

## Editorial

# Fetal Cardiology, the Frontier of Pediatric Cardiovascular Medicine

## Cardiología fetal, la frontera de la medicina cardiovascular

Constancio Medrano-Lopez<sup>a,\*</sup> and Jean-Claude Fouron<sup>b</sup>

<sup>a</sup> Servicio de Cardiología Pediátrica, Hospital General Universitario Gregorio Marañón, Madrid, Spain

<sup>b</sup> Cardiologie Pédiatrique et Foetal, Hopital Sainte Justine, Montreal, Quebec, Canada

Article history:

Available online 13 June 2012

### INTRODUCTION

Over many years, researchers and clinicians in pediatric and fetal cardiology have undertaken the study of the cardiovascular system during the time from conception until birth. The fastest and most crucial cardiac and vascular developments take place during this period. In humans, the heart is formed and functional at 8 weeks of gestation. Cardiac malformations during gestation can be observed in 0.8% to 1% of neonates and altered development of the cardiac muscle or conduction tissue can lead to cardiomyopathy or arrhythmias. These alterations may be determined by the interaction of genetic or environmental conditions to which the fetus is subjected.

In this overview, we will cover the historical background leading to the birth of fetal cardiology, the present state of development of this relatively new clinical discipline, and a speculation on what can be expected in the near future.

### HISTORICAL DEVELOPMENT

Experimental and clinical investigations carried out in the second half of the twentieth century by pioneers in fetal physiology and pediatric cardiology established the basic physiological concepts of fetal circulatory dynamics such as the parallel disposition of the two ventricles, the presence of shunts, and elevated pulmonary vascular resistance contrasting with low placental resistance.<sup>1–4</sup> The major circulatory changes of the transitional period surrounding birth have also been described.<sup>5</sup> Parallel to these fundamental observations, ultrasound technology was progressively introduced in pediatric cardiology practice for noninvasive study of patients with acquired and congenital heart disease (CHD), starting with B-mode and followed by M-mode, real-time two-dimensional imaging, and Doppler technology (continuous, pulsed, and color). The application of the same technology to prenatal life was explored both in the experimental and clinical settings, rapidly<sup>6–8</sup> paving the way to fetal cardiology as it is known today. It must be emphasized, however, that echocardiography is just a tool; even the best echocardiographer is not a fetal cardiologist.

### CONTEMPORARY FETAL CARDIOLOGY

Today fetal cardiology is a subspecialty of pediatric cardiology. Working groups within national and supranational medical societies in Europe have published training recommendations for future fetal cardiologists.<sup>9</sup> The increasing number of associations, congresses, and symposia as well as scientific publications related to the fetal cardiocirculatory system confirms the pertinence of this subspecialty and reflects the vitality of clinical and fundamental research in this new field.

Fetal cardiology encompasses: *a*) the management of fetuses with CHD; *b*) fetal arrhythmias, and *c*) the exploration of fetal myocardial function and cardiocirculatory conditions in high-risk pregnancies.

### Management of the Fetus With Congenital Heart Disease

#### *Prenatal Screening for Congenital Heart Disease*

A cost-efficient screening program for prenatal identification of CHD calls for a certain number of prerequisites: first, all pregnant women should undergo ultrasound assessment between 14 and 20 weeks of pregnancy to detect suspicious signs of fetal morphological abnormalities. Only those with suspected CHD are referred to the fetal cardiologist. Second, a systematic cardiocirculatory assessment should be performed in all cases with higher risk of malformation. In some instances, especially with stenotic lesions, follow-up screenings are mandatory due to the risk of increase in the hemodynamic impact of the malformation; for instance, cases of moderate aortic stenosis diagnosed early in the second trimester may present left heart hypoplasia at the end of gestation. A minority of CHD cases, those at risk of immediate postnatal hypoxia or circulatory collapse, will need to be delivered in tertiary centers where pediatric and surgical specialists are on hand, as in the case of severe left or right heart stenosis or complete transposition of the great arteries. As could be expected, the major impact of this screening process in terms of improvement in postnatal morbidity and mortality is observed in this group of malformations.

