Inverted Pyramid of Care

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KEYWORDS

• First trimester • Screening • Diagnosis • Anomalies • Maternal complications • Preeclampsia

KEY POINTS

- Most fetal chromosomal and structural anomalies can be diagnosed by the end of the first trimester of pregnancy.
- Cell free fetal DNA is a significant advance in screening for fetal aneuploidy; however, its use is limited and is best used in combination with first-trimester ultrasound and maternal serum screening.
- The risk of some pregnancy complications that become clinically evident only later in pregnancy can be established in the first trimester; the incidence of some of these disorders, such as preeclampsia, can be reduced if treatment is instituted early in pregnancy.
- First-trimester screening also shows some promise in other pregnancy-related problems (eg, spontaneous preterm birth, small for gestational age without preeclampsia, macrosomia, gestational diabetes) and represents a fertile field for future research.

INTRODUCTION

Pregnancy management typically involves reacting to maternal and fetal problems only after they develop. Because most fetal and maternal complications become apparent late in pregnancy, it has been traditionally thought that is when the most intensive surveillance should be implemented. Indeed, the initial prenatal care guidelines as put forth by the Ministry of Health in the United Kingdom in the early twentieth century reflects this fact.[1] In this schema, which has been accepted throughout the world, the frequency of antenatal visits progressively increases with advancing gestation and is recommended to be on a weekly basis from 36 weeks' gestation onwards.

Recent decades have seen a movement of fetal and maternal investigations to the first trimester of pregnancy.[2] The impetus for this phenomenon can be traced to the

No disclosures.

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Clin Lab Med 36 (2016) 305–317

http://dx.doi.org/10.1016/j.cll.2016.01.009 **labmed.theclinics.com**

0272-2712/16/$ – see front matter

development of first-trimester ultrasound screening for fetal aneuploidy using nuchal translucency (NT) measurement.[3,4] This screening was quickly followed by the realization that NT thickening can be associated with a whole host of other fetal abnormalities.[5,6] Furthermore, the increased use of ultrasound in the first trimester revealed that many fetal structural problems can already be accurately diagnosed at this point.[7]

The use of maternal serum biochemical screening followed a similar pattern. Free beta–human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) were first used to screen for trisomy 21, but subsequently they were also found to be useful in screening for trisomies 18 and 13 and for triploidy.[8,9] The use of first-trimester biochemistries was then further expanded to predict pregnancy complications that become apparent only later on in pregnancy, such as preeclampsia (PE) and severe intrauterine growth restriction.[10]

The recent introduction of screening using maternal plasma cell-free (cf) DNA represents a significant advance in antenatal detection of aneuploidy.[11] Even though this test analyzes fetal DNA, it still is a screening test, not a diagnostic one. Furthermore, its limited scope and high cost makes it impractical as a primary screening test.[12]

In this article, the authors aim to review the benefits of early pregnancy evaluation and how to best use the tests currently available. The authors also aim to show that some very important complications that occur later in pregnancy can be predicted in the first trimester; therefore, it is worthwhile to increase the focus of clinical evaluations in early pregnancy, thus, inverting the pyramid of prenatal care (**Fig. 1**). By selecting pregnancies that are at the highest risk for complications that become apparent only later in gestation and by identifying those that are at very low risk, a prenatal care plan can be developed that is tailored to individual patients.[13]

FIRST-TRIMESTER SCREENING FOR FETAL ANEUPLOIDY

Fetal aneuploidy is a major cause of perinatal morbidity and mortality as well as long-term disabilities. All diagnostic prenatal tests used to diagnose fetal aneuploidy carry a risk of miscarriage and are expensive.[14] Therefore, starting with a screening test that has the highest possible detection rate and lowest false-positive rate is of critical importance. However, because funds for health care are limited, from the standpoint of public health policy, a screening test that is deemed to be too expensive (ie, is not cost-effective) cannot be universally implemented.

