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The association between prenatal atrioventricular septal defects and chromosomal abnormalities

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Condensation

The rate of trisomy 21 among fetuses with an AVSD in the second trimester is high even in those that undergo first trimester combined screening.

Short version of title

AVSD and trisomy 21.

ABSTRACT

Objective: Atrioventricular septal defect is associated with a high risk of a chromosomal abnormality, particularly trisomy 21. The aim of this study is to assess the rate of trisomy 21 in fetuses diagnosed with an atrioventricular septal defect and to examine the influence of prior screening on the rate of trisomy 21.

Methods: Electronic ultrasound database was searched to identify fetuses diagnoses with an atrioventricular septal defect from 2002 to 2014. Rate of trisomy 21 and other aneuploidies was calculated among fetuses with normal situs. The prevalence of trisomy 21 and other aneuploidies was assessed in women with low and high first trimester risk for trisomy 21, using a cut-off value of 1:150 and 1:250.

Results: A total 110 fetuses with a diagnosis of atrioventricular septal defect were identified. Among the 98 fetuses with normal situs, the prevalence of trisomy 21 was 46% (95%CI: 36-56%). Using a 1:150 threshold, the rate of trisomy 21 within the low-risk group was 41% (95%CI: 27-57%) while in the high-risk group it was 70% (95% CI: 52-83%), significantly higher than in the low risk group (p= 0.028). Similar results were obtained when the 1:250 threshold was applied (66% versus 41%, p= 0.055).

Conclusions: The rate of trisomy 21 among fetuses identified with an atrioventricular septal defect in the second trimester is high even in those that undergo first trimester combined screening. Some fetuses with a high-risk screening result show a normal karyotype. Therefore, an offer of an invasive

procedure to check fetal karyotyping is indicated. Knowledge of these rates may be helpful for parents in the decision making process.

Key words: atrioventricular septal defect, AVSD, chromosomal abnormalities, trisomy 21, first trimester risk, combined risk.

INTRODUCTION

Atrioventricular septal defect (AVSD) is a common cardiac abnormality with an estimated incidence ranging from 0.24/1000 to 0.31/1000 live births.[1] Its anatomical hallmark involves the presence of a common atrioventricular junction, but a wide spectrum of abnormalities exists. In a complete AVSD there are variable size atrial and ventricular septal defects, and a single valve orifice. In a partial AVSD there are two atrioventricular valve orifices, and this is most commonly associated with a defect in the primum (inferior) part of the atrial septum, an ostium primum defect.[2]

Fetal AVSD has known associations with aneuploidies and situs abnormalities. The association is strongest for trisomy 21, which is present in about 40% of fetuses with an AVSD.[3,4,5] It is also known that in fetuses with trisomy 21, AVSD is a common malformation.[6] Because of this, the finding of an AVSD during a genetic sonogram represents an indication to offer fetal invasive prenatal testing for karyotype.[7]

First trimester screening using combined screening for trisomy 21 has led to large increases in antenatal detection.[8,9] As a consequence of this increased detection rate, one would expect a reduction in the prevalence of trisomy 21 in the second trimester overall, but also in the subgroup of fetuses with an AVSD – There is some evidence of this from published literature. [10] We undertook this study with two aims: to assess the rate of trisomy 21 in a population of fetuses diagnosed with an AVSD; and to examine the influence of prior screening on the rate of trisomy 21.

MATERIALS AND METHODS

The Fetal Medicine Unit of St. George's Hospital, London, UK, is a tertiary referral centre for the diagnosis and management of all fetal conditions. Pregnant women where a screening scan reveals a concern are referred to our unit both from our own hospital (approx. 5,000 births per year) and the South-West Thames region (five maternity units, with approx. 20,000 births per year).

We undertook a search of our electronic database (Viewpoint) to identify all those fetuses diagnosed with an AVSD from 2002 to 2014. Maternal details, the indication for referral, gestational age at the time of diagnosis of the AVSD, ultrasound findings, presence of any associated abnormalities, information regarding fetal karyotype, nuchal translucency (NT) measurement and the estimated risk for trisomy 21 at the first trimester screening, and pregnancy outcome were extracted. Details of fetal karyotype were cross-checked with a separate cytogenetic database maintained in the Department of Genetics.

