Review Article

Autoimmune-associated Congenital Heart Block: A New Insight in Fetal Life

Kai-Yu Zhou, Yi-Min Hua

Department of Pediatric Cardiology, Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases of Sichuan Province, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China

Abstract

Objective: Congenital heart block (CHB) is a rare but life-threatening disorder. More than half of CHB cases are associated with maternal autoimmune, which are termed as autoimmune-associated CHB. This review summarized the recent research findings in understanding autoimmune-associated CHB, discussed the current diagnostic approaches and management strategies, and summarized the problems and future directions for this disorder.

Data Sources: We retrieved the articles published in English from the PubMed database up to January 2017, using the keywords including "Autoimmune-associated", "Autoimmune-mediated", and "Congenital heart block".

Study Selection: Articles about autoimmune-associated CHB were obtained and reviewed.

Results: Observational studies consistently reported that transplacental maternal antibodies might recognize fetal or neonatal antigens in various tissues and result in immunological damages, but the molecular mechanisms underlying CHB pathogenesis still need illuminated. Multiple factors were involved in the process of atrioventricular block development and progression. While several susceptibility genes had been successfully defined, how these genes and their protein interact and impact each other remains to be explored. With currently available diagnostic tools, fetal ultrasound cardiography, and fetal magnetocardiography, most of CHB could be successfully diagnosed and comprehensively evaluated prenatally. The efficacy of current approaches for preventing the progression and recurrence of CHB and other autoimmune-mediated damages was still controversial.

Conclusions: This review highlighted the relationships between autoimmune injuries and CHB and strengthened the importance of perinatal management and therapy for autoimmune-associated CHB.

Key words: Autoimmune Diseases; Congenital; Disease Management; Heart Block; High-risk; Pregnancy; Prenatal Care

Introduction

Congenital heart block (CHB) is a rare but life-threatening disorder. More than half of CHB cases are associated with maternal autoimmune, which are termed as autoimmune-associated CHB. Although the association between maternal autoantibodies and CHB has been recognized for a long time, the molecular mechanisms underlying CHB pathogenesis are not fully understood yet. It is thought that transplacental maternal antibodies may recognize fetal or neonatal antigens in various tissues and result in immunological damages.

Recent studies in animal models as well as in patients demonstrated that anti-Ro52 antibody has a direct pathogenic effect on cardiac conduction system via disrupting calcium homeostasis. In addition, deposition of maternal antibodies in the heart of fetuses may initiate inflammatory responses, which in turn contribute to fibrosis and eventual calcification of the AV node, leading to complete atrioventricular block (CAVB). However, CHB develops only in 1–2% anti-Ro-positive pregnancies and the outcome varies

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Address for correspondence: Prof. Yi-Min Hua, Department of Pediatric Cardiology, Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases of Sichuan Province, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: nathan_hua@163.com

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greatly.[1-5] Obviously, multiple factors are involved in the process of atrioventricular block (AVB) development and progression. While several susceptibility genes have been successfully defined, how these genes and their protein interact and impact each other remains to be explored.

Since the first-degree AVB could rapidly progress to CAVB, early diagnosis, timely prenatal evaluation, and proper management are critical to prevent progression and avoid irreversible damage. Fortunately, with currently available diagnostic tools, fetal ultrasound cardiography (fUCG), and fetal magnetocardiography (fMCG), most of CHB can be successfully diagnosed and comprehensively evaluated prenatally.

Regarding the management of autoimmune-mediated CHB, the efficacy of current approaches for preventing the progression and recurrence of CHB and other autoimmune-mediated damages is still controversial. The parameters to weigh out the risk and benefit remain to be determined. Recently, several combined therapies have been proposed and attempted and appeared to be promising.

In the current study, we have reviewed the recent research findings in understanding autoimmune-associated CHB, discussed the current diagnostic approaches and management strategies, and summarized the problems and future directions for this disorder.

Prevalence and Current Understanding for Autoantibody-mediated Congenital Heart Block

CHB occurs approximately 1 in 20,000 live births. More than half of CHB cases are associated with autoimmune and CHB remains a severe life-threatening disorder.[1-9] Autoimmune-associated CHB occurs in 2–5% pregnancies with positive anti-Ro/SSA (the most common one) and La/SSB antibodies, and it has a recurrence rate of 12–25% in a subsequent pregnancy.[4-6,10] The perinatal mortality of neonate with CHB researches to 30%, and even higher in the presence of endocardial fibroelastosis (EFE) and/or dilated cardiomyopathy (DCM).[6,11] Previous studies revealed that 64–70% CHB survivors require permanent pacemaker implantation.[2,5,6,9-12]

Such autoimmune-mediated CHB has been found in a variety of maternal autoimmune disorders, such as Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, antiphon-spholipid syndrome, mixed connective tissue disorders, and undifferentiated connective tissue disease.[1-3,8-10] Multicenter prospective studies with large sample size have demonstrated that more than half of asymptomatic pregnant women were eventually confirmed with autoimmune disorders. Among fetal AVB, approximately one-third of anti-SSA/Ro-positive pregnant women were diagnosed with rheumatological disorders preceding the discovery of advanced fetal CHB.[4-6,11-13]

Previous studies support that autoimmune-associated fetal CHB is secondary to the autoantibody-mediated damages and fibrosis in fetal conduction system, especially in atrioventricular (AV) node. The first sign of CHB, such as persistent fetal bradyarrhythmia, is usually noted between 18th and 24th gestational weeks (GWs).[7,9,13,14] In the mean time, it has been demonstrated that CAVB and cardiomyopathy may occur within 1 week following a normal echocardiogram.[6,13,15] The rapid deterioration of the tissue damages in conducting system only allows a short-time window for urgent prenatal evaluation, management, and therapy.