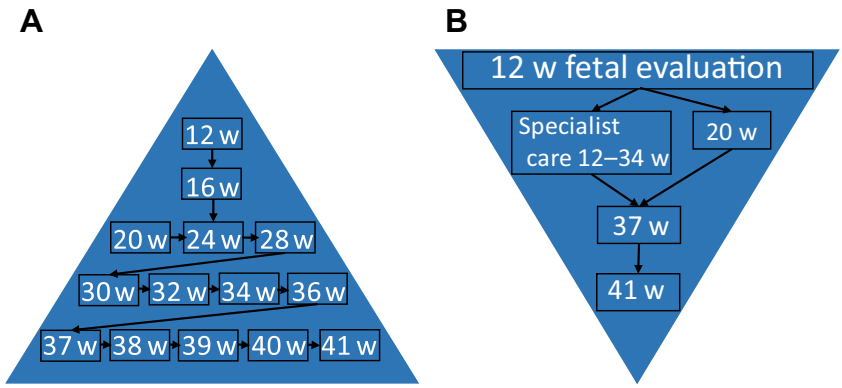

Fig. 1. Traditional pyramid of prenatal care (*A*) and a possible new pyramid (*B*). w, weeks. (*Adapted from* Nicolaides KH. Turning the pyramid of prenatal care. Fetal Diagn Ther 2011;29:184; with permission.)

Until the advent of cfDNA technology, first-trimester combined screening (maternal age and history, gestational age, NT measurement, PAPP-A, and free beta-hCG) performed at 11^{+0} to 13^{+6} weeks' gestation was arguably the most robust screening test for fetal aneuploidy available. For a positive rate of 3% to 5%, screening the combined test can identify more than 90% of fetuses with trisomy 21. The detection rate of trisomies 18 and 13 is about 95% for the same false-positive rate.[15]

The effectiveness of the first-trimester combined screen can be further augmented by the addition of other fetal markers, such as nasal bone evaluation and Doppler evaluations of the ductus venosus and blood flow across the tricuspid valve.[16–18] The additional ultrasound markers can be either obtained at the time of the combined screen or on a contingent basis.[19,20] The contingent protocol calls for patients to be initially divided into 3 categories based on the traditional combined screen: high risk ($\geq$1:50), intermediate risk (1:51–1:1000), and low risk ($\leq$1:1000). Patients in the high-risk category are offered an invasive procedure, and those in the low-risk category are reassured. Patients in the intermediate category then undergo stage-2 screening using the additional ultrasound markers. If the final risk assessment in this group is 1:100 or greater, an invasive test is offered. Those whose risk is less than 1:100 are reassured. The screening performance of both approaches is similar: the detection rate is approximately 93% to 96% for a 2.5% false-positive rate.

There is evidence that the effectiveness of first-trimester screening could also be further enhanced by including additional maternal serum markers, such as placental growth factor (PlGF) and maternal serum alpha-fetoprotein (AFP).[15,21]

First-Trimester Screening for Down Syndrome: Performance and Cost-Benefit

All of the currently available cfDNA tests have a higher detection rate (>99%) for trisomy 21 for a much lower false-positive rate (about 0.1%) than the first-trimester combined test. The performance of cfDNA in screening for trisomy 18 (detection: 96.4%–99.9%), trisomy 13 (detection: 91.7%–99.0%), and monosomy X (detection: 92.9%–96.6%) is lower but is still very good.[11] Despite the good test results, the positive predictive values are such (50%–90%) that it is imperative to confirm each positive result with a diagnostic test.[22]

Many laboratories have expanded the testing panel to include trisomy 9, trisomy 16, trisomy 22, 22q11 deletion (DiGeorge/velocardiofacial syndrome), 1p36 del, 4p- (Wolf-Hirschhorn syndrome), 5p- (Cri-du–chat syndrome), 8qdel (Langer-Giedion syndrome), 11qdel (Jacobsen syndrome), and 15qdel (Angelman/Prader-Willi syndrome).[23] It must be stressed that the true detection and false-positive rates of these diseases remains to be established. Additionally, it is questionable whether the low prevalence of these uncommon conditions justifies screening in the general population. The manner in which cfDNA is to be used in population screening continues to be a subject of debate. However, the most significant impediment to universal implementation is its current cost.

