

Editorial

Should sonographic screening for fetal Down syndrome be applied to low risk women?

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There have been startling advances in the use of ultrasound for the detection of second trimester fetuses with Down syndrome.

In particular, screening programs have begun using sonographic markers of Down syndrome among women at high risk for having affected fetuses¹⁻⁴.

Although much documentation exists to encourage the use of ultrasound screening in these women, the ultrasound community has begun to include in the reports any and all sonographic markers for aneuploidy among the low-risk patients as well.

Indiscriminate application of screening may actually do more harm than good, resulting in confusion and inappropriate anxiety among pregnant women undergoing sonography.

An increasing number of subtle sonographic markers has been linked to an elevated risk of fetal Down syndrome in the second trimester and these are used for detecting fetuses at risk for Down syndrome.

As this list of sonographic markers grows, the likelihood that a routine ultrasound will identify at least one marker rises dramatically.

Such sonographic findings are commonplace in karyotypically normal fetuses.

Although the sensitivity and specificity is constant, the positive predictive value for each marker is far less in low-risk than it is in high-risk patients, due to the application of Bayes' theorem.

It is therefore inappropriate to advocate that the same screen for high risk patients be expanded to low-risk patients without additional data.

The vast majority of data describing the ultrasound detection of the fetus with a chromosomal abnormality was collected on selected high-risk populations, and the extrapolation of these findings is problematic and probably overzealous among low-risk women.

The estimated risk that fetuses with sonographic markers are chromosomally abnormal may be inflated, resulting in unnecessary invasive procedures and even potential loss of normal fetuses.

The current climate of medical litigation, however, encourages the counseling of any women whose fetus exhibits these sonographic findings, regardless of prior probability of Down syndrome.

Although the risk may shift upward slightly in these low-risk patients for whom a sonographic marker has been identified, the risk may not reach the accepted threshold for warranting an invasive procedure.

Nevertheless, the current litigious atmosphere encourages indiscriminate counseling, perhaps unnecessarily alarming as much as 12-15% of the pregnant population.

The theory that a greater number of fetuses with trisomy 21 could be identified in the low-risk patient group, combined with the fear of missing an affected fetus if every minor marker is not reported, has fostered over diagnosis and excessive counseling.

THE MARKERS

In 1985, the first second trimester sonographic marker for Down syndrome, the thickened nuchal fold, was described as having a sensitivity of 40% for detecting affected fetuses, with a < 1% false-positive rate.

This feature remains the most sensitive and specific sonographic marker for the detection of trisomy 21, conveying a likelihood ratio of 18.6 times the age-based risk for Down syndrome.

Fetuses with trisomy 21 also exhibit structural malformations such as major cardiac defects, duodenal atresia, omphalocele, and hydrocephalus, among others.

These malformations are seen in 33% of second-trimester fetuses with Down syndrome, also with a low false-positive rate, conferring a likelihood ratio for Down syndrome of 25 times the age-based risk.

Due to the very high specificity for each of these two major markers, the thickened nuchal fold and major malformations, each has a high positive predictive value for the detection of chromosomal abnormalities - even in low-risk patients.

The minor markers, on the other hand, are findings which are more commonly seen among normal fetuses, although they have a higher frequency in fetuses with aneuploidy.

These include a slightly short humerus, slightly short femur, pyelectasis, small calcifications in the papillary muscle of the heart (bright papillary muscle), hyperechoic bowel, hypoplasia of the middle phalanx of the fifth digit, widened iliac angle, and choroid plexus cyst.

THE MINOR MARKERS

Individuals with Down syndrome have slightly shorter long bones compared to normals, not only in infancy and childhood but also in pathologic evaluations of second trimester fetal specimens.

Although it is well accepted that fetuses with Down syndrome have slightly short humeri and femora, the degree of shortening is very mild and overlaps extensively with the normal range.

Because the different bone dimensions in fetuses of different racial and ethnic backgrounds may also have an impact on this measurement, there is a wide variation in the use of this marker among different practitioners throughout the country.

In clinical use, slight shortenings of the femur and the humerus convey likelihood ratios of 2.2 and 2.5 times the age-based risk for Down syndrome, respectively.

