Ultrasound Obstet Gynecol 2007; **30**: 254–258
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.4098

Reversed end-diastolic flow in the umbilical artery at 10–14 weeks of gestation is associated with absent pulmonary valve syndrome

C. BERG*, Y. THOMSEN*, A. GEIPEL*, U. GERMER† and U. GEMBRUCH*

**Department of Obstetrics and Prenatal Medicine, University of Bonn and †Department of Prenatal Medicine, University of Regensburg, Germany*

KEYWORDS: absent pulmonary valve syndrome; congenital heart disease; first trimester; hydrops; prenatal diagnosis; pulmonary regurgitation; reversed end-diastolic flow; tetralogy of Fallot; umbilical artery

ABSTRACT

Objective *To determine the incidence of reversed end-diastolic flow (REDF) in the umbilical artery in high-risk first-trimester pregnancies and evaluate associated conditions.*

Methods *This was a prospective evaluation of the umbilical artery Doppler waveforms of 614 consecutive high-risk pregnancies between 10 and 14 weeks of gestation, to determine those with REDF. The associated anomalies and characteristics of these fetuses were then investigated.*

Results *In 278/614 (45.3%) fetuses, there was positive end-diastolic flow in the umbilical artery; in 331/614 (53.9%) end-diastolic flow was absent and in 5/614 (0.8%) there was REDF. Three of the five fetuses with REDF had tetralogy of Fallot (TOF) with absent pulmonary valve syndrome (APVS) and a patent ductus arteriosus, and all three showed signs of cardiac failure, with reversed blood flow in the ductus venosus during atrial systole and generalized skin edema. Another fetus had a large ventricular septal defect and the remaining fetus had agenesis of the ductus venosus. Three fetuses had trisomy 18 and one had trisomy 13.*

Conclusions *REDF in the umbilical artery is very rare in early pregnancy and mostly occurs in association with major fetal vascular anomalies and cardiac defects, particularly TOF with APVS and patent arterial duct. We propose that the patency of the arterial duct in TOF with APVS leads to heart failure with subsequent demise early in pregnancy. Therefore, the frequent absence of the arterial duct observed in APVS in later pregnancy is more likely to be a result of early selection than a prerequisite for the development of this lesion as has been proposed previously.*

INTRODUCTION

Typically, Doppler flow velocity waveforms of the umbilical artery in uncomplicated early pregnancies show absent end-diastolic flow (AEDF) up to the 11th week of gestation[1]. Between the 11th and 14th weeks, positive diastolic flow emerges and remains detectable from then onwards[1]. Reversed end-diastolic flow (REDF) in the umbilical artery in the first trimester is very rare and previous reports have found a strong association with chromosomal anomalies, fetal heart defects, early onset growth restriction and an unfavorable prognosis in affected fetuses[2–9]. Here, we report on five further cases of REDF in the umbilical artery detected in first-trimester pregnancies, and describe their associated anomalies. Three of the five cases were associated with tetralogy of Fallot (TOF) with absent pulmonary valve syndrome (APVS) and a patent ductus arteriosus. This unusual combination of APVS with patency of the arterial duct has, to the best of our knowledge, never been reported in the first trimester, and offers important new aspects to the ongoing discussion on the pathogenesis of this rare heart defect.

METHODS

Over a 12-month period in a tertiary referral center, we investigated prospectively the umbilical artery blood flow in 614 consecutive high-risk pregnancies at 10–14 weeks of gestation (calculated from maternal last menstrual period and confirmed by sonographic fetal crown–rump length (CRL)). Patients were referred either due to an abnormal scan or because they were deemed to be high risk for aneuploidies or other fetal anomalies. Of the 614 fetuses, 33 had an abnormal karyotype diagnosed in the pre- or postnatal period (trisomy 21, $n = 14$; trisomy 18, $n = 7$; monosomy X, $n = 5$; trisomy 13, $n = 3$; triploidy,

