

Complete atrioventricular septal defect in the era of prenatal diagnosis

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Abstract

Complete atrioventricular septal defect (CAVSD) is a fetal cardiac malformation (5% of all cardiac malformations) that can be detected prenatally with a reserved prognosis. The diagnosis can be suspected early at the end of the first trimester using the transabdominal or transvaginal ultrasound approach. Generally, the diagnosis can be established during the mid-trimester scan at 19-24 weeks of gestation. The percentage of antenatal diagnosis of CAVSD is between 57-92%. This review aims to analyze the anatomical principles and the ultrasound techniques that can improve the prenatal diagnosis of CAVSD. We have also analyzed the structural and genetic anomalies frequently associated with CAVSD.

Keywords: complete atrioventricular septal defect, linear insertion of atrioventricular valves, Spatio-Temporal Image Correlation, Doppler ultrasonography, prenatal diagnosis

Introduction

Congenital heart defects (CHD) are one of the most frequent fetal malformations, accounting for 4/1,000 to 50/1,000 live births and around 30 per 1,000 in stillbirths [1]. The reported incidence of atrioventricular septal defect (AVSD) is 348:100.000 representing 17.4% of all cardiac congenital malformations [1]. The frequency of complete AVSD (CAVSD) is higher in fetal life, many parents opting for pregnancy termination, especially in aneuploid fetuses with extracardiac associated malformations [2]. The frequency is estimated at 1:2120 [3].

During the last 10-15 years most cases of CAVSD were diagnosed during the second trimester of pregnancy, but nowadays the diagnosis became possible in the first trimester [4,5]. In a series of 99 cases of CAVSD diagnosed in the second trimester in a tertiary center a large majority of cases (74.74%) were referred for ab-

normal fetal heart screening, the rest of them being resuscitated in a tertiary center for suspicion of trisomy or a particular maternal or fetal condition [2]. A large study on 29,460 fetuses reported a rate of prenatal detection of CHD of 57% and CAVSD of 71% [6]. These patients with CAVSD were detected as following: 19% during the early scan (11-14 WG), 48% during the mid-trimester scan (19-24 WG), and 5% during late pregnancy [6]. The percentage of diagnosis for isolated CAVSD was of 67% and was almost 100% only when CAVSDs were associated with complex cardiac malformations [6]. Another major study, the Euroscan study, has reported a large variability of antenatal detection rate of cardiac malformation from country to country; overall the prenatal detection rate being of only 56% for isolated CAVSD [7]. A correct and complete prenatal diagnosis of CHD allows a better intrauterine and postnatal management of these children, and thus it will improve their long-term outcome [8].

Embryologically, the CAVSD is determined by an interference with the normal development of the endocardial cushions that takes place between the 34th and 36th day of intrauterine life [9]. The endocardial cushions being involved in the formation of septum primum, atrioventricular annuli, atrioventricular valves (tricuspid and mitral valves) and the posterior part of the interven-

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tricular septum [9,10], an abnormal development of these structures can lead to a broad spectrum of anomalies: CAVSD, atrial septal defects (ASD) and VSD.

The main goal of this paper is to review the actual role of different ultrasound techniques in the prenatal diagnosis of CAVSD. The frequently association with cardiac and extracardiac anomalies that can pinpoint to specific genetic syndrome is also review at the end of the paper.

Anatomical details

Three different types of AVSD have been described, with specific anatomic and ultrasound features [11] (table I). The complete form is detected in 75 % of cases.

Moreover, based on the morphology of the anterior valve and its attachment by the papillary muscles to the interventricular septum and to the ventricular walls, Rastellii classifies the complete form into three types [12]. This classification has a good correlation with the postnatal prognostic and with the results of surgical repair [13].

A comprehensive knowledge of the AV plan is essential in order to identify the different AVSD types, the main element being the plan of insertion of AV valves and the aspect of the pathological leaflets [14,15].

Normally in the fetal heart the mitral and tricuspid valves are not placed at the same level on the membranous part of the interventricular septum; the tricuspid valve being inserted more apically than the mitral valve [15]. This aspect of a differential insertion of atrioventricular valves (DIAAV) can be visualized during the ultrasound examination on so called “apical four chamber view” plan (fig 1a), the visualization of “the cross of the heart” being an important landmark of normality [16-18]. In CAVSD the AV valve insertion is linear, important clue for the diagnostic, the atrioventricular valve being located in the same plan [19]. The aspect can be easier visualized during the ventricular systole when the AV valve is closed [19]. This particular insertion of AV valve modifies the atrial-to-ventricular length (AVL) ratio; $AVL > 0.6$ is commonly seen in CAVSD [17].

