



Fetal Arrhythmias: Genetic Background and Clinical Implications

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Abstract

Fetal arrhythmias are a common phenomenon of pregnancies. However, debates remain with regard to the etiologies and early treatment of choices for severe fetal arrhythmias. The gene regulatory networks govern cardiac conduction system development to produce distinct nodal and fast conduction phenotypes. The slow conduction properties of nodes that display automaticity are determined by the cardiac ion channel genes, whereas the fast conduction properties are regulated by the transcription factors. Mutations of genes specific for the developmental processes and/or functional status of cardiac conduction system including ion channel promoter (*minK-lacZ*), GATA family of zinc finger proteins (*GATA4*), the homeodomain transcription factor (*Nkx2.5*), the homeodomain-only protein (*Hop*) and the T-box transcription factors (*Tbx2*, *Tbx3* and *Tbx5*), hyperpolarization-activated cyclic nucleotide-gated channel 4 (*HCN4*) and connexins, may cause fetal arrhythmias. It is expected that development of investigational antiarrhythmic agents based on genetic researches on cardiac conduction system, and clinical application of percutaneously implantable fetal pacemaker for the treatment of fetal arrhythmias would come to true.

Keywords Arrhythmia · Fetus · Genetics

Introduction

Fetal arrhythmias occur in 1–2% of all pregnant cases [1, 2], and only 10% of the cases with morbidity or even mortality [3]. In high-risk after-midterm pregnancies, the incidence of fetal arrhythmias was 16.7% (33/198), and the most common arrhythmias were premature atrial contractions (PACs), followed by premature ventricular contractions (PVCs), paroxysmal supraventricular tachycardias (SVTs) and atrial fibrillations/flutterers [4]. PACs are frequently diagnosed during pregnancy, while SVTs, including atrial tachycardia, atrioventricular (AV) nodal reentrant tachycardias and circus movement tachycardias, are less frequently diagnosed. In contrast, malignant ventricular tachyarrhythmias, such as sustained ventricular tachycardias, ventricular flutters and ventricular fibrillations, may occur [5]. Strasburger et al. [6] systematically categorized fetal cardiac arrhythmias

into three types: ectopic contractions, tachyarrhythmias and bradyarrhythmias (Table 1). Currently, the most commonly used diagnostic method to evaluate these rhythm disturbances is fetal echocardiography including M-mode and pulsed Doppler imaging [2]. Fetal arrhythmias are mostly benign in nature and usually do not require therapy. In most fetuses, tachyarrhythmias resolve spontaneously or only require short-term administration of antiarrhythmics. Approximately one-third of these may recur later on, especially during adolescence [7]. However, rhythm surveillance is necessary in order to prevent from evolving into SVTs [3].

The origin of cardiac conduction system (CCS) has been recognized to originate from the primary heart tube, in which some genes express to prevent this part of myocardium to differentiate into pacemaking cell phenotype. However, the mechanisms of cardiomyocyte differentiation into either a working cell or a CCS cell phenotype are still undetermined. The transcription factors have been identified to regulate CCS development [8]. Molecular studies have revealed that genes specific for the developmental processes and (or) functional status of CCS include the ion channel promoter (*minK-lacZ*), the GATA family of zinc finger proteins (*GATA4*), the homeodomain transcription factor (*Nkx2.5*), the homeodomain-only protein (*Hop*), the T-box

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Table 1 Classification of fetal arrhythmias

