Prenatal First Trimester Assessment of the Heart

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Abstract

An efficient first trimester cardiac scan offers the possibility to terminate earlier, safer, and with less economic and emotional costs the pregnancy in cases where major fetal abnormalities are detected.

FT anomaly scan was initially offered to high-risk groups and selected population, but because many CHD were found in low risk population, many authors agreed to screen all pregnancies for CHD. It was stated that two-dimensional ultrasound, performed on a standardized protocol, is feasible and repeatable within and between observers in visualizing the normal heart structures as early as 11-13.6 GW.

In terms of detection rate of major CHD, recent reports have advocated a percentage of 80-90% when an extended standardized heart screening protocol is used. Nevertheless, this detection rate can vary depending of several factors such as the protocol used, studied population (high or low-risk), scan route (transvaginal, transabdominal or both), definition and prevalence of major congenital heart disease (CHD). CHD early markers, as increased nuchal translucency, abnormal tricuspid and ductus venosus flowsare important indicators for further fetal echocardiographic investigation, as early as possible.

Despite the significant impact of the first trimester screening on pregnancies with major congenital heart diseases, we should not underestimate the value of the second trimester fetal anomaly scan, as some cardiac abnormalities are undetectable early in the first trimester, or the expression of the anomaly may be minimal.

Introduction

Sonography provided important data in understanding the anatomic development and physiology of the fetus since its early stages [1]. An efficient First Trimester (FT) morphologic scan would offer the possibility to terminate earlier the pregnancy in cases where severe fetal abnormalities are detected, safer, and with less economic and emotional costs. This provides a shift in the timing of fetal diagnosis and mortality, which is very important, because major fetal anomalies account for a quarter of the neonatal deaths and associate long-term disabilities with considerable societal cost if the parents elect the termination of pregnancy with severe anomalies detected [2,3].

Despite the significant impact of the FT screening on pregnancies with major Congenital Heart Diseases (CHD) [4], we should not underestimate the value of the second trimester fetal anomaly scan, as it still represents the main baseline against which earlier scans should be compared for the confirmation of fetal anatomical features [5-9].

Targeted Population or Screening Evaluation?

At first FT anomaly scan was offered to high-risk groups and selected population but because many CHD were found also in low risk population many authors agreed to screen all pregnancies for CHD [10-17]. The main inconvenience in examining low risk population is the high number of false negatives and costs in term of time and machines. The heart protocol is different when visualizing the heart in the FT in an unselected population or in a referral one, due to the difficulty of the early heart evaluation when dealing with high-risk pregnancy for cardiac defects [18].

Due to the latest advances in technology and machines, operators tried to examine the fetal heart as early as 10 Gestational Weeks (GW), when four heart chambers and outflow tracts of the great vessels views were obtained [19]. Thus, as gestational age increases the detection rate of fetal cardiac abnormalities is better from 20% at 11 GW to 92% at 13 GW with a Trans vaginal (TV) probe to 100% of visualization at 14 -15 GW [20-22]. Therefore, many authors concluded that the fetal cardiac anatomy is better accessible at the end of the FT [16,23-25].

Imaging Technique

The basic technique in scanning the fetal heart in the Second Trimester (ST) is the grey scale. Thus, important information can also be obtained using modern advanced sonographic techniques such as Doppler ultrasonography. With Doppler imaging, blood flow velocity and flow patterns across valves and within heart chambers are better evaluated. To analyze dysrhythmias, suspected ventricular dysfunction and abnormal wall thickness is indicated to use M-mode echocardiography. Many controversies exist regarding the routine use of color Doppler in low-risk populations and it is considered an optional method recommended for suspected cardiac flow abnormalities [26,27]. Nevertheless, the use of color Doppler in FT is necessary because of the low discrimination of the heart structures in B-mode and improved visualization of normal cardiac structures, early detection of conotruncal anomalies and assessing tricuspid and ductusvenosus flow patterns [28,29]. The use of color Doppler should be restricted according to "As Low As Reasonably Achievable" (ALARA) principle [30-32].

First trimester scan of the fetal heart has been performed Trans vaginally since the beginning of the 1990s [33-44]. The constant improving of ultrasound (US) systems' resolution over the past years enabled the sonographers to evaluate Trans abdominally the fetal anatomy at early scans [45-48]. Consecutively, basic cardiac views were incorporated in the routine 11–13 weeks' morpho-genetic scan and positive results were noted. We will discuss in this paper the achievements and the necessary settings for an adequate FT cardiac evaluation.