Correspondence to: Dr C. Berg, Abteilung für Pränatale Medizin und Geburtshilfe, Zentrum für Geburtshilfe und Frauenheilkunde, Rheinische Friedrich-Wilhelms-Universität, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany (e-mail: christoph.berg@ukb.uni-bonn.de)

Accepted: 3 May 2007

$n = 2$; other, $n = 2$), and of these, 17 had cardiac defects that were diagnosed in the pre- or postnatal period (ventricular septal defect, $n = 5$; atrioventricular septal defect, $n = 4$; TOF, $n = 4$; coarctation, $n = 3$; common arterial trunk, $n = 1$). Five fetuses had cardiac defects without associated aneuploidy (ventricular septal defect, $n = 2$; atrioventricular septal defect, $n = 2$; coarctation, $n = 1$).

Biparietal diameter, CRL and nuchal translucency thickness (NT) were measured in each fetus. Increased NT was defined as being > 95th percentile of the normal range for CRL[10]. Echocardiography and Doppler sonography of the umbilical artery and ductus venosus were performed using transvaginal and transabdominal phased array transducers (5.0 and 7.5 MHz) with color and pulsed wave Doppler options (HDI 5000 ATL, Philips, Hamburg, Germany). During pulsed wave Doppler measurement of the umbilical artery blood flow, the angle of insonation was near 0° or 180° and the high-pass filter setting was low (100 Hz). In fetuses with AEDF, several consecutive measurements were performed.

A diagnosis of TOF with APVS was made on demonstration of a ventricular septal defect with overriding aorta (Figure 1) as well as to-and-fro blood flow over the pulmonary valve. We differentiated this from severe pulmonary regurgitation in the presence of a pulmonary valve by demonstrating relatively low velocities of the regurgitant flow over the pulmonary valve (Figure 2).

RESULTS

Of the 614 fetuses, 331 (53.9%) had AEDF, 278 (45.3%) had positive end-diastolic flow and five (0.8%) had REDF in the umbilical artery (Table 1). All five of the fetuses with REDF had NT > 95th percentile

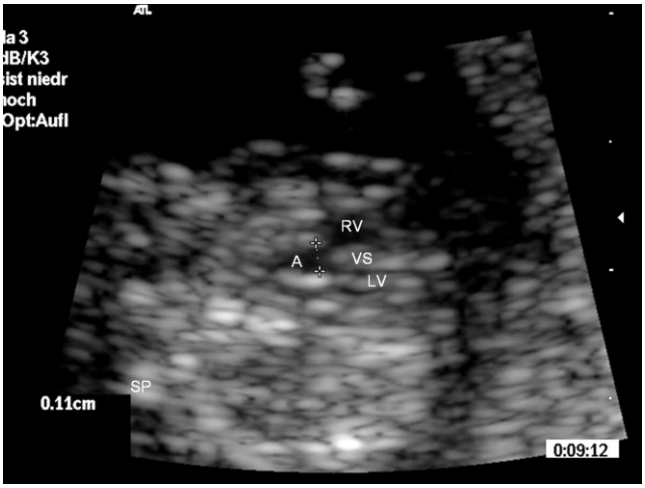

Figure 1 Five-chamber view in a fetus with trisomy 18, tetralogy of Fallot with absent pulmonary valve syndrome and patent ductus arteriosus at 10 + 3 weeks' gestation (Case 3). The anterior malalignment of the conal septum with overriding aorta (A) is demonstrated. Calipers mark the aortic value. LV, left ventricle; RV, right ventricle; SP, spine; VS, ventricular septum.

