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The 'question mark' sign as a new ultrasound marker of tetralogy of Fallot in the fetus

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KEYWORDS: congenital heart defects; pulmonary atresia with ventricular septal defect; tetralogy of Fallot; ultrasonographic marker; ultrasound screening

ABSTRACT

Objective *To describe a new ultrasonographic marker, the 'question-mark' sign, to assist in the diagnosis of tetralogy of Fallot (TOF) in the fetus, and to evaluate its prevalence in TOF as compared with other cardiac defects.*

Methods *A prospective evaluation over a 5-year period of a consecutive series of 3998 pregnant women undergoing fetal echocardiography from 12 to 40 weeks' gestation due to high risk for congenital heart disease (CHD). Standard echocardiographic planes with color Doppler assessment and evaluation of the whole aortic arch, from the left ventricular outflow tract to the descending aorta in the axial upper mediastinum views, were performed. The question-mark sign corresponded with an enlarged and dilated ascending aorta and aortic arch in the three-vessel view of the upper fetal mediastinum. The frequency of this sign was evaluated in cases with TOF and in other cases of cardiac defects, as well as in fetuses with normal cardiac scans in this series.*

Results *CHD was diagnosed in a total of 447 (11.2%) fetuses at a median gestational age of 24 (range, 12–40) weeks. Forty-two of the 447 (9.4%) had TOF, of which 29 cases (69.0%) had classical TOF (pulmonary stenosis), nine (21.4%) pulmonary atresia and four (9.5%) absent pulmonary valve syndrome. A question-mark sign was observed in 16/29 (55.2%) cases of classical TOF and in 8/9 (88.9%) cases of TOF with pulmonary atresia. The sign was never observed in any of the cases of TOF with a right-sided aortic arch. Likewise, the sign was observed in 1/405 (0.2%) cases with other cardiac anomalies (a fetus with a complex cardiac defect) and in none of the fetuses with normal hearts.*

Conclusions *The finding of an enlarged aorta with a question-mark shape should raise a strong suspicion of tetralogy of Fallot, in particular the variant with pulmonary atresia. This sign may be useful in screening considering that prenatal diagnosis of TOF by routine ultrasonography remains a challenge. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Tetralogy of Fallot (TOF) occurs in approximately 8–12% of infants with CHD[1–3]. TOF is frequently associated with chromosomal and extracardiac anomalies, and cases with severe obstruction of the pulmonary tract very often require assessment and treatment immediately after birth. Therefore, prenatal detection of TOF is critically important[4–8]. Unfortunately, the prevalence of TOF found in fetal series is much lower than that found in infant series[3,9], which indicates that TOF remains among the least diagnosed CHD during the prenatal period[2,4,10].

The use of key signs may be of great help in assisting in the identification of cardiac defects in fetal ultrasound screening. In our clinical experience, we have observed that fetuses with TOF often present a characteristic appearance of the ascending aorta in axial planes that strongly resembles a 'question-mark' ('?') sign; in fact, in most cases of TOF the question-mark sign was the first sign to suggest a cardiac defect. We have subsequently evaluated the frequency of this sign in our fetal cardiology unit during the last 5 years.

The aim of this study was to describe the question-mark sign as a potentially useful ultrasonographic marker to raise the suspicion of, or better document the diagnosis

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of, TOF in the fetus, and to evaluate its frequency in fetuses with TOF as compared with those with other cardiac defects and normal cardiac scans.

METHODS

This was a prospective study performed on all fetuses referred to our fetal cardiology unit because of the presence of risk factors for CHD, from January 2004 to January 2009. Gestational age at examination ranged between 12 and 40 weeks on the day of the examination, as determined by first-trimester fetal crown–rump length measurement. The study protocol was approved by the local ethics committee and all patients provided oral consent for the use of the images for clinical studies.

All patients underwent a detailed ultrasound scan in our fetal cardiology unit, which operates as a referral center for pregnancies at high risk for CHD. Obstetricians experienced in evaluating the fetal heart perform the fetal echocardiography, which includes standard planes with color Doppler assessment, obtained following the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology and others[11–13]. Briefly, the situs is checked at the abdominal level in an axial scanning plane through the stomach, aorta and inferior vena cava. Then, visualization of the four-chamber view (with atria, atrioventricular valves and ventricles), the origin and double-crossing of the great arteries, and systemic and pulmonary venous return is performed in a segmental approach. Finally, the three vessels and trachea view is obtained axially at the level of the upper mediastinum, as described by Yagel *et al.*[11]. Color Doppler to review normal flow at the level of the four chambers, the atrioventricular and semilunar valves, the interventricular and interatrial septa, and the ductal and aortic arches, is also routinely performed. Pulsed Doppler and M-mode are only used if indicated. The reliability of CHD diagnosis is always assessed by postnatal examination by pediatric cardiologists, or by autopsy in cases of termination of pregnancy or perinatal death.

