Review

Maternal-Fetal Medicine®

OPEN

Reappraising the Value of Fetal First-Trimester Ultrasonography

Huirong Tang, Mingming Zheng*

Abstract

In the last few years, the introduction of cell-free DNA has rapidly altered prenatal screening regimens and is increasingly offered as the second- or, at times, even the first-tier screening test. Should an early anomaly scan also be part of an up-to-date screening policy? This paper reappraises the value of fetal first-trimester ultrasonography. The primary aims of the first-trimester scan are to establish gestational age based on the measurement of fetal crown-rump length, to detect multiple pregnancy and chorionicity, and to measure fetal nuchal translucency thickness as part of a combined screening test for chromosomal abnormalities. With recent advancements in ultrasound technology, there is compelling evidence that a majority of fetuses with major structural abnormalities and almost half of them without chromosomal abnormalities can be detected in the first trimester. We focused on the first-trimester screening of fetal major defects, especially including fetal congenital heart disease and cleft lip and palate by ultrasound markers and views. Moreover, it is critical to highlight that after a detailed anomaly scan in the first trimester without major structural anomalies and positive genetic tests, the residual chance of favorable outcome in fetuses with isolated increased nuchal translucency is relatively high. The discussion on the role of cell-free DNA in prenatal screening is still ongoing. Even in the event of it becoming a first-line screening test for aneuploidies, the importance of a first-trimester fetal scan, including assessment of markers for other anomalies, remains undisputed.

Keywords: Ultrasonography, prenatal; First-trimester ultrasound; Fetal structural anomalies; Cell-free DNA; Chromosomal anomalies

Introduction

Since the 1990s, first-trimester ultrasonography has been widely performed to assess the risk of chromosomal abnormalities in the general population of pregnant women by measuring fetal nuchal translucency (NT) thickness between 11 and 13^{+6} weeks of gestation.[1] Previous studies showed that a combination of serum analytes (pregnancy-associated plasma protein A and β-human chorionic gonadotropin) and sonographic measurement of NT had a detection rate of 82%–95% for Down syndrome with a false-positive rate of 5%.[2] In contrast, in the last several years, prenatal screening using cell-free DNA (cf-DNA) has shown a detection rate of 99% for Down syndrome with a false-positive rate of <0.1%.[3] An increasing number of pregnant women choose cf-DNA instead of the first-trimester abovementioned combined screening test. Meanwhile, with recent advancements in ultrasound technology, there is compelling evidence that majority of fetuses with the major structural abnormalities, and almost half of fetuses without chromosomal abnormalities, can be detected in the first trimester. Hence, it is necessary to reappraise the role of the first-trimester scan in fetal morphological assessment in this cf-DNA era.

Department of Obstetrics and Gynecology, The Affiliated Drum and Tower Hospital of Medical School of Nanjing University, Nanjing, Jiangsu 210000, China.

** Corresponding author: Mingming Zheng, Department of Obstetrics and Gynecology, the Affiliated Drum and Tower Hospital of Medical School of Nanjing University, Nanjing, Jiangsu 210000, China.*
E-mail: drmingmingzheng@163.com

Maternal-Fetal Medicine (2023) 5:2

Received: 12 September 2021 / Accepted: 16 November 2021

First online publication: 14 December 2021

http://dx.doi.org/10.1097/FM9.0000000000000138

Who can benefit from the first-trimester scan?

The primary aims of the first-trimester scan at $11\text{-}13^{+6}$ weeks are to establish gestational age from the measurement of fetal crown-rump length to detect multiple pregnancy and chorionicity and to measure fetal NT thickness as part of a combined screening test for chromosomal abnormalities. Routine fetal anomaly ultrasound scan is recommended within 20–24 weeks of gestation.[4] Most fetal anomalies have already appeared and can therefore theoretically be identified in the majority of cases during early pregnancy. With higher resolution of ultrasound machine and recognition of fetal early development over the past few years, the ability to diagnose major fetal anomalies in the first trimester has been significantly improved.[5] The 2013 guidelines of the International Society of Ultrasound in Obstetrics and Gynecology have suggested anatomical assessment of the fetal head, neck, face, spine, chest, heart, abdomen, extremities, placenta, and cord during $11\text{-}13^{+6}$ gestational weeks.[6] Based on this guideline, some major structural abnormalities such as anencephaly, exencephaly, and limb reduction defects could be diagnosed by the first-trimester scan. A retrospective study involving 39,572 pregnant women compared the detection rates of fetal malformations between the first and second trimester.[7] It was seen that the detection rates of fetal structural abnormalities in the first and second trimester were 38% and 47%, respectively, which meant that around 70% of fetal major structural abnormalities detected prenatally could be detected in early pregnancy.