Fetuses who have an exposure to maternal pathogenic autoantibodies may have variegated cardiac manifestations. Irreversible CAVB is the main cardiac manifestation in over 80% of reported cases.[5] The spectrum of manifestation is still expanding and the followings are recently reported: fetal prolonged PR interval, first-and second-degree AVB, EFE, prolongation of corrected QT interval, sinus bradycardia (SB), late-onset DCM, atrial flutter, valvular insufficiency, ventricular/valvular hyperechogenicity, pericardial effusion, and other heart disorders even in the absence of cardiac block.[2,4-7]

Autoimmune-mediated damage is initiated at the fetal stage but may sustain postnatally. According to the latest opinions, once fetal cardiac involvement is determined, it should be included in the management of neonatal lupus syndrome (NLS), which is the most common presentation of autoimmunity in newborns.[4-7,13] The heart appeared to be particularly susceptible to damage in NLS. In addition to cardiac involvements, NLS may affect other systems and manifest involvement of multiple systems, such as cutaneous rashes, hepatobiliary disease, and/or thrombocytopenia or other types of cytopenia. While third-degree heart block, once occurred pre- or post-natally, is permanent, most of manifestations of NLS is transient. Cutaneous lesions and hepatobiliary diseases tend to resolve spontaneously, but they appear to pose an increased risk for autoimmune diseases later in childhood or adulthood. In the absence of prenatal cardiac involvements, there are still the possible autoimmune-mediated cardiac injuries, which could newly present during the 1st year of postnatal life. Accordingly, close monitoring and regular follow-up are strongly recommended.

Regarding the pathogenesis of neonatal autoimmune diseases, it is thought that the transplacental maternal antibodies are involved. These antibodies may recognize fetal or neonatal antigens in various tissues and result in immunological damages and may manifest as the cryopyrin-associated periodic syndromes (CAPS), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and neonatal onset multisystem inflammatory disease (NOMID), neonatal antiphospholipid syndrome, Behcet's disease, neonatal autoimmune thyroid disease, neonatal polymyositis and dermatomyositis, neonatal scleroderma, or neonatal type I diabetes mellitus.[14] The diseases vary greatly in severity and involvement of physiological systems, it could be from mild skin rash to severe involvements of the neurological, cardiac, hepatic, and hematological systems. Regarding

the molecular mechanism, it was found that the defect of *CIAS1* or *NALP3* gene (on chromosome 1) was a shared gene background in various neonatal autoimmune diseases, including CAPS, FCAS, NOMID, and some types of hematological cytopenia.[14] Therefore, aberrant functioning of the inflammasome may play an important role in the pathogenesis of autoimmune-mediated fetal/neonatal inflammatory diseases.[14,16,17]

Current Dilemma in Clinical Management of Autoantibody-mediated Congenital Heart Block

1. The mechanism for etiopathogenesis of autoantibody-mediated CHB remains to be elucidated.[2,6,8,16-25]
2. Diverse clinical presentations need to be further dissected and classified.[2-10]
3. Early detection of autoantibody-mediated CHB is critical but still challenging. It is urgently necessary to define the susceptible populations, from both maternal and fetal aspects.[2,15,26-37]
4. The efficacy of current approaches for preventing the CHB progression in affected fetus and recurrence in subsequent pregnancy as well as other autoimmune-mediated damages is still controversial. The parameters to weigh out the risk and benefit remain to be determined.[2,38-49]
5. The data from experiment-based research on NLS are not conclusive, and laboratory findings are not sufficient to guide clinical practice.[42-49]
6. Risk factors for NLS are not clearly defined and studies with racial/ethnic specificity remain to be performed.[2,8,12,15,49,50]

Mechanisms of Autoimmune-associated Congenital Heart Block

Although the association between maternal anti-Ro/SSA autoantibodies and CHB has been recognized for a long time, the molecular mechanisms underlying CHB pathogenesis are not fully understood yet. We discuss previously published findings and their clinical implications.

Relationships between autoimmune injuries and CHB

Anti-Ro/SSA and anti-La/SSB antibodies specifically recognize three different proteins: Ro 52, Ro 60, and La, as well as a set of noncoding RNAs called Y RNA particles. The Ro/SSA 60 kDa protein acts as a quality check for misfolded RNAs, which are subject to degradation when tagged by Ro/SSA particles.[6,16] Ro/SSA 52 kDa protein mediated a wide spectrum of biological function through ubiquitination, which modifies the functional roles or stability of different molecules.[6,16,17] La/SSB proteins bind Ro 60/Y RNA and facilitates the correct folding of newly synthesized small RNAs and protects them from exonuclease digestion.[6,16,17]

While autoantibodies against these proteins may be all involved in the development of CHB, anti-Ro52 antibody appears to play the dominating roles.[16,17] It was demonstrated that anti-Ro52 antibody have a direct pathogenic effect on cardiac conduction and calcium homeostasis both *in vitro* and *in vivo*.[6] First, animal models of heart block have indicated that anti-Ro52 antibody contributed to the occurrence of CHB. Briefly, first-degree AVB was observed in 9–45% of pups with exposure to Ro52 immunization, depending on the animal types and strains.[17-19] Second, a population-based investigations of the autoantibody profile in mothers of children with AVB also support the role of anti-Ro52 antibody. In this study, autoantibody profiles for the mothers of children with AVB were obtained and were analyzed. Among the entire panel of antibodies against Ro52, Ro60, La, SmB, SmD, RNP-70k, RNP-A, RNP-C, CENP-C, Scl-70, Jo-1, ribosomal RNP and histones, maternal anti-Ro52 antibody showed a dominating association with children's AVB.[3] Regarding the roles of other autoantibodies, a recent study showed that while low-titer and isolated anti-Ro/SSA 60kDa antibodies were correlated with positive pregnancy outcomes, high-titer anti-Ro/SSA 60kDa was associated with a high probability of fetal CHB.[17]