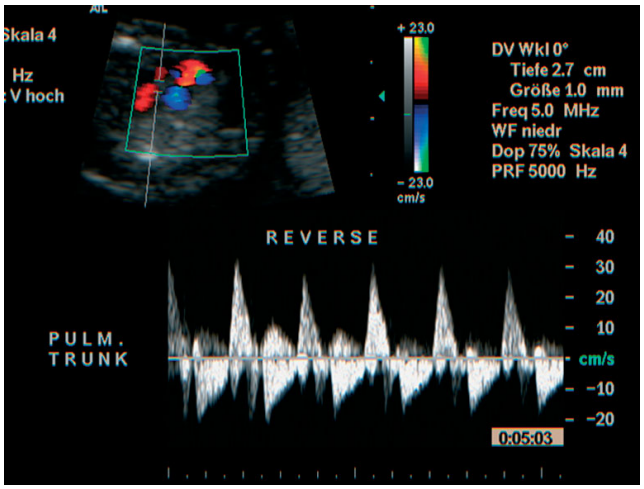

Figure 2 Doppler examination of the pulmonary valve in a fetus with trisomy 13, tetralogy of Fallot with absent pulmonary valve syndrome and patent ductus arteriosus at 12+3 weeks' gestation (Case 4). To-and-fro blood flow is demonstrated during systole and diastole, respectively. PULM, pulmonary.

(range, 2.6–12.0 mm) and generalized skin edema. Two had additional hydrothoraces. Chromosomal analysis revealed trisomy 18 in three of the five cases, trisomy 13 in one and a normal female karyotype in the other. Fetal heart defects were diagnosed in the four trisomic fetuses and the remaining fetus had agenesis of the ductus venosus with liver bypass and drainage of the umbilical venous blood flow directly into the inferior vena cava.

In two of the REDF fetuses with trisomy 18 and the one with trisomy 13, TOF with APVS and patent ductus arteriosus was diagnosed. These three fetuses showed severe pulmonary insufficiency throughout diastole, with to-and-fro flow in the pulmonary trunk, ductus arteriosus (Figure 3a,b), descending aorta (Figure 4a), middle cerebral artery (Figure 4b) and umbilical artery (Figure 4c). The venous blood flow velocities of these three fetuses showed pulsatile flow in the umbilical vein and reversed flow during atrial systole in the ductus venosus (Figure 4d). A ventricular septal defect was found in the third fetus with trisomy 18 that was not associated with APVS.

In four of the five REDF cases (three with trisomy 18 and one with agenesis of the ductus venosus), the parents decided to terminate pregnancy because of the unfavorable prognosis. The fifth case (a dichorionic twin pregnancy with trisomy 13 in one fetus and a normal cotwin), died *in utero* 7 days after chorionic villus sampling. In this fetus and another with trisomy 18 and TOF no autopsy was performed. In the other cases autopsy by a specialized pathologist comfirmed the prenatally diagnosed cardiac defects as well as the venous anomaly.

DISCUSSION

REDF in the umbilical artery between the 10th and 14th weeks of gestation is very rare; a total of 23 cases have been reported so far[2–9]. The associated conditions

Table 1 Clinical data and outcome of the five cases with reversed end-diastolic blood flow (REDF) in the umbilical artery

Case	GA (weeks)	Karyotype	NT (mm)	Sonographic findings	Umbilical artery	Ductus venosus	Outcome
1	12 + 6	47,XX,+18	7.8	VSD, tricuspid regurgitation, omphalocele, generalized hydrops, mild bilateral hydrothorax	PI, 5.77 RI, 1.35 REDF	PVIV, 1.63 PIV, 2.58 Reversed a-wave	TOP, autopsy
2	12 + 0	47,XY,+18	5.4	Tetralogy of Fallot with APVS but patent ductus arteriosus, single umbilical artery, generalized hydrops	PI, 6.50 RI, 1.44 REDF	PVIV, 2.50 PIV, 3.33 Reversed a-wave	TOP, autopsy
3	10 + 3	47,XY,+18	7.0	Tetralogy of Fallot with APVS but patent ductus arteriosus, single umbilical artery, generalized hydrops	PI, 14.03 RI, 1.55 REDF	PVIV, 2.00 PIV, 2.67 Reversed a-wave	TOP
4	12 + 3	47,XY,+13	2.6	Tetralogy of Fallot with APVS but patent ductus arteriosus, generalized hydrops	PI, 8.13 RI, 1.37 REDF	Not measured	IUFD
5	11 + 3	46,XX	12.0	Ductus venosus agenesis with liver bypass, generalized hydrops, mild left-sided hydrothorax	PI, 6.36 RI, 1.23 REDF	Agenesis	TOP, autopsy