Finally, it must be recognized that this screening approach is conceivable only in countries that have a public healthcare system with a skilled workforce and appropriate financial support. Interestingly enough, marked discrepancies in the success of this screening program have been observed within well-developed

\* Corresponding author: Juan Esplandiu 9 portal B, 6.º B, 28007 Madrid, Spain.  
E-mail address: [consmelu@yahoo.es](mailto:consmelu@yahoo.es) (C. Medrano-Lopez).

countries, with failure rates between 2.8% and 60% depending on the area evaluated.<sup>10</sup>

### *The Genetic Aspects*

Genetic counseling is a major part of fetal cardiology. In the presence of familial CHD, the risk of having a child with CHD increases from 0.8% to 4% and in some cases as high as 8%.<sup>11</sup> Some CHDs are associated with chromosomal syndromes such as atrioventricular (AV) canal with trisomy 21 or conotruncal anomalies with 22q11 deletion. For this reason, the study of the fetal karyotype, including deletions, with chorionic villous sampling or amniocenteses, is systematically recommended in routine assessment of fetuses with structural cardiac malformations. A family history of cardiomyopathy, especially in hypertrophic cases, may be due to gene mutations associated with sarcomeric proteins<sup>12</sup> whose inheritance is usually autosomally dominant (50% risk of transmission from a heterozygotic parent). Barth syndrome, an X-linked mutation in the *TAZ* gene, must be ruled out in the presence of a noncompacted cardiomyopathy.<sup>13</sup> Prenatal identification of conditions such as Marfan or Loeitz-Dietz syndrome darkens the prognosis of the associated aortic root dilation or valve anomalies found in the fetus.

### *Fetal Cardiac Intervention*

The approach for fetal cardiac intervention is guided by two principles: *a*) clear fetal benefits in the short term (avoiding in-utero or immediate postnatal death) or long term (changing the outcome of a progressive lesion such as stenosis causing ventricular hypoplasia), and *b*) no significant side effect to the fetus or to the pregnant mother. The indications and technical aspects of interventional catheterization in the fetus have been defined over the past decade.<sup>14</sup> Briefly, closed fetal intervention through puncture of the maternal abdomen, uterus, and the fetal ventricle with needles, transducers, guides, and small calibre balloon catheters allows dilatation of stenotic valves. This approach has been mostly advocated for critical aortic stenosis. Postnatal biventricular circulation has been shown to be maintained in those cases.<sup>15</sup> The criteria for choosing candidates for critical pulmonary stenosis or pulmonary atresia with an intact ventricular septum are more debatable, although there are series describing indications for the selection of fetuses.<sup>16</sup> One condition where interventional fetal catheterization has the greatest impact is the hypoplastic left heart syndrome with restrictive foramen ovale, a situation involving serious postnatal hypoxia and very poor outcomes after neonatal surgery (usually Norwood Stage I). The opening of the septum and/or placement of a stent reduces the left atrial pressure and increases pulmonary venous return, preventing neonatal acidosis prior to surgery. These techniques are currently performed in a few specific centers; they require expert multidisciplinary teams and, like other fetal interventions, are associated with a learning curve. Their long-term benefit remains to be demonstrated.

### *Information to the Parents*

If CHD is diagnosed, the critical counseling interview with the parents must be carried out with the utmost sensitivity. This is perhaps the least debated subject in forums or scientific publications. Meeting the parents nevertheless remains one of the most delicate aspects of fetal cardiology practice and certainly the one with major significance when final impacts of fetal cardiology are analyzed.

The cardiologist must present both the pre and postnatal prognosis of the disease. This information should be objective, based on local as well as other centers' experience. In extreme situations such as fetuses with complete AV block at 22 weeks of gestation and severe hydrops, an imminent exitus is easy to predict. On the other hand, as previously mentioned for aortic stenosis, it is sometimes difficult to predict the final morphological and hemodynamic pictures. The couple's ethical, moral, and religious convictions, especially the mother's, concerning the crucial decision on whether or not to continue with the pregnancy must always be taken into account, without forgetting compliance with the laws in different countries. If the heart disease is associated with other morbidities, especially neurological, this must be clearly stated. Consequently, this crucial information should be given by an experienced cardiologist, representing a multidisciplinary group of cardiologists, obstetricians, geneticists, cardiac surgeons, neonatologists, and other specialists who have studied the case from all perspectives. A meeting with the neonatologist and the surgeon should always be offered to the parents, and a social worker or a psychologist could also be involved, if needed.

