REVIEW ARTICLE

First Trimester Ultrasound Screening: An Update

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Abstract

For many years, the main use of ultrasound in the first trimester of pregnancy was to confirm viability and to establish gestational age. Indeed, the crown-rump length measurement in the first trimester remains the most accurate method to estimate the gestational age even today. However, improvements in ultrasound equipment and improvement in our understanding of normal and abnormal fetal development allows us now to perform a much more complete first trimester fetal evaluation. This pertains not only to the diagnosis of fetal anomalies but also to screening for fetal defects. The combination of the nuchal translucency measurement and maternal serum biochemistries (free β-hCG and PAPP-A) has been shown to be an extremely efficient way to screen for fetal aneuploidy. The addition of other first trimester markers such as the nasal bone evaluation, frontomaxillary facial angle measurement, and Doppler evaluation of blood flow across the tricuspid valve and through the ductus venosus improves the screening performance even further by increasing the detection rates and decreasing the false positive rates. Several of the first trimester markers also are useful in screening for cardiac defects. Furthermore, significant nuchal translucency thickening has been associated with a variety of genetic and nongenetic syndromes. A recently described first trimester marker called the intracerebral translucency appears to hold great promise in screening for open spine defects. Finally, it appears that a first trimester evaluation (uterine artery Doppler and the measurement of certain biochemical markers in the maternal serum) significantly improves the assessment of the risk of preeclampsia.

Keywords: First trimester screening, nuchal translucency, nasal bone, frontomaxillary angle, ductus venosus, tricuspid valve, intracranial translucency, uterine artery.

INTRODUCTION

The utility of the first trimester ultrasound examination of the gravid uterus and its contents continues to expand. The first trimester evaluation of the fetus, maternal pelvic vasculature, and maternal serum in conjunction with maternal history and physical examination may be used to establish the risk of fetal aneuploidy and some complications that do not become clinically evident until later in pregnancy. This paper reviews the current information regarding the benefits and limitations of this approach.

Gray scale examination of the fetal head and neck yields a great amount of information regarding the risk of trisomy 21 and other aneuploidies. Many of the ultrasound markers that are used in the first trimester to establish the risk of trisomy 21 have their equivalents in the postnatal phenotype. In 1866, Langdon Down[1] described individuals with the syndrome that later came to bear his name as "having skin that appears to be too large for their bodies" [hence the increased nuchal translucency (NT) thickness],[2] having a "small nose" [hence the nasal bone (NB) absence or hypoplasia],[3] and having a "flat face" [hence the shallow frontomaxillary facial (FMF) angle].[4]

Gray scale examination of the fetal heart in the first trimester may yield evidence of a cardiac defect, which is the most common structural anomaly seen in individuals with trisomy 21.[5] However, even in the absence of an overt structural defect, the function of the heart may be altered. There is ample evidence that the microscopic and ultrastructural anatomy of the myocardium and valve leaflets is abnormal.[6-8] These findings were exploited to develop a second type of ultrasound marker: Doppler evaluations of the cardiovascular system. The two tests of this type that are proving to be especially useful are the evaluation of blood flow across the tricuspid valve (TCV)[9-11] and through the ductus venosus (DV).[12-19] The third marker that falls into the general category of cardiovascular markers is evaluation of the fetal heart rate (FHR).[2,20] This marker is only marginally helpful in screening for trisomy 21 but, as will be discussed later, may be helpful in screening for other types of aneuploidy.

Pregnancy is associated with an alteration of levels of a number of substances that circulate in the maternal blood. Through empirical observations and studies, it has been noted that some of these are present in concentrations that are different in aneuploid pregnancies as compared to those

that are chromosomally normal. The two substances that have been shown to be especially useful in screening for trisomy 21 are free beta-human chorionic gonadotropin (free β-hCG) and pregnancy associated plasma protein-A (PAPP-A).[21] It should be stressed that it is the free β-hCG rather than other forms of hCG that has been tested most rigorously and that appear to perform the best.[22]

First trimester screening has been shown to be useful not only for trisomy 21 but for other types of aneuploidy (trisomies 18 and 13, monosomy X, other aneuploidies involving the sex chromosomes, and triploidy).[2,3,22-24] Some of these tend to have nuchal translucencies that are even thicker than trisomy 21 and are more likely to have major or minor structural defects. As a result the detection rates are in some cases even higher than for trisomy 21.[2,22]

A first trimester marker called the intracranial translucency (IT) has been recently described.[25] This marker appears to be useful in screening for open neural tube defects. It remains to be proven whether this marker is as powerful as the Chiari type II malformation and bifrontal scalloping in the second trimester.

First trimester Doppler evaluation of the maternal uterine arteries and measurement of levels of certain substances in the maternal serum along with maternal blood pressure measurement, have been shown to be useful in estimating the risk of preeclampsia.[26-29] This is especially true for early and severe preeclampsia, which is frequently associated with fetal growth restriction. The utility of this approach is limited by the fact that there is no proven method for the prevention of either one of these conditions. However, identification of the truly high risk patients early in pregnancy may lead to methods that improve pregnancy outcome in the future.

The Fetal Medicine Foundation (FMF) played an active role in the development and implementation of the above mentioned markers. They are included in the current FMF algorithm for the first trimester pregnancy evaluation.

An Argument for Screening in the First Trimester

There are a number of benefits that a pregnancy evaluation in the first trimester offers. Firstly, first trimester screening that combines ultrasound and maternal serum markers (PAPP-A and free β-hCG) has the highest detection rates for fetal aneuploidy currently available.[30] Secondly, NT measurements are helpful in establishing the risk of a number of fetal disorders other than aneuploidy.[31-79] Thirdly, a fairly complete fetal anatomic evaluation may be performed even in the first trimester.[80-91] Therefore, the patient is provided with a great amount of information early in pregnancy. If a fetal problem is detected, this approach preserves maximum privacy and autonomy as well as safety with regards to her reproductive choices. Lastly, first trimester ultrasound evaluation includes the (CRL) measurement which is the most accurate method for estimating the gestational age.[92] Arguably, an accurate gestational age is one of the most important pieces of information in the management of both at-risk and normal pregnancies.

The first trimester ultrasound has even more benefits in the case of multiple gestations. Firstly, the first trimester is the optimal time to establish the chorionicity and amniocity in a multiple gestation.[93-95] A distinct thickening of the dividing membrane ("lambda" or "twin peak" sign) as it approaches the placental surface indicates that the gestation is dichorionic (DC). If the membrane is thin throughout its entire length including the point, where it meets the placental surface ("T" sign), the diagnosis of a monochorinic/diamniotic (MC/DC) gestation may be confidently made. The knowledge of chorionicity is very useful in the overall management of the pregnancy; MC/DC gestations are at a significantly high risk for a variety of adverse perinatal outcomes than DC gestations. Furthermore, establishing the chorionicity helps to select the appropriate algorithm to calculate the aneuploidy risk.[96-98] Unlike maternal serum biochemistries, the use of ultrasound markers in multiple gestations allows for this risk to be assigned to each fetus individually, rather than establishing a risk for the pregnancy overall. Maternal serum markers in higher order multiple gestations (triplets and greater) are unreliable and first trimester ultrasound screening is the best option.

In monochorionic/diamniotic gestations, the risk of developing twin-to-twin transfusion syndrome (TTTS) later in pregnancy may be estimated by measuring the NT (the likelihood of TTTS increases with increasing difference in the NT measurements between the two fetuses),[99] and by evaluating the ductus venosus with Doppler (presence of reversed a-wave increases the risk of TTTS).[100]

An Argument for Confining the First Trimester Ultrasound Exam to 11-13 + 6 weeks' Gestation

The inclusion of an ultrasound examination in first trimester screening results in benefits that extend well beyond just screening for aneuploidy. Imposing the lower limit of 11 weeks' gestation for first trimester screening assures that the benefits of the ultrasound examination are maximized.