In a study involving 45,191 singleton pregnancies, Syngelaki *et al.*[8] reported that fetal non-chromosomal abnormalities can

be subdivided into three groups in relation to the first-trimester scan. The first group includes those that should be detectable, such as acrania, alobar holoprosencephaly, exomphalos, gastroschisis, and body-stalk anomaly. The second group includes abnormalities that are undetectable: some of them appear and develop till the second or third trimester of pregnancy, such as fetal tumors, ovarian cysts, microcephaly or ventriculomegaly; other defects evolve with advancing gestational age such as short limbs in achondroplasia, fractured limbs in some types of osteogenesis imperfecta or some cardiac defects, such as pulmonary or aortic stenosis. The last group includes abnormalities that are potentially detectable depending on the screening views, experience of the sonographers, and whether there are some soft markers to help detect anomalies. Some cardiac defects, orofacial clefts (OC), and open spina bifida are present within this group. Studies have shown 34% and 5% detection rate of congenital heart disease (CHD) and cleft lip and palate (CLP), respectively.[8] The prevalence of CHD and CLP is relatively high and fetuses with CHD and CLP have high risk of chromosomal abnormalities. Studies have also shown that the probability of chromosomal abnormalities in CHD and CLP were 37.8% and 40%, respectively, in the first trimester.[9,10] Therefore, the early detection of fetal CHD and CLP is crucial.

The early detection of CHD

Ultrasound markers in the screening of major CHD in the first trimester

Generally, the detection rate of fetal congenital heart in early pregnancy is relatively low (16%–48%),[11,12] and it requires experienced cardiac sonographers for the diagnosis. Assessment of sonographic markers has been shown to help detect underlying cardiac defects including NT, abnormal flow in the ductus venosus, and tricuspid regurgitation. When the fetal NT value is greater than the 99th percentile for crown-rump length, the risk of fetal CHD is 31.0%, and it increases as NT enlarges. When the NT >8.5 mm, the incidence of fetal CHD is 64.0%.[13] The ductus venous (DV) is a branch of the hepatic umbilical vein and is directly connected to the inferior vena cava. The DV blood flow can indirectly reflect the heart function status. About 50% of serious cardiac structural abnormalities have abnormal blood flow in the DV.[14] According to a large cohort study, reversed a-wave of DV can detect 32.9% and 28.2% of major cardiac defects with a false positive rate of 1.3% and 2.1%, respectively.[15] In addition, some studies have found that the measurement of fetal cardiac axis in early pregnancy is also closely related to fetal CHD. The retrospective case-control study by Sinkovskaya *et al.*[16] involving 197 CHD fetuses showed that 74.1% (146/197) of fetuses with major CHD had an abnormal cardiac axis during early pregnancy (>95th or <5th). Recently, our study indicated that the angle between ductal artery and aortic arches ("V" sign angle) was also associated with major CHD.[17] Abnormal angle was present in 66.7% of major cardiac defects in the first trimester. When combining fetal cardiac axis as another CHD screening marker, the sensitivity for predicting major cardiac defects can be substantially improved to 93.3% with a false-positive rate of 7.3%. Soft markers including fetal NT, tricuspid regurgitation, and a reversed a-wave of ductus venosus, cardiac axis, and abnormal "V" sign angle during early pregnancy are practicable and reproducible. It could be used for early fetal CHD screening, and positive cases could be further referred to superior hospitals for diagnosis and follow-up.

Ultrasound views in the detection of major CHD in the first trimester

Fetal heart develops from the 18th or 19th day in the embryonic period, and development is essentially completed by 8–10 weeks of pregnancy. After 11 weeks of gestation, the fetal cardiac structure can be assessed by transabdominal or transvaginal ultrasound scan. It has been shown previously that first-trimester assessment of the fetal heart using an approach similar to that of the second-trimester anomaly scan is feasible, with similar sensitivity for the detection of CHD. Detection of abnormal four-chamber view and three-vessel view images is considered an indication for referral to fetal echocardiography in the second trimester.[18] Some cardiac malformations such as left ventricular dysplasia syndrome and atrioventricular septal defect may show abnormal imaging on four-chamber view. The three-vessel view also has an important role in the diagnosis of major cardiac structural abnormalities such as transposition of great arteries, tetralogy of Fallot, double outlets of right ventricle, and other cardiac diseases. The International Society of Ultrasound in Obstetrics and Gynecology guideline suggest a four-chamber view with Doppler in the first trimester.[4] Several studies have confirmed that the detection rate of CHD in the first trimester combined with four-chamber view and three-vessel view is 88.6%, which is significantly higher than the detection rate of 45.1% through only four-chamber view.[19–21] Since December 2015, we have combined four-chamber view and three-vessel views in an unselected cohort population in the first trimester and achieved comparable detection rate to those views in the second trimester for major CHD.[17] Majority of severe cardiac abnormalities such as atrioventricular septal defect, tetralogy of Fallot, left ventricular dysplasia syndrome, right ventricular double outlet, tricuspid atresia, and ventricular aneurysm were usually diagnosed in early pregnancy. Among them, atrioventricular septal defect and left ventricular dysplasia syndrome were the most common CHDs in early pregnancy in this cohort study.[17] On the other hand, we also need to recognize that some types of CHD such as aortic and pulmonary stenosis gradually appear with increasing gestational age. Some CHDs such as cardiac tumors and cardiomyopathy may not be detected until the third trimester.