The first trimester risk was obtained by a combination of maternal age, fetal NT thickness and maternal serum free beta-human Chorionic Gonadotrophin (hCG) and pregnancy associated plasma protein-A (PAPP-A) at 11^{+0}–13^{+6} weeks.[11] When data regarding maternal serum data were not available, the first trimester risk was obtained by combination of maternal age and fetal NT.[12] Finally, when neither were available (women declining screening), the risk was calculated based on maternal age alone for the purposes of this study.[13]

Following referral, fetuses underwent complete ultrasound evaluation of fetal anatomy in addition to fetal echocardiography. Invasive testing was offered to all women, and the results were recorded. Fetal karyotype was obtained after birth where parents declined prenatal invasive testing.

Institutional Review Board approval was given for the collection of pregnancy outcome data as part of follow-up of fetal medicine unit patients.

Statistics

Descriptive data are presented as median and inter-quartile ranges (IQR). Proportions are presented as percentage and 95% CI. Statistical analysis was performed using the SPSS V20.0. The chi-squared test was used to evaluate inter-group differences. P-values of <0.05 have been considered statistically significant.

RESULTS

Overall 110 fetuses with a diagnosis of AVSD were identified. The median gestational age at diagnosis was 21 weeks (IQR: 17.6-22.4); median maternal age was 33 years (IQR: 27-38); median maternal BMI was 25.7 (IQR: 22.9-29.8); median NT value in the first trimester was 2.7 mm (IQR: 1.9 – 4.5); median first trimester risk for trisomy 21 was 1:184 (IQR: 1:918 – 1: 16). Information regarding fetal karyotype was available for 100 fetuses (91%). In 11 cases the parents declined invasive testing during pregnancy and the investigation for karyotyping was performed post-natally. Details regarding karyotype, indication for referral and pregnancy outcome of the 110 fetuses with an AVSD are given in Table 1. The rate of trisomy 21 among the 110 cases was

41% (95% CI: 32-50%). There were twelve cases where the AVSD was found in the presence of abnormal situs (Supplementary Table 1); in this group there was one case of trisomy 18 but none with trisomy 21. These fetuses were excluded from subsequent analysis.

Among the remaining 98 fetuses with AVSD and normal situs, the prevalence of trisomy 21 was 45 of 98 (46%, 95% CI: 36-56%), the karyotype was normal in 35 (36%, 95% CI: 27-46%) and not available in 9 (9%, 95% CI: 5-17%) cases. In these 98 fetuses with AVSD and normal situs we identified 69 with an isolated AVSD, and 29 with an AVSD associated with other abnormalities (listed in Table 2). In fetuses with isolated AVSDs, the most common karyotype abnormality was trisomy 21, found in 37 of 69 fetuses (54%, 95% CI: 42-65%). The karyotype was normal in 22 cases (32%, 95% CI: 22-44%), and unavailable in 5 (7%, 95% CI: 3-16%). When the AVSD was non-isolated, the prevalence of trisomy 21 was lower, with 8 of 29 fetuses showing trisomy 21 (28%, 95% CI: 15-46%), 13 with normal karyotype (45%, 95% CI: 28-63%) and 4 (14%, 95% CI: 5-31%) in which it was unavailable. Additional information is available in Table 3.

Within the isolated AVSD group (n=69), we further investigated the prevalence of trisomy 21 among the cases with low and high first trimester risk for trisomy 21. When the estimation of the first trimester risk was lower than 1:150, pregnancies were included in the low risk group (median risk = 1:814; IQR= 1:386 – 1:1681). Among these pregnancies the rate of trisomy 21 was 41% (95% CI: 27-57%), while the karyotype was normal in 49% (95% CI: 34-64%) of

cases. If the first trimester risk was equal or higher than 1:150, women were included in the high-risk group (median risk = 1:10; IQR= 1:2 – 1:45). Among them the prevalence of trisomy 21 was 70% (95% CI: 52-83%), and karyotype was normal in 10% (95% CI: 4-26%) of cases. The prevalence of trisomy 21 in the high risk group was significantly higher than in the low risk group (70% versus 41%, p= 0.028) (Table 4). In many European countries a different cut off of 1:250 is used to classify the pregnancies in high and low risk. Using a cut off of 1:250 the results did not vary. The risk in the low-risk group remained high, but lower than in the high-risk group (66% versus 41%, p= 0.055) (Table 4).

