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Prevalence and Outcome of Absence of Ductus Venosus at 11^{+0} to 13^{+6} Weeks

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Key Words
Agenesis of ductus venosus · Nuchal translucency · First-trimester screening · Prenatal diagnosis

Abstract
Introduction: To examine the prevalence and outcome of absent ductus venosus (DV) diagnosed at 11–13 weeks' gestation. ***Method:*** Prospective screening study for aneuploidies in 65,840 singleton pregnancies, including measurement of nuchal translucency (NT) thickness and examination of the DV. Prenatal findings and outcome of fetuses with absent DV were examined. ***Results:*** Absent DV was diagnosed in 26 cases giving a prevalence of 1 in 2,532. In 15 (57.7%) cases the NT was above the 95th centile for crown-rump length. In 11 (42.3%) cases, there was an aneuploidy, mainly Turner syndrome. The incidence of aneuploidies was 66.7% (10 of 15) for those with NT above the 95th centile and 9.1% (1 of 11) in those with normal NT ($p = 0.015$). In addition to the aneuploidies, there were 3 cases with other abnormalities, including one case each of Ebstein anomaly, Noonan syndrome and Pierre Robin sequence. In 9 of the 11 (81.8%) fetuses with NT below the 95th centile, absent DV was an isolated finding and the pregnancies resulted in healthy live births. ***Conclusion:*** The prognosis of fetuses with absent DV depends on the measurement of NT thickness, being poor if the NT is increased and good if the NT is normal.

Introduction

The ductus venosus (DV) plays an important role in the fetal circulation because it diverts oxygenated blood from the placenta towards the right atrium and through the foramen ovale to the left heart and thereafter the brain [1]. Previous studies have examined pregnancy outcome in fetuses with absent DV diagnosed during the second and third trimester of pregnancy (table 1) [2–27]. In the combined data from 26 reports on a total of 110 cases, about 40% had associated defects and aneuploidies. In the pregnancies with isolated absent DV, about 35% resulted in termination or perinatal death. However, this high prevalence of associated defects and adverse outcome may be exaggerated because the diagnosis of absent DV may have been the consequence of referral to specialist centres of fetuses with suspected abnormalities.

The aim of this study was to examine the prevalence of absent DV and the outcome of affected fetuses in a large population of pregnancies undergoing routine ultrasound examination at 11^{+0} to 13^{+6} weeks of gestation.

Methods

This was a prospective study in singleton pregnancies undergoing first-trimester screening for aneuploidies at King's College Hospital, London, the Fetal Medicine Centre, London, and Med-

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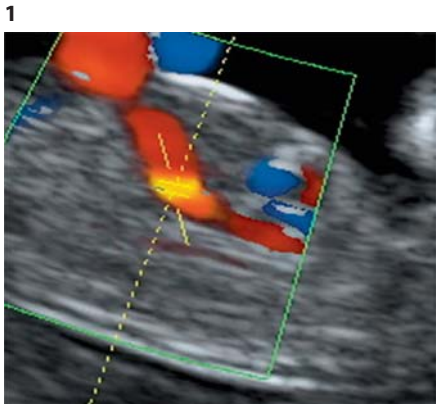

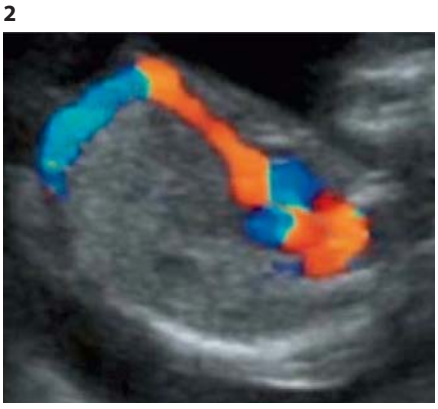

Fig. 1. Ultrasound picture of a 12-week fetus demonstrating a normal DV with the typical yellowish aliasing above the umbilical sinus.
Fig. 2. Ultrasound picture of a 12-week fetus demonstrating absence of the DV.