The screening of OC in the first trimester

OC are the most common congenital malformations of the facial region and are formed during 6–8 gestational weeks.[22] Approximately, 80% of cases of cleft lip are associated with cleft palate and are related to >180 genetic syndromes and chromosomal disorders.[10] Currently, fetal cleft palate is usually diagnosed in the second trimester of pregnancy as the result of routine examination of the upper lip and alveolar ridge using conventional two-dimensional ultrasound. There was considerable variety in the diagnostic accuracy of two-dimensional ultrasound in low-risk women, with prenatal detection rates ranging from 9% to 100% for cleft lip with or without cleft palate according to different studies.[23,24] In the prenatal diagnosis of OC, the typical recommended views during the second-trimester scan are the axial view of the maxilla and the coronal view of the lips. The diagnosis of CLP in the first

trimester is even more challenging. The detection rate of OC ranges from 5% to 46% and could be improved to 86% using three-dimensional ultrasound.[8,12,25] In 2010, Sepulveda *et al.*[26] first demonstrated the feasibility of evaluation of the retronasal triangle (RNT) at 11-13^{+6} gestational weeks. The coronal view of the RNT is then evaluated widely for early screening of cleft palate during the NT scan. In 2015, Chaoui *et* al.[27] proposed that a maxillary gap in the sagittal view could be used as a new marker for OC in the first trimester and increase the detection rate of CLP.

However, the images of RNT in the coronal view may be influenced by the shadowing of the nasal bone, and the visualization of maxillary gap in the mid-sagittal view may be theoretically effective for central and bilateral cleft palate, rather than unilateral cleft palate. Our previous study found that visualization of the maxilla in the axial view, which is a significant screening view for OC in the second-trimester scan can be easily obtained with 95.2% obtaining rate during the first trimester scan. The visualization of this view in the first trimester improved the detection of OC compared with the sagittal view of the palatine line and coronal view of the RNT in the first trimester.[28]

The re-evaluation of increased NT

For the last decade, first-trimester NT measurement has played an important role in early detection of fetal aneuploidies. An increased NT is associated with fetal chromosomal anomalies and structural defects such as CHD. Pregnant women carrying fetuses with an increased NT are offered an invasive genetic test. If the fetal karyotype or chromosomal array is normal, a detailed anomaly ultrasound examination is offered in the second trimester including fetal echocardiography. With advancements in ultrasound technology, the first-trimester scan has achieved compelling detection rates in the diagnosis of lethal or major abnormalities, as compared with the second trimester scan. A study conducted in our unit provided an overview of the pregnancy outcome of fetuses with increased NT based on a first-trimester detailed anomaly scan.[29] It confirmed that the fetuses with isolated increased NT are at much lower risk of aneuploidies (3.5%, 3/86) compared to those with major structural anomalies (43.8%, 32/73) detected in the first trimester anomaly scan. It is critical to highlight that after a detailed anomaly scan in the first trimester without major structural anomalies and positive genetic tests by invasive procedure, the residual chance of favorable outcome in fetuses with isolated increased NT is relatively high (79/86, 91.9%).

Should a first-trimester "anomaly" scan be part of an up-to-date screening policy?