Classification	Perinatal arrhythmia	Genetic or chromosomal abnormalities
Premature contraction	Premature atrial contraction; Premature ventricular contraction	— —
Tachyarrhythmia	Sinus tachycardia; Supraventricular tachycardia; Atrial flutter; Junctional tachycardia; Ventricular tachycardia	— — — — <i>LQT1</i> form of long QT syndrome
Bradyarrhythmia	Blocked atrial ectopy; Sinus bradycardia; Second-degree and complete atrio-ventricular block; Low atrial or junctional bradycardia	— <i>LQT1</i> form of long QT syndrome Morgagni–Adams–Stokes syndrome Holt–Oram syndrome

transcription factors (*Tbx2*, *Tbx3* and *Tbx5*), the hyperpolarization-activated cyclic nucleotide-gated channel 4 (*HCN4*) and connexins [9]. Moreover, the growth and differentiation factor neuregulin induces cardiomyocytes to a CCS phenotype by induction of ectopic CCS-lacZ expression [10]. Endothelin-1 other than neuregulin also shows differentiation of atrial derived cardiomyocytes into a pacemaking phenotype in murine embryonic stem cells [11]. Adenosine monophosphate (AMP)-activated protein kinase (*AMPK*) mutation modifies AV septation during cardiogenesis, leading to ventricular preexcitation as a result of presence of accessory pathways [12]. A novel mutation of *PRKAG2* gene in the γ_2 regulatory subunit of AMPK is responsible for some CCS disorders. In brief, the exact mechanisms of the cardiac structure and CCS to arrhythmogenicity have not been fully elucidated. The purpose of this article is to given an overview of the genetic and clinical aspects of fetal arrhythmias.

Genetic Backgrounds

Research works focusing on arrhythmogenicity of cardiac structures have helped the understanding of the mechanisms of cardiac arrhythmias. The pathway theories proposed by James representing a posterior pathway (along the crista terminalis), an anterior pathway (to the left atrium via Bachmann's bundle) and a medial pathway (in the interatrial septum) disclosed the specialized Purkinje-like and transitional cells based on histological studies primarily explained this phenomenon. Various cytokines found in different foci of the CCS inside the heart might be responsible for the conduction functions, for instance, the internodal tracts distinguished from the atrial myocardium in terms of expressions of the marker HNK1 may explain the underlying genetic backgrounds.

The origin of the CCS cells has become an issue of interest. In the past, cardiomyocytes were thought to originate from the cardiac neural crest cells. Nowadays, the

cardiomyocytes are considered derived from a common myogenic precursor in the embryonic tubular heart. It has been found that, in the process of cardiomyocyte differentiation into a working myocardial cell or into a CCS cell, multifactorial inheritance other than a single gene is involved, and the growth and differentiation factor neuregulin plays a pivotal role in inducing them into a CCS phenotype, indicated by ectopic CCS-lacZ expression [10]. Specific transcription factors with members of zinc finger transcription factor family (*GATA4*, *GATA6* and *HF-1b*), bHLH (*MyoD*), T-box (*Tbx5*) and homeodomain (*Msx2* and *Nkx2.5*) typically expressed in the cardiac conduction cells, such as the AV node, the Purkinje fibers and the His bundle [13]. Mutations of these genes link to the abnormalities of the CCS (Table 2). In experimental animals, the lethality was proved to be caused by genetic interactions of *GATA4* and *GATA6* with *Tbx5* in the CCS or due to abnormal contractile properties of the myocardium [14]. *Tbx5* is a T-box containing transcription factor that is critical for proper limb and heart development. *Tbx5* mutations that result in haploinsufficiency cause Holt–Oram syndrome, which is characterized by congenital heart defects, CCS abnormalities and upper-limb deformities [15].

The maturation of recently developed next-generation sequencing (NGS) technologies provides unprecedented sequencing capacity at dramatically lower cost, faster and more upgradable than other sequencing techniques. The NGS panels of fetal arrhythmias and their sensitivities are shown in Table 3. The price for an individual gene was \$690 and for a full panel was \$1670.00 [17].

Clinical Aspects

Premature Contractions

The majority of fetal arrhythmias are premature contractions. PVCs increased the risk to ventricular tachycardia and multiple PVCs usually increased the risk to PVTs.