Proposed mechanism

It has been observed that maternal autoantibodies can be transported across the placenta, and they may affect the developing fetus and contribute to the development of fetal CHB.[16] Regarding the molecular mechanisms leading to CAVB, several hypotheses have been proposed in the literature, but none of the proposed model was capable of explaining all aspects of CHB.[16,17] A relatively well-accepted model is that anti-Ro52 antibody may directly affect calcium homeostasis in the fetal heart, leading to disturbances in signal conduction and/or electrogenesis. In addition, deposition of maternal antibodies was found in the heart of fetuses who died of CHB. The accumulated antibodies were thought to be the initiator of fetal inflammatory responses, which in turn contribute to fibrosis and eventual calcification of the AV node, leading to CAVB.

Aurélie and Ambrosi *et al*.[16,17] proposed that a cascade of events occur in the pathogenesis of CHB. Briefly, during pregnancy, maternal IgG autoantibodies are transported across the placenta through neonatal Fc receptor to the fetal blood circulation. Mother-derived anti-Ro antibodies may have cross-reactivity with fetal epitopes on calcium-regulating molecules, such as ion channels. Binding of maternal anti-Ro antibody on the ion channel protein may disrupt the function of channel and cause the dysregulation of calcium homeostasis, and eventually cellular apoptosis. Subsequently, anti-Ro 60 and anti-La autoantibodies may bind their cognate antigens present on the surface of apoptotic cells. These molecular interactions in the early stages may correspond to clinical signs of fetal AV time prolongation or first-degree AVB. Concerning the different outcome among fetuses, the expression status of fetal susceptibility

genes, such as human leukocyte antigen (HLA), may determine the degree of severity and progression. In other words, in the absence of susceptibility gene, the local inflammation may be resolved, leading to recovery of fetal AV conduction. Otherwise, the inflammation and damage may be exacerbated and results in fibrosis and calcification, leading to permanent CAVB.

Genetic susceptibility factors

While it has been well recognized that there is an association between fetal CHB and maternal anti-Ro/La antibodies, two questions remain to be answered. First, why does CHB not develop in all anti-Ro-positive pregnancies but in only 1–2% of such pregnancies?[16] Second, why does first-degree AV block never progress in certain cases but progress rapidly to AVB II and AVB III in other cases? Although we do not have definitive answers for these two questions yet, the two observations suggested that there must be other unidentified important factors involved in the process of AVB development and progression. In the past decade, we have seen efforts made to reveal those undefined factors from both maternal and fetal aspects.

First, studies focusing on genetic polymorphisms of the proinflammatory and profibrotic cytokines, tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β), have revealed that the genetic profile of the fetus may be important determinants for the development of autoimmune-associated CHB. In addition, studies on myosin heavy chains (MHCs) demonstrated that genetic differences in MHCs influence the degree of susceptibility to CHB in both animal models and patients.[17,19-21] Furthermore, a family-based analysis of single-nucleotide polymorphisms (SNPs) in the HLA region demonstrated that HLA-DR104 and HLA-Cw5 genotypes were associated with high susceptibility to CHB, and HLA-DR13 and HLA-Cw6 genotypes appeared to have protective effect.[17,22] Consistently, a genome-wide association study for 116 children with NLS and 3551 controls has identified that the most significant N LS-associated candidate loci were in the HLA region at 6p21 and 21q22.[23] These loci include rs3099844 near *MIBC* gene, rs7775397 between *Notch4* and *BTNL2* genes, and several SNP loci near *TNF-α* gene. Last, recent studies revealed that some non-HLA genes, such as sialyltransferase *ST8SIA2*, the complement regulator *CSMD1*, and the integrin *ITGA1*, may also be associated with cardiac manifestations of NLS.[14,24] From maternal aspect, it was found that polymorphism in the interferon regulatory factor 5 gene was associated with asymptomatic mothers who had high-titer anti-Ro/SSA autoantibodies.[14,25]

Despite the success in searching for genetic factors for CHB, extensive effort is still necessary to elucidate their specific roles in the development of CHB. In addition, the environmental factors are poorly defined, and how these factors interact and impact each other also remains to be explored.[51]

Diagnosis and Heart Structure/Function Assessment

Fetal ultrasound cardiography

Currently, ultrasound cardiography (UCG), also known as echocardiography, is the leading tool for the diagnosis of fetal arrhythmia. Based on the rate and regularity of atrial and ventricular events, as well as the relationship among A-V conduction, A-V and V-A chronology, most types of fetal arrhythmia can be diagnosed prenatally. UCG has the capacity of simultaneously recording the heart rhythm and screening the cardiac structure, which provides necessary parameters for comprehensive evaluation of fetal heart function.[2,26-28] Although the diagnosis of certain types of fetal arrhythmia is still challenging, the effectiveness and accuracy of fUCG is sufficient for the evaluation of morbid state, prognosis, and therapeutic guidance.