The normal fetal heart bears particularities of the AV valves insertion that might be responsible for the high rate of false positive and false negative results; the aspects can be different at different sectional levels [20]. Just beneath the aortic outflow tract (level 1) there is an evident difference in AV valve insertion, that diminishes near the diaphragm (level 2), and disappears just above the diaphragm (level 3) where the mitral and the tricuspid valve have a linear insertion [20]. In hearts with CAVSD at the 1st and 3rd level of the section the AV valvular insertion is linear, but sometimes at the 2nd level the unique valve has a differential insertion in her left and right edge, thus having a “crux cordis” ultrasound appearance [20]. Moreover, some fetuses with trisomy 21 without any cardiac defect can have a linear insertion of AV valves. [19]. Therefore a linear insertion of AV valves or a modified AVL ration requires evaluation by a tertiary center [5].

In fetuses with AVSD the aspect of AV plane bears a range of abnormalities in the complete form where there is only one AV valve with five leaflets with different shape and insertions. The diagnosis is much more difficult in incomplete forms where one or two AV valvular rings might exist with an atypical leaflets features [11].

When to screen for a CAVSD?

Fetal heart structure can be evaluated with the latest ultrasound machines starting from the end of the first trimester using transvaginal or transabdominal approach [21,22].

During the first trimester scan the visualization of cardiac structures increase gradually from 43% at 11 weeks to 62% at 13+6 weeks, [23]. Color Doppler associated with 4D Spatio Temporal Image Corelation (STIC) can improve the identification of cardiac structures up to a percentage of 90% [24-26]. So, the detection of CAVSD is possible at the end of first trimester. A meta-analysis from 2013 that has included 14 studies that had evaluated fetal heart during the first trimester reported a detection rate of 42.9% for CAVSD [4]. The evaluation of the fetal heart is particularly important in the presence of other

Table I. Anatomical classification of AVSD [Boussion]

AVSD Types	Characteristics
Partial	two distinct valvular rings two atrioventricular orifices the atrioventricular (AV) valves are malformed. the most frequent situation is when the mitral valve has an aperture the ostium primum is absent with an atrial septal defect (ASD)
Intermediary	a single atrioventricular valve ring is present accompanied by an ostium primum type ASD and a small ventricular septal defect (VSD)
Complete	a single AV ring, an ASD and a posterior VSD.

first trimester sonographic markers such as increased nuchal translucency, tricuspid regurgitation, abnormal ductus venosus blood flow and abnormal maternal serum markers [4].

However, due to the late growth of atrioventricular septum and late identification of mitral and tricuspid offset after 14 weeks [27] most of the CAVSD are diagnosed or confirmed between 18-24 weeks with the occasion of second trimester morphological screening ultrasound [22]. A tertiary center from UK reported an overall antenatal detection rate of CAVSD of only 29% between 1996 and 2001 [28], while Euroscan in 2001 reported a 56% detection rate [7]. The overall detection rate of CHD was 57% in a large Norwegian study that has included 30 149 unselected fetuses that had been scanned at 18 weeks of gestation by four chamber view and sections of the great arteries of the heart; the CAVSD detection rate was 19% based on prior scan, 48% on routine scan and 5% in late scan leading to an overall antenatal 71% detection rate [6]. Interesting, the detection rate of CAVSD in aneuploid fetuses with associated malformation was 68%, comparable to the low risk population [6].

Ultrasounds examination protocols

The detection rates depicted above had encouraged regulations regarding major cardiac defects screening and the use of complementary ultrasound techniques in order to increase the detection rate.

The International Society of Ultrasound in Obstetrics and Gynecology [16] published in 2013 guidelines for the prenatal screening of cardiac heart disease (CHD) providing the methodology for fetal cardiac ultrasound scan. However, the diagnostic needs a sequential approach, the classical 2D examination representing the cornerstone and being mandatory [16]. The guide encourages, for screening purposes, the use of B mode with the evaluation of four chamber view and three vessels view; the CAVSD being potentially detected on four chamber view when an abnormal atrioventricular junction can be found with and absent cardiac crux.

The 2D ultrasound is the initial step while screening for a CHD. In the case of a CAVSD three characteristic features are found concomitant on this section: absent septum primum (ASD), abnormal atrioventricular valve and intraventricular defects [11,15]. First plan of scan is the apical 4 chamber view, which is the best incidence for the evaluation of the atrioventricular plane, ventricular and interatrial septal defect [29].