Table 2 Genetic backgrounds of cardiac arrhythmias

Gene	Site of expression	Function	Typical cardiac phenotype
T-box family of transcription factors (<i>Tbx2</i> and <i>Tbx3</i>)	Cardiac inflow tract, atrioventricular canal, outflow tract and inner curvatures of the heart (putative slow conducting areas, His bundle and proximal part of the bundle branches)	Repress <i>Nppa</i> (<i>ANF</i>) and <i>Cx40</i> genes	Holt–Oram syndrome
<i>Homeodomain transcription factors</i> (<i>Nkx2.5</i>)	AV conduction system	Suppress <i>ANF</i> promoter activity in the AV canal	Heart block, ion channel disorders, impaired depolarization in slow conduction tissue (hypoplasia of the AV node and His bundle, significantly reduced number of peripheral Purkinje fibers)
<i>Homeodomain transcription factor</i> (<i>Msx2</i>)	Central CCS (but not the peripheral Purkinje fibers)	A downstream target of Pax-3/splotch	
<i>Homeobox gene</i> <i>Hop</i>	AV node, His bundle and bundle branches of the adult CCS		Conduction defects below the AV node
The GATA family of transcription factors/zinc finger subfamilies	Adult and embryonic heart; Purkinje fibers (<i>GATA4</i>); atrioventricular CCS and AV node (<i>cGATA6</i>)		Cardiac dysmorphogenesis with early embryonic mortality
<i>Mink</i> gene (also known as <i>IsK</i> and <i>KCNE1</i>)	Electrical currents in the heart	Encoding protein modifying HERG and KvLQT1	Jervell-and Lange-Nielsen syndrome cardiac delayed rectifier currents <i>Ikr</i> and <i>Iks</i> (congenital long QT syndrome)
Cardiac conduction system (CCS)- <i>lacZ</i> gene Connexins	Developing conduction system of the heart Fast conducting cardiac tissues and in the atria (<i>Cx40</i>); slower conducting working myocardium of the atria and ventricles, and in the distal part of the conduction system (<i>Cx43</i>); slow conducting pathways and in the myocardium of the primary heart tube (<i>Cx45</i>)	Correlation with electrical activation Electrical and metabolic coupling between cells	Sinoatrial conduction defects (<i>Cx40</i>); sudden cardiac death from spontaneous ventricular arrhythmias (<i>Cx43</i>)
<i>PRKAG2</i> gene	Regulation of cardiac ion channels [12]	AV conduction	Ventricular preexcitation Heart block Wolff–Parkinson–White syndrome
<i>Cardiac voltage-gated sodium channel α-subunit gene</i> (<i>SCN5A</i>)	To drive the initial depolarization phase of the cardiac action potential and determine conduction of excitation [16]	Regulate sodium current and repolarization	Congenital long QT and Brugada syndromes
AV atrioventricular, CCS cardiac conduction system			

Table 3 NGS technologies for fetal arrhythmias [17–19]

Clinical indication	Genes	Sensitivity (%)
Arrhythmogenic right ventricular dysplasia	<i>CTNNA3, DES, DSG2, DSC2, DSP, JUP, LDB3, LMNA, PKP2, PLN, RYR2, TGFB3, TMEM43, TTN</i>	~73
Short QT syndrome	<i>KCNH2, KCNQ1, KCNJ2</i>	15–20
Long QT syndrome	<i>AKAP9, ANK2, CACNA1C, CALM1, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, NOS1AP, SCN4B, SCN5A, SNTA1</i>	~80
Brugada syndrome	<i>CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND3, KCNE1L, KCNE3, KCNH2, KCNJ8, RANGRF, SCN1B, SCN2B, SCN3B, SCN5A, SSCN5A, TRPM4</i>	20–35
Sick-sinus syndrome	<i>HCN4, MYH6, SCN5A</i>	
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	<i>RYR2, CASQ2, CALM1</i>	~52–60

Wloch et al. [20] reported 128 fetuses with PACs, 34% of which were benign. Most PAC cases have no genetic cause. However, some authors reported that PACs represented 22.2% (2/9) of a small fetal arrhythmia cohort next to SVT (66.7% (6/9)). They noted that PACs could also be a manifestation of Costello syndrome due to *HRAS* mutations [21]. In a clinical study involving 702 arrhythmic fetuses, 306 had an irregular rhythm, 298 (97.4%) of which had isolated premature contractions. PACs with first- or second-degree heart block or long PR duration were found in 3 (1.0%) cases at 23-, 28- and 32-week gestations, respectively. Many have aneurysmal septum primum with septum bowing and mechanical initiation of the PACs, and 1–2% of fetal cases of premature contractions were associated with other conditions, such as long QT syndrome or first- or second-degree heart block, or positivity of maternal SSA antibodies [22].