Most cardiac structural abnormalities can be detected by fUCG with a sensitivity of 93.8%, specificity of 98.8%, positive predictive value of 98.1%, and negative predictive value of 99.9%. A meta-analysis study for 81 studies in 63 articles by Li *et al.*[28] supported the notion that fUCG detection is a reliable method for diagnosis of fetal cardiac structural abnormalities. The overall performance of pooled sensitivities of spatiotemporal image correlation (STIC), extended cardiac echocardiographic examination (ECEE), and 4-chamber view (4CV) + outflow tract view (OTV) + 3 vessels and trachea view (3VTV) were around 0.90. The area under the summary receiver operating characteristic curves value of STIC, ECEE, 4CV + OTV + 3VTV, 4CV + OTV/3VTV, and 4CV were 0.9700, 0.9971, 0.9983, 0.9929, and 0.9928, respectively. Therefore, fUCG has a great diagnostic potential for detection fetal congenital cardiovascular malformations.[2,28]

The evaluation systems for fetal heart function include fetal cardiovascular profile score (CVPS) and Tei-index. CVPS included five parameters: hydrops, cardiomegaly (cardiac area/thoracic area), cardiac function, arterial umbilical Doppler, and venous/ductus umbilical Doppler. The maximal CVPS is 10 points, with 2 points given to normal findings and 1 or 2 points deduction for abnormal states. Decrease in CVPS indicates impaired overall fetal cardiac function. Tei-index, also known as the myocardial performance index, is a more sensitive indicator for mildly compromised fetal heart at early stage. It has been reported that there was a negative correlation between CVPS and Tei-index. Data of previous studies showed that combined evaluation of CVPS, Tei-index, and umbilical artery resistance index could provide a comprehensive and accurate estimation for fetal heart function.[2,29-31]

Fetal magnetocardiography

While most of fetal CHB cases can be reliably diagnosed through fUCG, it fails to provide conclusive information regarding electrophysiology of the fetal cardiac conducting system. fMCG is the magnetic analog of the fetal

electrocardiogram (fECG),[32] and fetal cardiac time intervals could be extracted from the fMCG recordings by predefined procedures. In addition, fMCG results may also be utilized to monitor disease progression. It has been demonstrated that PQ segment prolongation in fetuses from antoantibody-positive mothers is associated with a low-risk for progression. Furthermore, recent studies showed that fMCG can be effectively used in the prenatal diagnosis of atrial bigeminy (conducted and blocked), 2:1 AVB, CAVB, delayed AV conduction, PQ segment prolongation, and different types of long QT syndrome.[32-35]

In comparison with fMCG, conventional M-mode echocardiography failed to detect the exact AV interval unless full AVB was reached. It detected first-degree AVB with low sensitivity and specificity (44% and 88%, respectively), in contrast, fECG showed a sensitivity of 66.7% and specificity of 96.2% for these cases.[15,35] The availability of fMCG could help define low-risk and high-risk PQ normal ranges.

In summary, using currently available diagnostic tools, fUCG and fMCG, most of CHB can be successfully diagnosed and prenatally evaluated. Proper management should be followed with a goal to prevent progression and avoid irreversible damage.

Prenatal Management for Autoimmune-associated Congenital Heart Block

Necessity and importance of prenatal management for congenital heart block

Thus far, factors influencing the progression of cardiac lesions are not well defined. It was noticed that a small number of CHB patients who have prolonged PR and QT intervals could spontaneously return to normal.[15,36-37] However, a large portion of CHB, as first detected as first-degree AVB, progress rapidly to AVB II and III in a very short time. Previous studies in rator human heart isolated with the Langendorff technique indicated that maternal autoantibodies have a direct effect on the fetal heart conducting system, and induced fetal bradycardia and CAVB within 15 min.[17] Once CAVB occurs, it is irreversible and most of the children need permanent pacemaker implantation. Accordingly, upon the diagnosis of fetal CHB, timely treatments are necessary to exempt affected fetus/neonate from a poor outcome, such as intrauterine demise, pre- and post-natal heart failure, pacemaker implantation, and low quality of life.

Pre- and post-natal monitoring

The accurate prenatal diagnosis is the cornerstone of prenatal monitoring and therapy. Pregnant women with clinical and subclinical autoimmune diseases should be referred for fetal cardiac morphology screening and heart function evaluation. If fetal CHB is suspected, fetal cardiac conduction interval (PR, QT) should be closely monitored.[15,37] Fetal UCG is the leading tools to measure fetal cardiac PR intervals and fMCG can provide more detailed information. Thus far, it is still challenging to predict the prognosis for a specific individual. Usually, PR prolongation is considered an early manifestation of CAVB in autoantibody-mediated lesion. According to the perspective study for the PR Interval and Dexamethasone Evaluation conducted by Friedman *et al*.[13] and Phoon *et al.*,[15] we included a hierarchical management and monitoring regimen for fetal PR [Figure 1]. Regarding the prognostic factors,[3-6,27] multiple studies indicated that poor prognosis during fetal and neonatal periods included earlier gestational age at diagnosis, lower ventricular rate (<50 beats/min), as well as the presence of EFE, DCM, and fetal hydrops. Hydrops fetalis was revealed to be an independent risk factor for both neonatal and *in utero* death.[7-10,27] In contrast, fetuses/neonates with NLS, in the absence of hydrops fetalis and cardiac structural abnormality, have a documented 90% survival rate.[8-9,27] It was suggested that multiple factors should be taken into consideration for the risk evaluation.

Previous studies showed that these who experienced exposure to maternal autoantibodies in fetal life have a higher risk for autoimmune diseases in later life, when compared to normal subjects. In addition, it has been shown that while the offspring of lupus mothers develop mentally normal, some of them suffer from cognitive deficits, and >45% boys have dyslexia. Furthermore, cardiac involvement might sustain within 1 year after birth even after blocking progress. Therefore, these children still need follow-ups and monitoring routinely to 1 year after birth, or for even longer period.