In the case of a CAVSD the part of the interatrial septum closest to the AV valve is absent – ASD due to the *absence of the septum primum*, which gives the im-

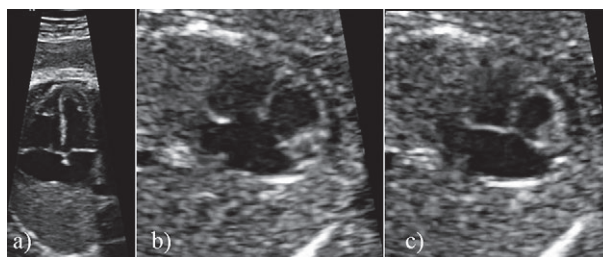


Fig 1. Aspect of the atrio-ventricular plane: a) normal with differential insertion of the atrio-ventricular valves; b) CAVSD with linear insertion of common atrio-ventricular valve in diastole, with the leaflets open; c) CAVSD with linear insertion of the atrio-ventricular valves during systole, with the leaflets closed.

pression of a common atrium [11,15,22]. Also there is a *common atrioventricular valve* due to the abnormal formation of the atrioventricular valves, which usually has 5 leaflets. The aspect of a common valve can be better evaluated during diastole, when the valves are open [11] (fig 1b). The characteristics of the leaflets and their attachment to the papillary muscles need to be evaluated next, and therefore the Rastelli type can be defined. The B mode techniques do not always allow to define the Rastelli type, because of the difficulty in obtaining the coronal plane of the valves [11].

Moreover, using the same apical 4 chamber view the AV plane appears linear and it bulges towards the ventricles during the systole. The normal aspect of the atrioventricular plane, with a differential insertion of the AV valves, the so called “crux cordis”, is absent. This aspect is generally the first ultrasound marker identified in a CAVSD and it gives the typical image of linear insertion of the AV valves (LIAVV) (fig 1c). The LIAVV was found in 69% of normal hearts of fetuses with trisomy 21 [17]. This may represent a particularity of trisomic hearts, and can also be used as an ultrasound marker for Down syndrome. For some authors it represents a minor form of AVSD continuum [19].

There is always a variable deficiency of the inter-ventricular septum inlet in its posterior part. This inter-ventricular septal defect is in contact with the common atrioventricular valve, and therefore might be sometimes difficult to identify [11,15,22]. In these situations, the modification of the angle of insonation with the examination in transverse view or in the long axis of the left ventricle, the use of color Doppler and 4D STIC may be useful [30].

The aspect of the ventricles is important for the prognosis. When the ventricles are equal in size, the CAVSD is known as a “balanced form” which is more frequently encountered in fetuses with Down syndrome. The form when the ventricles dimensions are different is known

as the “unbalanced form” of CAVSD, being usually detected in euploid fetuses with cardiac isomerism [31]. An postnatal objective measurement of the ventricular disproportion is the atrioventricular valve index (AVVI) calculated as the ratio between left atrioventricular valve area/total atrioventricular valve area expressed in centimeters squared [32,33]. The form is considered unbalanced if the $0.4 < AVVI < 0.6$, right dominant ($AVVI \leq 0.4$) or left dominant ($AVVI \geq 0.6$) [33]. The index can be used postnatally for the selection of the surgical procedure. Theoretically, the AVVI can be easily measured, even antenatal, using the apical four-chamber view, but no antenatal reports have been found yet to our knowledge.

Due to the apical displacement of the common valve in AVSD, the left atrium is elongated and left ventricle is shortened [17,18]. This anatomical feature was used by Machalitt et al, in 2004 to calculate the atrial-to-ventricular length (AVL) ratio [17]. This marker was analyzed in a study that included 123 normal pregnancies and 29 CAVSD pregnancies. The authors concluded that in normal pregnancies AVL ratio was constant during pregnancy (0.47%), but it was significantly increased (mean 0.77%) in AVSD pregnancies [17]. Therefore the calculation of AVL ratio is a useful tool that might optimize the detection of the CAVSD [17].

The ultrasound evaluation of these fetal hearts must also include the evaluation of the ventricular-arterial concordance and the crossing of the great arteries [16], most frequently normal. The association of CAVSD and Fallot tetralogy or double outlet right ventricle (DORV) has been reported especially related to trisomy 21 [34].