Respondek et al. [23] reported that 96% of the fetal arrhythmic cases had PACs as evidenced by fetal echocardiography at a mean of 34-week gestation. The fetal heart was structurally normal in most cases, and tricuspid valve regurgitation and atrial septal aneurysm were present in 14% cases each. Sole regular echocardiographic monitoring was applied in 86% of the cases and pharmacotherapy with digoxin, verapamil, or both was required in 14%.

Fetal PVCs were less common than PACs. Fetal echocardiogram is recommended to assess cardiac structure and function and to determine the mechanism of the arrhythmia in fetuses with isolated PACs and multiple ectopic beats (bigeminy, trigeminy, or more than every 3–5 beats on average) [24]. PACs may be associated with congenital heart defects. They are usually benign and often resolve spontaneously, but follow-up is warranted for monitoring the development of ventricular tachycardia [3].

Fetal PVCs can be associated with cardiomyopathy, cardiac tumors, long QT syndrome, electrolyte imbalances and complete heart block with slow ventricular escape rhythm. Most fetal isolated PVCs usually disappear spontaneously before birth. Fetuses with sustained PVCs may usually

resolve within 6 weeks. They usually do not cause more complicated arrhythmias [25].

Tachyarrhythmias

Fetal tachyarrhythmias typically include SVT, atrial flutter and ventricular tachycardia. Krapp et al. [26] reported that SVT accounted for 73.2% and atrial flutter accounted for 26.2% of fetal tachyarrhythmias. Hydrops fetalis was present in 38.6% and 40.5% of fetuses with atrial flutter and SVT, respectively. Fetal atrial flutter can be serious and fatal, especially in those with hydrops fetalis [27]. SVTs are frequently complicated by fetal congestive heart failure or even fetal death [3]. Idiopathic monomorphic ventricular tachycardia is probably caused by stationary vortex-like reentrant activity, while non-stationary reentry may be responsible for polymorphic ventricular tachycardia and ventricular fibrillation [28]. Timely prenatal pharmacotherapeutic intervention is generally advised to return it to sinus rhythm with an adequate heart rate [3].

The exact mechanism of fetal SVT was difficult to determine with Doppler magnetocardiogram, but currently Doppler myocardial deformation analysis is available for the diagnosis [29]. Mechanisms of SVT can be classified as AV reentrant, intraatrial reentrant and AV nodal reentrant [30, 31]. These three types of SVTs accounted for 73%, 14% and 13% of the cases, respectively, as reported by Ko et al. [30]. Kannankeril et al. [32] obtained similar results in their study of fetal tachycardias.

Spontaneous resolution of SVT may occur *in utero*, during delivery, or after birth. There have been no definite regimens, and the treatment of choice is controversial. Digoxin is the first-line drug of choice in treating fetal SVTs in many centers; and in other centers, flecainide or procainamide has been used as a first-line agent, but its use is limited due to its higher pro-arrhythmic activity and its fetal-negative inotropic actions, which may exacerbate hydrops fetalis [33–35]. Sotalol, a β -adrenergic antagonist, is effective for the treatment of SVT in fetuses with or without hydrops