Firstly, an anatomic survey of the fetus performed after 11 weeks' gestation is much more likely to produce usable information than an examination done prior to this gestational age. This applies not only to identification of anomalies but also to simply being able to visualize normal structures.[101] There are some transient structural alterations that are normal in the embryonic and early fetal period that

may make the diagnosis of certain anomalies more difficult. One is the presence of a physiologic extra-abdominal herniation of the bowel that makes the diagnosis of an omphalocele difficult prior to 11 weeks' gestation.[102-104] The absence of ossification of the cranial vault prior to 11 weeks' gestation reduces the accuracy of the diagnosis of the first trimester exencephaly/anencephaly sequence.[105] Finally, aside from the NT measurement, the effectiveness of first trimester markers prior to 11 weeks gestation is unknown but is likely to be reduced (e.g. the nasal bone is not normally ossified prior to 11 weeks' gestation,[106] almost 50% of normal fetuses have incompetent tricuspid valves at 10 weeks' gestation).[107]

There are several reasons for not extending the NT-based screening beyond 13 + 6 weeks' gestation. Firstly, the effectiveness of NT measurement as a marker of aneuploidy diminishes in effectiveness with advancing gestational age.[108] Secondly, the position of the fetus within the uterus tends to be such that the nuchal translucency measurement is more difficult to acquire.[109,110] Thirdly, the estimation of gestational age based on a CRL measurement is no longer accurate. Lastly, the patient now enters the second trimester thus reducing the benefits of early diagnosis and treatment.

ELEMENTS OF FIRST TRIMESTER FETAL SCREENING

General Principles of Screening

The development of a credible screening protocol has a number of essential components. Firstly, a marker (ultrasound or maternal serum) needs to be identified. A marker for aneuploidy is defined as a finding that has a different prevalence in the euploid and aneuploid populations. A likelihood ratio that is associated with the marker is calculated by dividing the two prevalences. The strength of the marker increases as this difference increases. It needs to be determined whether the likelihood ratio is influenced by maternal or fetal factors. If more than one marker is used, it needs to be established whether or not they perform independently of each other. If there is weak association between the two markers, this usually may be compensated for mathematically. If the association is strong, it may be best not to use them together. The technique, which is used to examine a marker, must be standardized so it is reproducible and may be implemented in more than one center.

The implementation of a credible screening protocol also has a number of essential components. Above all, only those operators that have the appropriate background and training should be involved in the performance of screening. It is equally important to establish a quality assurance system that reviews the performance of the screening on an ongoing basis.

General Principles of the Use of Ultrasound and Biochemical Markers

Each of the markers that are included in the FMF algorithm has its own likelihood ratio associated with it, which is appropriately adjusted for maternal and fetal factors. Some of the markers are measured as a quantitative parameter (NT, FMF angle, fetal heart rate, maternal serum biochemistries). They are used as continuous variables and each measurement has its own likelihood ratio associated with it. While using these types of variables, the detection rates and false positive rates may be changed by changing the cut-off value that is used to separate the "high-risk" group from the "low-risk" group. The remaining markers (NB, TCV, DV, "soft" markers, fetal anomalies) are evaluated qualitatively. They are assigned a likelihood ratio, which depends on whether they are present or absent. The detection rates and the false positive rates of these markers cannot be mathematically changed since their prevalences in the normal and abnormal populations are fixed.

The manner in which the majority of markers for fetal aneuploidy are used is to adjust the patient's a priori (background) risk. The only exception is certain fetal anomalies (see below). They have such a high association with aneuploidy that the a priori risk is irrelevant and the risk that they confer is fixed.

The a priori risk is usually based on the maternal age. However, other less common factors such as a prior offspring with aneuploidy or a balanced parental translocation also increase the a priori risk.[111,112]

Crown-rump Length

It is important to obtain an accurate crown-rump length (CRL) as the calculation of fetal risk must be based on the correct gestational age.[92] A midline longitudinal view of the fetus is obtained and the image is magnified so that the fetus fills most of the image. The fetus is measured from the top of the head to the rump. The measurement should be done with the fetus in a neutral position, i.e. not hyperflexed or extended.

Nuchal Translucency

The NT is formed by a layer of fluid beneath the nuchal skin extending for a variable distance over the head and neck.[113] This layer of fluid is present in all fetuses between 11 and 13 + 6 weeks of gestation. It has been shown that as

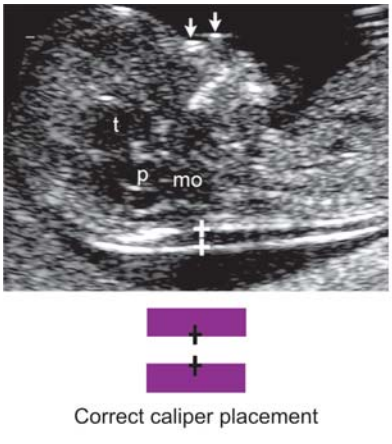
the amount of this fluid increases, there is an increasing chance of the fetus being affected by some type of a disorder. However, as is the case with every true marker, even a very significant increase in NT thickness does not make the diagnosis of a fetal problem. This can be determined only by the appropriate diagnostic test such as chorionic villus sampling or amniocentesis.

Possible Mechanisms for Thickened Nuchal Translucency

There are a number of mechanisms that have been proposed for the nuchal thickening: structural cardiovascular abnormalities and/or abnormalities of myocardial performance,[6,114-117] abnormalities of connective tissue composition,[7,8,118-120] abnormalities or delay in lymphatic system formation,[66,67,121,122] increase in intrathoracic pressure,[48,54-61] decrease in fetal movement,[50,70-72] fetal hypoproteinemia,[69,123] fetal anemia,[73-76] and fetal infection.[77-79,124] It is likely that under different clinical circumstances, different mechanisms are in effect. It is also likely that in many cases, especially in fetuses with chromosomal defects, the thickened NT is caused by more than one mechanism.

Nuchal Translucency Measurement

The relative amount of nuchal fluid may be estimated by measuring the thickness of the hypoechoic layer that it forms with the fetus in a longitudinal view. In order for this marker to be reproducible and usable in multiple centers, the method of measurement has been standardized by the FMF (Fig. 1). The magnification is such that the fetal head and the upper thorax occupy the majority of the image. This is done so the accuracy of the NT measurement is 0.1 mm.[125] A midline section is obtained with the fetus either facing towards or away from the transducer. There are a number of anatomic landmarks that help to establish that the ultrasound plane is in the midline: delineation of the fetal profile with echogenic lines representing the skin over the nasal bridge and nasal tip being visible in the same view (only if the fetus is facing the transducer) and the intracranial hypoechoic regions of the thalamus, the pons and the medulla oblongata (if the fetus is either facing towards or away from the transducer). The fetal neck should be neither extended or hyperflexed. Extension artificially increases the nuchal translucency measurement and hyperflexion decreases it.[126] Cross-shaped calipers should be used. This allows for optimal standardization of the caliper placement: the inner aspect of the caliper cross hatch should be flush with the inner aspect of the echodense lines bracketing the nuchal fluid. The ultrasound settings should be adjusted so these lines are as thin and sharply delineated as possible. The NT may be best visualized and the echogenic lines are sharpest if the face of the transducer is approximately parallel to the longitudinal axis of the fetus and the nuchal skin is insonated at 90°. The nuchal translucency must be clearly differentiated from the amniotic membrane, which has a similar ultrasound appearance to the skin line. The measurement, which is used for the risk calculation should be taken at the thickest part of the NT. Optimally, the measurement should be performed on at least three separate images and the largest measurement that meets the criteria should be used.