### **Fetal Arrhythmias**

This is one of the most rewarding fields of fetal cardiology. In the great majority of cases, the cardiac morphology is normal. Some fetuses with sustained tachycardia (heart rate >180 bpm) could develop life-threatening cardiac failure. Successful conversion of those tachycardias to normal sinus rhythm is presently the rule, especially in absence of hydrops fetalis.

#### *Investigation of Fetal Arrhythmia*

Identification of the mechanisms of fetal arrhythmia is based on the chronological relationship between atrial and ventricular contractions. This identification can be achieved with Doppler techniques such as tissue velocity imaging<sup>17</sup> or more simply with simultaneous recording of superior vena cava/ascending aorta or pulmonary artery/pulmonary vein Doppler flow recordings.<sup>18,19</sup> In our experience, the superior vena cava/ascending aorta Doppler approach has provided a consistent dynamic marker of atrial (venous "A" wave) and ventricular (aortic flow) contractions, allowing reliable analysis of the mechanism underlying the arrhythmia. Three types of arrhythmia are observed<sup>18</sup>:

1. *Irregular rhythm*: mostly atrial ectopies; and rarely isolated ventricular ectopies. These arrhythmias are usually self-limited and do not require any therapy.
2. *Sustained bradycardia*: usually related to blocked atrial bigeminy. Rare cases of sustained sinus bradycardia or complete AV block can also be observed, the latter in the context of either a complex cardiac malformation or more frequently as an immune reaction due to anti-RO and anti-LA antibodies in a mother with Lupus.
3. *Tachyarrhythmia (5 types)*: type I, short ventriculo-atrial tachycardia due to a re-entrant phenomenon; type II, long ventriculo-atrial tachycardia most frequently caused by atrial ectopic tachycardia; type III, simultaneous onset of atrial and ventricular contraction proven to be junctional tachycardia; type IV, atrial flutter with a 2:1 AV block, and type V, rare cases of accelerated ventricular rhythm.

#### *Therapeutic Approaches*

Extensive experience has been gained with prenatal use of digoxin, sotalol, flecainide and amiodarone. Currently, a more

specific approach is usually adopted in the choice of antiarrhythmic agents, based on the underlying mechanisms.<sup>20</sup> In the presence of sustained tachycardia associated with advanced heart failure and fetal hydrops, the transmaternal therapy is less efficient due to the placental edema. If fetal immaturity precludes preterm delivery, cautious intravenous injection of the anti-arrhythmic agent either to the mother or directly into the umbilical vein is advocated. It must be remembered that with short ventriculo-atrial re-entrant tachycardia, atrial and ventricular contractions occur at the same time; the AV valves are then closed and the atrial systoles generate giant reverse venous waves and elevated mean central venous pressures. This specific dynamic feature results in earlier peripheral edema with hydrops fetalis and not necessarily myocardial failure.

Although well-established immune complete AV block due to elevated maternal RO and SSA antibodies is insensitive to corticosteroids, isolated cases of pending complete AV block (second-degree AV block associated with intermittent periods of complete AV block) respond to anti-inflammatory therapy.<sup>21</sup> The benefit of systematic administration of steroids in well-established, immune-related, complete AV block to reduce the myocardial inflammatory process is presently a subject of debate.<sup>22,23</sup>