fetalis [29, 36]. Digoxin and combined digoxin and sotalol or flecainide were very successful for the treatment of fetal SVTs [37–39]. Parilla et al. [40] employed, in eight hydropic fetuses, maternal intravenous administration (MIV) of digoxin or a combination of fetal intramuscular (FIM) digoxin and MIV with a mean duration of antiarrhythmic therapy of 9.6 ± 5.9 weeks, and achieved a shorter conversion time and a better conversion effect into sinus rhythm. Most recently, Wacker-Gussmann et al. [41] emphasized the importance of continuous monitoring of fetal tachyarrhythmias by fetal magnetocardiography. They recommended that sotalol was better than digoxin for fetal atrial flutter in conjunction with SVT, and that digoxin and (or) amiodarone were effective in restoring into sinus rhythm or decreasing the heart rate, but for the latter, the conversion rate was low. Fetal antiarrhythmic therapy can be associated with a much better survival in comparison to those without treatment (5–10% vs. 27–50%) [29].

Bradyarrhythmias

Heart Block with Maternal Autoantibodies or Fetal Cardiac Structure Anomaly

Fetal bradycardias may develop in the condition of fetal hypoxia [1], congenital heart defects [42], maternal systemic lupus erythematosus or Sjögren syndrome [43], maternal autoantibodies to SSA/Ro and (or) SSB/La ribonucleoproteins [43], or with an unknown etiology [44]. Fetal complete heart block in a structurally normal heart is frequently associated with maternal anti-Ro/SSA and anti-La/SSB autoantibodies with an incidence of 2% [45]. Lee et al. [46] recommended a close echocardiographic monitoring of fetal heart block to prevent from progression into complete heart block, and they also shared their successful experiences of treating fetal first-degree heart block by dexamethasone. Perín et al. [47] reported a fetus whose mother was with positive anti-Ro and anti-La antibodies presented with alternative tachy- and bradycardias. The baby required postnatal pacemaker implant.

Jaeggi et al. [48] described 59 cases of fetal heart block with 24 (41%) having major congenital heart defects, 18 of which were left isomerism and 3 were transposition of the great arteries. Lopes et al. [49] reported a similar finding, showing that 59 of 116 (50.9%) cases of fetal heart block were associated with major structural heart disease, mainly left atrial isomerism. Miyoshi et al. [50] described 29 cases of fetal bradyarrhythmia associated with congenital heart defects and noted that the fetuses had a higher mortality rate, particularly in the context of fetal myocardial dysfunction and hydrops fetalis, irrespective of *in utero* treatment with ritodrine hydrochloride. Vesel et al. [51] reported a continuous infusion of isoprenaline failed to raise the very

low ventricular rate of a fetus with complete heart block; thus, a permanent ventricular rate modulated pacing endocardial pacemaker was implanted a few hours after birth. Donofrio et al. [24] reported two cases of fetal complete heart block. An early delivery was suggested for worsening cardiovascular conditions, and an epicardial pacemaker was implanted early after birth in both cases. Fetal heart block in relation to cardiac structural defects denotes poor prognosis and left atrial isomerism displays the highest mortality. Dismal effects were seen even with pacing or supportive treatments [44].

Sinus Bradycardia, Sinus Node Dysfunction (Ion Channelopathies and Long QT Syndrome) and Low Atrial and Junctional Rhythm (NKX2.5, HCN4, SCN5A and Left Atrial Isomerism, etc.)

The most common early manifestation of fetal long QT syndrome was sinus bradycardia, seen in fetuses of <25-week gestation, while other fetal arrhythmias associated with fetal long QT syndrome, between 28- and 40-week gestations [52]. The cardiotocogram study revealed persistent fetal sinus bradycardia was associated with long QT syndrome in 71% of the cases [53]. The diagnosis of fetal sinus bradycardia is feasible by revealing a prolonged QT interval by magnetocardiography [53]. It has been recognized that long QT syndrome is caused by delayed repolarization of the ventricular cells due to a decreased repolarizing current and (or) an increased depolarizing current [54]. Cuneo et al. [55] found, in fetal long QT syndrome, 18% polymorphic ventricular tachycardia resembling Torsades de Pointes. They proposed that early afterdepolarizations was the cause of Torsades de Pointes in such cases. Mutations of genes encoding potassium channels (*KCNQ1*, *KCNH2*, *KCNE1* and *KCNJ2*, etc), encoding sodium channels (*SCN5A* and *SCN4B*) and encoding calcium channels (*CACN1C*, *CACN2B* and *CACN2D1*) might be responsible for the development of long QT syndrome [54]. Long QT syndrome or other cardiac channelopathy warrants an electrocardiogram and genetic screening [56]. Change et al. [57] reported a case of fetal long QT syndrome underwent successful postnatal administration with the potassium channel opener nicorandil, by shortening the QT interval and improving the outcome. In addition, transplacental lidocaine could effectively treat fetal heart block and terminate ventricular tachycardia [55].