The examination Protocol of the Fetal Heart

The main planes investigated in the second trimester can be imagined also in the first trimester, with less detailed accuracy (Figure 1 and 2) [49]. Previously, using only the 4CV protocol, a wide range of CHD were prenatally diagnosed up to 77%, while adding the outflow tracts views (OTV) in the scanning protocol increases antenatal detection rate to 83%-92%. The four-Chamber View (4CV) is indeed insufficient as many conotruncal cardio-vascular anomalies may not be detected at that level of the fetal heart, thus imaging of the outflow tracts is mandatory and very helpful in the prenatal diagnosis of a coarctation of the aorta, hypoplastic left heart, tetralogy of Fallot, double outlet right ventricle, truncus arteriosus, corrected or non-corrected transposition of great vessels. During the last decades, five scan protocols for fetal CHD diagnosis have been commonly used: 4CV, 4CV + OTV/ three Vessels and Trachea View (3VTV), 4CV+OTV+3TV, Extended Cardiac Echography Examination (ECEE) and Four-Dimensional (4D) Spatiotemporal Image Correlation (STIC). Overall, prenatal ultrasound in the detection of CHD had a moderate sensitivity of 68.1% and a favourable specificity of 99.9%. The pooled sensitivities significantly increased to varying extents with the following echocardiographic views: 48.7% for four-Chamber View (4CV); 58.0% for a combination of 4CV and Outflow Tract Views (OTV); 73.5% for combination of 4CV, OTV and three Vessels and Trachea View (3VTV); 77.1% for Extensive Cardiac Echocardiography Examination (ECEE); and 89.6% for Spatiotemporal Image Correlation (STIC) [50]. The overall performance of pooled sensitivities of Spatiotemporal Image Correlation (STIC), Extend Cardiac Echography Examination (ECEE) and 4 chambers view + outflow tract view + 3 vessels and trachea view (4CV + OTV + 3VTV) were around 0.90, which was significant higher than that of 4 chambers view + outflow tract view

or 3 vessels and trachea view (4CV + OTV/3VTV) and 4 chambers view (4CV). Unfortunately the pooled specificity of STIC was 0.92, which was significantly lower than that of other 4 protocols which reached at 1.00 [51].

The pooled sensitivity of the first trimester was 60.3%, compared with 60.9% in second trimester and to 77.4% of the second to third trimester [52].

Sinkovskaya and colleagues measured the cardiac axis on the four-chamber view. In early pregnancy, the mean value for the cardiac axis, based on 94 fetuses with non-cardiac abnormalities, was approximately 47° with limits of normality set between 35° and 60° and it impossible to measure the cardiac axis in early pregnancy and this may help to identify pregnancies at risk of CHD [53,54].

4D-STIC is very useful well known tool for the assessment of fetal heart after 15 weeks of gestation. Recent studies have reported that STIC can be successfully used in evaluation of the fetal heart during 11–13 + 6 scan and is likely to improve the detection of CHD in expert hands [55,56]. The 2nd trimester rules for STIC do not work at this time. The acquisition angle, time and most importantly the original plane of acquisition placement have to be changed.

Satisfactory first trimester STIC acquisition is difficult due to motion artifact. When acquisition is satisfactory, diagnoses based on offline reconstruction correlate with the traditional two dimensional first trimester echocardiogram. Still STIC technology also offers advantages, such as access to virtual planes not available for direct visualization in 2D US demonstrated that volume datasets from a first-trimester fetal heart can be acquired in a high proportion of cases by properly trained non-expert operators and sent to an expert in ECEE for offline evaluation via telemedicine. Studies showed that the pooled specificity of STIC was 0.92, significantly lower than that of other 4 protocols which reached at 1.00. Thus, STIC technique should not be used alone in making a definite diagnosis, although it can be used in the fetal heart examination with the aim of providing more information for local details of defects.

It was stated that 2DUS, performed on a standardized protocol, is feasible and repeatable within and between observers in visualizing the normal heart structures as early as 11 GW-13.6 GW [28]. There are many factors that have consistently been incriminated on the low diagnostic performance of FT cardiac scan: some that operators cannot alter (the risk profile of the study population, high body mass index, anterior placenta, retroversion, surgical scars), and some that may be worked on: the training of examiners, the number of cardiac planes that are incorporated into the assessment, the addition of color Doppler imaging and the insonation angle used for data acquisition.