Prenatal treatment and management

The normal range of fetal PR interval varies depending on gestation weeks (GWs) and fetal heart rate (HR). If fetal PR interval is prolonged >140 ms, more frequent fUCG should be arranged. If fetal PR interval is >150 ms, first-degree AVB can be diagnosed,[15,37] and transplacental administration of corticosteroids should be considered. If it advanced to second-degree AVB and CAVB, maternal oral dexamethasone is strongly recommended [Figure 1], and intravenous immunoglobulin (IVIG) and plasmapheresis can be adopted.[15,37,38] Depending on the fetal ventricular rate and heart function, β-sympathomimetic agent can be selected as an alternative drug to increase fetal HR (fHR) and improve myocardial contractility. The currently used treatments are further discussed.

Transplacental administration of corticosteroids

The transplacental administration of corticosteroids is being used to treat congenital heart, but its effect versus risk is still controversial, especially for CAVB.[1,38-41] Accumulating data showed that corticosteroids have no beneficial effects on CAVB. While it appeared to improve the overall condition of the suffered fetus, it could not avoid pacemaker implantation or decrease the mortality. For some mild cases, dexamethasone could prevent the progression and

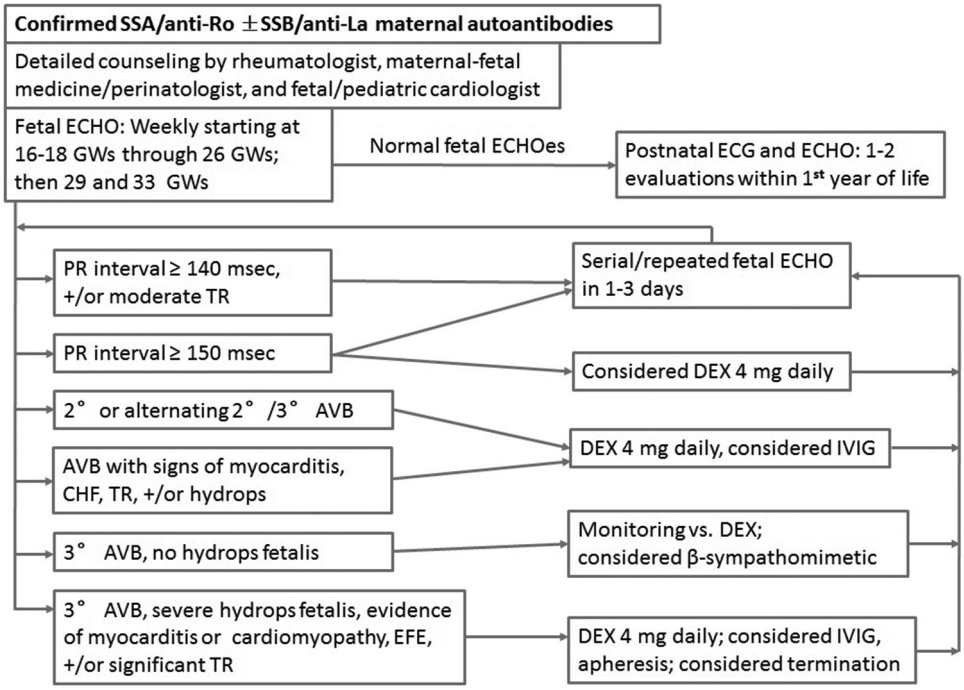

Figure 1: PR Interval and Dexamethasone Evaluation research: Hierarchical management and monitoring base on PR interval. GWs: Gestational weeks; ECHO: Echocardiography; ECG: Electrocardiogram; msec: Millisecond; AVB: Atrioventricular block; TR: Tricuspid regurgitation; CHF: Congestive heart failure; DEX: Dexamethasone; IVIG: Intravenous immune globulin; EFE: Endocardial fibroelastosis. (*The picture is original published in Congenit Heart Dis 2012; 7: 349-60 by Dr. Colin K.L. Phoon, Mimi Y. Kim, Jill P. Buyon, and Deborah M. Friedman).*

facilitate the recovery of normal sinus rhythm. In general, it is thought that benefit of corticosteroids may be limited to first- and second-degree AVB cases and cases complicated by fetal hydrops. In addition, prenatal dexamethasone might slow down or even halt the fetal growth and development, and long-term corticosteroids therapy has a strong association with intrauterine growth retardation (IUGR) and oligoamnios.[4,42] Thus, with the given data, as well as the potential side effects, it is necessary to weigh out the benefits and risks before use of steroids.[1,39]

Regarding different corticosteroids, prednisone and prednisolone have only a small proportion of active ingredients capable of passing the placenta and reach fetal circulation, and the therapeutic effects for fetus are not adequate to meet the expectation for clinical treatments. However, they can be used as single-aspect maternal therapy with less effect on fetus. In contrast, the placental transfer rate of dexamethasone and betamethasone is sufficient for prenatal treatment of fetal diseases, and they are also used for two-aspect therapy in pregnancy (both maternal and fetal disorders). In general, prenatal use of glucocorticoid may be beneficial for following conditions: fetal DCM, fetal AVB with high lethality, incomplete AVB, pregnancies of anti-SSA/SSB antibody-positive multigravida with previous fetus suffered from CHB, and other conditions with high risk of prenatal CHB recurrence, mortality, and disability. In addition, it is thought that dexamethasone could be beneficial with the fetal cardiac involvements, such as SB, echogenicity near AV node, and ventricular systolic dysfunction with valve regurgitation.[26,41,42-46]

Intravenous immunoglobulin, plasmapheresis, and combined strategies

Due to the side effect and limited benefit of steroids alone treatment, combined therapy has been proposed and attempted.