For the purposes of this study the aortic arch was assessed from the left ventricle outflow tract to the descending aorta in the axial upper mediastinum view. The question-mark sign was defined, in a fetus in cephalic position with posterior spine, as a typical sonographic shape of the ascending aorta and aortic arch in axial planes, almost at the level of the three vessels and trachea view, showing a very enlarged and dilated aorta, with a striking shape resembling a question mark (Figure 1). In this same sonographic plane, color Doppler was found to be very helpful for differentiating between classical TOF with pulmonary stenosis (antegrade flow in the short arm of the question-mark sign) and TOF with pulmonary atresia (retrograde flow) (Figure 2). The presence or absence of the question-mark sign was part of the standardized protocol and was included as an item in a check-list.

We measured the frequency of the question-mark sign in cases with TOF and analyzed the association with left/right aortic arch and with the degree of pulmonary obstruction. For each diagnosis of TOF, three experienced examiners (O.G., M.B. and J.M.M.) reached a consensus on the presence or absence of the question-mark sign. The frequency of the sign in other cardiac defects and in normal cardiac scans was also recorded. The data were stored in research databases and standard statistical analysis was performed using SPSS 14.0 (SPSS, Chicago, IL, USA).

RESULTS

During the 5-year study period a consecutive series of 3998 fetuses at high risk for CHD underwent echocardiography in our fetal cardiology unit. The median maternal age was 31 (range, 16–40) years and the median

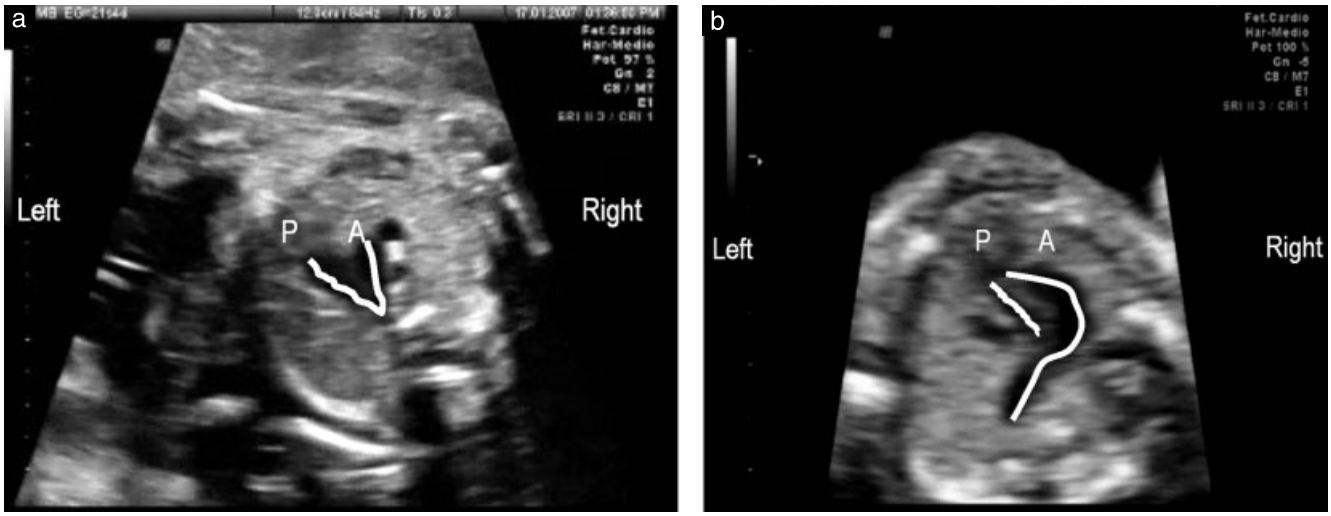

Figure 1 (a) Normal three vessels and trachea view, with both pulmonary artery and aorta showing similar size and a confluent shape ('V-shape'). (b) The 'question-mark' sign in a case of classical tetralogy of Fallot. The aorta is significantly larger than the pulmonary trunk, and resembles a question mark in shape. A, aorta; P, pulmonary artery.