Ultimately, the discussion regarding screening for aneuploidy centers on trisomy 21 because it is the most common type of aneuploidy and, compared with trisomies 18 and 13, it is more difficult to differentiate from euploid fetuses using ultrasound markers. Additionally, survival of fetuses with the other 2 types of aneuploidy is greatly diminished both during fetal life and after delivery, making the timing of the delivery slightly less critical.

Currently, the evaluation of cost-effectiveness of various prenatal screening protocols for trisomy 21 can be derived only from statistical modeling.[24] One such analysis was published recently, and the results are listed in **Table 1**.[25] It contains both the predicted screening performance and costs of screening protocols, 3 of which are

Table 1
Example comparing 3 existing and 4 cell-free DNA testing protocols: model-predicted screening performance and cost per Down-syndrome birth avoided under a set of particular conditions, unit costs and uptake

	Model-Predicted Screening Performance			Cost per Down Syndrome Birth Prevented ($)	
Protocol	**DR (%)**	**FPR (%)**	**PPV (%)**	**Average**	**Marginal[a]**
Existing					
Combined test	81.7	2.4	4.3	220,000	—
Contingent test	89.2	1.6	6.7	199,000	—
Combined test & NB	90.2	1.3	8.2	190,000	—
cfDNA					
Routine test	99.3	0.11	54	770,000	3,300,000
Contingent test	94.5	0.09	58	300,000	770,000
Contingent test, PlGF & AFP	96.6	0.09	59	290,000	690,000
AMA & contingent test	94.8	0.06	68	320,000	960,000

Maternal age distribution was standardized. Test conditions: Term (midtrimester) risk cutoff for combined test with or without nasal bone, 1 in 250 (1 in 190), for contingent test, 1 in 50 per 2500 (1 in 38 per 1900), and for contingent cfDNA test with or without PlGF and AFP, 1 in 10 per 2500 (1 in 8 per 1900); advanced maternal age cutoff, 35 years; hCG isoform, free beta; gestational age determined by serum markers at 10 weeks' gestation and NT at 11 weeks. Unit cost: combined test with or without nasal bone, $200; Quad markers, $50; cfDNA test, $1000; PlGF and AFP levels, $50; invasive prenatal diagnosis, $1500; uptake of screening, invasive prenatal diagnosis, and termination of Down syndrome pregnancies, 100%.

Abbreviations: AMA, advanced maternal age; DR, detection rate; FPR, false-positive rate; NB, nasal bone; PPV, positive predictive value.

[a] Cost of each additional birth prevented compared with combined test.

Adapted from Sonek JD, Cuckle HS. What will be the role of first-trimester ultrasound if cell-free DNA screening for aneuploidy becomes routine? Ultrasound Obstet Gynecol 2014;44:622; with permission.

existing traditional protocols and 4 include the addition of cfDNA. The conditions, unit costs, and uptake that were used for these calculations are specified in the footnote. The average cost applies to the cost of screening per case of Down syndrome detected. The marginal cost specifically refers to the cost of detection of each case of Down syndrome through the use of cfDNA that would not have been detected by traditional screening. When cfDNA is used as a primary screen, the average cost of preventing a Down syndrome birth is increased between 3- and 4-fold and the marginal cost is increased 15-fold (approximately $3,300,000). Using any of the approaches whereby cfDNA testing is done on a contingent basis, that is, using cfDNA only in those patients who are determined to be at an increased risk based on traditional screening, the average cost is less than doubled and the marginal cost is less than 4-fold. This approach retains much of the improved performance of routine cfDNA: The false-positive rate remains essentially the same with only a slightly diminished detection rate. This finding seems to be especially true if additional serum markers, PlGF and AFP, are included. Of note is that the approach of selecting older women (≥35 years of age) to undergo primary screening with cfDNA increases the cost without any apparent improvement in the overall screening performance (see Table 1).[25]