Previous investigators have shown that high maternal Body Mass Index (BMI) and small fetal size have a negative impact on success rates of first-trimester scans but more recent studies claim no influence of the BMI and crown-rump length in fetal cardiac assessment between 12 to14 gestational weeks [23,57-59].

During the standardized transverse scanning planes for fetal echocardiography the sonographer is sweeping the transducer beam in a transverse plane from the level of the four-chamber view towards the fetal neck as presented in the left of the image. By doing so, the following views become apparent: four-Chamber View (4CV), arterial outflow tracts: Left Ventricular Outflow Tract (LVOT), Right Ventricular Outflow Tract (RVOT) and the three-Vessel and Trachea View (3VTV).
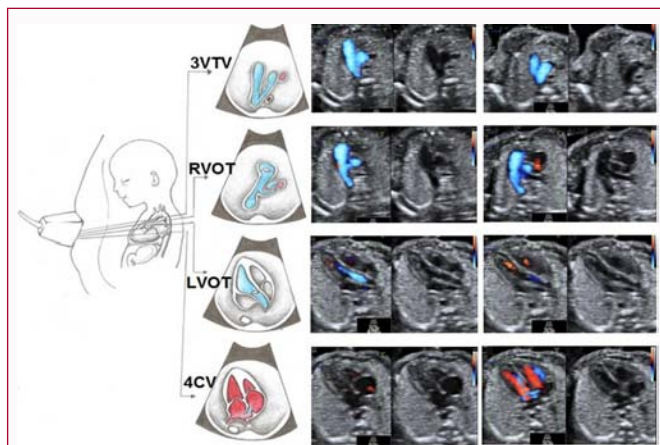
Figure 1: Second trimester fetal cardiac sweep.

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The following views become apparent: the upper abdominal view, showing the abdominal situs, the four-chamber view (B), left ventricular outflow tract (C), right ventricular outflow tract and the three-vessel and trachea view (D).

Obviously, the color Doppler technique is much superior in identifying and defining the cardiac features.

Detection Rate Accuracy

The advances in improving the first trimester examination include efforts for a better visualization of the fetal heart in an attempt to detect as many CHD as possible. Some time ago, the fetal cardiac examination was considered optimally performed in the second trimester between 18 and 22 weeks of gestation. There are anomalies that in expert hands can be detectable in the first trimester if an appropriate protocol is used. On the other hand, there can be cardiac lesions that evolve in utero as gestational age advances or even occur later during pregnancy: hypoplastic left heart syndrome, coarctation of the aorta, endocardial fibroelastosis due to aortic stenosis, pulmonary stenosis, and tetralogy of Fallot [28,60]. The absence of a CHD detected in the prenatal period does not entirely exclude the development of later cardiac anomalies such as cardiomyopathy or cardiac tumors that can evolve even after birth [61]. The FT scan is not a technique without blemish. The most missed lesions during the evaluation were the ventricular septal defects due to limited resolution, the small size of the lesion and low flow velocities in the FT.

The accuracy represents the ability of a measurement to match the actual value of the quantity being measured and should be reported concerning the FT US scan diagnose of major CHD. A recent systematic review of the literature reported that pooled sensitivity and specificity were 85% and 99% respectively [62]. This demonstrated a high accuracy (specificity approaching 100%). In terms of detection rate of major CHD, recent reports have advocated a percentage of 80-90% when an extended standardized heart screening protocol is used [10,63]. Nevertheless this detection rate can vary depending of several factors such as the protocol used, studied population (high or low-risk), scan route (transvaginal, transabdominal or both), definition and prevalence of major CHD.