Doppler ultrasound is valuable tool for the diagnosis of CAVSD. In color flow mode (CFM) in four chamber apical view the filling of ventricles is displayed with a common flux of blood towards the ventricles that separates over the ventricular septal defect, with a “Y” shape (fig 2a). The image was compared with the wings of a butterfly “*image en aire de papillon*” [11]. Frequently, the common AV valve is insufficient, therefore in CFM mode a central regurgitation can be visualized during the ventricular systole (fig 2b) which can be quantified in Pulsed-Wave (PW) Doppler mode. The amplitude of the regurgitation has an important predictive value for the postnatal evolution of the new-born [10,13]. CFM mode is also useful in the confirmation of ASD and VSD [36]. Even if the use of Doppler in the first trimester is controversial due to the lack of studies [37] CFM mode at the end of the first trimester allows a better characterization of the four chamber and of the crossing of the great arteries [38].

The *3D-4D ultrasound* is a useful tool for the diagnostic of AVSD due to its capability of reconstructing mul-

tiples planes [39]. These new technologies may improve the diagnostic proficiencies regarding the exact form and the association with others CHD [26,39,40]. The AV plane can be directly visualized and the morphology of the AV valves or of the unique valve can be assessed.

Practical tricks for 3/4D techniques

The acquisition of the volume can be made in four chamber apical view or in transverse view. The apical view is preferable because the AV plane is examined in a direct axial resolution, which is better than a reconstructed one. However, due to the improvements of ultrasound machines, also a transverse acquisition may give good results. The acquisition is made on STIC mode, with a minimum sweep angle and a high frame rate. The following step is the adjustment of the direction of view at 0 (or 90 degrees), and the selection of the volume set to be analyzed. The render box is resized for the region of interest (ROI) that are the AV valves with the reference dot at the level of the crux of the heart (fig 3). Then the morphology of the AV valves and the papillary muscles are examined

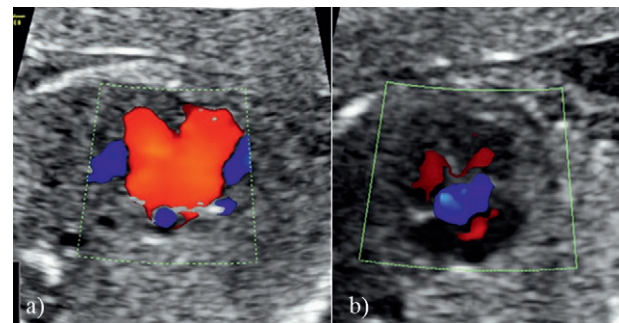


Fig 2. Doppler examination in a CAVSD: a) the common flux of blood towards the ventricles separates over the ventricular septal defect, with a “Y” shape; b) the common AV valve with a central reflux during ventricular systole.

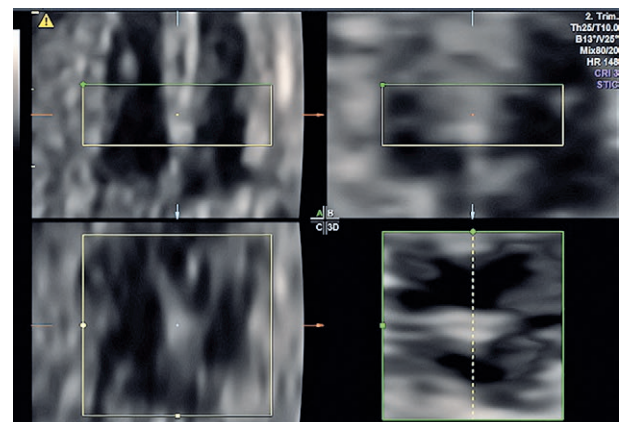


Fig 3. 3D examination of the atrio-ventricular plane in a normal heart with the render box resized for the region of interest (ROI) of AV valves with the reference dot at the level of the crux of the heart

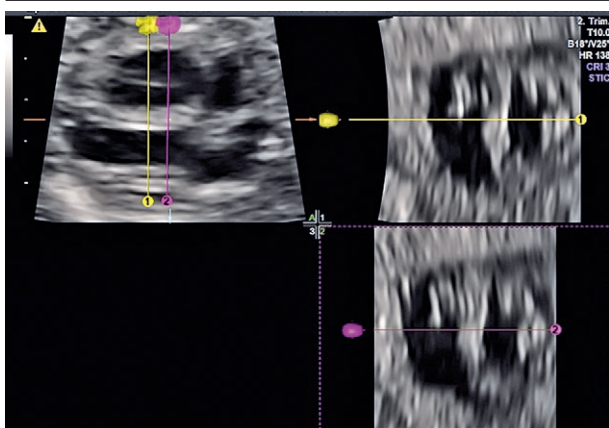


Fig 4. Omniview acquisition in a normal heart: the morphology of the papillary muscles are examined at the level of ventricles