APVS, absent pulmonary valve syndrome; GA, gestational age; IUFD, intrauterine fetal death; NT, nuchal translucency; PI, pulsatility index; PIV, pulsatility index for veins; PVIV, peak velocity index for veins; RI, resistance index; TOP, termination of pregnancy; VSD, ventricular septal defect.

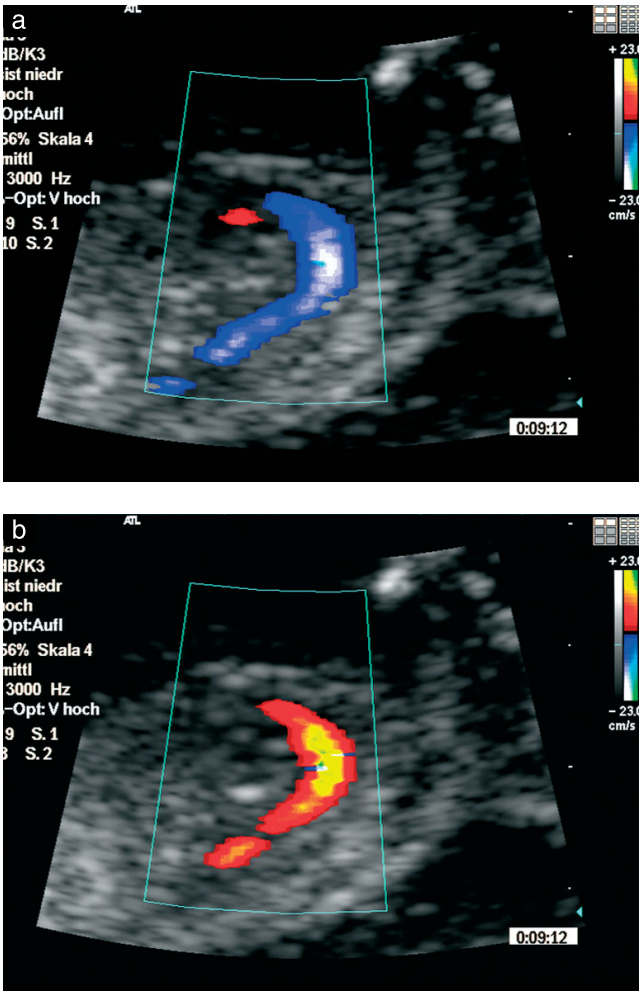

Figure 3 Longitudinal ultrasound image of the ductal arch in a fetus with trisomy 18, tetralogy of Fallot with absent pulmonary valve syndrome and patent ductus arteriosus at 10 + 3 weeks' gestation (Case 3). To-and-fro blood flow is demonstrated during systole (a) and diastole (b), respectively.

included 14 cases of chromosomal anomalies (six trisomy 18; three trisomy 13; five other aneuploidies), two cases with isolated cardiac defects (one pulmonary atresia; one atrioventricular septal defect), one VACTERL association and one early twin-to-twin transfusion syndrome, and there were five anatomically normal fetuses, of which two developed early onset growth restriction. Sixteen of these 23 cases were associated with increased NT. There were six terminations of pregnancy, 12 intrauterine deaths and one neonatal death; the only survivors were three of the anatomically normal children and one child with a Turner mosaicism.