COMMENT

The findings of the study show that the overall rate of trisomy 21 among fetuses with an AVSD and normal situs is 45.9% (95% CI: 36.4-55.6%). There was some evidence of an effect of first trimester screening on the prevalence of trisomy 21: the rate of trisomy 21 was significantly higher in women that had previously had a positive first trimester combined test (70%) than in those who were screen –negative (41%). Nevertheless this prevalence of 41% means that karyotipic examination should still be offered. The findings also show that four out of the 33 fetuses (12%) with AVSD from the high risk group had normal karyotype.

The rate of trisomy 21 among fetuses with a diagnosis of AVSD has been reported to be around 40%.[3,4,6] These studies were performed in the 1990s, before the introduction of the first trimester screening in the clinical practice. Since 2001, the introduction of the first trimester screening for trisomy 21, has

led to a 70% increase in the antenatal detection of trisomy 21.[8,9] Following this improvement, we expected to find a lower prevalence of trisomy 21 among fetuses diagnosed with an AVSD in the 2nd trimester, and a higher proportion of fetuses with an AVSD and normal karyotype, as a consequence of detection and subsequent termination of at least some of the affected pregnancies. Contrary to expectations, we found that the rate of trisomy 21 in fetuses with AVSD has remained stable since 1990s, being 45% in our series. A possible explanation to this is available in a UK epidemiological study investigating trends in diagnosis and live births of fetuses affected by Down's syndrome. This study[8] shows that the annual number of trisomy 21 live births has remained steady since 1990s, as the number of pregnancies that are detected and where the parents opt for pregnancy termination is balanced by the age-related increase. This may partly explain why the rate of trisomy 21 in fetuses with an AVSD in the second trimester is stable at around 40% in our study. We speculate that the number of pregnancies detected (and where parents choose termination) is balanced by those resulting from increased maternal age, leading to a similar number of fetuses with trisomy 21 and an AVSD reaching the second trimester.

A recent study[10] reported on trisomy 21 from 1992 – 2012. They reported that complex congenital heart defects were less common in the latter years in infants diagnosed with Down syndrome. This phenotypic shift could be a result of selective termination of fetuses with Down syndrome. In addition to this, a proportion of women with an increased first trimester risk opted against prenatal diagnosis; and of those undergoing prenatal diagnosis of trisomy 21,

approximately one in ten will opt to continue the pregnancy.[8] This is supported by our observation that the diagnosis of aneuploidy was already known at the time of fetal echocardiography in 15% of the fetuses and was the reason for the referral to the fetal cardiologist.

Another aim of this study was to assess the role of the first trimester risk in the prediction of trisomy 21 after detection of an AVSD in the 2nd trimester.[15] We wanted to explore if, in the presence of an AVSD and a low first trimester risk, the chance of trisomy 21 remains low. Indeed, the risk of trisomy 21 after detection of an AVSD is an important factor in parental decision making. We found that although the rate of trisomy 21 is higher in the group of women with a high first trimester risk (>1:150) and an AVSD (70%, 95%CI: 52-83%), the absolute rate remains high in the group with a low first trimester risk (41%, 95% CI: 27-57%), a difference which does not vary significantly when the chosen threshold is 1:250 (66% versus 41%). In a previous study[3] conducted before the introduction of screening by NT and combined testing, the risk of trisomy 21 in fetuses with an AVSD was assessed by taking into account the age-related maternal risk and the relative risk was found to be 107. The authors concluded that with such a high relative risk, even in the presence of a very low first trimester risk (e.g. 1:1000), the final risk calculated in the second trimester would still be high (e.g. 1:10). In our study, we examined the rate of trisomy 21 in fetuses with an AVSD in two separate groups with low and high risk in the first trimester. Although we found a significant difference, with a rate of 70% in the high-risk group compared with a rate of 41% in the low-risk group, we believe that in both groups the rates are still high and that an offer of

amniocentesis in the presence of an AVSD is still indicated, irrespective of the risk in the first trimester. Indeed, given that the final management is guided by parental choice, the rate of trisomy 21 in the low and high-risk group is still a useful information in the decision making process.