Sinus node dysfunction is most frequently caused by the presence of congenital defect and sinoatrial node deficiency. Patients with sinus node dysfunction may be asymptomatic or with tachy- or bradycardia. Bravo-valenzuela [58] reported a case of fetal bradycardia with sinus node dysfunction, in whom severe bradycardia developed after birth and surgical pacemaker implant was required.

Left atrial isomerism is characterized by “a large azygos continuation of an interrupted inferior vena cava, heart block and viscerocardiac heterotaxy on echocardiography” [59]. In some fetuses, persistent sinus or low atrial bradycardia may be present. A short PR interval bradycardia usually denotes a low atrial rhythm, as seen in left atrial isomerism due to the absence of the sinus node. Fetal sinus bradycardia and low atrial bradycardia usually demonstrate heart rate reactivity. However, either sinus or low atrial bradycardia does not need any specific treatment and is usually with no hemodynamic compromise after birth [44]. The prognosis of fetal junctional rhythm is also good. Wakai et al. [60] reported a case of fetal junctional rhythm associated with respiratory arrhythmia disclosed by fetal magnetocardiography, and the baby recovered to normal sinus rhythm at 10 days of life.

Blocked Atrial Bigeminy

Differential diagnostic criteria between blocked atrial bigeminy and heart block have drawn much attention regarding the distinct management policies. Blocked atrial bigeminy may persist for hours but is clinically benign with no need of treatment, while fetal complete heart block without structural heart disease has a better prognosis, which is mainly related to the transplacental passage of maternal autoantibodies directed to fetal Ro/SSA ribonucleoproteins [1]. Blocked atrial bigeminy can be a marker of a reentry pathway, which might cause tachycardia in 6–12% of cases [61]. A heart rate of <60 beats/min suggests the probable diagnosis is third-degree heart block [61]. Eliasson et al. [61] proposed the concept of “interval between two conducted atrial beats (acb/acc)”, which clearly differentiated fetal blocked atrial bigeminy from second-degree heart block: intermittent blocked atrial bigeminy was diagnosed at 21–40-week gestation and the acb/acc ratio was <0.35, whereas in cases with second-degree heart block, the ratio was 0.50. Wiggins et al. [62] proposed to distinguish blocked atrial bigeminy from 2:1 heart block by ectopic P wave on fetal magnetocardiography. Blocked atrial bigeminy usually resolves spontaneously in most fetal cases without the need of treatment; however, close rhythm monitoring is necessary to prevent it from developing into severe dysrhythmias [62]. In a fetus reported by Martucci et al. [47], blocked atrial bigeminy was evolving into SVT *in utero*. After birth, the baby required lanoxin syrup and subsequently sotalol, and the baby's condition was then improved.

Fetal echocardiography may disclose the mechanism of fetal arrhythmias and help in decision-making of antiarrhythmic therapy [63]. The maternal steroid therapy for fetal heart block is controversial. Breur et al. [64] summarized the steroid treatment (with prednisone or prednisolone, and with additional dexamethasone in two cases) of fetal heart block in 43 fetuses, the effective rate was 80%, while in

18% cases, complete heart block persisted in spite of steroid treatment, and in 2%, second-degree heart block during fetal life became first-degree at birth. Jaeggi et al. [65] reported that 22 fetuses with fetal complete heart block were treated with dexamethasone in 21 cases and with β -stimulation in 9 cases for an average of 7.5 weeks. The patients treated with dexamethasone had a much higher 1-year survival rate than those without (90% vs. 46%, $p < 0.02$).