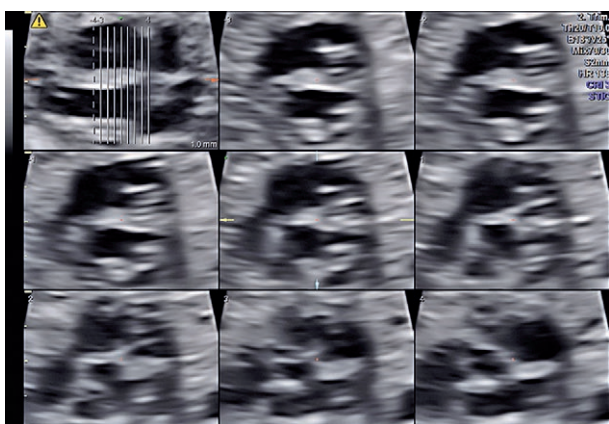


Fig 5. TUI acquisition: reconstruction of the AV plane at multiple levels from the atrial chamber

(with the render bar in the ventricles) from the apical direction. The reconstruction is made on coronal view [39].

Omniview and *TUI* (tomographic ultrasound imaging) in a transverse view can also be used with the render view direction from the atrial chamber (fig 4, fig 5) [37,40]. After the reconstruction, the analysis at slow speed allows the identification of anatomical structures and their movement during the cardiac cycle.

3D allows a better assessment of the morphology of the leaflets and of the papillary muscles, which are difficult to achieve in 2D sections [37,39-41]. Today the 3D/4D and Doppler ultrasound techniques have improved the diagnostic capabilities [42].

Pathologic associations

Once a CAVSD is diagnosed one should look for further cardiac and extracardiac malformations, because the anomaly is isolated in only 50% of cases. A very im-

portant clue is the distinction between the balanced and unbalanced form: the “balanced form” is usually associated with trisomy 21 [43] with or without Fallot tetralogy while the “unbalanced form” is present in euploid fetuses or in cases with cardiac isomerism [11,44]. If an isomerism is present (25-50%), more frequently left isomerism, the fetuses are euploid and other cardiac and extracardiac anomalies are expected [45-47]. In case of right isomerism usually an anomaly of the arterial and venous connection is present (double outlet right ventricle, anterior aorta, total anomalous pulmonary venous return [47]. The concomitant detection of a CAVSD with a Fallot tetralogy is highly evocative for trisomy 21 [46,48].

Several cardiac anomalies have been reported in relation to CAVSD: conotruncal anomalies in 30% of cases [46], aortic stenosis, hypoplasia or coarctation and aortic arch interruption. The aortic coarctation has been described in relation with partial AVSD [47].

Extracardiac anomalies were detected in a third of cases of CAVSD usually in syndromic association [11,47]. CHARGE syndrome has a dominant transmission having in 75% a cardiac malformation that is more frequently either of a Fallot tetralogy, either a CAVSD [49]. Noonan syndrome is considered as the second most frequent, when a cardiac malformation is detected, and has also a dominant transmission [50]. The spectrum of cardiac malformations in Noonan syndrome is represented classically by pulmonary stenosis, with or without dysplastic pulmonary valve and hypertrophic cardiomyopathy; CAVSD coming on the second place as frequency, being reported in 13.8% of cases [50]. Holt Oram syndrome is characterized by the concomitant presence of heart and limb anomalies, the cardiac malformation could be either ASD, VSD or CAV [51,52]. VACTERL association has also been reported in the presence of a CAVSD [31].

The partial forms of AVSD are less frequently associated with chromosomal anomalies [47]. The association of partial AVSD with a unique atrium is highly evocative for Ellis-van Creveld syndrome [53], while the presence of a left obstruction is characteristic for Noonan syndrome. In the case of Ellis-van Creveld syndrome the heart defect is present in 50-60% of cases, the most common anomaly being common atrium, but a characteristic pattern of atrioventricular canal defects in these fetuses is the association with systemic and pulmonary venous abnormalities [53].

When the diagnostic of isolated CAVSD has been made, this is associated with trisomy 21 in 58% of cases [31,54]. Several trisomies beside Down syndrome and chromosomal deletions or mutations have been reported especially in the presence of CAVSD: trisomy 18, trisomy 13, microdeletion 22q11, del 8p21-p23, 46XY, t(1;10)(p21p12) [47]. We have detected using noninva-

sive DNA fetal a 19 Mb microdeletion of chromosome 20 (20q11.21q13.13) in a fetus with a complete CAV without any other malformations (unpublished data).

