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Prenatal Incidence of Isolated Right Aortic Arch and Double Aortic Arch

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ABSTRACT

Objective: To define the incidence of variants of aortic arch sidedness in fetuses undergoing routine first trimester ultrasound examination.

Methods: The data for this study were derived from prospective routine ultrasound examination at 11^{+0} to 13^{+6} weeks' gestation in singleton pregnancies examined in a local population between January 2014 and March 2018. We examined the incidence of isolated right aortic arch (RAA) and double aortic arch (DAA) in the local, screened population and compared the group with and without these abnormalities.

Results: The study population of 33,202 pregnancies included 18 (5.4 per 10,000) cases with isolated RAA and 5 (1.5 per 10,000) with DAA. In the group with isolated RAA or DAA, compared to those without, the median maternal age was higher and the incidence of conceptions from *in vitro* fertilization (IVF) was 8-fold higher. The prevalence of 22q11microdeletion was 5% in patients with RAA from this local population.

Conclusions: The incidence of isolated RAA and DAA in a local population undergoing routine first-trimester ultrasound examination is 2-3 fold higher than that reported in postnatal studies and the risk for these abnormalities is substantially increased in fetuses conceived by IVF.

INTRODUCTION

Variants of aortic arch sidedness are increasingly diagnosed during routine prenatal ultrasound examination following incorporation of the three vessel and tracheal view (3VT) into regional and National prenatal screening programs.[1-3] A right aortic arch (RAA) with left arterial duct and double aortic arch (DAA) both form a vascular ring around the trachea and esophagus and patients are therefore at risk of developing tracheoesophageal symptoms. Patients with a RAA and DAA require allocation of fetal medicine, fetal cardiology and pediatric resources in order to confirm the diagnosis, identify co-morbidities, genetic associations, evaluate the postnatal presentation, investigate symptoms and undertake surgical repair of the lesion.[1,4,5] However, allocation of such resources is not possible without knowledge of the incidence of these diagnoses in the population. The reported postnatal incidence of DAA and RAA is 2.1-3.5 per 10,000,[6,7] which is considerably lower than the prenatal incidence of 4.7-10 per 10,000;[8,9] a possible explanation for this difference is that the latter is overestimated because it is based on studies from specialist referral centers.

The objective of this paper is to describe the incidence of isolated RAA and DAA in a local population undergoing routine ultrasound examination in pregnancy.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women from the local population attending for routine ultrasound examination at 11^{+0} to 13^{+6} weeks' gestation at King's College Hospital, London, UK between January 2014 and March 2018. This visit included recording of maternal demographic characteristics, obstetric history, medical history, measurement of maternal weight and height and ultrasound examination for the measurement of fetal crown-rump length (CRL) to determine gestational age,[10] measurement of the fetal nuchal translucency (NT) thickness and examination of fetal anatomy for the diagnosis of major defects. The policy in our hospital was to

offer routinely a second ultrasound examination at 20^{+0} to 23^{+6} weeks and a third ultrasound examination at 35^{+0} to 37^{+6} weeks. All scans involved systematic detailed examination of the fetus, including a sweep through the heart in the transverse plane to include the four-chamber view, outflow tracts and three vessel and tracheal view, augmented with color Doppler.[11-13]

All cases of suspected fetal abnormality were examined by a fetal medicine specialist. Likewise, all cases of suspected fetal cardiac defect were examined by a fetal cardiologist. In addition, fetal cardiologists carried out fetal echocardiography at 11-14 weeks in those with NT above the 99th centile and at 20 weeks in those with NT between the 95th and 99th centiles.[14] All neonates were examined by a pediatrician. Prenatal and neonatal findings were recorded in computerized databases. Data on pregnancy outcome is ascertained from electronic records in all women who underwent prenatal ultrasonography in our unit. Children suspected to have heart disease at the postnatal assessments or community checks are referred to our paediatric cardiac service and therefore symptomatic, missed cases of congenital heart disease would be identified. Outcome was obtained from women who were booked for obstetric care in our hospital but delivered in other hospitals were obtained either from the maternity computerized records in these hospitals or from the general medical practitioners of the women.

Inclusion and exclusion criteria

We included all cases with isolated RAA or DAA with normal cardiac situs diagnosed by fetal cardiologists antenatally. For the purposes of this study the definition of isolated RAA or DAA included those fetuses with a RAA and minor associated cardiac findings such as a small ventricular septal defect or persistent left superior vena cava which did not require cardiac surgery. A DAA was defined as two limbs of the aortic arch (figure 1) and included balanced right and left aortic arches and those with dominance of either limb. All livebirths with RAA or DAA underwent echocardiography after birth in our pediatric cardiac unit at Evelina London Children's Hospital and the final diagnosis of the aortic arch anatomy was based on a combination of fetal echocardiography, fetal cardiac MRI, postnatal echocardiography and postnatal CT or surgical findings. The prenatal diagnosis of RAA or DAA in cases of termination of pregnancy and miscarriage at <24 weeks was assumed to be correct (in these cases,

postmortem examination was not performed systematically). Array comparative genomic hybridization (CGH) was offered in all pregnancies with RAA or DAA.