- **CRL:** 45-84 mm (11+0 to 13+6 weeks' gestation)
- **Mid-sagittal view** (fetus may either be facing towards or away from the transducer)
- **Landmarks on the profile:** skin over the nasal bridge and the nasal tip (solid arrows)
- **Intracranial structures:** thalamus (t), pons (p), medulla oblongata (mo)
- **Image size:** head and upper thorax occupies most of the screen (measurement accuracy 0.1 mm)
- **Neutral fetal position** (avoid neck extension or flexion)
- **Skin line needs to be seen separately from the amnion**
- **Nuchal cord** (5% of the cases): measure NT above and below the nuchal cord and average the measurements
- **"On-to-on"** caliper placement
- **Motivated sonographer**

Fig. 1: Nuchal translucency measurement

In approximately 5% of the cases, a nuchal cord is identified.[127] This is usually first suspected when a segment of the nuchal translucency cannot be clearly visualized. Often, faint echodense lines are seen in this region, which represent a cross-section of the tortuous umbilical vessels. The presence of a nuchal cord is best confirmed with color Doppler. It is felt that a nuchal cord causes redistribution of the nuchal fluid. An acceptable method to compensate for this redistribution is to measure the NT above and below the nuchal cord. The risk assessment is based on the average of the two measurements.

For a given measurement, the appearance of the NT does not change the risk of a fetal abnormality being present. Therefore, the risk assessment should be based on the NT measurement alone. On close inspection, septations may be seen in essentially all thickened nuchal translucencies.[128] Therefore, attempting to differentiate between simple nuchal translucency and a "cystic hygroma" is not useful. Assigning different risks based on the appearance of the NT was proposed as a part of the FASTER study.[129] The statistical analysis used in this article was questioned by some.[130] Additionally, subsequent analysis of the same data by the FASTER group did suggest that NT size rather than appearance is most important.[131]

Nuchal Translucency and Fetal Aneuploidy

The prevalence of chromosomal defects increases with increasing NT thickness.[132,133] The relation between fetal NT and chromosomal defects was initially derived from a multicenter screening study involving 96,127 singleton pregnancies.[132] The distribution of these measurements has slightly changed since that time. This is due to minor changes in the technique used to measure the NT and due to changes in ultrasound equipment. The distribution of normal measurements that is currently used for risk estimation is based on 37,078 fetuses examined in a standardized fashion at the Fetal Medicine Center in London between 1999 and 2005.[108]

The mathematical description of the NT measurement distribution and the manner in which the likelihood ratios are generated have evolved over the past 15 years. Recently, a mixture model of the NT measurement distributions has been introduced.[108] This model is based on the observation that the NT measurement distributions in both the euploid and the aneuploid fetuses follow two distinct patterns. In a certain proportion of the fetuses, the nuchal translucency measurements increase between 11 and 13 + 6 weeks' gestation, whereas in another proportion, the NT measurements are independent of the gestational age and remain constant over this time period. The percentage of populations that fit into these two categories is different depending on the chromosomal complement.

If done correctly, NT measurement is arguably the most robust single marker for fetal aneuploidy.[30] Therefore, NT measurement should be a part of any screening protocol that includes first trimester ultrasound examination. Using just the combination of maternal age and NT measurement, the detection rates for a 5% false positive rate are about 75% for trisomies 21, 18 and 13, and are 90% and 60% for monosomy X and triploidy respectively.[132,134,135]

Maternal serum analytes that have been shown to be most effective in first trimester screening for aneuploidy are free β-hCG and PAPP-A. Nuchal translucency measurements and the serum analytes levels are independent of each other. Therefore, the two may be used together along with maternal age-related risk (combined first trimester screen) without the need for additional mathematical manipulation.[21,136-140] The combined screening improves the detection rate for trisomies 21, 18 and 13, monosomy X, and triploidy to 90% or more for a 5% false positive rate.[2,141,142]

Nasal Bone

The logic behind using the prenatal nasal bone evaluation in screening for trisomy 21 is based on the characteristic facial features found in individuals with Down syndrome and anthropometric, radiological, and histological studies.[143-147] All of these studies demonstrate a significant difference in either the size of the nasal bone or in the degree of ossification between euploid individuals and those with trisomy 21.[148]

Since the confirmation that this phenomenon appears to be present on prenatal ultrasound,[149] a number of studies have been published indicating that absence of the nasal bone is highly associated with trisomy 21 in both the first and the second trimesters.

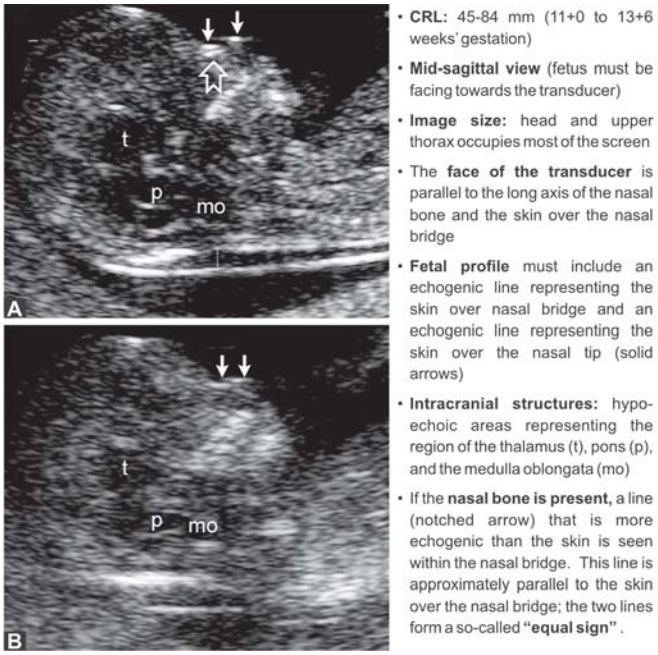
Recently, the routine evaluation of the nasal bone (absence or hypoplasia) in postmortem fetal examinations has been proposed as a marker for developmental disturbances in the frontonasal region.[150]

Mechanism for the Nasal Bone Absence in Trisomy 21

The exact mechanism leading to the nasal bone abnormalities seen in trisomy 21 is unknown. However, it is likely that the changes in connective tissue known to exist in trisomy 21 are at least in part responsible.[118-120,146,147]

Ultrasound Evaluation of the Fetal Nasal Bone

In the first trimester, the nasal bridge is evaluated only for the presence or absence of the nasal bone.[148,151-156] Unlike in the second trimester, measuring the nasal bone does not appear to improve the screening performance of the test.[148,157]



Figs 2A and B: Nasal bone assessment (A) nasal bone present, (B) nasal bone absent

The protocol for an ultrasound evaluation of the nasal bone is shown in Figures 2A and B. The fetal profile needs to be insonated in the midline plane. This is determined by visualizing the following fetal structures: the hypoechoic region of the thalamus, pons, and medulla oblongata, the echogenic line over the nasal bridge representing the skin, and an echogenic line that is located anteriorly and slightly superiorly to the nasal bridge, which represents the skin over the nasal tip. If the nasal bone is present, an echogenic line is also seen within the substance of the nasal bridge. This line is approximately parallel to the line representing the nasal bridge skin. These two lines form a so-called "equal sign". The echogenicity of the nasal bone needs to be greater than that of the skin in order for the nasal bone to be identified as present. The reason for this requirement is that even if the nasal bone is not ossified (i.e. sonographically absent), a very faint echodense line may be seen within the nasal bridge.

In order to be able to visualize the required anatomic landmarks and to see the nasal bone as a separate structure from the nasal skin, significant magnification is required: the fetal head an upper thorax should occupy the majority of the image.