Therefore in case of a suspected CAVSD a complete morphological scan has to be performed. An amniocentesis with a full karyotype preferably with array comparative genomic hybridization is also mandatory.

Prognosis

The main prognostic factor for the fetus is represented by the presence of cardiac, extracardiac and genetic anomalies. The intrinsic prognosis of CAVSD is related to specific ultrasound characteristics: the type of CAVSD, the symmetry of the ventricles, the dimensions of the valvular defect and the amplitude of the AV transvalvular regurgitation [11,13]. The most frequent form of CAVSD are of Rastelli type C, and they are more frequently associated with extracardiac malformations [55]. The largeness of the atrioventricular defect is critical; with a larger defect more likely a rapid installation of pulmonary hypertension can be foresaw with a poor outcome. Also the detection of an in utero transvalvular regurgitation has a negative impact upon the prognosis: it can anticipate a rapid installation of cardiac failure, it can be a contraindication for pulmonary cerclage or it can lead to a mitral reflux after corrective surgery. The balanced form has a better intrinsic prognosis but the association with Down syndrome aggravates the outcome: more than 50% of the couples asked for termination of pregnancy [45,47]. Last but not least, the complete form has a more unfavorable outcome than the incomplete form [11].

If an isolated CAVSD has been diagnosed, the frequency of Down syndrome and others aneuploidies is increased.

In the absence of the surgical treatment half of the infants will die until the age of six months [34], the major causes of death being the cardiac failure and pneumonia. The surgical procedures are usually performed around the age of 6 month with good results [10,13].

The detection of cardiac or extracardiac anomalies, especially in case of a syndrome, malformation sequences or chromosomal anomalies has to be assessed by a pluridisciplinary team (obstetrician, pediatric cardiologist, pediatric heart surgeon, and genetic specialist) with realistic data regarding survival rate and surgical corrections for a correct prenatal counseling. [31].

Conclusions

The diagnostic of CHD is still not perfect. It can be diagnosed starting from the first trimester, but it is usu-

ally identified during the mid-trimester scan. The diagnostic of CAVSD needs an experimented operator with skills and experience. 3D ultrasound, STIC and Doppler techniques may improve our ability in diagnosing CAVSD especially when it is isolated. These techniques permit a complementary evaluation of the AV plane and may help in the exact identification of the anomaly. Also, a complete morphologic and genetic evaluation of the fetus will allow a better management of these pregnancies.

Conflict of interest: none

References

- Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; 19:39:1890-1900.
- Rasiah SV, Ewer AK, Miller P, Wright JG, Tonks A, Kilby MD. Outcome following prenatal diagnosis of complete atrioventricular septal defect. *Prenat Diagn* 2008;28:95-101.
- Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol* 2010;88:1008-1016.
- Khalil A, Nicolaides KH. Fetal heart defects: potential and pitfalls of first-trimester detection. *Semin Fetal Neonatal Med* 2013;18:251-260.
- Abramowicz JS. The fetal heart in early pregnancy. In: Hernandez-Andrade Edgar, Patwardhan MS. *First-Trimester Ultrasound*. Springer 2016:173-194.
- 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;27:252-265.
- Garne E, Stoll C, Clementi M; Euroscan Group. Evaluation of prenatal diagnosis of congenital heart diseases by ultrasound: experience from 20 European registries. *Ultrasound Obstet Gynecol* 2001;17:386-391.
- van Velzen CL, Clur SA, Rijlaarsdam ME, et al. Prenatal diagnosis of congenital heart defects: accuracy and discrepancies in a multicenter cohort. *Ultrasound Obstet Gynecol* 2016;47:616-622.
- Combs MD, Yutzey KE. Heart valve development: regulatory networks in development and disease. *Circ Res* 2009;105:408-421.
- Calabrò R, Limongelli G. Complete atrioventricular canal. *Orphanet J Rare Dis* 2006;5:1-8.
- Boussion F, Pézard P. *Echocardiographie fœtale*. Elsevier Masson, 2013:129-137.
- Rastelli G, Kirklin JW, Titus JL. Anatomic observations on complete form of common atrioventricular canal with special reference to atrioventricular valves. *Mayo Clin Proc* 1966;41:296-308.