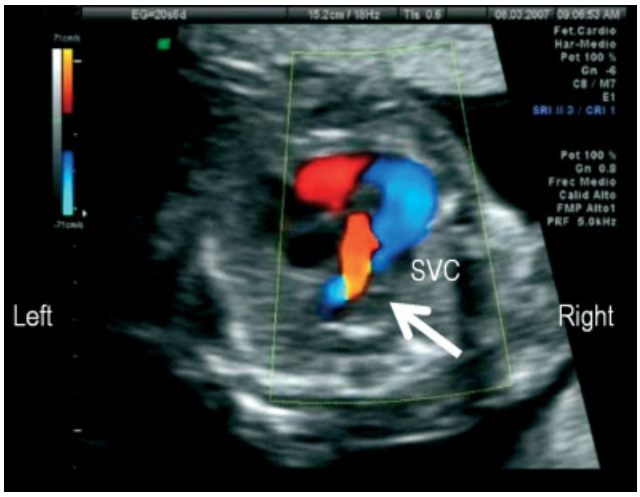

Figure 2 The 'question-mark' sign in a case of tetralogy of Fallot with pulmonary atresia. Both the trachea (arrow) and the superior vena cava (SVC) are positioned normally to the right of the aorta. Color Doppler echocardiography demonstrates retrograde flow (red) in the whole pulmonary artery, from the outflow tract to the ductus arteriosus, while antegrade flow (red then blue) is shown in the whole aortic arch.

gestational age at ultrasound examination was 21 (range, 12–40) weeks.

Complete follow-up was obtained in 98.2% of the pregnancies, among which 447 fetuses with CHD were identified, with an incidence of 11.2%. In this group a total of 42 (9.4%) cases were diagnosed with TOF. Among those were 29 cases (69.0%) with classical TOF (pulmonary stenosis), nine (21.4%) with pulmonary atresia and four (9.5%) cases of absent pulmonary valve syndrome. A right aortic arch was diagnosed in eight of the 29 cases (27.6%) with classical TOF and in one of the nine (11.1%) with pulmonary atresia. Termination of pregnancy was performed in 24 cases (57.1%) at parental request because of the presence of associated structural or chromosomal anomalies (including four cases of 22q11 microdeletion). The prenatal diagnosis of TOF was confirmed in all 42 cases, either by postnatal evaluation or by necropsy.

The prevalence of the question-mark sign in the whole population and with regard to the type of anomaly and the side of the aortic arch is summarized in Table 1. Overall, the question-mark sign was found in 24/42 (57.1%) fetuses diagnosed with TOF, of which 16/29 (55.2%) were in fetuses with classical TOF and 8/9 (88.9%) were in fetuses with TOF and pulmonary atresia. The sign was not present in any of the nine (21.4%) cases in which the aortic arch was right sided (Figure 3). Therefore, if only cases with left-sided aorta are considered, the detection rate was 76.2% (16/21) for classical TOF and 100% (8/8) for pulmonary atresia.

The question-mark sign was observed in none of the 3551 fetuses with a normal cardiac scan and in 1/405 (0.2%) fetuses with cardiac anomalies other than TOF. This case was a fetus with a complex cardiac malformation consisting of tricuspid and pulmonary atresia with a large perimembranous ventricular septal defect. Thus, the positive predictive value of the question-mark sign for the diagnosis TOF was 96.0% (24/25) in this series.

Table 1 Prevalence of the 'question-mark' ('?') sign in the studied population with regard to the type of anomaly and the side of the aortic arch

Fetal heart	n	*'?' absent (n (%))*	*'?' present (n (%))*
Normal	3551	3551 (100)	0
CHD	447	422 (94.4)	25 (5.6)
TOF	42	18 (42.9)	24 (57.1)
Type of TOF			
PS-TOF	29	13 (44.8)	16 (55.2)
PA-TOF	9	1 (11.1)*	8 (88.9)
AbsP-TOF	4	4 (100)	0
Side of aortic arch			
TOF + RAA	9	9 (100)	0
TOF + LAA	33	9 (27.3)	24 (72.7)
Other CHD	405	404 (99.8)	1 (0.2)†

*Case with right aortic arch. †Complex malformation: pulmonary and tricuspid atresia with a large perimembranous ventricular septal defect. AbsP, absent pulmonary valve; CHD, congenital heart disease; LAA, left aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RAA, right aortic arch; TOF, tetralogy of Fallot.

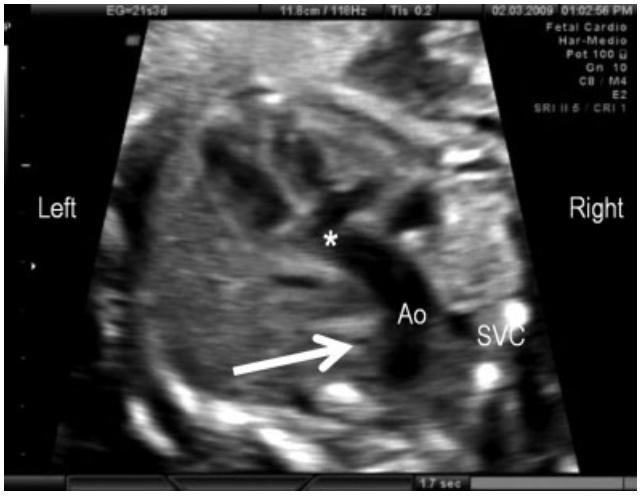

Figure 3 Absence of the 'question-mark' sign in a case of tetralogy of Fallot with pulmonary atresia and right aortic arch, showing the malaligned ventricular septal defect with the overriding aorta (*). The trachea is located to the left of the aorta (arrow) while the superior vena cava is normally placed to the right of the aorta. Ao, aorta; SVC, superior vena cava.