In the last few years, the introduction of cf-DNA has rapidly altered prenatal screening regimens and cf-DNA is increasingly offered as the second-, or, at times, even the first-tier screening test. cf-DNA testing is supported by the American College of Obstetricians and Gynecologists and the Society of Maternal-Fetal Medicine as a screening modality in patients with singleton pregnancies at increased risk for aneuploidy.[30,31] Should an early "anomaly" scan also be part of an up-to-date screening policy? The advantage of early pregnancy structural screening is that, on the one hand, a relatively complete evaluation of fetal anatomy can be performed during early pregnancy, which provides an initial confirmation of the general health of the fetus for most pregnant women in whom an abnormal fetal structure is not found during early pregnancy. On the other hand, early detection of structural abnormalities can give clinicians, pregnant women, and family members more time to conduct targeted genetic examination including karyotype testing to detect chromosomal aneuploidies and chromosomal microarray analysis to identify smaller microdeletions and duplications, which are collectively referred to as copy number variants. Further, in recent years, whole-exome sequencing (WES) has been more widely used and may provide more genetic information, especially in the face of ultrasound anomalies or positive family history. A recent cohort study of pregnancies with unselected fetal structural anomalies showed that WES identified a well-described genetic cause in 10% of cases, in which standard testing by karyotype and chromosomal microarray analysis were negative.[32] Noticeably, another prospective cohort study showed that in fetuses with isolated increased NT (≥4.0 mm), the WES had limited identification of diagnostic genetic variants (in three (3.2%) of 93 fetuses).[33]

Conclusion

The discussion on the role of cf-DNA in prenatal screening is still ongoing. Even in the event of it becoming a first-line screening test for aneuploidies, the importance of a first-trimester fetal scan, including assessment of markers for other anomalies, remains undisputed. Meanwhile, there is an increasing development in genome-wide sequencing strategies for evaluation and clinical triage of fetal structural anomalies. Early detection of fetal structural anomalies with the first-trimester ultrasound scan can help clinicians to conduct targeted genetic examinations earlier.

Funding

None.

Conflicts of Interest

None.

References

[1] Hackshaw AK, Wald NJ, Haddow JE. Down's syndrome screening with nuchal translucency. Lancet 1996;348(9043):1740. doi: 10.1016/S0140-6736(05)65871-0.
[2] Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011;31(1):7–15. doi: 10.1002/pd.2637.
[3] Gil MM, Accurti V, Santacruz B, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated metaanalysis. Ultrasound Obstet Gynecol 2017;50(3):302–314. doi: 10.1002/uog.17484.
[4] Salomon LJ, Alfirevic Z, Berghella V, et al. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2011;37(1):116–126. doi: 10.1002/uog.8831.
[5] Ding WP, Li N, Chen M. Ultrasound screening of fetal anomalies at 11-13+6 weeks. Maternal Fetal Med 2020;2(3):175–180. doi: 10.1097/FM9.0000000000000045.
[6] Salomon LJ, Alfirevic Z, Bilardo CM, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan [published correction appears in Ultrasound Obstet Gynecol. 2013 Feb;41(2):240]. Ultrasound Obstet Gynecol 2013;41(1):102–113. doi: 10.1002/uog.12342.
[7] Saltvedt S, Almström H, Kublickas M, et al. Detection of malformations in chromosomally normal fetuses by routine ultrasound at 12 or 18 weeks of gestation-a randomised controlled trial in 39,572 pregnancies. BJOG 2006;113(6):664–674. doi: 10.1111/j.1471-0528.2006.00953.x.

