of the Rh isoimmunization. Although numerous other clinical applications are on the horizon, much more information is needed to determine objectively the benefits and risks of these newer applications.

References

[1] Allfirevic Z, Neilson JP. Doppler ultrasonography in high risk pregnancies: systematic review with meta-analysis. Am J Obstet Gynecol 1995;172:1379–87.
[2] Milnor WR. Pulsatile blood flow. N Engl J Med 1972;287:27–34.
[3] Stuart B, Drumm J, FitzGerald DE, Duignan NM. Fetal blood velocity waveforms in normal pregnancy. Br J Obstet Gynaecol 1980;87:780–5.
[4] Pourcelot L. Application cliniques de l'examen Doppler transcutane. In: Perronneau P, editor. Velocimetrie ultrasonore' Doppler. Paris: Seminaire INSERM; 1974. p. 213–40.
[5] Gosling RG, King DH. Ultrasound angiology. In: Marcus AW, Adamson L, editors. Arteries and veins. New York: Churchill Livingstone; 1975. p. 61–98.
[6] FitzGerald DE, Drumm J. Noninvasive measurements of human fetal circulation using ultrasound: a new method. BMJ 1977;2:1450–1.
[7] Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveform indices: AB ratio, pulsatility index and Pourcelot ratio. Br J Obstet Gynaecol 1988;95:589–91.
[8] Trudinger BJ, Stevens D, Connelly A, Hales JR, Alexander G, Bradley L, et al. Umbilical artery flow velocity waveforms and placental resistance: the effects of embolization of the umbilical circulation. Am J Obstet Gynecol 1987;157:1443–8.
[9] Trudinger BJ, Giles WB, Cook CM, Bombardiere J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol 1985; 92:23–30.
[10] Mari G, Moise KJ, Deter RL, Kirshon B, Carpenter RJ, Huhta JC. Doppler assessment of the pulsatility index in the cerebral circulation of the human fetus. Am J Obstet Gynecol 1989;160: 698–703.
[11] Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. Am J Obstet Gynecol 1992;166:1262–70.
[12] Mari G, Adrignolo A, Abuhamad AZ, Pirhonen J, Jones DC, Ludomirsky A, et al. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. Ultrasound Obstet Gynecol 1995;5:400–5.
[13] Dobbing J, Sands J. Timing of neuroblast multiplication in developing human brain. Nature 1970;226:639–40.
[14] Fleischer A, Schulman H, Farmakides G, Bracero L, Blattner P, Randolph G. Umbilical ar-