The angle of insonation is extremely important in the evaluation of the nasal bone. The face of the transducer should be parallel to the longitudinal axis of the nasal bridge and the nasal bone (90^o angle of insonation). The nasal bone may become sonographically invisible, if there is a significant deviation from this angle. This is due to the fact that the NB is an extremely thin structure. The lateral resolution of the ultrasound equipment is insufficient to visualize the NB if it is viewed "on-end" (close to 0^o angle of insonation). Finally, the nasal bone evaluation may be done only with the fetus facing the transducer.

Three-dimensional ultrasound does not appear to significantly improve the success of examination of the nasal bone.[158] However, one advantage that it holds over the 2D examination is that it can reliably identify unilateral absence of the nasal bone.[158] The exact likelihood ratio associated with this finding has not been established. However, since it has been seen in association with trisomy 21, unilateral nasal bone absence has been for now assigned the same significance as bilateral nasal bone absence.

Nasal Bone and Fetal Aneuploidy

The likelihood ratio associated with the NB findings needs to be adjusted for gestational age.[159] Overall, the prevalence of an identifiable NB increases with increasing gestational age. If the NB is not visualized at 11-12 weeks' gestation, it is recommended to repeat the ultrasound examination one week later and use the results of the second examination for the risk calculation. This approach decreases the false positive rate.

The prevalence of NB presence and absence is also influenced by ethnicity.[159] The prevalence of NB absence is the lowest in Caucasians and it is most common in persons of African origin. The prevalence in Asians falls between the two. This difference in prevalence applies to both euploid fetuses and fetuses with trisomy 21.

There is a relationship between the NT measurement and the prevalence of NB absence. However, this does not appear to be significant until the NT measurement exceeds the 99th percentile (3.5 mm).[159] Therefore, most of the time the likelihood ratio based on the nasal bone evaluation does not have to be adjusted for the NT measurement.

A review of several major studies demonstrates that based on examinations of approximately 49,000 fetuses the prevalence of NB absence in euploid fetuses in the first trimester is 1-3% and is 65% in fetuses with trisomy 21.[148] An increased prevalence of NB absence has also been found in trisomy 18 (55%), trisomy 13 (34%), monosomy X (11%) but not in triploidy.[159]

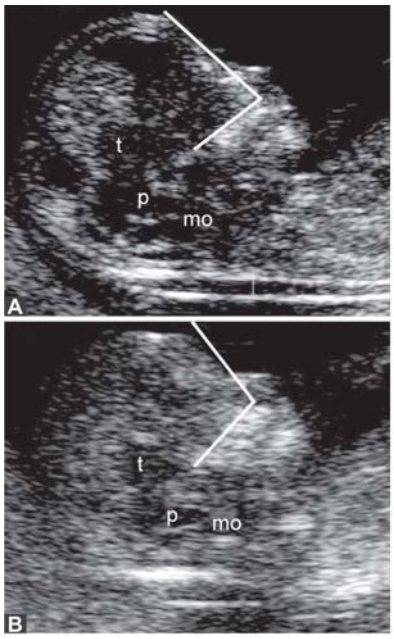
The presence or absence of NB is independent of the maternal serum markers (free β-hCG and PAPP-A).[3, 151,160,161] Therefore, this evaluation may be added to the first trimester combined screen. A study involving 19,614 fetuses demonstrates that with the addition of NB evaluation to the combined screen, for a false positive rate of 3% the detection rate of trisomy 21 was 92% and the detection rate for trisomies 18,13, and for monosomy X was 100%.[3]

Frontomaxillary Facial Angle

Flat facies is recognized as a common dysmorphic features in individuals with Down syndrome. This may be subjectively assessed even on prenatal ultrasound by examining the fetal profile. However, in order for this facial feature to be exploited for screening purposes, a method had to be found to evaluate it using a standardized measurement. The frontomaxillary facial (FMF) angle measurement is an objective way to estimate mid-face hypoplasia; the deeper the location of the front edge of the maxilla is with respect to the forehead, the shallower the FMF angle.[162] The reason for the mid-face hypoplasia in trisomy 21 also appears to be the presence of abnormal connective tissue. Theoretically, abnormal bone modeling due to hypotonia of the tongue may also be a contributing factor.

Frontomaxillary Facial Angle Measurement

The image requirements for the FMF angle measurement (Fig. 3) are very similar to those for the NB evaluation. The



- **CRL: 45-84 mm** (11+0 to 13+6 weeks' gestation)
- **Mid-sagittal view** (fetus must be facing towards the transducer)
- **Image size:** head and upper thorax occupies most of the screen
- **Face of the transducer** is approximately parallel to the long axis of the nasal bone
- **Fetal profile** must include an echogenic line representing the skin over nasal bridge and an in front of it an echogenic line representing the skin over the nasal tip
- **Intracranial structures:** hypoechoic areas representing the region of the thalamus (t), pons (p), and the medulla oblongata (mo)
- Space between the upper palate and the nose should be **devoid of an echogenic structure** representing the zygomatic process
- **FMF angle: first ray** is drawn along the upper edge of the hard palate, apex of the angle is at the anterior edge of the maxilla, second ray runs upwards from the apex resting on the echogenic line beneath the skin (the noncalcified metopic suture)

Figs 3A and B: Frontomaxillary facial angle measurement. (A) an acute angle in an euploid fetus, (B) an obtuse angle in a fetus with trisomy 21

head and the upper thorax should fill the majority of the image and the fetus needs to be facing the transducer. The greatest of care must be taken to obtain a precise midline view as only a small deviation from the midline significantly affects the measurement.[163] The landmarks that are used to determine this are also similar to those, which are used for the NB evaluation: echogenic skin over the nasal bridge and nasal tip seen in the same view on the surface of the profile and the intracranial hypoechoic regions of the thalamus, pons, and the medulla oblongata.[163] Additionally, in the precise midline view, the area between the upper edge of the hard palate and the nasal bone is relatively echo free. As the plane of insonation deviates slightly from the midline, an echogenic structure comes into view. This represents the zygomatic process of the maxilla, a finding that should be absent in the correct view. The use of 3D ultrasound may be helpful to establish the correct view.[163]

\ The angle of insonation is also similar to the one required for the nasal bone evaluation: the face of the transducer should be roughly parallel to the long axis of the NB and the skin over the nasal bridge. The hard palate, which is composed of the maxilla and the vomer bones, is seen as a roughly trapezoid echogenic structure with the posterior portion being slightly thicker than the front one.

In order to measure the frontomaxillary angle, the following lines are generated. The first one runs along the upper edge of the hard palate. The vertex of the angle is at the anterior-most portion of the maxilla. The second line of the angle runs upwards from the vertex towards the forehead. It is positioned so its inner edge rests upon the metopic suture, which lies a short distance beneath the skin. In the first trimester, the metopic suture is not yet ossified. Therefore, it is seen as a line of similar echogenicity as the skin.

The deep position of the front edge of the maxilla in fetuses with trisomy 21 may be due to maxillary hypoplasia, dorsal displacement of the maxilla, or a combination of the two. Figures 3A and B illustrates the difference between FMF measurements in a fetus with trisomy 21 and in a euploid fetus.

In the first trimester, the division between the vomer bones and the maxilla is usually difficult to see. However, towards the end of the first trimester, this division may become evident as an oblique hypoechoic line running from the upper edge of the hard palate anteriorly to the lower edge of the hard palate posteriorly.[164] This line should not be used to form the lower ray of the FMF angle.