One limitation of our study is that fetal karyotype was unknown in about the 9% of cases and clearly, this may have led to a underestimation of the rate of chromosomal abnormalities. One more limitation is the missing maternal serum-free beta-hCG and PAPP-A levels in 12 pregnancies and missing NT measurements in 18 pregnancies. It may be also argued that the present study tends to overestimate the real incidence of AVSD due to a selection bias. Some fetuses had been referred because of increased NT, which in itself, is associated with heart defects regardless of karyotype.[16,17] However only 17% of our series had this indication (increased NT), and exclusion of these fetuses from our analysis did not change our results. Some other fetuses were referred for a known trisomy 21. This may have led to an increase in the rate of trisomy 21 among the group with a high first trimester risk, as most of them (11 out of 16) belonged to that group. Another limitation is related to an intervention bias: this was likely to occur in the high-risk group as many trisomy 21 cases could have been terminated. These predominantly increased NT cases would have had a high incidence of cardiac anomalies – hence the prevalence of trisomy 21 in the high-risk group in this study might be lower than would naturally be observed. We cannot be sure that all the AVSDs diagnosed after birth were detected antenatally. Such defects might have been less likely to be affected with trisomy 21. Hence the study prevalence of trisomy 21 in the low-risk group

may be higher than would naturally be observed. Alternatively, it has been reported that fetuses with AVSD associated with trisomy 21 have less distorted cardiac anatomy. [18] Therefore, some fetuses with isolated AVSD with trisomy 21 may not have been detected antenatally. However, the database was matched with the regional genetic database of chromosomal abnormalities, and prenatally undiagnosed cases of trisomy 21 with AVSD were not found. Observational bias may affect the low-risk group. A proportion of women knew that the fetus was affected with trisomy 21. The data from this study is of no use to these prospective parents. However, the data are still useful to couple faced with a diagnosis of AVSD in the second trimester. It will help them in making an informed choice. Access to cell-free DNA testing technology has provided additional alternatives to couples with a fetus suspected to have Down syndrome. However, this technology was not available during the study period.

Despite the introduction of the first trimester combined screening the rate of trisomy 21 among fetuses diagnosed with an AVSD in the second trimester is still high. Given the high rates both in the low and high-risk group, the option of karyotyping should be given to the parents. At the same time, a small proportion of fetuses with AVSD and high risk on antenatal screening have a normal karyotype. Therefore, karyotyping should be carried out before concluding that the fetus with AVSD and a high risk screening result is affected with Down syndrome. The knowledge of these rates may be helpful for parents in the decision making process.

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REFERENCES

1. Craig B. Atrioventricular septal defect: from fetus to adult. Heart. 2006 Dec;92(12):1879-85.

2. Allan LD. Atrioventricular septal defect in the fetus. 1999 Am J Obstet Gynecol 181: 1250–1253.

3. Paladini D, Tartaglione A, Agangi A, et al. The association between congenital heart disease and Down syndrome in prenatal life. Ultrasound Obstet Gynecol. 2000 Feb;15(2):104-8.

4. Langford K, Sharland G, Simpson J. Relative risk of abnormal karyotype in fetuses found to have an atrioventricular septal defect (AVSD) on fetal echocardiography. Prenat Diagn. 2005 Feb;25(2):137-9.

5. 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 Aug;36(2):593-601.

6. Ferencz C, Neill CA, Boughman JA. Congenital cardiovascular malformations with chromosome abnormalities: an epidemiologic study. J Pediatr 1989; 144: 79–86.

7. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015 Jan;45(1):16-26.

8. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. BMJ. 2009 Oct 26;339:b3794.

9. UK National Screening Committee. Fetal anomaly screening programme—screening for Down's syndrome: UK NSC policy recommendations 2007-2010: model of best practice.

10. Bergström S, Carr H, Petersson G et al. Trends in Congenital Heart Defects in Infants With Down Syndrome. Pediatrics. 2016 Jul;138(1).

11. Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999; 13: 231–237.

12. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Lancet. 1998;352(9125):343-6.

13. Snijders RJM, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age and gestation-specific risk for trisomy 21. Ultrasound Obstet Gynecol 1999; 13: 167–170.

14. Berg C, Geipel A, Smrcek J, et al. Prenatal diagnosis of cardiosplenic syndromes: a 10 year experience. 2003 Ultrasound Obstet Gynecol 22: 451–459.

15. Vintzileos AM, Egan JF. Adjusting the risk for trisomy 21 on the basis of second-trimester ultrasonography. Am J Obstet Gynecol 1995; 172: 837–844.

16. Hyett JA, Perdu M, Sharland GK, Snijders RS, Nicolaides KH. Increased nuchal translucency at 10–14 weeks of gestation as a marker for major cardiac defects. Ultrasound Obstet Gynecol 1997; 10: 242–6.