Considering the variety of associated conditions in fetuses with REDF in the umbilical artery in the first trimester, the etiology is most likely multifactorial. Vascular anomalies and heart defects are a possible explanation for the altered flow velocity waveforms in four of the five cases in our present series. In the three cases of TOF with APVS, patent ductus arteriosus and non-restrictive ventricular septal defect, the altered arterial to-and-fro blood flow could be explained by the absence of 'Windkessel' function in the pulmonary trunk (the Windkessel effect is the recoil effect of large arteries that converts the pulsatile ejection of the heart into a steady flow) that results from the missing pulmonary valve as well as the large capacity of both ventricles. Fetuses like our Case 5, with absence of the ductus venosus and liver bypass, have been reported in previous studies[11–15] with high output cardiac failure due to chronic volume overload of the central venous system and the cardiac chambers, and could therefore also be associated with altered flow in the umbilical artery early in gestation. However, the ventricular septal defect in the remaining fetus with trisomy 18 in our cohort is unlikely to have caused the REDF. In this case it is more likely that the increased vascular impedance was due to a decrease

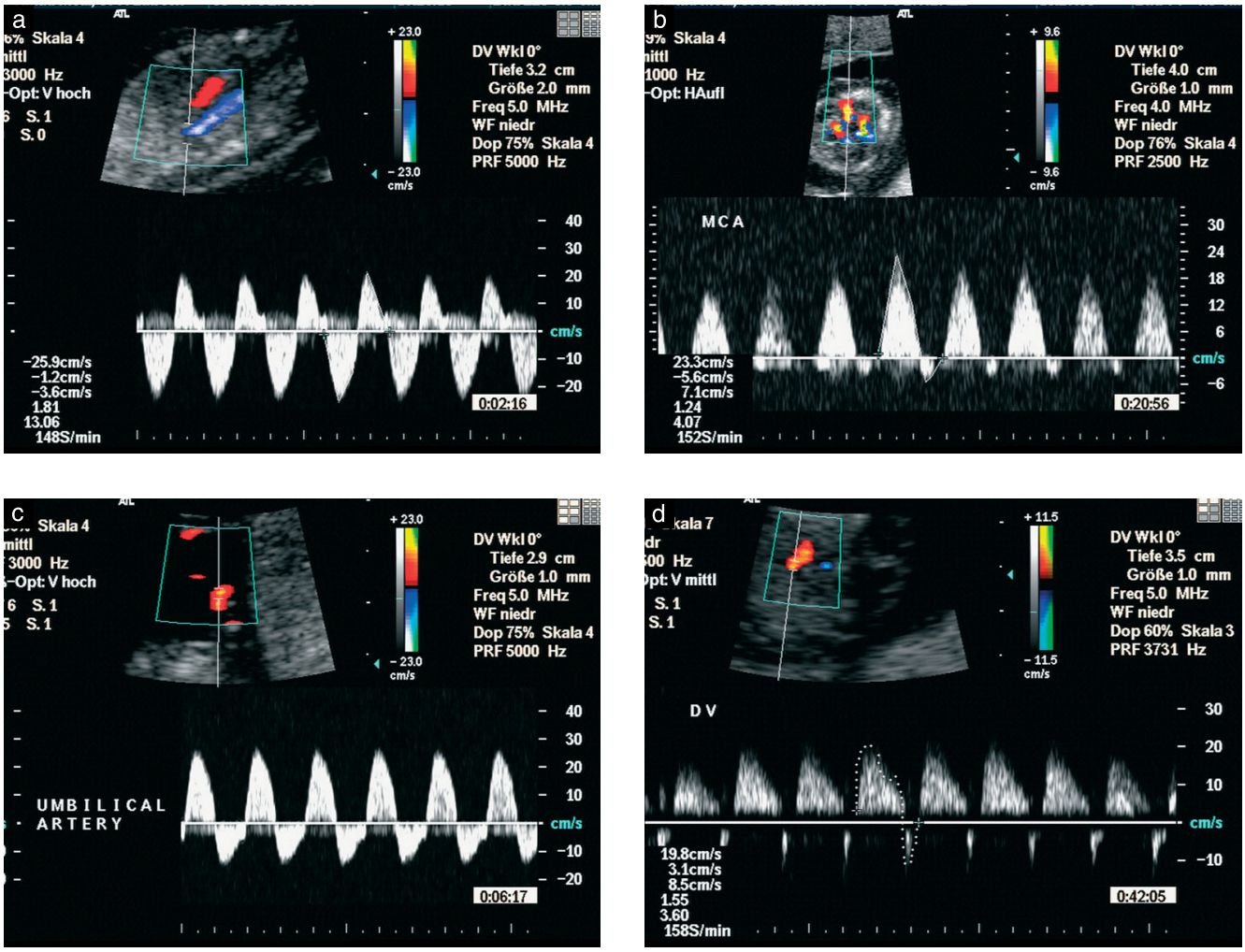

Figure 4 Doppler examination in a fetus with trisomy 18, tetralogy of Fallot with absent pulmonary valve syndrome and patent ductus arteriosus at 10 + 3 weeks' gestation (Case 3). Reversed flow during diastole is demonstrated in the descending aorta (a), middle cerebral artery (b) and umbilical artery (c), and reversed flow during atrial contraction is demonstrated in the ductus venosus (d).

in trophoblast invasion, as has been demonstrated in previous studies in aneuploid fetuses[16] and in fetuses that developed early-onset growth restriction in the further course of pregnancy[9].