Ion Channelopathies

A genetic linkage has been found between ion channel gene mutations and long QT syndrome, and the major genes that have been found are *KCNQ1*, *KCNH2* and *SCN5A* [66]. Inherited arrhythmogenic syndromes caused by ion channel dysfunctions at membrane level (mutations in protein-encoding genes with gain or loss of function) may lead to life-threatening arrhythmias, syncope and sudden death [67]. Research showed that the 470+ allelic mutations induce loss of function in the passage of mainly potassium ions, and gain-of-function in the passage of sodium ions through their respective ion channels. The resultant early afterdepolarizations could lead to a polymorphic form of cardiac bradycardia [68]. Addison et al. [69] examined the postmortem muscle or heart tissue samples from 46 unexplained stillbirths. In total 11 variants, three in *LQT* genes (*AKAP9*, *KCNJ2* and *KCNE2*) and four in GWAS genes (*BAZ2B*, *RYR2*, *TRPM7* and *CAV2*) were predicted to be functionally damaging. Dysfunction of the cardiac L-type calcium channel $Ca_v1.2$ and de novo $Ca_v1.2$ missense mutation *G406R* cause prolonged calcium ion current, delayed cardiomyocyte repolarization and an increased risk of arrhythmia [70]. CPU 86017, a new derivative of berberine, exerts its blockade directly on the ion channel itself [71].

Familial Bradyarrhythmia

Family bradycardia is associated with mutations of the pacemaker channel gene *hHCN4*, which contributes to negative *f*-channel in the sinoatrial node [72]. *S672R* mutation in the cAMP-binding domain of HCN4 is a direct cause of familial bradycardia or arrhythmia [73]. Familial bradycardia is rarely reported in fetal cases. In a case of postnatal bradycardia with syncope due to severe bradyarrhythmia, implantation of a permanent ventricular demand pacemaker was indicated. His family history was positive in five persons of four generations for bradyarrhythmias. A high-grade heart block and ST–T changes in precordial leads recorded in all affected family members suggested familial conduction abnormality [74]. A case of fetal bradycardia at a heart rate of 50 beats/min noted at 28-week gestation persisted until 42-week gestation when an asymptomatic male baby was delivered. Electrocardiography at 3 weeks of age revealed an incessant

atrial fibrillation with slow ventricular response. He continued to be asymptomatic; however, at 16 year of age, a heart rate of 23 beats/min and pauses of up to 6 s warranted an endocardial pacing system of a ventricular rate modulated pacing program. He seemed to have a good prognosis [75].

Familial forms of primary sinus bradycardia have sometimes been attributed to mutations of *HCN4*, *SCN5A* and *ANK2*, but mutations of *HCN4* ion channel gene may be associated with cardiac structural anomalies [76]. A basic study in mouse revealed that *HCN4* was a novel target for posttranscriptional repression by miR-423-5p and the training-induced downregulation of *HCN4*, and the bradycardia was a result of upregulated *Nkx2.5* and consequently miR-423-5p in the sinus node [77]. *Tbx5* mutations can be a mechanism of Holt–Oram syndrome and responsible for the associated long QT syndrome, while *SCN5A* mutations cause Brugada syndrome [78].

Bradyarrhythmias can be benign and requires no treatment; however, acute unstable bradycardia can lead to cardiac arrest. Management of bradycardia is based on the severity of symptoms, the underlying causes, the presence of adverse signs, and the risk of progression to asystole. Pharmacologic therapy and (or) pacing is used to manage unstable or symptomatic bradyarrhythmias [79].

Basic Science

The T-type calcium channels are normally expressed in fetal ventricular myocytes. Basic research revealed that the T-type calcium channel currents were enhanced in hypoxic conditions, thereby disturbing the cardiac contraction pattern and leading to occurrence of arrhythmias [80]. When the dominant-negative form of neuron-restrictive silencer factor transgenic mice (dnNRSF-Tg) was treated with efonidipine or mibefradil, the selective T-type calcium channel antagonists, by reversing depolarization of the resting membrane potential, the incidence of sudden death and arrhythmogenicity in mice was significantly reduced [81].