First, IVIG and plasmapheresis have been used to desensitize patients with alloantibodies and they are also effective to decrease antoantibodies in patient's circulation. Accordingly, they were used in combination with steroids to treat fetal CHB in mothers with autoimmune conditions. A treatment regimen consisting of dexamethasone 4 mg/d throughout pregnancy, weekly plasmapheresis, and IVIG 1 g/kg every 2 weeks were carried out; it appeared to provide benefit for fetuses with second- and third-degree block.[39,41,42] However, administration of low dose of IVIG ($0.4\ g \cdot kg^{-1} \cdot d^{-1}$, 5 days continuously) failed to prevent the progression and recurrence of CHB in high-risk pregnancies.[39,43] Despite possible benefit, combination therapy with IVIG and plasmapheresis could not reverse the progression to CAVB either.[40,43]

Second, it has been reported that hydroxychloroquine (HCQ) could reduce the incidence of heart block in fetuses exposed to autoantibodies prenatally and has been used in the combination of glucocorticoid. HCQ has been recommended to be used in these patients at a dose of 200 mg, two times/day.[44,46-48]

The efficacy of combined therapy may be achieved through multiple mechanisms simultaneously. From the maternal aspect, they may be more efficient to remove

maternal autoantibodies, and/or maintaining them at a low level, decreasing autoimmune-mediated inflammation via anti-idiotypic regulation, induction of inhibitory Fc receptors, and inhibition of placental anti-Ro/La transport.[40] From the fetal aspect, glucocorticoid and HCQ may be transported cross placenta and directly modulate autoimmune-mediated inflammation in fetal heart.[39,40,48] While these combined therapies could be effective in treating fetal cardiac manifestations mediated by autoantibodies, their beneficial effect can be achieved only when they are administered within a strict time window. Larger prospective studies are still necessary to comprehensively evaluate the efficacy of therapy in different drug combinations.[39]

Pre- and post-natal pacing

A large number of studies have reached consensus that fHR is an important parameter for the outcomes. When fHR is beyond 75 beats/min, fetal cardiac output can meet the requirement of fetal growth and development; prenatal cardiomyopathy and cardiac insufficiency are usually not present. If fHR is between 55–75 beats/min, close monitoring and comprehensive evaluation are strongly recommended, since compromised fetal cardiac function will gradually appear in the absence of proper intervention. Furthermore, if fHR is <55 beats/min, cardiomegaly and fetal hydrops are inevitable. A well-accepted recommendation is that drug or pacing therapy should be performed prenatally when fHR is <75 beats/min.[1,39-41]

Among all sympathomimetic agents, terbutaline and salbutamol have a favorable transplacental transfer rate and β-sympatheticomimetic action, and they can increase fetal HR and play a positive inotropic action on fetal myocardium. When fHR is <55 beats/min or associated cardiac dysfunction and hydrops, sympathomimetic therapy should be started. Terbutaline is recommended with an initial dose of 2.5 mg q6h, salbutamol of 2.5 mg q8h. Dosage and administration time can be adjusted according to maternal and fetal dynamic assessments. Regarding fetal pacing therapy, percutaneous transparietal *in utero* fetal cardiac pacing has been attempted as a possible solution for providing fHR support. However, with currently available techniques and instruments, it appears to be associated with high risk, as fetal demise occurred after the procedure in a high proportion of studied cases.[1,38-41]

Indications for postnatal cardiac pacing and the decision-making process can be more complicated in patients with more subtle symptoms, such as tiredness, poor fetal growth, frequent nightmares, and napping. If clinical bradycardia is the most likely cause of the symptoms, then the pacing is usually recommended. However, the decision regarding implantation of pacemaker needs careful consideration for the benefits of symptom improvement against the risks associated with long-term pacing therapy.[38-41] The pacemaker implantation is recommended for symptomatic patients and asymptomatic patients who have profound bradycardia, left ventricular dysfunction, a wide QRS interval, or a prolonged QT interval. Recently, it is recognized that a subset of paced patients develop DCM, heart failure, and they are also at a high risk of developing complications associated with intracardiac material. Therefore, regular follow-up is strongly recommended for patients with pacemaker implantation.[1,5,7,49]

Future Research Directions for Autoimmune-associated Fetal Congenital Heart Block

As discussed in the preceding sections, during the past decades, extensive research has been performed for autoimmune-associated fetal CHB, and the acquired knowledge allowed us to understand better for this disease from multiple aspects. Yet, there are still questions to be answered and problems to be resolved. First, in addition to the maternal antibodies and genetic factors, many other factors that significantly contribute to CHB pathogenesis remain to be defined. Second, while we have more information to understand pathogenic effect of anti-Ro52 antibody, more investigations are necessary to elucidate the molecular mechanisms of other autoantibodies and genetic factors in promoting or regulating the development of CHB. Third, the data supporting the association between certain HLA genotypes and CHB susceptibility are convincing, but the relationship between different expression patterns of HLA genes and CHB variants remains to be established. Furthermore, the relationship between racial specificity of HLA and the occurrence, progression, and therapeutic outcomes of CHB in different ethnic groups remains to be determined. Fourth, no therapy is currently available to effectively slowdown, halt, or reverse the malignant progression of CHB. It is urgently needed to find method to prevent the progression of CHB. Finally, from the perspective of developmental origins of health and disease, also called fetal origin and programming hypothesis,[52] long-term investigation from fetal stage to adulthood is needed to determine the disease spectrum mediated by autoantibodies.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jaeggi E, Öhman A. Fetal and neonatal arrhythmias. Clin Perinatol 2016;43:99-112. doi: 10.1016/j.clp.2015.11.007.
2. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA,