Frontomaxillary Angle and Fetal Aneuploidy

The normal ranges of the frontomaxillary angle measurements decrease with advancing gestational age.[165] They are independent of NT measurements, presence or absence of the nasal bone, and maternal serum biochemistries.[4, 162]

Shallow FMF angles are seen not only in trisomy 21 but also in trisomies 18 and 13. Fetuses with trisomies 21, 18, and 13 have FMF angle measurements that are above the 95th percentile in 45%, 58%, and 48% cases respectively.[4,166,167] In a study, which included 782 euploid fetuses and 108 fetuses with trisomy 21, a 92% detection rate for a 3% false positive rate was achieved by adding FMF angle measurement to the combined screen.[4]

Doppler Evaluations of Fetal Blood Flow as Markers for Aneuploidy

The fetal cardiovascular system has a number of structural and functional features that differentiate it from the cardiovascular system *ex utero*. The arrangement of the myocytes within the fetal heart is less well-organized and there are fewer sarcomeres per unit mass.[6] The fetal myocardium has lower compliance resulting in a higher intraventricular pressure at any cardiac volume. Early in pregnancy, the placental vascular resistance is relatively high placing additional strain on the heart. As a consequence, the fetal heart functions at the upper limits of the Frank-Starling curve. In the first trimester, abnormalities of cardiac structure and/or performance may lead to detectable changes in blood flow through certain structures. The two structures that have been investigated the most and hold promise in screening for aneuploidy are the tricuspid valve (TCV)[168]

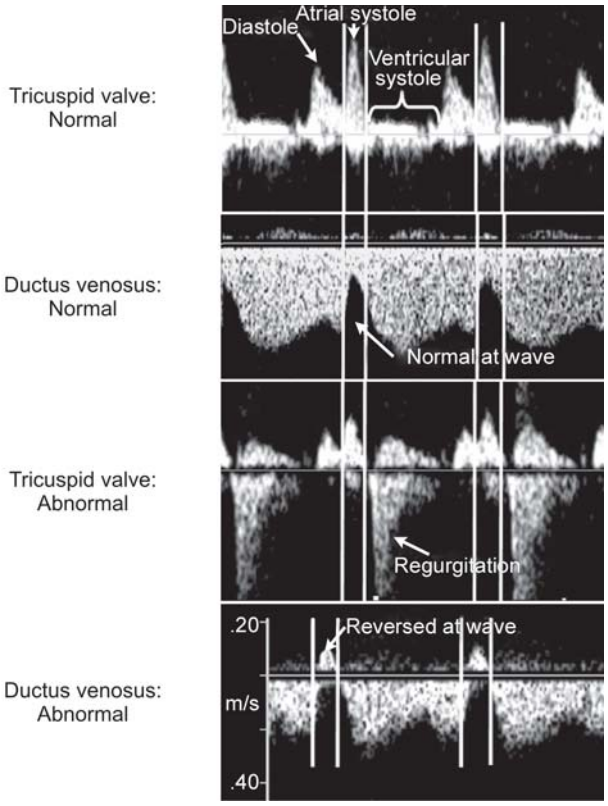


Fig. 4: Temporal relationship of pulsed Doppler waveforms across the TCV and the DV: normal and abnormal

and the ductus venosus (DV).[169] The DV is strictly a fetal structure that carries 50% of the oxygenated blood from the umbilical vein and empties into the inferior vena cava at a point that is very close to the right atrium. Its proximity to the right side of the heart makes it susceptible to changes in the cardiac function.[170-182] Tricuspid valve flow is considered abnormal in the presence of regurgitation and the DV venous flow is considered abnormal if the a-wave is reversed (see below). The temporal relationship between the Doppler flow patterns across the TCV and DV are demonstrated in Figure 4.

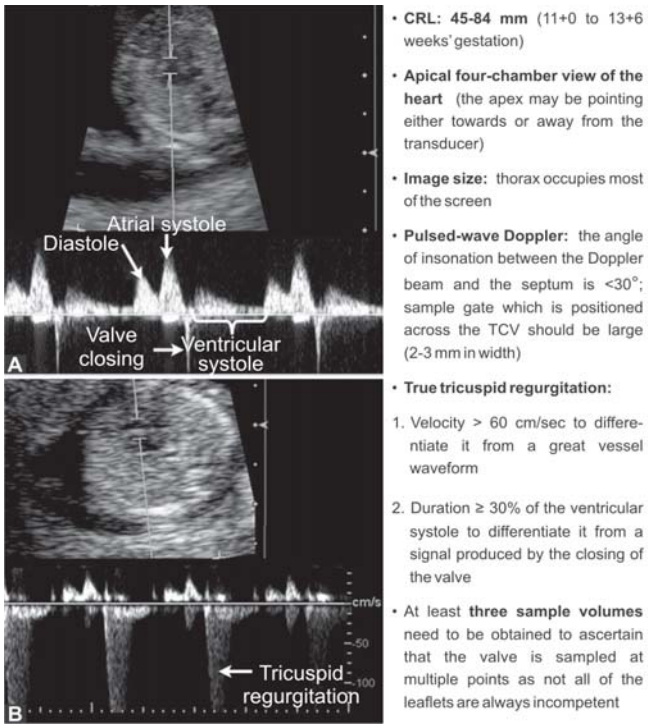
Tricuspid Valve Regurgitation

The exact reason for the increased prevalence of tricuspid valve regurgitation in fetuses with trisomy 21 is not completely clear. However, it is likely that it is related to the structural and ultrastructural changes in the heart that are known to be associated with trisomy 21: decreased number of myocytes, abnormal orientation of myocytes and myofibrils, and abnormal connective tissue.[6, 8,118-120] It may be that these changes result in a relative dilatation of the right ventricle. It is also recognized that dilatation of the right ventricle may lead to tricuspid regurgitation by dilating the tricuspid valve annulus. Finally, the connective tissue abnormalities that affect the myocardium are also present in the valve itself.[8] It may be that both of these mechanisms are involved in causing TCV incompetence and regurgitation.

Pulsed Doppler Evaluation of Blood Flow across the Tricuspid Valve

The protocol for TCV evaluation using pulsed Doppler is shown in Figures 5A and B. A magnified transverse section of the fetal thorax containing a four chamber view is obtained. The angle of insonation is important. The heart view should be apical so that the angle of insonation with respect to the ventricular septum is less than 30°. The Doppler gate is placed across the TCV. The gate should be relatively large (2-3 mm) to make certain that it covers both sides of the valve. It should be kept in mind that not all of the leaflets of the TCV are necessarily incompetent. Therefore, at least three Doppler evaluations should be obtained. It is also helpful to interrogate the TCV flow in real time sweeping through the valve to make sure that it is interrogated in its entirety.

The normal TCV waveform demonstrates biphasic pattern of blood flow into the right ventricle. The first one represents diastole and the second one represents the atrial systole (Figs 4 and 5). There should be no flow seen across the valve during the ventricular systole. Since the size of the first trimester heart is quite small the Doppler is often contaminated by the flow in one of the great vessels. The direction of blood flow in the great vessels is the same as that of the regurgitant jet and they are seen at the same point in the cardiac cycle. Therefore, it is imperative to be able to differentiate between the two. There are two consistent differences in their flow pattern. Firstly, the velocity in the great vessels is less than 50 cm/sec whereas the velocity of the regurgitant jet is always >> 60 cm/sec. Therefore, in order to be able to diagnose TCV regurgitation, the blood flow velocity has to be in excess of 60 cm/sec. Secondly, the regurgitant jet makes a typical high pitched hissing sound on Doppler, which is absent from the flow through the great vessels. It is often this sound that first alerts the operator to the presence of TCV regurgitation. Since a signal from a closing tricuspid valve (Fig. 5A) and trivial tricuspid regurgitation are fairly common findings and are of no clinical significance, regurgitation must last at least 30% of the ventricular systole in order to be called an abnormal finding.