Fetal pyelectasis, also a minor marker for Down syndrome, is common among normal fetuses.

There is an increased incidence of pyelectasis in fetuses with Down syndrome compared with the normal population, with 20-25% of fetuses with Down syndrome having dilatation of the renal pelvis.

Considering the relatively high false positive rate, however, pyelectasis conveys a likelihood ratio of 1.6 times the age-based risk for Down syndrome.

In routine scanning of low-risk women, isolated fetal hydronephrosis is not generally considered an indication for amniocentesis unless accompanied by other markers.

Hyperechoic bowel was first shown to be a sonographic marker for Down syndrome in 1993.

Despite this low sensitivity, the specificity is high since the incidence of hyperechoic bowel in the general population is only 0.6%.

Hyperechoic bowel is, in most cases, a normal variant although it has also been associated with an increased risk for cystic fibrosis, severe placental insufficiency, and infection with cytomegalovirus.

Hyperechoic bowel has a likelihood ratio of 5.5 times the age-based risk for the detection of trisomy 21.

By far, the most prevalent marker among the normal population is the bright papillary muscle.

Small calcifications in the papillary muscle, particularly in the left ventricle, are common in second-trimester fetuses and are present in approximately 5-10% of normal fetuses.

An association between this finding and chromosomal abnormalities was demonstrated in 1995.

On subsequent studies, we found that 18% of fetuses with Down syndrome and 5% of normal fetuses displayed this sonographic marker.

As an isolated finding, the likelihood ratio for Down syndrome is twice the age-based risk.

Although this marker was associated with the high positive predictive value of 1.5% in women starting out with an age-based risk of 1/300, the positive predictive value in patients initially at low risk (1/1000) for carrying a fetus with Down syndrome did not reach the accepted threshold for recommending amniocentesis.

In addition an echogenic intracardiac focus is much more common in fetuses of Asian mothers, with a 30% incidence of this finding in normal Asian fetuses.

It is clear that, despite the association with Down syndrome, most fetuses with an isolated echogenic intracardiac focus are normal - particularly in the low risk population.

Choroid plexus cysts are small transient fluid collections in the substance of the choroid plexus that occur in 1-2% of second trimester fetuses, and regress spontaneously within 6-8 weeks.

Although the vast majority of fetuses with choroid plexus cysts are normal, there is an association between these cysts and fetal trisomy 18, a rare lethal aneuploidy.

Trisomy 18 is not only very rare but associated with a multitude of major structural fetal malformations which are easy to identify sonographically.

A meta-analysis of the 13 largest studies of fetuses with choroid plexus cysts showed that the incidence of trisomy 18 was only 0.27% among fetuses with isolated cysts.

This low risk of trisomy 18 in fetuses with isolated choroid plexus cysts on an otherwise normal scan does not justify the risk of pregnancy loss of 0.5% imposed by amniocentesis.

Furthermore, choroid plexus cysts are not associated with an increased risk of Down syndrome, supporting the view that an invasive procedure for karyotyping is not indicated unless other findings (sonographic or biochemical) exist.

There are other characteristic fetal Down syndrome sonographic markers that are even more difficult to use clinically than those described above.

These include hypoplasia of the middle phalanx of the fifth digit, separation of the great toe ('sandal-gap foot'), iliac angle widening, slight heart rate disorders, fetal ear measurement abnormalities and others.

Due to the substantial overlap between Down syndrome fetuses and the normal population, these markers are not commonly part of the genetic sonogram but have been used occasionally as an adjunct to other findings among high-risk patients.

THE GENETIC SONOGRAM

A genetic sonogram, in the form of a scoring index was developed to optimize the detection of fetuses with aneuploidy³ 2s. The following scoring system was developed for detecting fetuses with aneuploidy:

Nuchal fold = 2 Major structural defect = 2 Short femur = 1 Short humerus = 1
Pyelectasis = 1 Hyperechoic bowel = 1 Echogenic intracardiac focus = 1 Choroid
plexus cyst = 1

It is recommend that only if the sum of the sonographic markers reach a score of 2 should an amniocentesis be suggested for patients not otherwise at risk for chromosomal abnormalities.