Sensitivity of FT US examination in detection of fetal major CHD
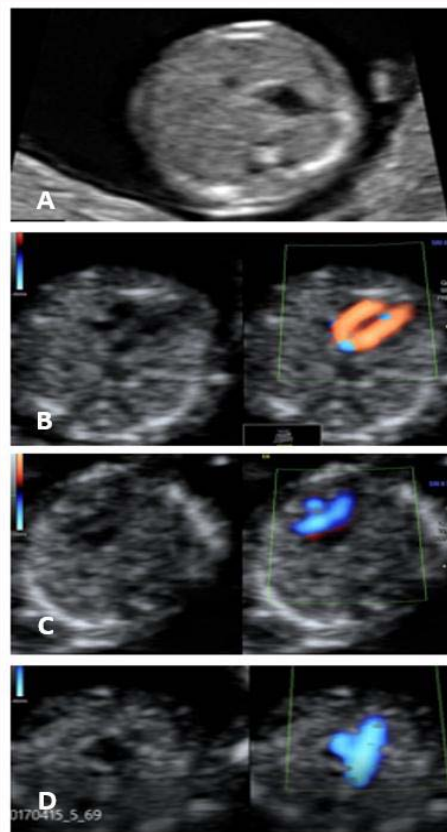
Figure 2: First trimester fetal cardiac sweep. In a similar manner the sonographer is sweeping the transducer beam in a trans verse plane from the level of the four-chamber view towards the fetal neck.

has wide variations in low risk populations in the literature: 36.8% , 57 % , 84.2% ,90% (61), 93.1% sometimes close to sensitivity of study on high risk with increased nuchal translucency (NT) population [10,46,47,64,65].

The Utility of the FT Screening Markers for CHD

NT measurement, Ductusvenosus (DV) assessment and Tricuspid Regurgitation (TR) identification were proposed in the literature as early screening markers for fetal CHD.

A nuchal scan is a sonographic prenatal screening scan to help identifying higher chances for chromosomal conditions in a fetus [29,65]. Increased NT is also associated with congenital heart defect even in fetuses with normal karyotype [9,24,29,66]. A significant drawback when using the NT as a marker for cardiac anomalies is represented by the differences in cut-offs used to define an increased NT (95th or 99th percentile, 1.7, 2, 2.5 or 3 Multiples of Median (MoM)), gestational ages at the time of NT measurement (10+4 to13+6 vs. 11 to14 weeks' gestation), study populations (high versus low-risk), study design (prospective vs. retrospective) and even the definition of a major CHD. On one hand, the percentages of reported prevalence of CHD differ from 2 to 20% when using the 95th percentile cut-off for the NT and when using the 99th percentile cut-off for the NT, the risk of CHD is six times higher in an unselected population [29,67]. On the other hand, the sensitivity and the specificity vary and a recent meta-analysis reported a 31% detection rate for CHD and a specificity of 98.7% using the 99th centile for NT cut-off and 37% sensitivity

and 96.6% using the 95th centile. The prevalence of major CHD can increase exponentially with increasing NT thickness from 0.6% - 6.2% in those with NT of 2.5 to 3.4 mm to 2.3% - 12.2% in those with a NT of 3.5 mm or more. From these pooled data resulted an overall detection rate of 28.4% and a false positive rate of 3% for major CHD in chromosomally normal fetuses with increased NT.

In summary, most studies consider the NT an important marker in screening for cardiac anomalies even in chromosomally normal fetuses, with a detection rate of below 5% when only maternal risk factors are considered and without any relation to a particular type of cardiac malformation. Several studies rule out the significance of the NT measurement in FT CHD detection in unselected or low-risk populations [68].

Beside the NT scan there are 2 other parameters proposed to improve the assessment of early screening for cardiac defects: the DV flow evaluation and the identification of TR. An abnormal DV flow pattern is represented by an absent or reversed a-wave and when present may be associated with a three-fold risk for major CHD, or an increased PI (pulsatility index) [69]. The finding of a reversed a-wave can increase the risk of cardiac defects by almost 10 times, with a predominance of right-heart anomalies regardless of the measurement of NT. [70,71] Considering DV regardless of NT status, it was reported a sensitivity of 50% and a specificity of 93%. When DV was associated with increased NT, the summary sensitivity and specificity were 83 and 80%, and for those with normal NT, they were 19 and 96%, respectively[70].

If chromosomally normal fetus presents TR at first trimester ultrasound evaluation, there have been reported an increased risk for CHD by 8 times [72].

Sensitivity of at least one of the ultrasound markers, NT measurement between 95th-99th percentile, >99th percentile (>3.5 mm), TR or inverted a-wave at the DV for detection of major CHD cases was 74%, 22%, 39%, 35%, 30%, respectively. Specificity of different first trimester ultrasound markers for detection of CHD cases: specificity of NT measurement between 95th-99th percentile, >99th percentile (>3.5 mm), TR or inverted a-wave at the DV for detection of major CHD cases was 4.30%, 0.58%, 0.92%, 1.94% [73].