tery velocity waveforms and intrauterine growth retardation. Am J Obstet Gynecol 1985;151: 502–6.
[15] Devoe LD, Gardner P, Dear C, Faircloth D. The significance of increasing umbilical artery systolic-diastolic ratios in third-trimester pregnancy. Obstet Gynecol 1992;80:684–7.
[16] Rochelson BL, Schulman H, Fleischer A, Farmakides G, Bracero L, Ducey J, et al. The clinical significance of Doppler umbilical artery velocimetry in the small for gestational age fetus. Am J Obstet Gynecol 1987;156:1223–6.
[17] Trudinger BJ, Cook CM, Giles WB. Fetal umbilical artery velocity waveforms and subsequent neonatal outcome. Br J Obstet Gynaecol 1991;98:378–84.
[18] Gudmundsson S, Marsal K. Umbilical and uteroplacental blood flow velocity waveforms in pregnancies with fetal growth retardation. Eur J Obstet Gynecol Reprod Biol 1988;27: 187–96.
[19] Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 1974;120:817–24.
[20] Rudolph AM. Distribution and regulation of blood flow in the fetal and neonatal lamb. Circ Res 1985;57:811–21.
[21] Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of the cerebral blood flow in the human fetus. Br J Obstet Gynecol 1986;93:471–5.
[22] Richardson BS, Rurak D, Patrick JE, Homan J, Carmichael L. Cerebral oxidative metabolism during sustained hypoxemia in fetal sheep. J Dev Physiol 1989;11:37–43.
[23] Mari G, Wasserstrum N. Flow velocity waveforms of the fetal circulation preceding fetal death in a case of lupus anticoagulant. Am J Obstet Gynecol 1991;164:776–8.
[24] Vyas S, Nicolaides KH, Bower S, Campbell S. Middle cerebral artery flow velocity waveforms in fetal hypoxemia. Br J Obstet Gynaecol 1990;97:797–803.
[25] Sepulveda W, Peek MJ. Reverse end-diastolic flow in the middle cerebral artery: an agonal pattern in the human fetus. Am J Obstet Gynecol 1996;174:1645–7.
[26] Chandran R, Serra Serra V, Sellers SM, Redman CW. Fetal middle cerebral artery flow velocity waveforms: a terminal pattern. Case report. Br J Obstet Gynaecol 1991;98:937–8.
[27] Respondek M, Woch A, Kaczmarek P, Borowski D. Reversal of diastolic flow in the middle cerebral artery of the fetus during the second half of the pregnancy. Ultrasound Obstet Gynecol 1997;9:324–9.
[28] Wladimiroff JW, van den Wijngaard JA, Degani S, Noordam MJ, van Eyck J, Tonge HM. Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. Obstet Gynecol 1987;69:705–9.
[29] Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, et al. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J Obstet Gynecol 1999;180:750–6.
[30] Abuhamad AZ, Mari G, Cortina RM, Croitoru DP, Evans AT. Superior mesenteric artery Doppler velocimetry and ultrasonographic assessment of fetal bowel in gastroschisis: a prospective longitudinal study. Am J Obstet Gynecol 1997;176:985–90.
[31] Mari G, Uerpairojkit B, Abuhamad AZ, Copel JA. Adrenal artery velocity waveforms in the appropriate and small-for-gestational-age fetus. Ultrasound Obstet Gynecol 1996;8:82–6.
[32] Finne PH, Halvorsen S. Regulation of erythropoiesis in the fetus and newborn. Arch Dis Child 1972;47:683–7.
[33] Fischer JW. Control of erythropoietin production. Proc Soc Exp Biol Med 1984;173:289–305.
[34] Abuhamad AZ, Mari G, Bogdan D, Evans AT. Doppler flow velocimetry of the splenic artery in the human fetus: is it a marker of chronic hypoxia? Am J Obstet Gynecol 1995;172:820–5.
[35] Rhee E, Detti L, Mari G. Superior mesenteric artery flow velocity waveforms in small for gestational age fetuses. J Matern Fetal Med 1998;7:120–3.
[36] Rizzo G, Arduini D, Romanini C. Umbilical vein pulsations: a physiologic finding in early gestation. Am J Obstet Gynecol 1992;167:675–7.
[37] Stigter RH, Mulder EJ, Bruinse HW, Visser GH. Doppler studies on the fetal renal artery in the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2001;18:141–5.

[38] Uerpairojkit B, Chan L, Reece AE, Martinez E, Mari G. Cerebellar Doppler velocimetry in the appropriate and small-for-gestational-age fetus. Obstet Gynecol 1996;87:989–93.
[39] Baschat AA, Gembruch U. Examination of fetal coronary sinus blood flow by Doppler ultrasound. Ultrasound Obstet Gynecol 1998;11:410–4.
[40] Gudmundsson S, Tulzer G, Huhta JC, Marsal K. Venous Doppler in the fetus with absent end-diastolic flow in the umbilical artery. Ultrasound Obstet Gynecol 1996;7:262–7.
[41] Nakai Y, Miyazaki Y, Matsuoka Y. Pulsatile umbilical venous flow and its clinical significance. Br J Obstet Gynaecol 1992;99:977–80.
[42] Rizzo G, Arduini D, Romanini C. Inferior vena cava flow velocity waveforms in appropriate- and small-for-gestational-age fetuses. Am J Obstet Gynecol 1992;166:1271–80.
[43] Kiserud T, Rasmussen S, Skulstad S. Blood flow and degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 2000;182:147–53.
[44] Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR. Foramen ovale: an ultrasonographic study of its relation to the inferior vena cava, ductus venosus and hepatic veins. Ultrasound Obstet Gynecol 1992;2:389–96.
[45] Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. Ultrasound Obstet Gynecol 1994;4:109–14.
[46] Hecher K, Bilardo CM, Stigter RH, Ville Y, Haskeloer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 2001;18:564–70.
[47] Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002;19:140–6.
[48] Hofstaetter C, Gudmundsson S, Dubiel M, Marsal K. Ductus venosus velocimetry in high-risk pregnancies. Eur J Obstet Gynecol Reprod Biol 1996;70:135–40.
[49] Rizzo G, Capponi A, Ardin D, Romanini C. The value of fetal arterial cardiac and venosus flows in predicting pH and blood gases measured in umbilical blood at cardiocentesis in growth-retarded fetuses. Br J Obstet Gynecol 1995;102:963–9.
[50] Montenegro N, Matias A, Areias JC, Castedo S, Barros H. Increased fetal nuchal translucency: possible involvement of early cardiac failure. Ultrasound Obstet Gynecol 1997;10:265–8.
[51] Kiserud T, Eik-Nes SH, Hellevik LR, Blaas HG. Ductus venosus blood flow velocity changes in fetal cardiac diseases. J Matern Fetal Invest 1993;3:15–20.
[52] Mavrides E, Sairam S, Hollis B, Thilaganathan B. Screening for aneuploidy in the first trimester by assessment of blood flow in the ductus venosus. BJOG 2002;109:105–19.
[53] Reed KL, Anderson CF, Shenker L. Changes in intracardiac Doppler blood flow velocities in fetuses with absent umbilical artery diastolic flow. Am J Obstet Gynecol 1987;157:774–9.
[54] Rizzo G, Arduini D, Romanini C, Mancuso S. Doppler echocardiographic assessment of atrioventricular velocity waveforms in normal and small-for-gestational-age fetuses. Br J Obstet Gynaecol 1988;95:65–9.
[55] Shapiro I, Degani S, Leibowitz Z, Ohel G, Tal Y, Abinader EG. Fetal cardiac measurements derived by transvaginal and transabdominal cross-sectional echocardiography from 14 weeks of gestation to term. Ultrasound Obstet Gynecol 1998;12:404–18.
[56] Fouron JC, Carceller AM. Determinants of the Doppler flow velocity profile through the mitral valve of the human fetus. Br Heart J 1993;70:457–60.
[57] Hata T, Hata K, Takamiya O, et al. Fetal ventricular relaxation assessed by Doppler echocardiography. Journal Cardiovascular Ultrasonography 1988;7:207–13.
[58] Kenny JF, Plappert T, Doubilet P, Saltzman DH, Cartier M, Zollars L, et al. Changes in intracardiac blood flow velocities and right and left ventricular stroke volumes with gestational age in the normal human fetus: a prospective Doppler echocardiographic study. Circulation 1986;74:1208–16.
[59] Al-Ghazali W, Chita SK, Chapman MG, Allan LD. Evidence of redistribution of cardiac output in asymmetrical growth retardation. Br J Obstet Gynaecol 1989;96:697–704.