Another published cost-effectiveness assessment arrived to a similar conclusion. In this study, the most cost-effective approach was to use a contingent strategy whereby

the initial risk assessment was based on maternal age, NT measurement, PAPP-A, free beta-hCG, and nasal bone with a 1 per 1000 risk cutoff.[26]

FIRST-TRIMESTER DETECTION OF FETAL STRUCTURAL ABNORMALITIES

About half of the congenital structural defects can now be diagnosed in the first trimester[27,28] because of improvements in ultrasound technology, NT thickening and the presence of other ultrasound markers can herald the presence of structural defects, and detailed evaluation of fetal anatomy is becoming widely recognized as an integral part of the first-trimester ultrasound.

Screening and Diagnosis of Structural Congenital Defects

It has been recognized now for more than 15 years that a thickened NT increases the risk of congenital fetal defects even in the absence of aneuploidy.[5] An evaluation of 4697 euploid fetuses that had an NT measurement greater than the 95th percentile revealed that 7% of them had a major abnormality. This risk increases significantly for an NT greater than 3.5 mm. In fetuses with an NT of 6.5 mm or greater, this risk is almost 50%. Since that time, case reports and case-control studies have confirmed that an increased NT can be associated with a large variety of genetic syndromes and structural defects, such as diaphragmatic hernia, omphalocele, facial clefts, body-stalk anomaly, skeletal defects, congenital adrenal hyperplasia, fetal akinesia deformation sequence, Noonan syndrome, Smith-Lemli–Opitz syndrome, and spinal muscular atrophy.[29]

A recent population-based study of 75,899 pregnancies also demonstrated a correlation between the prevalence of fetal structural defects and NT measurement.[30] After excluding fetuses with aneuploidy and critical cardiac defects, the analysis showed that an NT *greater than* the 95th percentile increased the risk of central nervous system, pulmonary, gastrointestinal, genitourinary, and musculoskeletal defects 1.6 to 2.7-fold. Certain anomalies had an increased risk that was 3-fold or greater: congenital hydrocephalus; agenesis, hypoplasia and dysplasia of the lung; atresia and stenosis of the small intestine; osteodystrophies; and diaphragmatic anomalies.

A recently published meta-analysis by Rossi and Prefumo[27] looked at the detection rates of fetal anomalies in the first trimester. The meta-analysis included 19 studies and a total of 78,002 fetuses, of which 996 has a structural anomaly. The overall detection rate was 51%. Detection rates were higher (62%–65%) in cases whereby both transabdominal and transvaginal ultrasound were used and in cases with a thickened NT.

A prospective analysis of 3094 fetuses confirmed that major fetal abnormalities can be diagnosed with a great reliability in the late first trimester even in a low-risk population (prevalence of major fetal anomalies was 2.8%). The overall detection rate of major anomalies, including congenital heart defects (CHDs), was 84%. In those cases whereby the NT measurement was 2.5 mm or greater, the detection rate was 98%.[31]

First-Trimester Detection of Congenital Cardiac Defects

The association between CHDs and NT measurement is well documented. In a meta-analysis that included 20 studies, the detection rate for major CHDs based on NT measurement alone was estimated at 44% for a 5.5% false-positive rate.[32] The risk of CHDs increases progressively with increasing NT measurement. Analysis that included combined data from 5 studies showed a risk of 3% for NTs 3.5 to 4.4 mm, 7% for NTs 4.5 to 5.4 mm, 20% for NTs 5.5 to 6.4 mm, and 30% for NTs 6.5 mm or

greater.[5] Doppler evaluation of blood flow across the tricuspid valve and ductus venosus further improves screening for CHDs.[32–34]

In a first-trimester screening study involving almost 41,000 normal fetuses and 85 with major cardiac defects, Pereira and colleagues[34] found tricuspid regurgitation (TR) and a reversed flow in the ductus venosus each in about 30% of the affected cases. They showed that the combination of 3 markers (NT >99th percentile, TR, and abnormal a-wave) resulted in a detection rate of 52% for a false-positive rate of 4.1%.