In conclusion, when detected at 11-14 weeks gestation, the association of an increased NT with TR and/or abnormal DV indicates the highest risk for a major CHD. Increased NT, TR and abnormal DV flow can be important indicators for echocardiography, which is favorable to early prenatal diagnosis of CHD.

Follow up by Diagnostic Fetal Echocardiography

Following a suspected cardiac abnormality in mid-gestation, the accepted recommendation in the UK is that the pregnant woman be offered an appointment as soon as possible, but preferably within a week. An unexpected abnormal ultrasound finding leads to parental anxiety, vacillation between emotional confusion and sense of reality. Parents adapt but they need additional information about diagnosis, achievable by extensive multidisciplinary counseling, genetics and perinatal autopsy assay. Thus, prenatal counseling for the subsequent pregnancies has its best premises. However, these important interventions are related to the availability of qualified practitioners and equipment, local medical practice and legal considerations. In many countries, insurance-related cost reimbursements strongly influence the extent and implementation of routine pregnancy scans.

References

1. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. PrenatDiagn. 2011;31(1):3-6.

2. Filly RA, Crane JP. Routine obstetric sonography. J Ultrasound Med. 2002;21(7):713-8.

3. Ecker JL, Frigoletto FD. Routine ultrasound screening in low-risk pregnancies: imperatives for further study. Obstet Gynecol. 1999;93(4):607-10.

4. Jicinska H, Vlasin P, Jicinsky M, Grochova I, Tomek V, Volaufova J, et al. Does first-trimester screening modify the natural history of congenital heart disease? Analysis of outcome of regional cardiac screening at 2 different time periods. Circulation. 2017;135(11):1045-55.

5. Schwärzler P1, Senat MV, Holden D, Bernard JP, Masroor T, Ville Y. Feasibility of the second-trimester fetal ultrasound examination in an unselected population at 18, 20 or 22 weeks of pregnancy: a randomized trial. Ultrasound Obstet Gynecol. 1999;14(2):92-7.

6. Saltvedt S1, Almström H, Kublickas M, Valentin L, Grunewald C. 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):664-74.

7. Tegnander E, Williams W, Johansen OJ, Blaas HG, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population of 30,149 fetuses--detection rates and outcome. Ultrasound Obstet Gynecol. 2006;27(3):252-65.

8. Grandjean H1, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. Am J Obstet Gynecol. 1999;181(2):446-54.

9. Makrydimas G1, Sotiriadis A, Huggon IC, Simpson J, Sharland G, Carvalho JS, et al. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. Am J Obstet Gynecol. 2005;192(1):89-95.

10. Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11-13-week scan. Ultrasound Obstet Gynecol. 2006;27(6):613-8.

11. Bellotti M, Fesslova V, De Gasperi C, Rognoni G, Bee V, Zucca I, et al. Reliability of the first-trimester cardiac scan by ultrasound-trained obstetricians with high-frequency transabdominal probes in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol. 2010;36(3):272-8.

12. Yagel S, Weissman A, Rotstein Z, Manor M, Hegesh J, Anteby E, et al. Congenital heart defects: natural course and in utero development. Circulation. 1997;96(2):550-5.

13. Achiron R, Glaser J, Gelernter I, Hegesh J, Yagel S. Extended fetal echocardiographic examination for detecting cardiac malformations in low risk pregnancies. BMJ. 1992;304(6828):671-4.

14. Rustico MA, Benettoni A, D'Ottavio G, Fischer-Tamaro L, Conoscenti GC, Meir Y, et al. Early screening for fetal cardiac anomalies by transvaginal echocardiography in an unselected population: the role of operator experience. Ultrasound Obstet Gynecol. 2000;16(7):614-9.

15. Jorgensen DE, Vejlstrup N, Jorgensen C, Maroun LL, Steensberg J, Hessellund A, et al. Prenatal detection of congenital heart disease in a low risk population undergoing first and second trimester screening. PrenatDiagn. 2015;35(4):325-30.

16. Mavrides E, Cobian-Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, et al. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart defects. Ultrasound Obstet Gynecol. 2001;17(2):106-10.