Prenatal diagnosis of TOF with APVS is feasible and has been reported in four case series[17–19] and several case reports[20–22]. However, this defect is usually detected in the second half of pregnancy and has not yet been reported in the first trimester. In the second and third trimesters and postnatally, TOF with APVS only appears in combination with absence of the ductus arteriosus, except for rare cases in which the left pulmonary artery is discontinuous and supplied solely by the ductus arteriosus and in fetuses with intact ventricular septum[19]. In both situations, the volume of the pulmonary regurgitation is restricted.

Our observations in three fetuses with TOF and APVS combined with a patent ductus arteriosus in early gestation gives important insights into the pathogenesis of this disease. It was previously hypothesized that primary absence of the ductus arteriosus avoids adequate decompression of pulmonary high-resistance flow, may alter the development of the pulmonary valve apparatus and causes the additional widening of pulmonary trunk and pulmonary arteries typically seen in later fetal and neonatal life[23–25]. This theory, proposing that agenesis of the ductus arteriosus plays an important etiological role in the genesis of APVS, has been questioned by some[19,26,27]. They hypothesized that the non-restrictive ventricular septal defect in fetuses with TOF and APVS equalizes the pulmonary and aortic pressures and allows adequate decompression of pulmonary blood flow regardless of the presence or absence of the ductus arteriosus. These authors suggest that up to 80–90% of fetuses with TOF and APVS may have a ductus arteriosus, as is the case for TOF in general, but that this subset of fetuses miscarries early in gestation. In fetuses with TOF, APVS, patent ductus arteriosus and an unrestrictive ventricular septal defect, the regurgitant flow from the aorta through the ductus arterious and the absent pulmonary valve fills not only the right ventricle but also the left ventricle. This diastolic overload of both ventricles is probably incompatible with further fetal life and results in cardiac failure, hydrops and fetal death[19,26,27]. A possible additional mechanism causing fetal demise could be a significant diastolic run-off not only from the systemic vascular bed of the fetus but also from the critical

placental vascular bed, thus leading ultimately to fetal hypoxemia.