#### Genetic Aspects

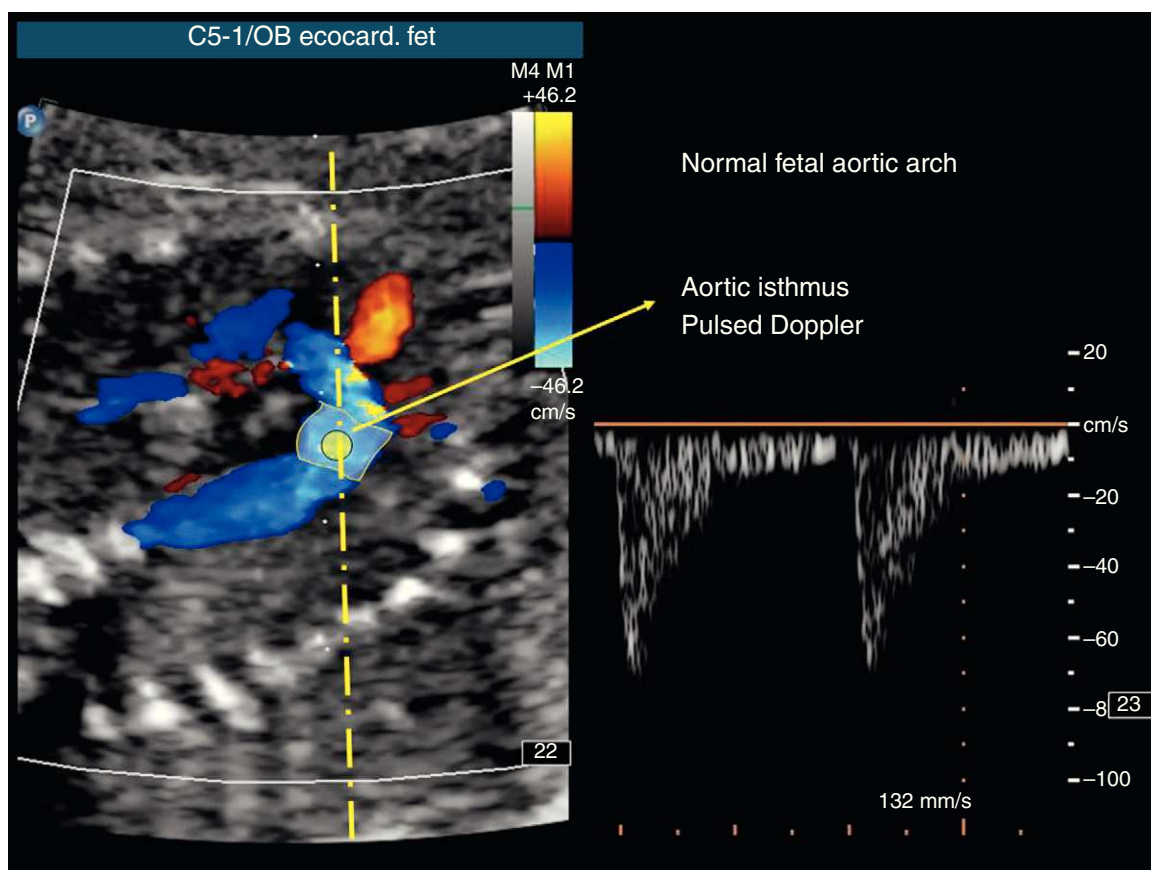
Channelopathies such as long QT syndrome, Brugada, and others are associated with autosomally dominant mutations. The identification of those mutations is especially useful for the prenatal prediction of postnatal clinical manifestations.<sup>24</sup> Recent

evidence of mutations in the gene encoding the pacemaker HCN4 ion channel has been detected in families with sinus bradycardia.<sup>25</sup> Finally, presence of prenatal myocardial rhabdomyoma justifies the search for gene mutations associated with late appearance of cerebral tuberous sclerosis.

#### Exploration of the Myocardial Function and Fetal Cardio-Circulatory Condition in High Risk Pregnancies

Echocardiography has not only served in detecting structural heart disease but has also been a fundamental tool in the assessment of fetal well-being. The cardiothoracic ratio, the systolic myocardial shortening fraction obtained with M-mode, as well as the diastolic filling pattern through the AV valves have been used in the functional assessment of the fetal heart with variable reproducibility. More consistent information on right ventricular compliance is obtained with the study of the depth of the "A" wave through the ductus venosus on Doppler flow recordings.