way Maritime Hospital, Gillingham, UK, between March 2006 and September 2009. In this visit, which was held at 11^{+0} to 13^{+6} weeks of gestation, maternal characteristics and medical history were recorded, an ultrasound scan was performed transabdominally (using 3–7.5 MHz curvilinear transducers), and at King's College Hospital and the Fetal Medicine Centre, maternal blood was also taken for measurement of serum free β-hCG and PAPP-A [28]. The ultrasound examination included assessment of gestational age from the measurement of the fetal crown-rump length (CRL) [29], basic anatomical examination for the diagnosis of any major fetal abnormalities [30], estimation of patient-specific risk for aneuploidies by measurement of fetal NT thickness [31], and assessment of flow across the DV [32, 33].

Examination of the DV was undertaken during fetal quiescence, the image was magnified so that the fetal thorax and abdomen occupied the whole screen, a right ventral mid-sagittal view of the fetal trunk was obtained and colour flow mapping was used to demonstrate the umbilical vein, DV and fetal heart [34]. The DV is characterized by a yellowish aliasing area which is the portion immediately above the umbilical sinus (fig. 1).

During the study period, the scans were carried out by one of 165 sonographers who had obtained the Fetal Medicine Foundation Certificate of Competence in the 11–13 weeks' scan or by trainees under the supervision of certified sonographers. All cases of suspected fetal abnormalities were examined by a fetal medicine specialist.

We searched the database to identify all cases of absent DV and examined their records to determine the prevalence of associated abnormalities and pregnancy outcome.

Results

During the study period, a first-trimester scan, including Doppler assessment of the DV, was carried out in 65,840 singleton pregnancies at a median gestation of 12^{+5} (range 11^{+0} to 13^{+6}) weeks. In 26 of these, there was absent DV giving a prevalence of 1 in 2,532. In the cases of absent DV, there was no systematic assessment of the neighbouring vessels to define the abnormal umbilical venous drainage.

The prenatal findings and outcome of the 26 cases of absent DV (fig. 2) are summarized in table 2 [35, 36]. In the cases where the pregnancy was terminated, the procedure was carried out at 12–13 weeks and it was not possible to undertake a pathological examination for confirmation of the diagnosis.

The fetal karyotype was abnormal in 11 (42.3%) cases, including 7 with Turner syndrome, 2 with trisomy 21, and 1 each of trisomy 18 and complex unbalanced rearrangement involving chromosomes 1, 2, 10 and 12. In the total population of 65,840 cases fetal aneuploidies were diagnosed either prenatally or postnatally in 657 cases, including 41 cases of Turner syndrome, 334 cases of trisomy 21, 113 of trisomy 18, and 169 with other aneuploidies. Therefore, absent DV was observed in 17.1% (7 of 41) with Turner syndrome, 0.6% (2 of 334) with trisomy 21, 0.9% (1 of 113) with trisomy 18 and 0.6% (1 of 169) with other aneuploidies. The incidence of aneuploidies was related to fetal NT thickness being 15.4% (2 of 13) for NT below 3 mm and 69.2% (9 of 13) for NT of 3 or more ($p = 0.015$; Fisher's exact test).

In the 15 euploid fetuses with absent DV, there was 1 case of Ebstein anomaly diagnosed prenatally and 1 case each of Noonan syndrome and Pierre Robin sequence where the diagnosis was made postnatally. In the 12 cases with isolated absence of the DV, there were 11 healthy live births and one miscarriage in a fetus with high NT.