DISCUSSION

Our investigation has shown that the finding of an enlarged aorta with a marked '?' shape at the mediastinum level can be considered as a valuable marker for improving the detection of TOF in the fetus; the sign was found to be particularly associated with the variant of TOF with pulmonary atresia. The question-mark sign was never observed in cases with right aortic arch, in which the

aorta always follows a straight anteroposterior trajectory due to its right disposition with respect to the trachea.

TOF is a cardiac malformation characterized by an anterior aorta overriding a subaortic ventricular septal defect, caused by malalignment between the infundibular and the trabecular septum, and obstruction of the right outflow tract with varying severity. Consequently, there is hypertrophy of the right ventricle, but it is not usually patent after birth. The prenatal diagnosis of TOF remains a challenge, with detection rates as low as 15–40%[7,9,14]. A main reason for this low detection rate is that the four-chamber view in TOF is usually unremarkable in the majority of cases[4–7], apart from a leftward deviation of the cardiac apex[15,16]. Likewise, in cases of TOF with absent pulmonary valve the four-chamber view may demonstrate some degree of cardiomegaly, although this is not a constant feature in the second trimester[17,18].

The diagnosis of TOF cannot be made unless the outflow tracts are evaluated, thus the aorta overriding a ventricular septal defect has to be demonstrated[4–6,19–21]. Once a suspicious diagnosis has been arrived at, color Doppler sonography can be used to demonstrate either antegrade or reversed flow through the pulmonary outflow tract and arterial duct. Importantly, the severity of the pulmonary obstruction may evolve during pregnancy. Thus, pulmonary stenosis, which can be absent at the time of diagnosis in the second trimester, may become evident later on in gestation. In addition, in some cases a narrow pulmonary outflow may progress to atresia, which entails a significantly worse prognosis for the newborn[22]. Serial ultrasound monitoring is therefore warranted in order to detect retrograde flow through the pulmonary artery late in gestation, thus warning of the need for prostaglandin therapy immediately after birth[4–6,15–17].

Although comprehensive fetal echocardiography may detect most cases of TOF, such an examination cannot be routinely offered in most settings because it is time-consuming and requires advanced knowledge of cardiac anatomy and substantial sonographic skills. That is the reason why any effort to improve the prenatal detection of TOF should be encouraged, and several authors have suggested the inclusion of other sonographic planes or measurements of aortic and pulmonary artery diameters[11,23]. The addition of the direction of flow by color Doppler examination provides further support for the establishment of normal outflow tract examination and complements the four-chamber view[24]. The findings of this study suggest that the question-mark sign could constitute an additional marker that might help to raise the suspicion of, or confirm the diagnosis of, TOF during the standard anomaly screening examination, given that the sonographic demonstration of an overriding aorta has proved to be difficult. However, it is important to emphasize that sequential examination of the heart, paying particular attention to the origin of the aorta from the left ventricle, cannot be replaced by observation or not of the question-mark sign.

Since morphology of the vessels and functional hemodynamic abnormalities are closely related, we hypothesize that a possible explanation for the '?' shape might be the presence of increased flow through the overriding aorta together with reduced flow through the pulmonary valve. This hypothesis is consistent with the fact that the question-mark sign was not observed in any case of TOF with absent pulmonary valve, in which there is high to-and-fro flow through the right outflow tract. However, we acknowledge that we do not have a clear explanation for the fact that the sign was not present in any other conotruncal anomaly – such as truncus arteriosus or double outlet right ventricle – in which similar patterns of outflow tract hemodynamics may be found, so other factors may be related to the anatomical morphology of the vessels. On the other hand, in cases of TOF with a right aortic arch the straight course of the aorta seems logical and is most probably forced by the anatomical position of the aorta to the right of the trachea, thus precluding observation of the '?' shape.

The major drawback of our study is that it was performed in a high-risk population by experts in fetal echocardiography. It remains an open question whether observation of the question-mark sign is reproducible enough in other settings. In our opinion, the fact that the sign was found to be obvious in most of the cases with TOF supports the potential contribution of the question-mark sign during non-specialized examination at universal screening.

To conclude, when exploring the fetal heart the finding of the question-mark sign at the three vessels and trachea view strongly suggests the presence of TOF in the fetus, particularly the form with pulmonary atresia, but not in the form with either pulmonary stenosis or absent pulmonary valve, nor in cases with right aortic arch. We suggest that the potential value of this sign for improving the prenatal diagnosis of TOF deserves to be further explored in the general screening population.

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