First-Trimester Detection of Open Neural Tube Defects

Once it was recognized that the appearance of anencephaly is different in the first trimester from that in the second trimester, early diagnosis of this defect has become routine. However, the diagnosis of open spina bifida has remained a challenge. This situation changed when it was recognized that examination and measurements of structures located in the posterior fossa can provide clues to the presence of open neural tube defects (ONTDs) even in the first trimester. This relies mainly on changes in the appearance of the fourth ventricle (in this context, termed *intracranial translucency* [IT]) and the size of the brainstem (BS) in the sagittal section.[35] It was noted that in fetuses with an ONTD the IT is often obliterated. This is accompanied by other posterior fossa anomalies, such as an increase in the anteroposterior diameter of the BS. In order to assess changes in the posterior fossa objectively, a ratio of the thickness of the BS estimated by a measurement from the sphenoid bone to the floor of the fourth ventricle to a measurement from the floor of the fourth ventricle to the inner edge of the occipital bone (BSOB) was developed. A ratio that is greater than the 95th percentile of a gestational age–adjusted normal range was associated with the presence of ONTDs in 97% of the cases. In a prospective, multicenter first-trimester screening study including about 15,500 normal fetuses and 11 fetuses with open spina bifida, all affected cases were identified or at least suspected by a detailed assessment of the posterior fossa at 11 to 13 weeks' gestation.[36]

Other markers that may be helpful are narrowing of the frontomaxillary angle (detection rate of approximately 90%), biparietal diameter (BPD) measurement less than the fifth percentile (detection rate of approximately 50%), or a small BPD to transabdominal diameter ratio (detection rate of approximately 75%).[37–39]

The use of the BS/BSOB ratio has now expanded beyond simply screening of ONTDs. It has been suggested that if the ratio is less than the fifth percentile (ie, the opposite of what occurs with ONTDs), the risk of abnormalities that originate in the posterior fossa (Dandy-Walker malformation, partial vermian dysgenesis, and Blake cyst) is increased; but further research is necessary in this field.[40]

FIRST-TRIMESTER ASSESSMENT OF MULTIPLE GESTATIONS

Perinatal risk of morbidity and mortality is always increased in multiple gestations. However, the level of risk depends greatly on chorionicity.[41] This assessment is best accomplished in the first trimester, as at this time the ultrasound appearance of a dichorionic/diamniotic dividing membrane is vastly different from that of a monochorionic/diamniotic membrane. This difference becomes more blurred as the pregnancy progresses. Estimation of chorionicity in the first trimester allows accurate counseling regarding the risk of the pregnancy. In monochorionic-diamniotic twin pregnancies, a large difference between the NT measurements of the 2 fetuses or the presence of ductus venosus blood flow abnormalities may be helpful in identifying pregnancies with an increased risk for twin-twin transfusion syndrome.[42,43] All these

evaluations allow the most appropriate plan of prenatal care to be outlined and implemented.[44] This aspect for first-trimester ultrasound evaluation has especially gained in importance recently as the incidence of twins has increased significantly in the past few decades.[45]

FIRST-TRIMESTER PREDICTION OF MATERNAL-FETAL COMPLICATIONS

Discussion regarding first-trimester screening often focuses on fetal aneuploidy and structural anomalies. However, maternal and fetal complications that are related to abnormal placentation are much more common than both of these problems combined.