Figs 5A and B: Pulsed Doppler evaluation of the tricuspid valve: normal (A); abnormal (B)

Tricuspid Valve Doppler and Fetal Aneuploidy

The prevalence of tricuspid regurgitation varies with gestational age. The prevalence of tricuspid regurgitation also increases as the NT measurement increases.[11] These associations are factored into the algorithm developed by the fetal medicine foundation. It should be noted that tricuspid regurgitation is also associated with an increased risk of congenital heart defects.[10] Therefore, a careful examination of the fetal heart should be performed at the time when the TCV regurgitation is noted and repeated in the mid second trimester.

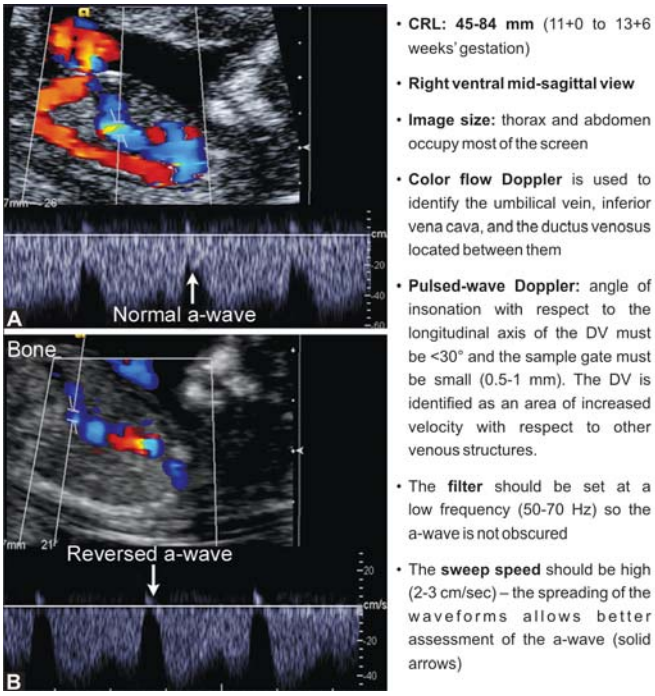
Tricuspid regurgitation is seen not only in trisomy 21 but also in trisomies 18 and 13, and monosomy X. The prevalence of tricuspid regurgitation in fetuses with trisomies 21, 18, and 13 and monosomy X is 56%, 33%, 30%, and 38% respectively. The prevalence of tricuspid regurgitation in euploid fetuses is 1%.[11] In a study, which included 19, 614 fetuses, a 96% detection rate for a 3% false positive rate was achieved for trisomy 21 by adding tricuspid valve evaluation to the combined screen. The detection rates for trisomies 18 and 13, and monosomy X were 92%, 100%, and 100% respectively.[11]

Reversed a-wave in the Ductus Venosus

The exact reason for a reversal of the a-wave in the ductus venosus in association with trisomy 21 is also not clear. However, it is likely that this abnormality is not a result of a change in the DV itself but rather due to a change in the fetal heart performance. Therefore, the ultrastructural changes in the cardiac anatomy described earlier in the "tricuspid valve regurgitation" section may also be responsible for this phenomenon.[6,8,118-120] However, the abnormality is likely to be the result of decreased compliance of the ventricular walls rather than ventricular dilitation. The mechanical explanation for the a-wave reversal may be that the atrial wall is contracting against a relatively stiffer wall and has to generate more pressure to push the blood across the TCV. The increased back pressure that would be inevitably generated in this situation may be sufficient to either stop or reverse the blood flow during atrial systole (absent or reversed a-wave). In the current FMF algorithm, the DV flow is considered abnormal only if the a-wave is reversed.

Pulsed Doppler Evaluation of Blood Flow through the Ductus Venosus

The fetus is examined in the longitudinal view slightly to the right of the midline (Figs 6A and B). The DV is identified as a short continuation of the hepatic portion of the umbilical vein (UV). The identification of the DV is greatly aided by using color Doppler. The DV is distinguishable from the UV by a distinctly higher velocity. The pulsed Doppler gate



Figs 6A and B: Pulsed Doppler evaluation of the ductus venosus: normal (A); abnormal (B)

that is placed within the lumen of the DV needs to be small (0.5-1 mm). This is to minimize contamination of the signal by venous structures that are in close proximity such as the hepatic veins and the inferior vena cava. The magnification should be such that the fetal abdomen and thorax fill the majority of the image. The angle of insonation of the Doppler beam should < 30° with respect to the longitudinal axis of the DV.

On pulsed Doppler, a normal DV waveform demonstrates forward blood flow throughout the cardiac cycle. There are two adjoining periods of increased blood flow: the ventricular systole and the diastole. Normally, the blood flow is diminished during the atrial systole but the forward flow is maintained (Figs 4 and 6).

Ductus Venosus Doppler Flow and Fetal Aneuploidy

The prevalence of a-wave reversal changes with gestational age. There is also an association in the prevalence of a-wave reversal and thickening of the NT. These associations are mathematically accounted for in the FMF algorithm.[17]

It should be noted that a-wave abnormalities are also associated with an increased risk of cardiac anomalies.[18,19,179] Therefore, a careful examination of the fetal heart should be performed at the time when the reversed a-wave is noted and be repeated in the mid second trimester.

Reversed a-wave is seen not only in trisomy 21 but also in trisomies 18 and 13, and monosomy X. The prevalence of tricuspid regurgitation in fetuses with trisomies 21, 18, and 13 and monosomy X is 66%, 58%, 55%, and 75% respectively. The prevalence of reversed a-wave in euploid fetuses is 3%.[17] In a study, which included 19,614 fetuses, a 96% detection rate for a 3% false positive rate was achieved for trisomy 21 by adding tricuspid valve evaluation to the combined screen. The detection rates for trisomies 18 and 13, and monosomy X were 92%, 100%, and 100% respectively.[17]

Fetal Heart Rate in Screening for Aneuploidy

It has been noted that aneuploid fetuses tend to have different heart rates from the euploid fetuses at the time of the first trimester screening.[2,20] The largest difference is seen in trisomy 13 and monosomy X where the heart rate is above the 95th percentile in 69% of the cases and 53% of the cases respectively. The heart rate also tends to be increased in trisomy 21 but much less so (14% are above the 95th percentile). Both trisomy 18 and triploid fetuses tend to be bradycardic (19% and 36% below the 5th percentile respectively). If FHR is included in first trimester screening, it needs to be adjusted for gestational age as the normal ranges decrease between 11 and 13 + 6 weeks of gestation.[2,20]

Acquiring Proficiency in Ultrasound Marker Evaluation

The proper use of prenatal ultrasound requires appropriate training and experience. This is especially true for the first trimester ultrasound evaluation. It is estimated that a sonographer needs to perform approximately 60 to 80 ultrasound examinations in order to be able to evaluate each of the first trimester markers correctly on consistent basis.[182-184] However, an improvement in skill is often noticeable even after the first few examinations.

First Trimester Screening for Aneuploidy using Multiple Ultrasound Markers

The ultrasound markers and maternal serum biochemical markers that are described above are sufficiently independent of each other to be used in combination. This can be done either by evaluating all of them in every fetus, using only some of them in every fetus, or using them on contingent basis. As more markers are added, the detection rate increases and the false positive rate decreases. Mathematical modeling predicts that if all of the ultrasound markers described above are used along with maternal age and maternal serum PAPP-A and free α-hCG levels, the detection rate for trisomy 21 would be 96% for a 2% false positive rate.[3,4,11,17]

An algorithm using ultrasound markers for aneuploidy on contingent basis in the first trimester was developed by the Fetal Medicine Foundation.[139] The first step taken in using this approach is to perform the combined screen (maternal age, NT measurement, free α-hCG level, PAPP-A level) in every patient. Based on the results of the combined screen, the patients are divided into three categories: high risk (trisomy 21 risk of ≥ 1:50), intermediate risk (trisomy 21 risk of 1:51 to 1:1,000) and low risk category (trisomy 21 risk <1:1,000). The patients that fall into the high risk category are offered an invasive diagnostic procedure without any additional screening. This category constitutes only 1.3% of the total screened population but contains 82% of the fetuses with trisomy 21. The low risk group constitutes the majority of the screened population (86.7%) but contains only 4% of fetuses with trisomy 21. These patients are reassured and invasive diagnostic testing is done only upon maternal request. However, a targeted scan at approximately 20 weeks' gestation is still recommended. The intermediate risk category constitutes 12% of the screened population and includes 14% of the trisomy 21 fetuses. The persons in this group undergo additional screening by evaluating the additional ultrasound

markers (NB, FMF angle, TCV, DV). If the resultant risk of trisomy 21 exceeds 1:100, an invasive diagnostic test is offered. If it is less than that, they are treated in the same way as the low risk group.