13. Suzuki T, Bove EL, Devaney EJ, et al. Results of definitive repair of complete atrioventricular septal defect in neonates and infants. *Ann Thorac Surg* 2008;86:596–602.
14. Vettraiño IM, Huang R, Comstock CH. The normal offset of the tricuspid septal leaflet in the fetus. *J Ultrasound Med* 2002;21:1099-1104.
15. Abuhamad AZ, Chaoui R. *A Practical Guide to Fetal Echocardiography: Normal and Abnormal Hearts*. Second Edition. LWW, Philadelphia 2009.
16. International Society of Ultrasound in Obstetrics and Gynecology, Carvalho JS, Allan LD, et al. ISUOG practice guidelines (updated): sonographic screening examination of the fetal heart. *Ultrasound Obstet Gynecol* 2013;41:348-359.
17. Machlitt A, Heling KS, Chaoui R. Increased cardiac atrial-to-ventricular length ratio in the fetal four-chamber view: a new marker for atrioventricular septal defects. *Ultrasound Obstet Gynecol* 2004;24:618=622.
18. Yoo SJ. What does an increased atrial-to-ventricular length ratio mean in fetus with atrioventricular septal defect? *Ultrasound Obstet Gynecol* 2004;24:597–598.
19. Fredouille C, Piercecchi-Marti MD, Liprandi A, et al. Linear insertion of atrioventricular valves without septal defect: a new anatomical landmark for Down's syndrome? *Fetal Diagn Ther* 2002;17:188-192.
20. Adriaanse BM, Bartelings MM, van Vugt JM, Chaoui R, Gittenberger-de Groot AC, Haak MC. Differential and linear insertion of atrioventricular valves: a useful tool? *Ultrasound Obstet Gynecol* 2014;44:568-574.
21. Huhta JC. First-trimester screening for congenital heart disease. *Curr Opin Cardiol* 2016;31:72-77.
22. Volpe P, De Robertis V, Campobasso G, Tempesta A, Volpe G, Rembouskos G. Diagnosis of congenital heart disease by early and second-trimester fetal echocardiography. *J Ultrasound Med* 2012;31:563-568.
23. Vimpelli T, Huhtala H, Acharya G. Fetal echocardiography during routine first-trimester screening: a feasibility study in an unselected population. *Prenat Diagn* 2006;26:475-482.
24. Lima AI, Araujo Júnior E, Martins WP, Nardoza LM, Moron AF, Pares DB. Assessment of the fetal heart at 12-14 weeks of pregnancy using B-mode, color Doppler, and spatiotemporal image correlation via abdominal and vaginal ultrasonography. *Pediatr Cardiol* 2013;34:1577-1582.
25. 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;42:659-668.
26. Turan S, Turan OM, Desai A, Harman CR, Baschat AA. First-trimester fetal cardiac examination using spatiotemporal image correlation, tomographic ultrasound and color Doppler imaging for the diagnosis of complex congenital heart disease in high-risk patients. *Ultrasound Obstet Gynecol* 2014;44:562-567.
27. Gardiner HM. First-trimester fetal echocardiography: routine practice or research tool? *Ultrasound Obstet Gynecol* 2013;42:611-612.
28. ter Heide H, Thomson JD, Wharton GA, Gibbs JL. Poor sensitivity of routine fetal anomaly ultrasound screening for antenatal detection of atrioventricular septal defect. *Heart* 2004;90:916-917.
29. El Yaman M, Edwards WD, Cetta F. Atrioventricular septal defects. In: Eidem BW, Cetta F, O'Leary PW, eds. *Echocardiography in Pediatric and Adult Congenital Heart Disease*. Wolters Kluwer/Lippincott Williams & Wilkins Health; Philadelphia, PA 2010:5-115.
30. Yagel S, Valsky DV, Messing B. Detailed assessment of fetal ventricular septal defect with 4D color Doppler ultrasound using spatio-temporal image correlation technology. *Ultrasound Obstet Gynecol* 2005;25:97-98.
31. Calkoen EE, Hazekamp MG, Blom NA, et al. Atrioventricular septal defect: From embryonic development to long-term follow-up. *Int J Cardiol* 2016;202:784-795.
32. Cohen MS, Jacobs ML, Weinberg PM, Rychik J. Morphometric analysis of unbalanced common atrioventricular canal using two-dimensional echocardiography. *J Am Coll Cardiol* 1996;28:1017–1023.
33. Jegatheeswaran A, Pizarro C, Caldarone CA, et al. Echocardiographic definition and surgical decision-making in unbalanced atrioventricular septal defect: a Congenital Heart Surgeons' Society multiinstitutional study. *Circulation* 2010;122(11 Suppl):S209-S215.
34. Craig B. Atrioventricular septal defect: From fetus to adult. *Heart* 2006;92:1879–1885.
35. Renna MD, Pisani P, Conversano F, et al. Sonographic markers for early diagnosis of fetal malformations. *World J Radiol* 2013;5:356-371.
36. Salvesen KÅ, Lees C, Abramowicz J, Brezinka C, Ter Haar G, Maršál K. Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible? *Ultrasound Obstet Gynecol* 2011;37:625-628.
37. Votino C, Kacem Y, Dobrescu O, et al. Use of a high-frequency linear transducer and MTI filtered color flow mapping in the assessment of fetal heart anatomy at the routine 11 to 13 + 6-week scan: a randomized trial. *Ultrasound Obstet Gynecol* 2012;39:145-151.
38. Paladini D, Vassallo M, Sglavo G, Lapadula C, Martinelli P. The role of spatio-temporal image correlation (STIC) with tomographic ultrasound imaging (TUI) in the sequential analysis of fetal congenital heart disease. *Ultrasound Obstet Gynecol* 2006;27:555-561.
39. Turan S, Turan O, Baschat AA. Three- and four-dimensional fetal echocardiography. *Fetal Diagn Ther* 2009;25:361-372.
40. Viñals F, Pacheco V, Giuliano A. Fetal atrioventricular valve junction in normal fetuses and in fetuses with complete atrioventricular septal defect assessed by 4D volume rendering. *Ultrasound Obstet Gynecol* 2006;28:26-31.
41. Chaoui R, Heling KS. New developments in fetal heart scanning: three- and four-dimensional fetal echocardiography. *Semin Fetal Neonatal Med* 2005;10:567-577.
42. Dalla PR, Römer U, Kozlik-Feldmann R, Netz H. Real-time three-dimensional ultrasound - a valuable new tool in preoperative assessment of complex congenital cardiac disease. *Images Paediatr Cardiol* 2003;5:10-12.