Sklansky MS, Abuhamad A, *et al.* Diagnosis and treatment of fetal cardiac disease: A scientific statement from the american heart association. Circulation 2014;129:2183-242. doi: 10.1161/01.cir.0000437597.44550.5d.
3. Salomonsson S, Dzikaite V, Zeffer E, Eliasson H, Ambrosi A, Bergman G, *et al.* A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block. Scand J Immunol 2011;74:511-7. doi: 10.1111/j.1365-3083.2011.02610.x.
4. Brito-Zerón P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol 2015;11:301-12. doi: 10.1038/nrrheum.2015.29.
5. Levesque K, Morel N, Maltret A, Baron G, Masseau A, Orquevaux P, *et al.* Description of 214 cases of autoimmune congenital heart block: Results of the french neonatal lupus syndrome. Autoimmun Rev 2015;14:1154-60. doi: 10.1016/j.autrev.2015.08.005.
6. Tonello M, Hoxha A, Mattia E, Zambon A, Visentin S, Cerutti A, *et al.* Low titer, isolated anti ro/SSA 60 kd antibodies is correlated with positive pregnancy outcomes in women at risk of congenital heart block. Clin Rheumatol 2017;36:1155-60. doi: 10.1007/s10067-017-3572-2.
7. Brooks P. Fetal manifestations of maternal anti-Ro and La antibodies – More than complete heart block. Australas J Ultrasound Med 2015;18:124-8. doi: 10.1002/j.2205-0140.2015.tb00212.x.
8. Chang C. Neonatal autoimmune diseases: A critical review. J Autoimmun 2012;38:J223-38. doi: 10.1016/j.jaut.2011.11.018.
9. Hunter LE, Simpson JM. Atrioventricular block during fetal life. J Saudi Heart Assoc 2015;27:164-78. doi: 10.1016/j.jsha.2014.07.001.
10. Pike JI, Donofrio MT, Berul CI. Ineffective therapy, underpowered studies, or merely too little, too late? Risk factors and impact of maternal corticosteroid treatment on outcome in antibody-associated fetal heart block. Circulation 2011;124:1905-7. doi: 10.1161/CIRCULATIONAHA.111.061267.
11. Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, *et al.* Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation 2011;124:1927-35. doi: 10.1161/CIRCULATIONAHA.111.033894.
12. Christine C, Jill PB, Deborah MF, William HF. Cardiac manifestations of neonatal lupus a review of autoantibody-associated congenital heart block and its impact in an adult population. Cardiol Rev 2012;20:72-6. doi: 10.1097/CRD.0b013e31823c808b.
13. Friedman DM, Kim MY, Copel JA, Davis C, Phoon CK, Glickstein JS, *et al.* Utility of cardiac monitoring in fetuses at risk for congenital heart block: The PR interval and dexamethasone evaluation (PRIDE) prospective study. Circulation 2008;117:485-93. doi: 10.1161/CIRCULATIONAHA.107.707661.
14. Chang C. The pathogenesis of neonatal autoimmune and autoinflammatory diseases: A comprehensive review. J Autoimmun 2013;41:100-10. doi: 10.1016/j.jaut.2012.12.010.
15. Phoon CK, Kim MY, Buyon JP, Friedman DM. Finding the "PR-fect" solution: What is the best tool to measure fetal cardiac PR intervals for the detection and possible treatment of early conduction disease? Congenit Heart Dis 2012;7:349-60. doi: 10.1111/j.1747-0803.2012.00652.x.
16. Aurélie A, Marie WH. Congenital heart block evidence for a pathogenic role of maternal autoantibodies. Arthritis Res Ther 2012;14:208-18. doi: 10.1186/ar3787.
17. Ambrosi A, Sonesson SE, Wahren-Herlenius M. Molecular mechanisms of congenital heart block. Exp Cell Res 2014;325:2-9. doi: 10.1016/j.yexcr.2014.01.003.
18. Madhusudan D, Raju A, Vijaya N. Correlation of maternal autoantibodies with fetal congenital heart block. J Obstet Gynaecol India 2016;66:112-6. doi: 10.1007/s13224-015-0813-7.
19. Skog A, Lagnefeldt L, Conner P, Wahren-Herlenius M, Sonesson SE. Outcome in 212 anti-Ro/SSA-positive pregnancies and population-based incidence of congenital heart block. Acta Obstet Gynecol Scand 2016;95:98-105. doi: 10.1111/aogs.12785.
20. Strandberg LS, Ambrosi A, Jagodic M, Dzikaite V, Janson P, Khademi M, *et al.* Maternal MHC regulates generation of pathogenic antibodies and fetal MHC-encoded genes determine susceptibility in congenital heart block. J Immunol 2010;185:3574-82. doi: 10.4049/jimmunol.1001396.
21. Clancy RM, Marion MC, Kaufman KM, Ramos PS, Adler A, Harley JB, *et al*. Genome-wide association study of cardiac manifestations of neonatal lupus identifies candidate loci at 6p21 and 21q22. Arthritis Rheum 2010;62:3415-24. doi: 10.1002/art.27658.
22. Meisgen S, Östberg T, Salomonsson S, Ding B, Eliasson H, Mälarstig A, *et al.* The HLA locus contains novel foetal susceptibility alleles for congenital heart block with significant paternal influence. J Intern Med 2014;275:640-51. doi: 10.1111/joim.12179.
23. Clancy RM, Marion MC, Kaufman KM, Ramos PS, Adler A, International Consortium on Systemic Lupus Erythematosus Genetics, *et al.* Identification of candidate loci at 6p21 and 21q22 in a genome-wide association study of cardiac manifestations of neonatal lupus. Arthritis Rheum 2010;62:3415-24. doi: 10.1002/art.27658.
24. Ramos PS, Marion MC, Langefeld CD, International Consortium on Systemic Lupus Erythematosus Genetics, Buyon JP, Clancy RM, *et al.* Brief report: Enrichment of associations in genes with fibrosis, apoptosis, and innate immunity functions with cardiac manifestations of neonatal lupus. Arthritis Rheum 2012;64:4060-5. doi: 10.1002/art.34663.
25. Cherian TS, Kariuki SN, Franek BS, Buyon JP, Clancy RM, Niewold TB, *et al.* Brief report: IRF5 systemic lupus erythematosus risk haplotype is associated with asymptomatic serologic autoimmunity and progression to clinical autoimmunity in mothers of children with neonatal lupus. Arthritis Rheum 2012;64:3383-7. doi: 10.1002/art.34571.
26. Krishnan A, Arya B, Moak JP, Donofrio MT. Outcomes of fetal echocardiographic surveillance in anti-SSA exposed fetuses at a large fetal cardiology center. Prenat Diagn 2014;34:1207-12. doi: 10.1002/pd.4454.
27. Lai J, Clark TJ, Tan JH, Delaney S, Jolley JA. Ultrasound findings in fetal congenital heart block associated with maternal anti-Ro/SSA and anti-La/SSB antibodies. Ultrasound Q 2015;31:34-6. doi: 10.1097/RUQ.0000000000000112.
28. Li Y, Hua Y, Fang J, Wang C, Qiao L, Wan C, *et al.* Performance of different scan protocols of fetal echocardiography in the diagnosis of fetal congenital heart disease: A systematic review and meta-analysis. PLoS One 2013;8:e65484. doi: 10.1371/journal.pone.0065484.
29. Zhou K, Zhou R, Zhu Q, Li Y, Wang C, Wan C, *et al.* Evaluation of therapeutic effect and cytokine change during transplacental digoxin treatment for fetal heart failure associated with fetal tachycardia, a case-control study. Int J Cardiol 2013;169:e62-4. doi: 10.1016/j.ijcard.2013.08.130.
30. Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL. A cardiovascular profile score in the surveillance of fetal hydrops. J Matern Fetal Neonatal Med 2006;19:407-13. doi: 10.1080/14767050600682446.
31. Zhou K, Hua Y, Zhu Q, Liu H, Yang S, Zhou R, *et al.* Transplacental digoxin therapy for fetal tachyarrhythmia with multiple evaluation systems. J Matern Fetal Neonatal Med 2011;24:1378-83. doi: 10.3109/14767058.2011.554924.
32. Wacker-Gußmann A, Paulsen H, Kiefer-Schmidt I, Henes J, Muenssinger J, Weiss M, *et al.* Atrioventricular conduction delay in fetuses exposed to anti-SSA/Ro and anti-SSB/La antibodies: A magnetocardiography study. Clin Dev Immunol 2012;2012:432176. doi: 10.1155/2012/432176.
33. Wiggins DL, Strasburger JF, Gotteiner NL, Cuneo B, Wakai RT. Magnetophysiologic and echocardiographic comparison of blocked atrial bigeminy and 2:1 atrioventricular block in the fetus. Heart Rhythm 2013;10:1192-8. doi: 10.1016/j.hrthm.2013.04.020.
34. Wacker-Gussmann A, Paulsen H, Stingl K, Braendle J, Goelz R, Henes J, *et al.* Atrioventricular conduction delay in the second trimester measured by fetal magnetocardiography. J Immunol Res 2014;2014:753953. doi: 10.1155/2014/753953.
35. Kiefer-Schmidt I, Lim M, Preissl H, Draganova R, Weiss M, Abele H, *et al.* Fetal magnetocardiography (fMCG) to monitor cardiac time intervals in fetuses at risk for isoimmune AV block. Lupus 2014;23:919-25. doi: 10.1177/0961203314527364.