Statistical analysis

Data from continuous variables are expressed as median and interquartile range (IQR) and from categorical data as n (%). Comparison of the maternal characteristics between the outcome groups was by the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. A p value of <0.05 was considered significant. The measured fetal NT was expressed as a difference from the expected normal mean for fetal CRL (delta value).[15] Univariate and multivariate analysis was undertaken to evaluate the relation between maternal characteristics and diagnosis.The statistical software package SPSS Statistics v. 24.0 (IBM Corp., Armonk, NY, USA) was used for the data analyses.

RESULTS

Study population

During the study period routine ultrasound examination was carried out in 34,011 singleton pregnancies from the local population by 256 sonographers. There were 809 (2.4%) which were lost to follow up, thus the study population comprised 33,202 pregnancies and included 18 (5.4 per 10,000 screened) cases with isolated RAA, 5 (1.5 per 10,000 screened) with isolated DAA and 33,179 without isolated RAA or DAA. No infants presented after birth with a RAA or DAA during the study period. Demographic and pregnancy characteristics of those with and without isolated RAA or DAA are compared in Table 1. In the group with isolated RAA or DAA, compared to those without, the median maternal age was higher and the incidence of IVF conceptions was 8-fold higher; there were no other significant differences between the groups. Univariate logistic regression analysis demonstrated that maternal age (OR 1.120; 95% CI: 1.031-1.218, p=0.007) and IVF conception (OR 11.175; 95% CI 4.589-27.212, p<0.0001), but not maternal weight (p=0.460) or height (p=0.769), Black (p=0.929) or South Asian (p=0.472) racial origin, ovulation induction drugs (p=0.996), cigarette smoking (p=0.990) or nulliparity (p=0.233) were associated with the risk of RAA/DAA. Multivariate logistic regression analysis demonstrated that

IVF conception (OR 11.175; 95% CI 4.589-27.212, p<0.0001), but not maternal age (p=0.130) was associated with the risk of RAA/DAA.

Findings in the cases of right aortic arch or double aortic arch

In 19 (79.2%) cases of RAA or DAA the diagnosis was suspected by the sonographers at the time of the 11-13 week scan and subsequently confirmed by a fetal cardiologist. The remaining 4 (20.8%) were confirmed at the 20 weeks scan. There were 15/18 (83%) cases of RAA with left arterial duct of which 12/15 (80%) cases had an aberrant left subclavian artery and 3 (20%) cases mirror image branching pattern. There were 3 cases (17%) of RAA with right arterial duct of which 2 had mirror image branching pattern and one with an aberrant left subclavian artery. The arterial duct was left sided in all cases of DAA.

In 15 cases invasive testing with array CGH was carried out and in 13 the result was normal in one there was 22q11 microdeletion and in another a 16p13.11 duplication. The remaining eight pregnancies resulted in livebirth of phenotypically normal neonates. Thus, 22q11microdeletion was seen in 5 .6% of RAA. In the case of 16p13.11 duplication the pregnancy was terminated at the request of the parents. In one of the cases with normal array CGH there was a miscarriage.

DISCUSSION

Main findings of the study

This is the first study reporting on the prenatal diagnosis of fetal RAA and DAA in a general population attending for routine ultrasound examination in pregnancy. We found that the incidence of isolated RAA and DAA, of 6.9 per 10,000, is 2-3 fold higher than that reported in postnatal studies.[8,9] Although our Fetal Medicine and Cardiology unit is a tertiary referral center we took great care to ensure that the study population was confined to women undergoing routine pregnancy care in our local hospital.

We found that in the group with isolated RAA or DAA, compared to those without, the median maternal age was higher and the incidence of IVF conceptions was 8-fold higher.

Comparison with findings of previous studies

A RAA and DAA constitute the commonest vascular rings identified on prenatal ultrasound examination and there are various morphological variants of these two entities which may be under-recognized as a vascular ring. In our study we included all the variants which may have impact on the trachea and bronchi; some of the previous studies excluded those cases of RAA with mirror image branching pattern and left duct,[8] which constitute 20% of our population.