If all women whose fetuses have a sonographic score of 22 undergo amniocentesis, 73% of fetuses with Down syndrome and 85% of fetuses with trisomy 18, along with 4% of normal fetuses, will be identified .

To optimize sensitivity at the cost of decreasing specificity, the lower threshold of 21 can be used for older patients at increased risk for Down syndrome.

Women 35 years of age have a risk of fetal Down syndrome estimated at 1/300 or more, increasing steadily with age.

A score of 1 is sufficient to increase the risk of fetal Down syndrome for those patients, whereas we showed that a score of 0 can convey a > 50% reduction in risk in these high-risk patients.

This notion prompted the development and rapid dissemination of the genetic sonogram for higher-risk women (of advanced maternal age) who wanted to avoid amniocentesis and who were attempting to diminish their risks of having a chromosomally abnormal fetus.

Our data and those of Nyberg shows that women between the age of 35 and 39 years are able to decrease the risk of having a fetus affected with Down syndrome by 50%, thus, in most cases, below the threshold of 1/300 (for which amniocentesis is recommended).

It is in these high-risk women that the genetic sonogram has had the greatest impact.

Over the age of 40, the age-based risk is high enough that even decreasing the risk by 50% still leave the odds that a woman could have an affected fetus at greater than 1/200.

Vintzileos reports that the utilization rates of the genetic sonogram in high risk patients have risen from 16% in 1994 to 55% in 1996, before their deciding whether or not to undergo amniocentesis.

Together with development of the sonographic markers for Down syndrome, the concurrent identification of three biochemical serum markers has aided the identification women who may be carrying fetuses with chromosomal abnormalities (in particular, Down syndrome).

In the early 1990s, the use of the serum 'triple screen' test (maternal serum alpha-fetoprotein, unconjugated estriol, and human chorionic gonadotropin) was combined with maternal age to render a revised risk that a woman could be carrying a fetus with Down syndrome.

This approach detects 57% of fetuses with Down syndrome, with a 3.2% false-positive rate.

Currently, all pregnant women in the United States are offered this serum triple screen, which is then combined with maternal age data to refine their individual risks of fetal Down syndrome.

Although a specific revised risk of having an affected fetus is generated for each pregnant woman, it is reported as normal (screen negative) unless it reaches 1/300, a level considered the risk of a woman aged 35, the threshold at which amniocentesis is offered.

Women who screen positively for serum markers may also become candidates for the genetic sonogram, to refine further their risks by evaluating their fetus for possible sonographic markers.

Investigators have shown that the lack of any sonographic markers present (a sonographic score of 0) can convey a 50% reduction in risk of fetal Down syndrome for patients with an abnormal triple screen, just as it is able to do for patients at increased risk based on maternal age only.

Although the European community has adopted nuchal translucency screening at 11-14 weeks as a standard test for fetal aneuploidy, unfortunately, this test has not become popular in the United States, possibly due to the reluctance of managed care companies to pay for any prenatal screening sonogram.

In an attempt to reduce costs, most of the ultrasound focus on screening has resided with the 18-week scan with the expectation of accomplishing both an anomaly and aneuploidy screen simultaneously.

In Europe, where the standard of care is moving towards first trimester screening, using primarily nuchal translucency together with first trimester biochemical markers, the utilization of the second trimester genetic sonogram may play a different role compared to the United States where first trimester screening is only done occasionally for high-risk patients.

However, even after first trimester screening, there is evidence that the second trimester markers still play a role in identifying aneuploid fetuses not detected earlier.

Karilas *et al.* presented an abstract at the last World Congress of Ultrasound in Obstetrics and Gynecology in Buenos Aires which described a group of 5500 patients studied with first trimester nuchal translucency, followed by the second trimester sonographic markers described above.

They showed that of the 3548 patients with normal nuchal translucency, five fetuses still had autosomal trisomies not detected earlier and two of these five (40%) were detectable using the second trimester markers.

One or more second trimester markers had a likelihood ratio of 7.7, and no markers had a likelihood ratio of 0.6 for fetal aneuploidie.