For a 2% false positive rate, the detection rate for trisomy 21 using one additional marker is 90%, 94% for two additional markers, 95% for three additional markers, and 96% using all four additional markers. These detection rates are the same whether the contingent approach is used or the additional markers are used in every patient.[3,4,11,17,138]

Variations in Fetal Anatomy as Markers for Aneuploidy (Minor Markers)

Ultrasound markers for fetal aneuploidy are simply those findings that are seen more commonly in fetuses in the aneuploid population *vs* the euploid population. These may be divided into two broad categories: "pure" markers and fetal anomalies that act as markers for fetal aneuploidy.

Pure ultrasound markers are those findings that are not detrimental to the fetus per se but are associated with an increased risk of aneuploidy. This group of markers includes the ones discussed above. It also includes a number of other anatomic deviations from the normal (also referred to as "minor markers") that have been shown to increase the risk of fetal aneuploidy even in the first trimester. These include choroid plexus cysts (>1.5 mm), echogenic intracardiac focus, hyperechogenic bowel, and hydronephrosis (antero-posterior diameter of the renal pelvis >1.5 mm).[185] These markers are included in the FMF algorithm in screening for trisomy 21. It should be stressed that the minor markers must be interpreted in the context of presence or absence of other markers. The presence of an isolated minor marker probably does not increase the risk of aneuploidy. This is due to the fact that the absence of other markers acts as a counterbalance and decreases the risk sufficiently to negate the effect of the presence of a single marker.[185]

Variations in Fetal Anatomy as Markers for Aneuploidy (Anomalies)

Fetal anomalies that act as markers for fetal aneuploidy are those fetal defects that not only have a clinical significance in their own right but also increase the risk of an underlying chromosomal defect being present. The ones that are diagnosable in the first trimester and that have a well-defined fixed risks associated with them are the following: holoprosencephaly (risk of 1:2 for trisomy 13), diaphragmatic hernia (risk of 1:4 for trisomy 18), atrioventricular septal defect (risk of 1:2 for trisomy 21), omphalocele (risk of 1:4 for trisomy 18 and risk of 1:10 for trisomy 13), megacystis defined as bladder length of ≥ 7 mm (risk of 1:10 for either trisomy 18 or 13).[186-189] The fixed risks associated with these anomalies are also included in the FMF algorithm for aneuploidy risk calculation.

FIRST TRIMESTER SCREENING FOR FETAL ANOMALIES OTHER THAN CHROMOSOMAL DEFECTS

Nuchal Translucency Measurement as a Marker for Fetal Abnormalities in Chromosomally Normal Fetuses

Nuchal translucency thickening is associated with an increase in poor pregnancy outcome even if the fetus is chromosomally normal.[190-199] However, this increase does not become statistically significant until the NT measurement exceeds the 99th percentile. Conveniently, the 99th percentile cut-off remains constant at 3.5 mm across the 11-13 + 6 weeks' gestation period.[200]

A number of different fetal conditions may result in NT thickening making this measurement a useful test across a broad range of fetal anomalies.

Nuchal Translucency Thickening and Fetal Structural Defects

The prevalence of major fetal abnormalities increases exponentially as the nuchal translucency measurement increases beyond the 99th percentile (> 3.5 mm). The prevalence is approximately 2.5% for an NT of 3.5 mm and reaches 45% for an NT of 6.5 mm or more.[51,201]

One of the most important areas where NT screening appears to offer an advantage is the prenatal diagnosis of cardiac defects. Cardiac defects are some of the most common congenital structural anomalies but their prenatal diagnosis is in many cases challenging. However, if an accurate prenatal diagnosis of CHD is made, the outcome overall is improved by allowing for the fetus to be delivered in a setting where appropriate neonatal treatment is available. Combined data from a number of screening studies demonstrates that the prevalence of major cardiac defects is 1 to 2% in fetuses with a < 3.5 mm NT measurement. A significant increase in the prevalence of CHD is noted with NT measurements ≥ 3.5 mm: 3% (3.5-4.5 mm), 7% (4.5-5.4 mm), 20% (5.4-6.4 mm), 30% (≥ 6.5 mm).[26,35,38,40-42,190]

A meta-analysis of screening studies showed a detection rate of 31% for CHD using an NT measurement of 3.5 mm as the cut-off. It is estimated that fetal echocardiography in all chromosomally normal fetuses with NT above the 99th percentile would identify one major cardiac defect in every

16 patients examined.[45] Furthermore, this analysis showed that an increased NT measurements increase the risk of a variety of heart defects. Results of another study arrived at the same conclusion.[202] In this multicenter study, nuchal thickening was found to be present in all types of heart defects: left as well as right heart lesions, septal defects, outflow tract disorders, laterality disorders, and complex heart lesions.

With improvements in the resolution of ultrasound equipment, a detailed fetal cardiac evaluation may be performed even in the first trimester of pregnancy. Many of the major cardiac defects may now be diagnosed at the time of the 11-13 + 6 week scan.[36,51,89,203,204] Even if the specific diagnosis cannot be made, the cardiac examination often will indicate whether or not a cardiac structural defect is present.

There are a number of other types of fetal defects that are seen more commonly in fetuses with NT measurements of 3.5 mm or greater than in fetuses with normal NT measurements.[51-53,201] These include diaphragmatic hernia,[48] omphalocele,[47] body stalk anomaly,[49] skeletal defects,[54-65] and certain genetic syndromes such as congenital adrenal hyperplasia,[68] fetal akinesia deformation sequence,[70] Noonan syndrome,[66] Smith-Lemli-Opitz syndrome,[205] and spinal muscular atrophy.[71,72] There are many additional disorders that have been reported in association with a thickened NT that are quite rare. However, in many of these a definite association with a thickened NT is difficult to prove because of their rarity.[52]

Finally, the prevalence of fetal demise is increased in chromosomally normal fetuses in which the NT measurement ≥ 3.5 mm even if a specific fetal defect cannot be diagnosed. An analysis of 4, 540 fetuses categorized based on the NT measurement showed an increase in intrauterine loss from 1.3% in the 95th-99th percentile group to 20% in those that had NT measurements ≥ 6.5 mm.[51,201] The majority of fetal losses occur by 20 weeks' gestation. In fetuses that survive to the mid second trimester and in which a targeted ultrasound fails to reveal any anomalies or increased nuchal fold thickness, the risk for perinatal or long-term morbidity and mortality does not appear to be increased.[197,198, 206-210]

Screening for Open Neural Tube Defects

One of the major failings of the first trimester fetal ultrasound examination had been the inability to consistently diagnose open neural tube defects other than the exencephaly/anencephaly sequence. However, a recently described intracranial marker [intracerebral translucency (IT)] may overcome this deficiency.[25] The fetal image required to evaluate the IT is identical to those needed for the NT, NB and FMF angle evaluation. A magnified midline view of the fetal head and upper thorax is obtained and the following intracranial structures need to be visualized: hypoechoic regions of the thalamus, the pons (brain stem) and the medulla oblongata (Fig. 7). The IT represents the fluid filled fourth ventricle, which is located posteriorly to the pons. The combination of the posterior border of the pons and the floor of the fourth ventricle is seen as a single thin echogenic line, which forms the anterior border of the IT. The posterior border of the IT is the roof of the fourth ventricle. This is seen also as a relatively thin echogenic line accentuated by the choroid plexus of the fourth ventricle.