The myocardial performance index has also been applied in prenatal life for a more global functional cardiac evaluation;<sup>26</sup> this index is based on time intervals during the cardiac cycles. The fast fetal heart rate resulting in relatively short time intervals increases the margin of error in the calculation of the myocardial performance index. A cardiovascular profile score based on 5 distinct variables has been proposed.<sup>27</sup> Similarly, the pulsed Doppler of the aortic isthmus (Figure) between the origin of the left subclavian artery and the aortic end of the ductus arteriosus has been shown to provide reliable information on the peripheral fetal circulatory dynamics as well as the relative systolic performance of each



**Figure.** Fetal echocardiography image of aortic arch with color Doppler (left panel). Highlighted aortic isthmus with localization of pulsed Doppler and registry of normal velocities (right panel).

ventricle.<sup>28</sup> During fetal life, the aortic isthmus occupies a unique position, at a cross-road between the two parallel arterial systems. It represents the only shunt between the aortic and pulmonary arches as well as the supradiaphragmatic (towards the brain) and infradiaphragmatic (towards the placenta) circulations. Hence, any changes either in individual ventricular performance or in peripheral vascular resistances are reflected in the isthmus Doppler flow pattern. This new physiological concept has been found useful in clinical conditions such as intrauterine growth restriction, cardiac malformations, arrhythmia, maternal diabetes, among others.<sup>29,30</sup> Aortic isthmus Doppler is increasingly used in the evaluation of fetal hemodynamics by obstetrical sonographers.<sup>31–34</sup>

## THE FUTURE OF FETAL CARDIOLOGY

Fetal cardiology has become a dynamic subspecialty of fetal medicine. Future developments in this discipline will, in all likelihood, involve the following:

- Continuous integration of the latest echocardiographic techniques allowing the study of fetal cardiac mechanics. Normal patterns have been described in fetuses of different gestational ages with tissue Doppler.<sup>35</sup> With the speckle tracking technique, longitudinal and circumferential strains<sup>36</sup> are investigated, opening new fields for clinical monitoring of fetal heart disease and hemodynamic alterations. More research and publications will undoubtedly appear in this domain.
- Improvement in prenatal therapeutic approaches for complex cardiac CHD, which will probably be one of the major developments in the future of fetal cardiology. Fetal cardiac surgery via cardiopulmonary bypass or by fetoscopy techniques have so far not resulted in postoperative fetal viability. A more promising therapeutic perspective could be in the field of in vitro organogenesis, from cells collected in utero from a fetus with complex cardiac disease, who would then receive a normal immunocompatible heart after birth.
- Fetal arrhythmia is another field where the need for more specific anti-arrhythmic agents for fetal life is obvious. At least three drawbacks must be addressed: first, the relatively slow transfer of drugs through the placenta; second, a pharmaceutical adaptation to the specific electrophysiological characteristics of the immature heart, and third, absence of any side effects interfering with the development and maturing of other organs such as the thyroid or the brain. In this respect, instead of relying on steroids for the prevention of inflammatory reaction against anti-RO antibodies in a mother with lupus, immunological research might lead to the development of specific monoclonal antibodies blocking the anti-RO antigenic activities.
- Finally, in the near future, one can hope that fetal medicine, and more specifically fetal cardiology, will reach beyond national frontiers to populations with the highest rates of pre- and perinatal mortality. The need for an “International Society of Fetal and Perinatal Cardiovascular Disease” is obvious. This society should have multiple objectives, from the discussion of pre- and perinatal management of cardiovascular problems (not only structural heart disease) to the creation of a training program with special conditions for underprivileged countries. This training program should cover pre- and perinatal physiology and pathophysiology, various clinical conditions, and technical, genetic, and psychosocial aspects. “Thinkers” in ethics, philosophy, and sociology should be welcomed in this international society. This is where fetal cardiology, a specialty dependent on sophisticated technology, would display its most humanistic side, caring with compassion for both an unborn patient and his/her entire surrounding family.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