17. Mogra R, Alabbad N, Hyett J. Increased nuchal translucency and congenital heart disease. Early Hum Dev. 2012 May;88(5):261-7.

18. Berg C, Kaiser C, Bender F, et al. Atrioventricular septal defect in the fetus--associated conditions and outcome in 246 cases. Ultraschall Med. 2009 Feb;30(1):25-32.

Table 1

Details regarding fetal karyotype, indication for referral to fetal cardiologist and pregnancy outcome among 116 fetuses diagnosed with an atrioventricular septal defect in the second trimester. NT: nuchal translucency; u/k: unknown; IUD: intra-uterine death; NND: neonatal death.

Karyotype	**n**	**% (95%CI)**		**Indication**	**n**	**% (95%CI)**		**Outcome**	**n**	**% (95%CI)**
Normal	49	42.2 (33.6-51.3)		Suspected cardiac defect	62	53.4 (44.4-62.3)		Livebirth	62	53.4 (44.4-62.3)
Trisomy 21	46	39.7 (31.2-48,8)		Increased NT, u/k karyotype	18	15.5 (10-23.2)		Termination	36	31.0 (23.3-39.9)
Trisomy 18	7	6.0 (3.0-11.9)		Trisomy 21	16	13.8 (8.7-21.2)		IUD	12	10.3 (6-17.2)
Trisomy 13	1	0.9 (0.2-4.7)		Increased NT, normal karyotype	9	7.8 (4.1-14.1)		NND	5	4.3 (1.9-9.7)
45X	1	0.9 (0.2-4.7)		Multiple abnormalities	4	3.4 (1.3-8.5)		Ongoing	1	0.9 (0.2-4.7)
XXY	1	0.9 (0.2-4.7)		Heart difficult to image	5	4.3 (1.9-9.7)				
Not available	11	9.5 (5.4-16.2)		Family history	2	1.7 (0.5-6.1)				

Table 2

Associated abnormalities. Data are given as absolute numbers. In the presence of any of the listed soft markers the AVSD was considered isolated if only one soft marker was identified, while in the presence of two of more soft markers the AVSD was defined non-isolated.

*: fetuses found with any of the marked cardiac abnormalities were excluded from analysis as such fetuses are well known to have a very low rate of chromosomal abnormalities (Berg 2003, Langford 2005).

Associated abnormalities	**n**	**Cardiac abnormalities**	**n**
Brachycepahly	5	*Left isomerism	6
Persistent increased NT/cystic hygroma	4	*Right isomerism	6
Hemivertebra	2	Tetralogy of Fallot	8
Strawberry shaped head	1	Pulmonary atresia	5
Micrognathia	1	Pleural effusion	5
Cleft lip	1	Bilateral SVCs	4
		Heart block	4
Posterior fossa cyst	2	Pericardial effusion	2
Partial agenesis of cerebellar vermis	1	Double outlet right ventricle	1
Small cerebellum	1	Double inlet right ventricle	1
Congenital diaphragmatic hernia	1	**Soft markers**	**n**
Thoracic dysplasia	1	Ventriculomegaly	6
		Choroid plexus cysts	5
Absent radius	1	Hydronephrosis	4
Bilateral talipes	1	2 vessels cord	4
Rocker bottom feet	1	Short long bones	2
Oesofageal atresia	2		
Exomphalos	1		
Enlarged kidneys	1		

Duodenal atresia	1		

Table 3 Details regarding fetal karyotype, indication for referral to fetal cardiologist and pregnancy outcome among 103 fetuses with an atrioventricular septal defect (AVSD) diagnosed in the second trimester and normal situs, among 72 fetuses with normal situs and an isolated AVSD, and among 31 fetuses with normal situs and non-isolated AVSD. NT: nuchal translucency; u/k: unknown; IUD: intra-uterine death; NND: neonatal death.