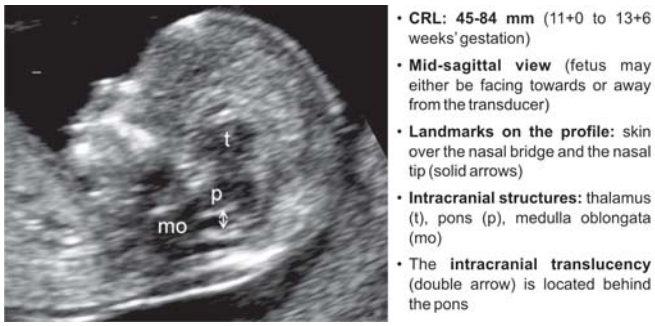


Fig. 7: Evaluation of the intracranial translucency

The IT was consistently visualized and was found to be normal at the 11-13 + 6 week scan in the 200 consecutive fetuses that were subsequently shown not to have spina bifida aperta.[25] In the same study, each of the four fetuses that were diagnosed with spina bifida aperta in the second trimester had an absent first trimester IT (i.e. the fourth ventricle was obliterated).[25] The proposed mechanism for this finding is similar to that of the Chiari type II malformation ("banana sign") seen in second trimester fetuses with spina bifida aperta: decreased pressure in the subarachnoid spaces leading to the caudal displacement of the brain. It appears that measuring the IT does not provide additional information. Therefore, the IT is simply reported as present or absent.

It would be premature to state that the absence or presence of IT has the same predictive value as the intracranial findings in the second trimester. However, the absence of the IT should lead to an extremely careful ultrasound evaluation of the spine at the time of the first trimester ultrasound. If the appearance of the spine is normal on the initial scan, the fetus should be reexamined at approximately 16 weeks. A 20 week scan should also be performed if the 16 week scan is normal.

First Trimester Screening for Preeclampsia

It is recognized that the development of preeclampsia is associated with vascular problems within the placental bed.

Even though the diagnosis of preeclampsia is not made until the second half of the pregnancy, the maldevelopment of the placental bed vessels occurs well before that time.[211]

The resistance of the vascular blood supply to the placenta and the placental bed normally decreases as the pregnancy progresses. This process is inhibited in many of those patients that are destined to develop preeclampsia. Additionally, the different degrees of placental vessel problems may result in a variety pregnancy associated hypertensive disorders: early-onset preeclampsia [< 34 weeks' gestation, very often associated with intrauterine growth restriction (IUGR)], late-onset preeclampsia (≥ 34 weeks' gestation), and gestational hypertension.

Pulsed Doppler Evaluation of Blood Flow through the Uterine Arteries

The impedance of the maternal blood supply to the placental bed may be estimated by measuring the pulsatility index (PI) of the uterine arteries using Doppler ultrasound. It has been shown that the risk of developing preeclampsia increases with increasing uterine artery PI.[26-29]

The first trimester Doppler examination of the uterine artery begins by obtaining a sagittal view of the cervix and the lower uterine segment. The cervical canal and the endocervix are identified. The transducer is then tilted from side to side and the location of the uterine artery at the level of the endocervix is identified with the aid of color Doppler (Fig. 8). The PI is measured using pulsed Doppler with the sample gate set at 2 mm. The angle of insonation with respect to the longitudinal axis of the uterine artery should be less than 30°. The magnification needs to be such that the uterine artery can be identified with confidence and the Doppler may be placed accurately within the lumen. At least three waveforms similar in shape should be obtained and the PI should be measured in both uterine arteries. The lowest PI is used for risk assessment.

In addition to identifying the artery in its proper location, there are two main ways to confirm that the vessel being interrogated with Doppler is the uterine artery. Firstly, the direction of the blood flow should be towards the transducer when the transabdominal approach is used. This assures that the cervical branches are not being insonated. Secondly, the peak velocity of the insonated vessel should be 60 cm/sec or greater. This assures that the main uterine artery is being insonated rather one of its branches.

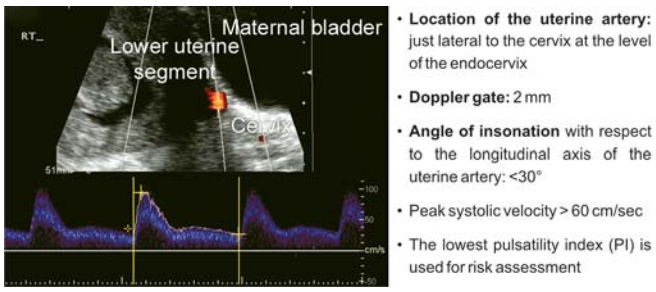


Fig. 8: Pulsed Doppler evaluation of the uterine artery [pulsatility index (PI) measurement]

Uterine Artery Doppler and Preeclampsia

Based on a recent publication that included 7,797 patients, it appears that the most efficient method of screening for preeclampsia in the first trimester is based on the following parameters: maternal history, uterine artery pulsatility index (increased PI increases the risk of preeclampsia), mean arterial pressure (increased MAP increases the risk of preeclampsia), pregnancy-associated plasma protein-A (decreased PAPP-A increases the risk of preeclampsia), and placental growth factor (decreased PlGF increases the risk of preeclampsia).[26] The factors in the maternal history that appear to make a significant independent contribution to the preeclampsia risk assessment included maternal BMI, age, ethnicity, smoking, and parity. For a 5% false positive rate, the combination of the above mentioned risk factors was shown to predict 90% of early preeclampsia, 35% of late preeclampsia, and 20% of gestational hypertension.[26] This compares favorably with screening based on maternal history alone where only 30% of early and 20% of late preeclampsia are predicted for a 5% false positive rate.

CONCLUSIONS

Over the past 40 years, the use of ultrasound has been clearly established as an invaluable tool in obstetric management. There has been a steady increase in our understanding of normal and abnormal fetal physiology along with an improvement in the quality of ultrasound equipment. This has not only lead to our ability to diagnose an ever increasing number of fetal conditions but also has moved the time of diagnosis to an earlier point in pregnancy. This benefits the patient in a number of ways not the least of which is maintaining the maximum level of privacy and preservation of reproductive choices.

The improvements in the screening capabilities of the first trimester scan have lead to an improved detection of fetal abnormalities, especially aneuploidy, and resulted in a decreased false positive rate. The latter has two very important benefits: fewer women have to go through the stress of being told that they fall into the "increased risk" category and fewer women undergo invasive diagnostic procedures. The decrease in the number of invasive diagnostic procedures being performed in turn leads to a

decrease in cost and a decrease in the number of normal fetuses being lost as a result of the invasive procedures.

Evaluation of maternal blood supply to the uterus along with maternal serum screening and history appears to accurately estimate the risk of developing preeclampsia later in pregnancy. This allows for an improved selection of at-risk patients early in pregnancy and may lead to treatments that reduce the development of preeclampsia in the future.

As the utility of ultrasound examination expands, our responsibility to perform the best possible ultrasound examination increases as well. This can be achieved only with proper training and expertise followed by an ongoing and rigorous external quality assurance program. A factor that is difficult to quantify but is none-the-less crucial in performing a thorough ultrasound examination is a high level of commitment on the part of each individual operator.

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