1. Rudolph AM. Distribution and regulation of blood flow in the fetal and neonatal lamb. *Circ Res*. 1985;57:811–20.
2. Dawes GS. The fetal circulation. In: Dawes GS, editor. *Fetal and neonatal physiology*. Chicago: Year Book Medical; 1968. p. 91–105.
3. Friedman WF. The intrinsic physiologic properties of the developing heart. *Prog Cardiovasc Dis*. 1972;15:87–111.
4. Hislop A, Reid L. Intrapulmonary arterial development during fetal life—branching pattern and structure. *J Anat*. 1972;113:35–48.
5. Teitel DF, Iwamoto HS, Rudolph AM. Effects of birth-related events on central blood flow patterns. *Pediatr Res*. 1987;22:557–66.
6. Allan LD, Tynan M, Campbell S, Wilkinson JL, Andersen RH. Echocardiographic and anatomical correlates in the fetus. *Br Heart J*. 1980;44:444–51.
7. Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H. Qualitative real-time cross-sectional echocardiographic imaging of the unborn human fetus during the second half of pregnancy. *Circulation*. 1980;62:799–806.
8. Huhta JC, Strasburger JF, Carpenter RJ, Reiter A, Abinadeet E. Pulsed Doppler fetal echocardiography. *J Clin Ultrasound*. 1985;13:247.
9. Allan L, Dangel J, Fesslova V, Marek J, Mellander M, Oberhansli I, et al.; Fetal Cardiology Working Group; Association for European Paediatric Cardiology. Recommendations for the practice of fetal cardiology in Europe. *Cardiol Young*. 2004;14:109–14.
10. Khoo NS, Van Essen P, Richardson M, Robertson T. Effectiveness of prenatal diagnosis of congenital heart defects in South Australia: a population analysis 1999–2003. *Aust N Z J Obstet Gynaecol*. 2008;48:559–63.
11. Thangaroopan M, Wald RM, Silversides CK, Mason J, Smallhorn JF, Sermer M, et al. Incremental diagnostic yield of pediatric cardiac assessment after fetal echocardiography in the offspring of women with congenital heart disease: a prospective study. *Pediatrics*. 2008;121:e660–5.
12. Hinton RB, Michelfelder EC, Marino BS, Bove KE, Ware SM. A fetus with hypertrophic cardiomyopathy, restrictive, and single-ventricle physiology, and a beta-myosin heavy chain mutation. *J Pediatr*. 2010;157:164–6.
13. Steward CG, Newbury-Ecob RA, Hastings R, Smithson SF, Tsai-Goodman B, Quarrell OW, et al. Barth syndrome: an X-linked cause of fetal cardiomyopathy and stillbirth. *Prenat Diagn*. 2010;30:970–6.
14. Mäkilä K, McElhinney DB, Levine JC, Marx GR, Colan SD, Marshall AC, et al. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. *Circulation*. 2006;113:1401–5.
15. Arzt W, Wertaschnigg D, Veit I, Klement F, Gitter R, Tulzer G. Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. *Ultrasound Obstet Gynecol*. 2011;37:689–95.
16. Gómez-Montes E, Herraiz I, Mendoza A, Albert L, Hernández-García JM, Galindo A. Pulmonary atresia/critical stenosis with intact ventricular septum: prediction of outcome in the second trimester of pregnancy. *Prenat Diagn*. 2011;31:372–9.
17. Nii M, Hamilton RM, Fenwick L, Kingdom JC, Roman KS, Jaeggi ET. Assessment of fetal atrioventricular time intervals by tissue Doppler and pulse Doppler echocardiography: normal values and correlation with fetal electrocardiography. *Heart*. 2006;92:1831–7.
18. Fouron JC. Fetal arrhythmias: the Saint-Justine hospital experience. *Prenat Diagn*. 2004;24:1068–80.
19. Carvalho JS, Perfumo F, Ciardelli V, Sairam S, Bhida A, Shinebourne EA. Evaluation of fetal arrhythmias from simultaneous pulsed wave Doppler in pulmonary artery and vein. *Heart*. 2007;93:1448–53.
20. Fouron JC, Fournier A, Proulx F, Lamarche J, Bigras JL, Boutin C, et al. Management of fetal tachyarrhythmia based on superior vena cava/aorta Doppler flow recordings. *Heart*. 2003;89:1211–6.
21. Raboisson MJ, Fouron JC, Sonesson SE, Nyman M, Proulx F, Gamache S. Fetal Doppler echocardiographic diagnosis and successful steroid therapy of Luciani-Wenckebach phenomenon and endocardial fibroelastosis related to maternal anti-Ro and anti-La antibodies. *J Am Soc Echo*. 2005;18:375–80.
22. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation*. 2004;110:1542–8.
23. Eliasson H, Sonesson S, Sharland G, Granath F, Simpson JM, Carvalho JS, et al. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation*. 2011;124:1919–26.
24. Horigome H, Nagashima M, Sumitomo N, Yoshinaga M, Ushinohama H, Iwamoto M, et al. Clinical characteristics and genetic background of congenital long-QT syndrome diagnosed in fetal, neonatal, and infantile life: a nationwide questionnaire survey in Japan. *Arrhythm Eletrophysiol*. 2010;3:10–7.
25. Milanese R, Baruscotti M, Gnecci-Ruscione T, DiFrancesco D. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. *N Engl J Med*. 2006;354:151–7.
26. Friedman D, Buoyon J, Kim M, Glickstein JS. Fetal cardiac function assessed by Doppler myocardial performance index (Tei Index). *Ultrasound Obstet Gynecol*. 2003;21:33–6.