Our results show that, during the first and early second trimesters, TOF with APVS can be associated with a patent ductus arteriosus; therefore, a critical role of an absent ductus arteriosus in the genesis of APVS seems unlikely. Our findings support the hypothesis that agenesis of the ductus arteriosus is essential for primary fetal survival in fetuses with TOF and APVS[26,27]. The enormous volume load prevents survival of fetuses with APVS and a patent ductus arteriosus beyond the early second trimester, so only the subset of fetuses with agenesis of the ductus arteriosus can be found later in gestation. In contrast, TOF with APVS, patent ductus arteriosus and discontinuous left pulmonary artery is compatible with survival because only a minimal amount of aortic blood fills the ductus arteriosus and the left pulmonary artery. Similarly, in the rare case of APVS with intact ventricular septum, the regurgitant volume is limited to the right ventricle and this is therefore compatible at least with early survival. Apart from fetuses with absent ductus arteriosus, only these latter two groups can be detected in the second trimester, and they are eventually complicated by intrauterine death or hydrops later in gestation or result in severely ill neonates[17,18,28].

REFERENCES

1. Fisk NM, MacLachlan N, Ellis C, Tannirandorn Y, Tonge HM, Rodeck CH. Absent end-diastolic flow in first-trimester umbilical artery. *Lancet* 1988; **2**: 1256–1257.
2. Borrell A, Martinez JM, Farre MT, Azulay M, Cararach V, Fortuny A. Reversed end-diastolic flow in first-trimester umbilical artery: an ominous new sign for fetal outcome. *Am J Obstet Gynecol* 2001; **185**: 204–207.
3. Borrell A, Costa D, Martinez JM, Farre MT, Palacio M, Mortera C, Fortuny A. Reversed end-diastolic umbilical flow in a first-trimester fetus with congenital heart disease. *Prenat Diagn* 1998; **18**: 1001–1005.
4. Martinez Crespo JM, Comas C, Borrell A, Puerto B, Antolin E, Ojuel J, Fortuny A. Reversed end-diastolic umbilical artery velocity in two cases of trisomy 18 at 10 weeks' gestation. *Ultrasound Obstet Gynecol* 1996; **7**: 447–449.
5. Ariyuki Y, Hata T, Kitao M. Reverse end-diastolic umbilical artery velocity in a case of intrauterine fetal death at 14 weeks' gestation. *Am J Obstet Gynecol* 1993; **169**: 1621–1622.
6. Comas C, Carrera M, Devesa R, Munoz A, Torrents M, Cusi V, Ribas I, de la Iglesia C, Carrera JM. Early detection of reversed diastolic umbilical flow: should we offer karyotyping? *Ultrasound Obstet Gynecol* 1997; **10**: 400–402.
7. Montenegro N, Beires J, Leite LP. Reverse end-diastolic umbilical artery blood flow at 11 weeks' gestation. *Ultrasound Obstet Gynecol* 1995; **5**: 141–142.
8. Murta CG, Moron AF, Avila MA. Reversed diastolic umbilical artery flow in the first trimester associated with chromosomal fetal abnormalities or cardiac defects. *Obstet Gynecol* 2000; **95**: 1011–1013.
9. Bellver J, Lara C, Rossal LP, Remohi J, Pellicer A, Serra V. First-trimester reversed end-diastolic flow in the umbilical artery is not always an ominous sign. *Ultrasound Obstet Gynecol* 2003; **22**: 652–655.
10. 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. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998; **352**: 343–346.
11. Jaeggi ET, Fouron JC, Hornberger LK, Proulx F, Oberhansli I, Yoo SJ, Fermont L. Agenesis of the ductus venosus that is associated with extrahepatic umbilical vein drainage: prenatal features and clinical outcome. *Am J Obstet Gynecol* 2002; **187**: 1031–1037.