17. Westin M, Saltvedt S, Bergman G, Kublickas M, Almström H, Grunewald C, et al. Routine ultrasound examination at 12 or 18 gestational weeks for prenatal detection of major congenital heart malformations? A randomised controlled trial comprising 36,299 fetuses. BJOG. 2006;113(6):675-82.

18. Aboulghar M, Shaker S, Mahmoud A. EP06.05: Early ultrasound detection of congenital heart anomalies in high risk pregnancies: first and second trimester scans compared to postnatal echocardiography. Ultrasound Obstet Gynecol. 2016;48Suppl 1:288.

19. Smrcek JM, Berg C, Geipel A, Fimmers R, Diedrich K, Gembruch U. Early fetal echocardiography: heart biometry and visualization of cardiac structures between 10 and 15 weeks' gestation. J Ultrasound Med. 2006;25(2):173-82; quiz 83-5.

20. Haak MC, Bartelings MM, Gittenberger-De Groot AC, Van Vugt JM. Cardiac malformations in first-trimester fetuses with increased nuchal translucency: ultrasound diagnosis and postmortem morphology. Ultrasound Obstet Gynecol. 2002;20(1):14-21.

21. Souka AP, Pilalis A, Kavalakis Y, Kosmas Y, Antsaklis P, Antsaklis A. Assessment of fetal anatomy at the 11-14-week ultrasound examination. Ultrasound Obstet Gynecol. 2004;24(7):730-4.

22. Smrcek JM, Berg C, Geipel A, Fimmers R, Axt-Fliedner R, Diedrich K, et al. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. J Ultrasound Med. 2006;25(2):187-96.

23. Huggon IC, Ghi T, Cook AC, Zosmer N, Allan LD, Nicolaides KH. Fetal cardiac abnormalities identified prior to 14 weeks' gestation. Ultrasound Obstet Gynecol. 2002;20(1):22-9.

24. Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005;192(4):1005-21.

25. Carvalho JS1. Fetal heart scanning in the first trimester. PrenatDiagn. 2004;24(13):1060-7.

26. International Society of Ultrasound in Obstetrics and Gynecology, Carvalho JS, Allan LD, Chaoui R, Copel JA, DeVore GR, et al. ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart. Ultrasound Obstet Gynecol. 2013;41(3):348-59.

27. Eggebø TM, Heien C, Berget M, Ellingsen CL. Routine use of color Doppler in fetal heart scanning in a low-risk population. ISRN Obstet Gynecol. 2012;2012:496935.

28. Tudorache S, Cara M, Iliescu DG, Novac L, Cernea N. First trimester two- and four-dimensional cardiac scan: intra- and interobserver agreement, comparison between methods and benefits of color Doppler technique. Ultrasound Obstet Gynecol. 2013;42(6):659-68.

29. Clur SA, Ottenkamp J, Bilardo CM. The nuchal translucency and the fetal heart: a literature review. PrenatDiagn. 2009;29(8):739-48.

30. Salvesen KA, Lees C, Abramowicz J, Brezinka C, TerHaar G, MarÅ¡ál K. Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible? Ultrasound Obstet Gynecol. 2011;37(6):625-8.

31. Campbell S, Platt L. The publishing of papers on first-trimester Doppler. Ultrasound Obstet Gynecol. 1999;14(3):159-60.

32. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(2):233-39.

33. Bronshtein M, Siegler E, Yoffe N, Zimmer EZ. Prenatal diagnosis of ventricular septal defect and overriding aorta at 14 weeks' gestation, using transvaginalsonography. PrenatDiagn. 1990;10(11):697-702.

34. Gembruch U, Knopfle G, Chatterjee M, Bald R, Hansmann M. First-trimester diagnosis of fetal congenital heart disease by transvaginal two-dimensional and Doppler echocardiography. Obstet Gynecol. 1990;75(3 Pt 2):496-8.

35. Bronshtein M, Zimmer EZ, Milo S, Ho SY, Lorber A, Gerlis LM. Fetal cardiac abnormalities detected by transvaginalsonography at 12-16 weeks' gestation. Obstet Gynecol. 1991;78(3 Pt 1):374-8.