Discussion

Assessment of the blood flow pattern across the DV at 11–13 weeks' gestation is useful in screening for fetal aneuploidies and major cardiac defects [33, 37]. Consequently, examination of the DV may become an integral part of the 11–13 weeks' scan which is now performed

Table 1. Reports on the findings of fetuses with absence of DV diagnosed in the 2nd and/or 3rd trimester of pregnancy and the outcome of the cases with isolated absence of DV

Author	Total	Defects (cardiac)	Aneuploidy			Isolated absence of DV			
			n	Turner	trisomy 21	n	alive	perinatal death	termination
Jouk et al., 1991 [2]	1	–	–			1	1		
Greiss et al., 1992 [3]	1	1 (–)	–			–			
Chaoui et al., 1994 [4]	1	–	–			1	1		
Jörgensen et al., 1994 [5]	4	1 (–)	–			3		1[a]	2
Moore et al., 1996 [6]	1	1 (1)	–			–			
Shih et al., 1996 [7]	1	–	–			1		1[a]	
Avni et al., 1997 [8]	1	–	–			1	1		
Cayol et al., 1997 [9]	1	–	–			1	1		
Cohen et al.,1997 [10]	1	–	–			1			1
Gembruch et al., 1998 [11]	2	1 (–)	1			1	1		
Achiron et al., 2000 [12]	4	–	–			4	2	1[a]	1
Hoffstaetter et al., 2000 [13]	5	1 (1)	1	1		4	4		
Hoppen et al., 2000 [14]	1	–	–			1	1		
Kiserud et al., 2000 [15]	1		–			1	1		
Contratti et al., 2001 [16]	10	2 (–)	2		1	8	5	3 (2[a])	
Langmann et al., 2001 [17]	1	1 (–)	–			–			
Jaeggi et al., 2002 [18]	12	7 (5)	–			5	4	1[a]	
Volpe et al., 2002 [19]	12	3 (2)	3	2		7	4	2[a]	1
Perles et al., 2003 [20]	1	–	–			1	1		
Sau et al., 2004 [21]	9	4 (3)	–			5	4	1	
Sothinathan et al., 2005 [22]	1	1 (–)	–			–			
Berg et al., 2006 [23]	23	14 (11)	4	1	1	8	6		2
Achermann et al., 2007 [24]	6	3 (1)	1		1	3	3		
Hajdu et al., 2008 [25]	3	1 (1)	–			2	1		1
Taddei et al., 2008 [26]	1	–	–			1	1		
Achiron et al., 2009 [27]	6	1 (–)	1		1	4	1		3
Total	110	42 (23)	13	4	4	64	43 (67.2%)	10 (15.6%)	11 (17.2%)

[a] Hydrops fetalis.

routinely in early screening for aneuploidies. The findings of this study demonstrate that firstly, at 11–13 weeks' gestation the prevalence of absent DV is about 1 in 2,500, secondly, in more than half of the cases, the fetal NT is above the 95th centile and in this group more than 40% of fetuses have chromosomal abnormalities, and thirdly, in most fetuses with NT below the 95th centile, absent DV is an isolated finding and the pregnancies result in healthy live births.

In previous reports, absent DV was most often an incidental finding in the second or third trimester following the detection of malformations or hydrops fetalis. In a study of 1,000 cases referred for fetal echocardiography because of suspected cardiac or extracardiac defects, there were 6 cases of absent DV (prevalence 1 in 166) [24].

In our series, 42% of fetuses with absent DV had aneuploidies and this is considerably higher than the prevalence of 12% in the combined data from previous reports of fetuses with absent DV diagnosed in the second and third trimester of pregnancy. In the majority of our fetuses with aneuploidies the NT thickness was very high and the most common aneuploidy was Turner syndrome. In the total population, absent DV was found in 17% of the fetuses with Turner syndrome and in less than 1% of

Table 2. Ultrasound findings, fetal karyotype and pregnancy outcome in the cases of absent DV