12. Contratti G, Banzi C, Ghi T, Perolo A, Pilu G, Visentin A. Absence of the ductus venosus: report of 10 new cases and review of the literature. *Ultrasound Obstet Gynecol* 2001; **18**: 605–609.
13. Volpe P, Marasini M, Caruso G, Lituania M, Marzullo A, Volpe G, Gentile M. Prenatal diagnosis of ductus venosus agenesis and its association with cytogenetic/congenital anomalies. *Prenat Diagn* 2002; **22**: 995–1000.
14. Sau A, Sharland G, Simpson J. Agenesis of the ductus venosus associated with direct umbilical venous return into the heart – case series and review of literature. *Prenat Diagn* 2004; **24**: 418–423.
15. Berg C, Kamil D, Geipel A, Kohl T, Knöpfle G, Hansmann M, Gembruch U. Absence of ductus venosus – importance of umbilical venous drainage site. *Ultrasound Obstet Gynecol* 2006; **28**: 275–281.
16. Drugan A, Johnson MP, Isada NB, Holzgreve W, Zador IE, Dombrowski MP, Sokol RJ, Hallak M, Evans MI. The smaller than expected first-trimester fetus is at increased risk for chromosome anomalies. *Am J Obstet Gynecol* 1992; **167**: 1525–1528.
17. Razavi RS, Sharland GK, Simpson JM. Prenatal diagnosis by echocardiogram and outcome of absent pulmonary valve syndrome. *Am J Cardiol* 2003; **91**: 429–432.
18. Volpe P, Paladini D, Marasini M, Buonadonna AL, Russo MG, Caruso G, Marzullo A, Arciprete P, Martinelli P, Gentile M. Characteristics, associations and outcome of absent pulmonary valve syndrome in the fetus. *Ultrasound Obstet Gynecol* 2004; **24**: 623–628.
19. Yeager SB, Van Der Velde ME, Waters BL, Sanders SP. Prenatal role of the ductus arteriosus in absent pulmonary valve syndrome. *Echocardiography* 2002; **19**: 489–493.
20. Becker R, Schmitz L, Guschmann M, Wegner RD, Stiemer B, Entezami M. Prenatal diagnosis of familial absent pulmonary valve syndrome: case report and review of the literature. *Ultrasound Obstet Gynecol* 2001; **17**: 263–267.
21. Sleurs E, De Catte L, Benatar A. Prenatal diagnosis of absent pulmonary valve syndrome in association with 22q11 deletion. *J Ultrasound Med* 2004; **23**: 417–422.
22. Fouron JC, Sahn DJ, Bender R, Block R, Schneider H, Fromberger P, Hagen-Ansert S, Daily PO. Prenatal diagnosis and circulatory characteristics in tetralogy of Fallot with absent pulmonary valve. *Am J Cardiol* 1989; **64**: 547–549.
23. Emmanoulides GC, Thanopoulos B, Siassi B, Fishbein M. "Agenesis" of ductus arteriosus associated with the syndrome of tetralogy of Fallot and absent pulmonary valve. *Am J Cardiol* 1976; **37**: 403–409.
24. Alpert BS, Moore HV. "Absent" pulmonary valve with atrial septal defect and patent ductus arteriosus. *Pediatr Cardiol* 1985; **6**: 107–111.
25. Fischer DR, Neches WH, Beerman LB, Fricker FJ, Siewers RD, Lenox CC, Park SC. Tetralogy of Fallot with absent pulmonic valve: analysis of 17 patients. *Am J Cardiol* 1984; **53**: 1433–1437.
26. Ettedgui JA, Sharland GK, Chita SK, Cook A, Fagg N, Allan LD. Absent pulmonary valve syndrome with ventricular septal defect: role of the arterial duct. *Am J Cardiol* 1990; **66**: 233–234.
27. Zach M, Beitzke A, Singer H, Hofler H, Schellmann B. The syndrome of absent pulmonary valve and ventricular septal defect–anatomical features and embryological implications. *Basic Res Cardiol* 1979; **74**: 54–68.
28. Galindo A, Gutierrez-Larraya F, Martinez JM, Del Rio M, Graneras A, Velasco JM, Puerto B, Gratacos E. Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve. *Ultrasound Obstet Gynecol* 2006; **28**: 32–39.