43. De Biase L, Di Ciommo V, Ballerini L, Bevilacqua M, Marcelletti C, Marino B. Prevalence of left-sided obstructive lesions in patients with atrioventricular canal without Down's syndrome. *J Thorac Cardiovasc Surg* 1986;91:467-469.
44. Dickinson DF, Arnold R, Wilkinson JL. Congenital heart disease among 160 480 liveborn children in Liverpool 1960 to 1969. Implications for surgical treatment. *Br Heart J* 1981;46:55-62.
45. Huggon IC, Cook AC, Smeeton NC, Magee AG, Sharland GK. Atrioventricular septal defects diagnosed in fetal life: associated cardiac and extra-cardiac abnormalities and outcome. *J Am Coll Cardiol* 2000;36:593-601.
46. Machado MV, Crawford DC, Anderson RH, Allan LD. Atrioventricular septal defect in prenatal life. *Heart* 1988;59:352-355.
47. Paladini D, Volpe P, Sglavo G, et al. Partial atrioventricular septal defect in the fetus: diagnostic features and associations in a multicenter series of 30 cases. *Ultrasound Obstet Gynecol* 2009;34:268-273.
48. Marino B, Digilio MC. Congenital heart disease and genetic syndromes: specific correlation between cardiac phenotype and genotype. *Cardiovasc Pathol* 2000;9:303-315.
49. Lalani SR, Hefner MA, Belmont JW, Davenport SL. Charge Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al. Editors. GeneReviews. <http://www.ncbi.nlm.nih.gov/books/NBK1117/> Accessed on 11/08/2016.
50. Digilio M, Marino B. Clinical manifestations of Noonan syndrome. *Images Paediatr Cardiol* 2001;3:19-30.
51. Baban A, Pitto L, Pulignani S, et al. Holt-Oram syndrome with intermediate atrioventricular canal defect, and aortic coarctation: functional characterization of a de novo TBX5 mutation. *Am J Med Genet A* 2014;164A:1419-1424.
52. Irving CA, Chaudhari MP. Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. *Arch Dis Child* 2012;97:326-330.
53. Hills CB, Kochilas L, Schimmenti LA, Moller JH. Ellis-van Creveld syndrome and congenital heart defects: presentation of an additional 32 cases. *Pediatr Cardiol* 2011;32:977-982.
54. Cetta F, Minich LL, Maleszewski JJ, et al. Atrioventricular septal defects. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF. Eds. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*. 8th ed. Lippincott Williams & Wilkins; Baltimore 2012:691-712.
55. Li J, Sun Y, Zhu Y, et al. OP18.05. Complete atrioventricular septal defect: prenatal diagnosis with fetal echocardiography, classification and associated malformations. *Ultrasound Obstet Gynecol* 2015;46(Suppl S1):54-121.