Most placental architecture, including placental maternal blood circulation, is established by the end of the first trimester; no further anatomic modifications are evident after the fourth month of pregnancy. These 2 facts serve to support the 2 following assertions. First, the validity of methods used at the end of the first trimester in screening for placental dysfunction has a sound physiologic basis. Second, in order for any treatment to be successful in reducing the risk of complications related to placental dysfunction, it must be instituted early in pregnancy.

The 2 often-interrelated complications of pregnancy that are major causes of maternal-fetal morbidity and mortality are PE and small-for-gestational-age (SGA) fetuses. A meta-analysis of 9 published studies has shown that the use of low-dose aspirin (75 mg/d) reduces the risk of PE but only if treatment is initiated before 16 weeks' gestation.[46] This finding was confirmed in a more recent meta-analysis.[47]

As a result of these studies, it is now recommended that prophylactic low-dose aspirin treatment should be initiated before 12 weeks' gestation in women who are found to be at an increased risk of PE based on a combination of factors, such as body mass index, parity, and personal as well as family history.[48] However, these factors alone are not adequate to achieve a high enough detection rate and they are nonspecific.

First-trimester screening for these complications can be improved by using additional markers.[49] One is the estimation of downstream resistance by measuring the pulsatility index (PI) in the uterine arteries.[50] Second is maternal blood pressure measurement in the late first trimester. Third is evaluation of certain placental product levels in maternal serum, such as PAPP-A and PlGF. Modeling using the Fetal Medicine Foundation (FMF) algorithm suggests that, for a false-positive rate of 10%, detection of early PE (requiring delivery before 34 weeks' gestation) would be approximately 90% based only on historical factors, maternal blood pressure measurement, and uterine artery PI. The addition of PAPP-A and PlGF levels increases the detection rates to 96%.[51]

The performance of the FMF PE algorithm was validated in a recent Australian study.[52] The algorithm was subsequently used by the same group to evaluate the effectiveness of aspirin treatment (150 mg at night) in those women who were screen positive. There were 12 women (incidence 0.4%) who developed PE in the observation cohort. Of those, 11 (92%) were screen positive. In the intervention group, only one (0.04%) developed PE. Based on the prevalence in the observational group, it was estimated that 10 women in the intervention group should have developed PE. There were 264 (9.9%) women in the intervention cohort who screened positive for PE. Therefore, for every 29 women advised to take aspirin, one case of PE was prevented. There were no apparent adverse effects of this therapy identified. Of note is that the screening algorithm included measurement of PAPP-A but not PlGF, which was not available for their use at that time.[53]

It has also been shown that early administration of low-dose aspirin reduces the incidence of intrauterine growth restriction as well as its related pregnancy and neonatal complications.[54] Using the same FMF screening algorithm mentioned earlier, the estimated detection rates for early onset PE, late-onset PE, preterm SGA, and term SGA were 95%, 46%, 56%, and 44%, respectively, with an overall false-positive rate of 11%.[47,54]

Gestational hypertensive disorders are not only a major cause of perinatal morbidity and mortality but they are also responsible for a large proportion of expenditure for pregnancy and neonatal care. In 2011, the state of California looked at the cost of treating women and their neonates who are affected by hypertensive complications. Using the Medi-Cal fee-for-service fee schedule and reimbursement to private hospitals, they found that the annual incremental cost for gestational hypertensive disorders over that of unaffected pregnancies was $226 million. This number does not even include the lifetime medical costs of treating complications due to prematurity, such as neurologic and developmental disabilities.[55] It is clear that a robust screening program and prophylaxis with low-dose aspirin instituted early in pregnancy has the potential to result in a significant cost saving.