The *second trimester* sonographic markers described above are well established in the ultrasound literature and practice when dealing with high-risk women in the United States, and have been shown to work quite well for refining the risk of Down syndrome in these womenl.

Unfortunately, the same standards and practices are starting to be imposed upon women at low-risk (younger women or women with normal serum screens) who are presenting for their standard 18-week sonographic fetal surveys with minor markers suggesting an increased risk for Down syndrome.

The litigious community in which we practice has encouraged disclosure to the patient of every finding, no matter how minor, and every marker, regardless of how weak.

This practice has resulted in confusion among patients. Imagine for a moment that a woman, aged 25, has a routine 18-week ultrasound and has a fetal echogenic intracardiac focus.

This raises her estimated risk of fetal Down syndrome from 1/1000 to 1/500 (odds ratio 2).

If this finding was not mentioned to the patient and she were to deliver a child with Down syndrome, she could have the films reviewed and allege that she had not been informed of this increased risk owing to the echogenic intracardiac focus.

However, a risk of 1/500 is not considered high enough to warrant amniocentesis.

When the triple serum screen result alters a risk of 1/1000 to 1/500, it is reported to the patient as screen-negative because it does not reach 1/300 (which is considered the threshold for a positive screen).

Why, then, have we undertaken to inform patients of their sonographic findings - irrespective of their a priori risks?

Down syndrome is the most common malformation in humans, with an incidence of 1/600 to 1/700 in the general population.

It carries a very high incidence of mental deficiency and a prognosis of moderate mental and physical limitations.

It is therefore tempting, whenever a single sonographic maker is seen prenatally, to share this information with the patient, even though she may not have presented to the ultrasound unit for an increased risk of aneuploidy.

The thought of taking home a child with Down syndrome terrorizes many prospective parents, who then opt to undergo amniocentesis despite an unreasonable risk: benefit ratio.

In our overzealousness to share all information with the patients, we have lost sight that *two* minor markers were considered necessary before amniocentesis should be recommended for low-risk women.

Is it too late to return to this recommendation, and is the cat out of the bag?

There is a double standard for the way that serum markers are treated and the way that sonographic markers are utilized.

Although it has been demonstrated that the presence of a thickened nuchal fold in low-risk patients carries a significantly increased risk for Down syndrome and should trigger an amniocentesis, just as an amniocentesis should be recommended for any fetus with a major structural defect, the minor markers are another story.

For example, a prospective study specifically shows that isolated fetal pyelectasis in low-risk women should not be considered an indication for amniocentesis.

Choroid plexus cysts have been shown to be associated with trisomy 18, an extremely rare trisomy, but not with an increased risk of Down syndrome²¹.

Therefore, as an isolated finding, choroid plexus cysts should *not* be considered an indication for amniocentesis.

The ultrasound community should consider whether perhaps an increased risk estimate for fetal Down syndrome should only be communicated to the patient if it reaches a certain threshold, such as 1/300, based on maternal age or triple screen as a baseline and then multiplied by the relative risk of any marker identified.

We provide a disservice to the low-risk pregnant population by divulging those increased risks for fetal Down syndrome which remain well below the risk of fetal loss from amniocentesis itself (1/200 procedures).

Currently, approximately 12-15% of pregnant women have one or more sonographic markers identified during a routine 18 week scan, and it is unlikely that invasive procedures on all of these is truly indicated.

The loss rates due to amniocentesis may in fact make this practice harmful. A large, multicenter study of the sonographic markers on *low-risk* patients is needed to replace the data extrapolated from high-risk patients to the low-risk population.

Alarm ing so many low-risk women because of minor findings (which are probably normal) on ultrasound is detrimental and definitely a liability of the indiscriminate use of the genetic sonogram.

Although perhaps an occasional fetus with Down syndrome is detected in the low-risk population by reporting each isolated marker as an abnormal finding, this practice should be reserved for high-risk women.

Applying the high-risk population's screening criteria to the low-risk population has resulted in unnecessarily terrifying prospective parents and has contributed to the loss of normal fetuses through non indicated amniocenteses.