[60] Copel JA, Grannum PA, Green JJ, Belanger K, Hobbins JC. Pulsed Doppler flow-velocity waveforms in the prediction of fetal hematocrit of the severely isoimmunized pregnancy. Am J Obstet Gynecol 1989;161:341–4.
[61] Copel JA, Grannum PA, Green JJ, Belanger K, Hanna N, Jaffe CC, et al. Fetal cardiac output in the isoimmunized pregnancy: a pulsed Doppler-echocardiographic study of patients undergoing intravascular intrauterine transfusion. Am J Obstet Gynecol 1989;161:361–5.
[62] Nicolaides KH, Bilardo CM, Campbell S. Prediction of fetal anemia by measurement of the mean blood velocity in the fetal aorta. Am J Obstet Gynecol 1990;162:209–12.
[63] Mari G, Rahman F, Oloffson P, Ozcan T, Lopel JA. Increase of fetal hematocrit decreases the middle cerebral artery peak systolic velocity in pregnancies complicated by rhesus alloimmunization. J Matern Fetal Med 1997;6:206–8.
[64] Mari G, Detti L, Oz U, Zimmerman R, Duerig P, Stefos T. Accurate prediction of fetal hemoglobin by Doppler ultrasonography. Obstet Gynecol 2002;99:589–93.
[65] Detti L, Mari G, Akiyama M, Cosmi E, Moise KJ, Stefor T, et al. Longitudinal assessment of the middle cerebral artery peak systolic velocity in healthy fetuses and in fetuses at risk for anemia. Am J Obstet Gynecol 2002;187:937–9.
[66] Zimmerman R, Carpenter RJ, Durig P, Mari G. Longitudinal measurement of peak systolic velocity in the fetal middle cerebral artery for monitoring pregnancies complicated by red alloimmunisation: a prospective multicentre trial with intention-to-treat. BJOG 2002;109: 746–52.
[67] Bahado-Singh R, Oz U, Deren O, Kovanchi E, Hsu CD, Onderoglu L, et al. Splenic artery Doppler peak systolic velocity predicts severe fetal anemia in rhesus disease. Am J Obstet Gynecol 2000;182:222–6
[68] Cosmi E, Mari G, Delle Chaiaie L, Detti L, Akiyama M, Murphy J, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia resulting from parvovirus infections. Am J Obstet Gynecol 2002;187:1290–3.