Animal experiments in a passive antibody transfer model by using several different rat strains and major histocompatibility complex (MHC)/non-MHC congenics revealed that intraperitoneal injection of the Ro52 monoclonal antibody (7.8C7) was associated with significant PR prolongation and that both fetal MHC and non-MHC genes regulated susceptibility to complete heart block, determining the fetal outcomes in the presence of maternal anti-Ro52 positivity [82]. Hoxha et al. [83] investigated the reactivity of a monoclonal anti-Ro52 antibody in inducing heart block in rats (7.8C7) and of sera from anti-Ro52p200 antibody-positive mothers of complete heart block offsprings. Their results supported the hypothesis that maternal anti-Ro/SSA positivity might predispose to fetal heart block.

Breast cancer resistance protein (BCRP) is known for its protective function against the toxic effects of the exogenous compounds. A pharmacokinetic model of the placental perfusion study using rat placental HRP-1 cell line and dually perfused rat placenta revealed that the transporter had a two-level defensive role in placenta: to reduce passage of its substrates from mother to fetus, and to remove the drug in the fetal circulation [84]. Drugs for transplacental treatment of fetal tachyarrhythmias include digoxin, sotalol, flecainide, amiodarone, propranolol, verapamil, procopone and procaine, etc. However, in the transplacental approach, the drug from mother to fetus passes through the placental trophoblast cells, which may be affected by the efflux of BCRP, affecting the amount of the trophoblast into the fetus, and leading to treatment failure. It has been reported that digoxin and verapamil are not the substrates of BCRP [85, 86]. Wang et al. [87] carried out an experiment by using MDCKII-BCRP and MDCKII cell monolayer models to investigate the candidatures of antiarrhythmic drugs as BCRP substrates. They found that flecainide, instead of sotalol, propranolol, propafenone and procainamide, can be a substrate of BCRP. Thus, the effect of flecainide may be affected by the BCRP in the maternal placental trophoblast membrane layer when treating fetal tachyarrhythmias.

The Medical Device Development Facility in Los Angeles, CA, USA has invented a percutaneously implantable fetal pacemaker. Preclinical testing of the pacemaker in fetal sheep models has preliminarily proved the advantages of the device, including minimally invasive implantation, successful ventricular capture, effective myocardial contraction, and device reliability and durability. The newly developed fetal pacemaker could be a feasible treatment of choice for fetal bradyarrhythmias, especially in those fetuses with hydrops fetalis [88, 89].

Conclusions

Genes like *minK-lacZ*, *GATA4*, the homeodomain transcription factor *Nkx2.5*, *Hop* and the T-box transcription factors *Tbx2*, *Tbx3* and *Tbx5*, *HCN4* and connexins, etc., might be involved in the developmental processes and (or) functional status of CCS. For most fetal cases with benign arrhythmias, maternal autoantibody screening and close follow-up are necessary in order to define the possible etiology and to prevent from progression into malignant arrhythmias, while for severe cases even those with heart dysfunction or hydrops fetalis, maternal or fetal antiarrhythmic medications are necessary. The selective T-type calcium channel antagonists can be a treatment of choice of fetal arrhythmias. Precaution with substrates of BCRP is recommended when using antiarrhythmic agents by transplacental approach. Immediate postnatal pacemaker implantation may be warranted in

the refractory cases. It is anticipated that the investigational agents in virtue of the genetic background of the CCS and early clinical use of the percutaneously implantable fetal pacemaker for the treatment of fetal arrhythmias could come to true in the near future to facilitate the management of fetal arrhythmias.

Compliance with Ethical Standards

Conflict of interest Author declares that he has no conflict of interest.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by the author.

Informed Consent Informed consent is not applicable for this study.

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