AVSD with NORMAL SITUS (n: 103)										
Karyotype	**n**	**% (95%CI)**		**Indication**	**n**	**% (95%CI)**		**Outcome**	**n**	**% (95%CI)**
Normal	38	36.9 (28.2-46.5)		Suspected cardiac defect	53	51.5 (41.9-60.9)		Livebirth	56	54.4 (44.8-63.7)
Trisomy 21	**46**	**44.7 (35.4-54.3)**		Increased NT, u/k karyotype	17	16.5 (10.6-24.9)		Termination	32	31.1 (22.9-40.5)
Trisomy 18	6	5.8 (2.7-12.1)		Trisomy 21	16	15.5 (9.8-23.8)		IUD	11	10.7 (6.1-18.1)
Trisomy 13	1	1.0 (0.2-5.3)		Increased NT, normal karyotype	7	6.8 (3.3-13.4)		NND	3	2.9 (1-8.2)
45X	1	1.0 (0.2-5.3)		Multiple abnormalities	4	3.9 (1.5-9.6)		Ongoing	1	1.0 (0.2-5.3)
XXY	1	1.0 (0.2-5.3)		Heart difficult to image	4	3.9 (1.5-9.6)				
Not available	10	9.7 (5.4-17)		Family history	2	1.9 (0.5-6.8)				
ISOLATED AVSD (n: 72)										
Karyotype	**n**	**% (95%CI)**		**Indication**	**n**	**% (95%CI)**		**Outcome**	**n**	**% (95%CI)**
Normal	23	31.9 (22.3-43.4)		Suspected cardiac defect	39	54.2 (42.7-65.2)		Livebirth	44	61.1 (49.6-

										71.5)
Trisomy 21	**38**	**52.8 (41.4-63.9)**		Increased NT, u/k karyotype	11	15.3 (8.8-25.3)		Termination	18	25 (16.4-36.1)
Trisomy 18	3	4.2 (1.4-11.5)		Trisomy 21	15	20.8 (13.1-31.6)		IUD	8	11.1 (5.7-20.4)
Trisomy 13	0	0		Increased NT, normal karyotype	1	1.4 (0.2-7.5)		NND	1	1.4 (0.2-7.5)
45X	1	1.4 (0.2-7.5)		Multiple abnormalities	0	0		Ongoing	1	1.4 (0.2-7.5)
XXY	1	1.4 (0.2-7.5)		Heart difficult to image	4	5.6 (2.2-13.4)				
Not available	6	8.3 (3.9-17)		Family history	2	2.8 (0.8-9.6)				
NON-ISOLATED AVSD (n: 31)										
Karyotype	**n**	**% (95%CI)**		**Indication**	**n**	**% (95%CI)**		**Outcome**	**n**	**% (95%CI)**
Normal	15	48.4 (32-65.2)		Suspected cardiac defect	14	45.2 (29.2-62.2)		Livebirth	12	38.7 (23.7-56.2)
Trisomy 21	8	25.8 (13.7-43.2)		Increased NT, u/k karyotype	6	19.4 (9.2-36.3)		Termination	14	45.2 (29.2-62.2)
Trisomy 18	3	9.7 (3.3-24.9)		Trisomy 21	1	3.2 (0.6-16.2)		IUD	3	9.7 (3.3-24.9)
Trisomy 13	1	3.2 (0.6-16.2)		Increased NT, normal karyotype	6	19.4 (9.2-36.3)		NND	2	6.5 (1.8-20.7)
45X	0	0		Multiple abnormalities	4	12.9 (5.1-28.9)		Ongoing	0	0
XXY	0	0		Heart difficult to image	0	0				
Not available	4	12.9 (5.1-28.8)		Family history	0	0				

Table 4

Prevalence of chromosomal abnormalities among women a diagnosis of isolated atrioventricular septal defect (AVSD) in the second trimester, according to the first trimester risk for trisomy 21. *Low-risk group: women with isolated AVSD, normal situs, first trimester risk <1:150. °High risk group: women with isolated AVSD, normal situs, first trimester risk >1:150.

	***Low-risk group (n: 39)**		**°High risk group (n: 33)**		
	n	**% (95%CI)**	**n**	**% (95%CI)**	***p***
Karyotype	39	%	33		
Normal	19	48.7 (33.9-63.8)	4	12.1 (4.8-27.3)	p=0.001
Trisomy 21	16	41.0 (27.1-56.6)	22	66.7 (49.6-80.2)	p=0.036
Trisomy 18	2	5.1 (1.4-16.9)	1	3.0 (0.5-15.3)	
Trisomy 13	0		0		
45X	0		1	3.0 (0.5-15.3)	
XXY	1	2.6 (0.5-13.2)	0		
Not available	1	2.6 (0.5-13.2)	5	15.2 (6.7-30.9)	p=0.087