[8] Syngelaki A, Chelemen T, Dagklis T, et al. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. Prenat Diagn 2011;31(1):90–102. doi: 10.1002/pd.2642.
[9] Dmitrovic A, Jeremic K, Babic UM, et al. Early fetal heart ultrasonography as additional indicator for chromosomopathies. Clin Exp Obstet Gynecol 2016;43(2):245–249. doi: 10.12891/ceog2091.2016.
[10] Hassan WA, Lees CC. Facial cleft detected: is the palate normal. Best Pract Res Clin Obstet Gynaecol 2014;28(3):379–389. doi: 10.1016/j.bpobgyn.2014.01.010.
[11] Khalil A, Nicolaides KH. Fetal heart defects: potential and pitfalls of first-trimester detection. Semin Fetal Neonatal Med 2013;18(5):251–260. doi: 10.1016/j.siny.2013.05.004.
[12] Rossi AC, Prefumo F. Accuracy of ultrasonography at 11-14 weeks of gestation for detection of fetal structural anomalies: a systematic review. Obstet Gynecol 2013;122(6):1160–1167. doi: 10.1097/AOG.0000000000000015.
[13] Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. Am J Obstet Gynecol 2003;189(5):1330–1335. doi: 10.1067/s0002-9378(03)00645-8.
[14] Papatheodorou SI, Evangelou E, Makrydimas G, et al. Firsttrimester ductus venosus screening for cardiac defects: a metaanalysis. BJOG 2011;118(12):1438–1445. doi: 10.1111/j.1471-0528.2011.03029.x.
[15] Huhta JC. First-trimester screening for congenital heart disease. Curr Opin Cardiol 2016;31(1):72–77. doi: 10.1097/HCO.0000000000000248.
[16] Sinkovskaya ES, Chaoui R, Karl K, et al. Fetal cardiac axis and congenital heart defects in early gestation. Obstet Gynecol 2015;125(2):453–460. doi: 10.1097/AOG.0000000000000608.
[17] Zheng MM, Tang HR, Zhang Y, et al. Contribution of the fetal cardiac axis and V-sign angle in first-trimester screening for major cardiac defects. J Ultrasound Med 2019;38(5):1179–1187. doi: 10.1002/jum.14796.
[18] Gynecology ISoUiOa, Carvalho JS, Allan LD, et al. ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart. Ultrasound Obstet Gynecol 2013;41(3):348–359. doi: 10.1002/uog.12403.
[19] Tongsong T, Tongprasert F, Srisupundit K, et al. The complete three-vessel view in prenatal detection of congenital heart defects. Prenat Diagn 2010;30(1):23–29. doi: 10.1002/pd.2404.
[20] Galindo A, Herraiz I, Escribano D, et al. Prenatal detection of congenital heart defects: a survey on clinical practice in Spain. Fetal Diagn Ther 2011;29(4):287–295. doi: 10.1159/000322519.
[21] Randall P, Brealey S, Hahn S, et al. Accuracy of fetal echocardiography in the routine detection of congenital heart disease among unselected and low risk populations: a systematic review. BJOG 2005;112(1):24–30. doi: 10.1111/j.1471-0528.2004.00295.x.
[22] Mossey PA, Little J, Munger RG, et al. Cleft lip and palate. Lancet 2009;374(9703):1773–1785. doi: 10.1016/S0140-6736(09)60695-4.
[23] Gillham JC, Anand S, Bullen PJ. Antenatal detection of cleft lip with or without cleft palate: incidence of associated chromosomal and structural anomalies. Ultrasound Obstet Gynecol 2009;34(4):410–415. doi: 10.1002/uog.6447.
[24] Offerdal K, Jebens N, Syvertsen T, et al. Prenatal ultrasound detection of facial clefts: a prospective study of 49,314 deliveries in a non-selected population in Norway. Ultrasound Obstet Gynecol 2008;31(6):639–646. doi: 10.1002/uog.5280.
[25] Martinez-Ten P, Adiego B, Illescas T, et al. First-trimester diagnosis of cleft lip and palate using three-dimensional ultrasound. Ultrasound Obstet Gynecol 2012;40(1):40–46. doi: 10.1002/uog.10139.
[26] Sepulveda W, Wong AE, Martinez-Ten P, et al. Retronasal triangle: a sonographic landmark for the screening of cleft palate in the first trimester. Ultrasound Obstet Gynecol 2010;35(1):7–13. doi: 10.1002/uog.7484.
[27] Chaoui R, Orosz G, Heling KS, et al. Maxillary gap at 11-13 weeks' gestation: marker of cleft lip and palate. Ultrasound Obstet Gynecol 2015;46(6):665–669. doi: 10.1002/uog.15675.
[28] Zheng MM, Tang HR, Zhang Y, et al. Improvement in early detection of orofacial clefts using the axial view of the maxilla. Prenat Diagn 2018;38(7):531–537. doi: 10.1002/pd.5257.
[29] Tang HR, Zhang Y, Ru T, et al. Prospective cohort study of fetal nuchal translucency in first-trimester and pregnancy outcome (in Chinese). Zhonghua Fu Chan Ke Za Zhi 2020;55(2):94–99. doi: 10.3760/cma.j.issn.0529-567X.2020.02.007.
[30] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion no. 545: noninvasive prenatal testing for fetal aneuploidy. Obstet Gynecol 2012;120(6):1532–1534. doi: 10.1097/01.AOG.0000423819.85283.f4.
[31] Committee opinion no. 640: cell-free dna screening for fetal aneuploidy. Obstet Gynecol 2015;126(3):e31–31e37. doi: 10.1097/AOG.0000000000001051.
[32] Petrovski S, Aggarwal V, Giordano JL, et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. Lancet 2019;393(10173):758–767. doi: 10.1016/S0140-6736(18)32042-7.
[33] Lord J, McMullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet 2019;393(10173):747–757. doi: 10.1016/S0140-6736(18)31940-8.

Edited By Yang Pan

How to cite this article: Tang H, Zheng M. Reappraising the Value of Fetal First-Trimester Ultrasonography. Maternal Fetal Med 2023;5(2)115–118. doi: 10.1097/FM9.0000000000000138.