The incidence of isolated RAA and DAA in our study was considerably higher than in postnatal reports.[3,6] One postnatal study reported an incidence of 2.1 per 10,000 live births; this study included a variety of types of vascular ring and did not differentiate between isolated RAA or DAA and cases associated with major congenital heart disease.[6] Another study of isolated RAA combined data of cases diagnosed prenatally with those detected postnatally and reported an incidence of 3.5 per 10,000 live births.[7] A likely explanation for this apparent difference between our findings and those of previous reports is that in postnatal series there is under ascertainment of this abnormality because there is no routine neonatal screening for vascular rings and consequently only those that are symptomatic in early childhood present to cardiac services. Furthermore, symptoms of a vascular ring overlap with many other common conditions such as asthma and therefore may not reach a threshold for specialist referral and this is evidenced by the delay reported between onset of symptoms and surgical relief of the vascular ring. Another possible explanation for a lower incidence of vascular rings in postnatal series is that some affected fetuses die in utero because of associated genetic abnormalities.[16]

The association between IVF and increased risk for congenital heart disease was raised from the early days of the introduction of this technology in clinical practice.[17] A recent systematic review and meta-

analysis, involving a total of 25,856 children conceived from IVF techniques and 287,995 children conceived spontaneously, reported that IVF was associated with a 45% increase in the incidence of congenital heart disease.[18]

Increased maternal age is apparent in the patients with an isolated RAA or DAA and this may be related to the higher use of IVF techniques.[19] Increased maternal age has not been shown to be a risk factor for congenital heart disease and is not considered an indication for specialist fetal echocardiography in our practice.

We have also demonstrated, that despite routine screening of a local population, chromosomal or genetic conditions were diagnosed in 2/23 (8.7%) of this cohort and this is higher than other reported cohorts. We acknowledge the limitations of the sample size, but this is the first population-based study with a protocolized follow-up of children born with RAA and DAA which includes reviews by senior pediatricians specifically to ascertain dysmorphisms or suggestions of genetic/chromosomal disorders. This incidence of chromosomal / genetic conditions is similar to our previous reports[1] and the incidence of these conditions remains considerable and warrants discussion with the expectant parents.

Implications for clinical practice

Prenatal diagnosis of isolated RAA and DAA provides the option of undertaking further genetic investigations and counselling the parents of the need for postnatal follow-up. Some patients with RAA or DAA with left arterial duct become symptomatic with respiratory or swallowing difficulties in infancy and these require surgery. Some may only present in later childhood/adulthood and despite a technically good result from surgery, there is ongoing respiratory morbidity.[20-22] Others remain asymptomatic but demonstrate tracheal compression in infancy[4] and the appropriate management of this group, including intensity of surveillance and need for surgery, is under investigation.

Limitations

The main limitation of the study is that despite the examination of a large population of pregnancies undergoing routine ultrasound examination, the number of cases of isolated RAA and DAA was small and therefore the observed 8-fold increased incidence of IVF conception needs to be interpreted with caution.

Conclusion

The incidence of isolated RAA and DAA in a local population undergoing routine first-trimester ultrasound examination is 2-3 fold higher than that reported in postnatal studies and the risk for these abnormalities is substantially increased in fetuses conceived by IVF.

Contributions: Study conceived and drafted by TV. Study design by TV, VZ, KN. Data collection by SJ, TV, AS. Critical review of the manuscript by all authors.

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FIGURE LEGENDS

Figure 1. a: Normal three vessel and tracheal view at 13weeks with colour Doppler demonstrating a left aortic arch (LAA) and left sided arterial duct.

b: Right aortic arch (RAA) with left arterial duct in a fetus at 12 weeks' gestation. The trachea (T) is encircled.

c: Right aortic arch with an aberrant left subclavian artery (ALSA) at 11 weeks.

d: Double aortic arch in a fetus at 11 weeks' gestation. The left aortic arch is marked with a star. The right and left aortic arches encircle the trachea.

Variables	**No RAA or DAA (n=33,179)**	**RAA or DAA (n=23)**	**P value**
Maternal age in years	32.6 (28.8-35.9)	35.9 (34.5-38.4)	0.001
Maternal weight in kg	67.0 (59.4-77.0)	71.4 (63.1-79.1)	0.163
Maternal height in cm	165 (160-170)	165 (161-169)	0.823
Gestational age at scan in weeks	12.7 (12.3-13.2)	12.6 (12.3-13.2)	0.909
Crown-rump length in mm	63.8 (58.5-69.5)	62.0 (58.3-70.3)	0.908
Racial origin			
White	22,234 (67.0)	16 (69.6)	0.969
Black	6,963 (21.0)	5 (21.7)	0.929
South Asian	1,756 (5.3)	2 (8.7)	0.793
East Asian	922 (2.8)	-	0.860
Mixed	1,304 (3.9)	-	0.665
Cigarette smokers	1,382 (4.2)	-	0.633
Conception			
Spontaneous	31,700 (95.5)	16 (69.6)	<0.0001
Ovulation induction drugs	229 (0.7)	-	0.689
In vitro fertilization	1,250 (3.8)	7 (30.4)	<0.0001

Parity			
Nulliparous	16,027 (48.3)	15 (65.2)	0.157
Parous	17,152 (51.7)	8 (34.8)	0.157
Nuchal translucency >95th percentile	1,512 (4.6)	3 (13.0)	0.147

Table 1. Maternal and pregnancy characteristics of the study population.

Data presented in n (%) or median (interquartile range). RAA = Right aortic arch; DAA = Double aortic arch.