36. D'Amelio R, Giorlandino C, Masala L, Garofalo M, Martinelli M, Anelli G, et al. Fetal echocardiography using transvaginal and transabdominal probes during the first period of pregnancy: a comparative study. PrenatDiagn. 1991;11(2):69-75.

37. Dolkart LA, Reimers FT. Transvaginal fetal echocardiography in early pregnancy: normative data. Am J Obstet Gynecol. 1991;165(3):688-91.

38. Johnson P, Sharland G, Maxwell D, Allan L. The role of transvaginalsonography in the early detection of congenital heart disease. Ultrasound Obstet Gynecol. 1992;2(4):248-51.

39. Bronshtein M, Siegler E, Eshcoli Z, Zimmer EZ. Transvaginal ultrasound measurements of the fetal heart at 11 to 17 weeks of gestation. Am J Perinatol. 1992;9(1):38-42.

40. Bronshtein M, Zimmer EZ, Gerlis LM, Lorber A, Drugan A. Early ultrasound diagnosis of fetal congenital heart defects in high-risk and low-risk pregnancies. Obstet Gynecol. 1993;82(2):225-9.

41. Homola J1, Satrapa V. [Transvaginal echocardiography in the early diagnosis of congenital heart defects in the human fetus]. CeskPediatr. 1993;48(12):711-3.

42. Gembruch U, Knopfle G, Bald R, Hansmann M. Early diagnosis of fetal congenital heart disease by transvaginal echocardiography. Ultrasound Obstet Gynecol. 1993;3(5):310-7.

43. Achiron R, Weissman A, Rotstein Z, Lipitz S, Mashiach S, Hegesh J. Transvaginal echocardiographic examination of the fetal heart between 13 and 15 weeks' gestation in a low-risk population. J Ultrasound Med. 1994;13(10):783-9.

44. Achiron R, Rotstein Z, Lipitz S, Mashiach S, Hegesh J. First-trimester diagnosis of fetal congenital heart disease by transvaginal ultrasonography. Obstet Gynecol. 1994;84(1):69-72.

45. Carvalho JS, Moscoso G, Ville Y. First-trimester transabdominal fetal echocardiography. Lancet. 1998;351(9108):1023-7.

46. Persico N, Moratalla J, Lombardi CM, Zidere V, Allan L, Nicolaides KH. Fetal echocardiography at 11-13 weeks by transabdominal high-frequency ultrasound. Ultrasound Obstet Gynecol. 2011;37(3):296-301.

47. Yagel S, Cohen SM, Porat S, Daum H, Lipschuetz M, Amsalem H, et al. Detailed transabdominal fetal anatomic scanning in the late first trimester versus the early second trimester of pregnancy. J Ultrasound Med. 2015;34(1):143-9.

48. Introduction to fetal echocardiography. Dominic Gabriel Iliescu. SMGroup, 2016.pp:7.

49. Liu H, Zhou J, Feng QL, Gu HT, Wan G, Zhang HM, et al. Fetal echocardiography for congenital heart disease diagnosis: a meta-analysis, power analysis and missing data analysis. Eur J PrevCardiol. 2015;22(12):1531-47.

50. Li Y, Hua Y, Fang J, Wang C, Qiao L, Wan C, et al. Performance of different scan protocols of fetal echocardiography in the diagnosis of fetal congenital heart disease: a systematic review and meta-analysis. PLoS One. 2013;8(6):e65484.

51. Zhang YF, Zeng XL, Zhao EF, Lu HW. Diagnostic value of fetal echocardiography for congenital heart disease: A systematic review and meta-analysis. medicine (Baltimore). 2015;94(42):e1759.

52. Sinkovskaya E, Horton S, Berkley EM, Cooper JK, Indika S, Abuhamad A. Defining the fetal cardiac axis between 11 + 0 and 14 + 6 weeks of gestation: experience with 100 consecutive pregnancies. Ultrasound Obstet Gynecol. 2010;36(6):676-81.

53. Sinkovskaya ES, Chaoui R, Karl K, Andreeva E, Zhuchenko L, Abuhamad

AZ. Fetal cardiac axis and congenital heart defects in early gestation. Obstet Gynecol. 2015;125(2):453-60.

54. Bennasar M, Martínez JM, Olivella A, del Río M, Gómez O, Figueras F, et al. Feasibility and accuracy of fetal echocardiography using four-dimensional spatiotemporal image correlation technology before 16 weeks' gestation. Ultrasound Obstet Gynecol. 2009;33(6):645-51.