CRL mm	NT mm	Karyotype	Fetal abnormality	Follow-up		
				outcome	gestation, weeks	birth weight, g
51.7	1.4	normal	none	live birth	40	3,080
60.6	1.5	normal	none	live birth	40	3,500
54.6	1.5	normal	Ebstein anomaly	live birth	40	3,980
65.4	1.7	normal	none	live birth	39	3,178
60.0	1.7	normal	none	live birth	41	3,720
68.4	1.8	normal	none	live birth	41	3,489
58.0	1.9	normal	none	live birth	36	2,895
68.5	2.0	normal	none	live birth	38	3,377
75.4	2.1	normal	none	live birth	39	3,320
67.3	2.2	normal	none	live birth	39	3,500
77.1	2.2	trisomy 18	none	termination	14	–
48.3	2.5[a]	normal	none[b]	live birth	37	1,930[d]
52.7	3.0[a]	rearrangement	Dandy Walker malformation	miscarriage	14	–
58.8	3.8[a]	normal	none[c]	infant death	34	2,340
69.0	4.5[a]	normal	none	live birth	41	3,377
67.4	5.9[a]	turner	none	termination	13	–
68.1	6.2[a]	trisomy 21	atrioventricular septal defect	termination	13	–
45.1	6.7[a]	turner	coarctation of the aorta	termination	12	–
76.8	7.1[a]	trisomy 21	none	termination	13	–
60.1	7.3[a]	normal	none	live birth	39	–
62.3	7.9[a]	turner	coarctation of the aorta	termination	13	–
61.0	9.3[a]	normal	none	miscarriage	16	–
63.5	9.5[a]	turner	none	termination	13	–
54.9	9.9[a]	turner	none	termination	13	–
64.1	10.2[a]	turner	none	termination	13	–
62.5	10.9[a]	turner	coarctation of the aorta	termination	13	–

CRL = Crown-rump length; NT = nuchal translucency. [a] NT above the 95th centile for crown-rump length [35]. [b] Pierre Robin sequence. [c] Noonan syndrome. [d] Birth weight below the 10th centile for gestation [36].

fetuses with trisomy 21 or other aneuploidies. The most likely explanation for the higher prevalence of aneuploidies in our series compared to previous reports is that most affected fetuses die in the first or early second trimester. The prevalence of Turner syndrome is approximately 1 per 1,500 fetuses at 12 weeks and this decreases to 1 per 3,000 at 20 weeks [38].

In the combined data from previous reports, major cardiac defects were found in 20.9% (23 of 110) of the cases of absent DV, suggesting an association between these abnormalities. However, these findings may merely reflect that in many cases the primary indication for the detailed scan leading to the diagnosis of absent DV was the suspicion of a cardiac defect. In our euploid fetuses, one had Ebstein anomaly and it is not possible from such small numbers to suggest an association between absent DV and major cardiac defects. The same is true for Noonan syndrome which was diagnosed in one of our cases with high NT and was reported in one of the fetuses from the previous studies [19].

In pregnancies with apparently isolated absent DV, the prognosis is good with the live birth of appropriately grown normal babies. In our series of 12 such cases, there were 11 healthy live births and one miscarriage in a fetus with high NT. In the combined data from previous reports, 43 of the 64 cases with isolated absent DV resulted in healthy live births, but in 10 (15.6%), there was an intrauterine or neonatal death. The most likely explanation for such high perinatal mortality is the high frequency of hydrops fetalis in such cases which was the indication for the detailed scan leading to the diagnosis of absent DV.

In conclusion, the prognosis of fetuses with absent DV diagnosed at 11–13 weeks depends on the measurement of NT thickness, being poor if the NT is increased and

good if the NT is normal. In the increased NT group, there is a high incidence of chromosomal abnormalities and it is likely that the natural history of such aneuploid fetuses with very high NT is early miscarriage. In euploid fetuses with high NT, there is an increased incidence of cardiac defects, other abnormalities and genetic syndromes and in such cases the high NT in the first trimester evolves into hydrops fetalis during the second and third trimesters of pregnancy. This is the most likely explanation for the apparent discordance between our findings and those of previous reports on the associations and outcome of fetuses with absent DV.

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