FUTURE APPLICATIONS OF FIRST-TRIMESTER SCREENING PROTOCOLS

Screening for SGA without PE has shown some promise. The risk is increased with an increase in the uterine PI and maternal mean arterial pressure. Decreased maternal serum PAPP-A, free beta-hCG, PlGF, placental protein 13 (PP13), and A disintegrin and metalloproteinase 12 (ADAM12) also increase the risk of SGA.[56,57] For a false-positive rate of 10%, the combination of these markers along with maternal characteristics could identify approximately 75% of SGA fetuses delivering before 37 weeks' gestation and 45% that deliver at term.[58]

The fact that risk of *spontaneous preterm delivery* is associated with cervical shortening is well established in the second trimester, and the same seems to hold in the first trimester.[59,60] Cervical length measurement obtained transvaginally and adhering to strict guidelines in combination with maternal characteristics is likely to be used in the future to select a high-risk group that may benefit from close follow-up and possible treatment. Preterm delivery prediction does not seem to be improved by the use of either maternal serum biochemistries or uterine artery PI.[56]

First-trimester screening for *gestational diabetes mellitus* (GDM) is possible using maternal serum biochemistries. Adiponectin and sex hormone–binding globulin are reduced and visfatin is increased in association with increased risk for GDM. Combination of maternal characteristics and biochemical markers can identify about 75% of pregnancies that will develop GDM for a 20% false-positive rate.[57,61,62]

Screening fetal *macrosomia/large for gestational age (LGA)* using first-trimester parameters has shown some promise. The risk of LGA increases with increased NT measurement, increased levels of maternal serum free beta-hCG and PAPP-A, and a decreased level of adiponectin.[63] For a 10% false-positive rate, the combination of these factors and maternal characteristics can detect approximately 40% of LGA fetuses.[57]

FIRST-TRIMESTER ESTIMATION OF GESTATIONAL AGE

Finally, first-trimester crown-rump length measurement represents the most accurate method for establishing the gestational age in the general population.[64] Accurate gestational age is a critical piece of information that influences essentially all decisions

throughout the pregnancy, including such basic aspects of prenatal care as evaluating fetal growth and timing of delivery.

SUMMARY

There are several arguments that can be made to encourage pregnancy evaluation in the late first trimester. This evaluation is not only to benefit patients but also in order to implement a responsible public health policy.

The benefit of first-trimester screening and diagnosis of fetal anomalies is clear. Patients become aware of these conditions early in pregnancy when they can make their decisions in the greatest degree of privacy. In those cases whereby termination is elected, it can be done at a point where it is safest for patients and the least expensive.[65] Furthermore, in many countries, including the United States, attempts are being made by the state legislatures to limit access to termination, especially those done beyond midgestation, making an early diagnosis of fetal problems that much more important.

A responsible public health approach must take into account not only the benefits of any new technology but also the potential disruptive effect that a new technology may have on those that are currently in use. It also needs to take into account all of the benefits of each technology rather than comparing a single aspect of their performance in isolation. Even though both combined screening and cfDNA technology provide an efficient screen for aneuploidy early in pregnancy, cfDNA is more accurate. However, combined first-trimester screening casts a much wider net in terms of the variety of fetal defects it can detect. Therefore, it does not make sense to think of cfDNA technology as a replacement for traditional first-trimester screening. Rather, it should be implemented in a logical and cost-effective manner that complements existing technologies.

Screening for gestational hypertensive disorders and SGA in the first trimester has 2 significant advantages. One is that those patients who are at an increased risk can be monitored more closely later in pregnancy. Second is the fact that treatment with a fairly benign medication (low-dose aspirin), if instituted early in pregnancy, can lead to a significant reduction in the incidence of these conditions. This treatment, in turn, cannot only result in a reduction of perinatal morbidity and mortality but also in a significant cost saving.

First-trimester ultrasound evaluation provides a very accurate estimation of gestational age. In those pregnancies whereby multiple fetuses are identified, the first trimester represents an ideal time to determine the chorionicity. Both of these bits of information are invaluable in designing a plan of management for the rest of the pregnancy.

Aside from all of these applications of first-trimester pregnancy evaluations that have a proven benefit in management for the rest of the pregnancy, there are others, such as screening for SGA without PE, spontaneous preterm delivery, GDM, and fetal macrosomia, that show some promise. It is likely that with time these will also be perfected to make them more clinically pertinent.

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