55. Goncalves LF, Espinoza J, Romero R, Lee W, Treadwell MC, Huang R, et al. Four-dimensional fetal echocardiography with spatiotemporal image correlation (STIC): a systematic study of standard cardiac views assessed by different observers. J Matern Fetal Neonatal Med. 2005;17(5):323-31.

56. Haak MC, Twisk JW, Van Vugt JM. How successful is fetal echocardiographic examination in the first trimester of pregnancy? Ultrasound Obstet Gynecol. 2002;20(1):9-13.

57. Carvalho JS. Screening for heart defects in the first trimester of pregnancy: food for thought. Ultrasound Obstet Gynecol. 2010;36(6):658-60.

58. Pares DB, Lima AI, Araujo Junior E, Nardozza LM, Martins WP, Moron AF. F, et al. Heart assessment in the first trimester of pregnancy: influence of crown-rump length and maternal body mass index. Rev Bras Cir Cardiovasc. 2013;28(4):477-81.

59. Carvalho JS, Moscoso G, Tekay A, Campbell S, Thilaganathan B, Shinebourne EA. Clinical impact of first and early second trimester fetal echocardiography on high risk pregnancies. Heart. 2004;90(8):921-6.

60. Haak MC, van Vugt JM. Echocardiography in early pregnancy: review of literature. J Ultrasound Med. 2003;22(3):271-80.

61. Rasiah SV, Publicover M, Ewer AK, Khan KS, Kilby MD, Zamora J. A systematic review of the accuracy of first-trimester ultrasound examination for detecting major congenital heart disease. Ultrasound Obstet Gynecol. 2006;28(1):110-6.

62. Iliescu D, Tudorache S, Comanescu A, Antsaklis P, Cotarcea S, Novac L, et al. Improved detection rate of structural abnormalities in the first trimester using an extended examination protocol. Ultrasound Obstet Gynecol. 2013;42(3):300-9.

63. Chen M, Lee CP, Lam YH, Tang RY, Chan BC, Wong SF, et al. Comparison of nuchal and detailed morphology ultrasound examinations in early pregnancy for fetal structural abnormality screening: a randomized controlled trial. Ultrasound Obstet Gynecol. 2008;31(2):136-46; discussion 46.

64. Grande M, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers. Ultrasound Obstet Gynecol. 2012;39(2):157-63.

65. Clur SA, Oude Rengerink K, Mol BW, Ottenkamp J, Bilardo CM. Fetal cardiac function between 11 and 35 weeks' gestation and nuchal translucency thickness. Ultrasound Obstet Gynecol. 2011;37(1):48-56.

66. Westin M, Saltvedt S, Bergman G, Almström H, Grunewald C, Valentin L. Is measurement of nuchal translucency thickness a useful screening tool for heart defects? A study of 16,383 fetuses. Ultrasound Obstet Gynecol. 2006;27(6):632-9.

67. Bilardo CM, Timmerman E, Pajkrt E, van Maarle M. Increased nuchal translucency in euploid fetuses--what should we be telling the parents? PrenatDiagn. 2010;30(2):93-102.

68. Muller MA, Clur SA, Timmerman E, Bilardo CM. Nuchal translucency measurement and congenital heart defects: modest association in low-risk pregnancies. PrenatDiagn. 2007;27(2):164-9.

69. Maiz N, Nicolaides KH. Ductusvenosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. Fetal DiagnTher. 2010;28(2):65-71.

70. Papatheodorou SI, Evangelou E, Makrydimas G, Ioannidis JP. First-trimester ductusvenosus screening for cardiac defects: a meta-analysis. BJOG. 2011;118(12):1438-45.

71. Martinez JM, Comas M, Borrell A, Bennasar M, Gomez O, Puerto B, et al. Abnormal first-trimester ductusvenosus blood flow: a marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. Ultrasound Obstet Gynecol. 2010;35(3):267-72.

72. Faiola S, Tsoi E, Huggon IC, Allan LD, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan. Ultrasound Obstet Gynecol. 2005;26(1):22-7.

73. Yang Y, Zhang Y. Ultrasound soft markers and fetal cardiac structural assessment at 11-14 weeks. Zhonghua Fu Chan Ke ZaZhi. 2014;49(3):188-92.