27. Huhta JC, Paul JJ. Doppler in fetal heart failure. *Clin Obstet Gynecol.* 2010;53:915–29.
28. Fouron JC. The unrecognized physiological and clinical significance of the fetal aortic isthmus. *Ultrasound Obstet Gynecol.* 2003;22:441–7.
29. Fouron JC, Gosselin J, Raboisson MJ, Lamoureux J, Tison CA, Fouron C, et al. The relationship between an aortic isthmus blood flow velocity index and the postnatal neurodevelopmental status of fetuses with placental circulatory insufficiency. *Am J Obstet Gynecol.* 2005;192:497–503.
30. Zielinsky P, Frajndlich R, Nicoloso LH, Manica JL, Piccoli Jr AL, De Morais MR, et al. Aortic isthmus blood flow in fetuses of diabetic mothers. *Prenat Diagn.* 2011;31:1176–80.
31. Acharya G, Tronnes A, Rasanen J. Aortic isthmus and cardiac monitoring of the growth-restricted fetus. *Clin Perinatol.* 2011;38:113–25.
32. Figueras F, Benavides A, Del Río M, Crispi F, Eixarch E, Martínez JM, et al. Monitoring of fetuses with intrauterine growth restriction: longitudinal changes in ductus venosus and aortic isthmus flow. *Ultrasound Obstet Gynecol.* 2009;33:39–43.
33. Kennelly MM, Farah N, Turner MJ, Stuart B. Aortic isthmus Doppler velocimetry: role in assessment of preterm fetal growth restriction. *Prenat Diagn.* 2010;30:395–401.
34. Benavides-Serralde A, Scheier M, Cruz-Martínez R, Crispi F, Figueras F, Gratacos E, et al. Changes in central and peripheral circulation in intrauterine growth-restricted fetuses at different stages of umbilical artery flow deterioration: new fetal cardiac and brain parameters. *Gynecol Obstet Invest.* 2011;71:274–80.
35. Comas M, Crispi F, Gómez O, Puerto B, Figueras F, Gratacos E. Gestational age- and estimated fetal weight-adjusted reference ranges for myocardial tissue Doppler indices at 24–41 weeks' gestation. *Ultrasound Obstet Gynecol.* 2011;37:57–64.
36. Di Salvo G, Russo MG, Paladini D, Felicetti M, Castaldi B, Tartaglione A, et al. Two-dimensional strain to assess regional left and right ventricular longitudinal function in 100 normal foetuses. *Eur J Echocardiogr.* 2008;9:754–6.