36. Cuneo BF, Ambrose SE, Tworetzky W. Detection and successful treatment of emergent anti-SSA-mediated fetal atrioventricular block. Am J Obstet Gynecol 2016;215:527-8. doi: 10.1016/j.ajog.2016.07.002.
37. Friedman DM, Kim MY, Copel JA, Llanos C, Davis C, Buyon JP, *et al.* Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR interval and dexamethasone evaluation (PRIDE) study. Am J Cardiol 2009;103:1102-6. doi: 10.1016/j.amjcard.2008.12.027.
38. Bordachar P, Zachary W, Ploux S, Labrousse L, Haissaguerre M, Thambo JB, *et al.* Pathophysiology, clinical course, and management of congenital complete atrioventricular block. Heart Rhythm 2013;10:760-6. doi: 10.1016/j.hrthm.2012.12.030.
39. DeNoble AE, Kuller JA, Rhee EJ. Controversies in the management of isolated congenital atrioventricular block. Obstet Gynecol Surv 2015;70:518-23. doi: 10.1097/OGX.0000000000000208.
40. Martínez-Sánchez N, Robles-Marhuenda Á, Álvarez-Doforno R, Viejo A, Antolín-Alvarado E, Deirós-Bronte L, *et al.* The effect of a triple therapy on maternal anti-ro/SS-A levels associated to fetal cardiac manifestations. Autoimmun Rev 2015;14:423-8. doi: 10.1016/j.autrev.2015.01.005.
41. Izmirly PM, Saxena A, Sahl SK, Shah U, Friedman DM, Kim MY, *et al.* Assessment of fluorinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fetal conduction system. Ann Rheum Dis 2016;75:1161-5. doi: 10.1136/annrheumdis-2015-208311.
42. Eliasson H, Sonesson SE, 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. doi: 10.1161/CIRCULATIONAHA.111.041970.
43. Friedman DM, Llanos C, Izmirly PM, Brock B, Byron J, Copel J, *et al.* Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis Rheum 2010;62:1138-46. doi: 10.1002/art.27308.
44. Lateef A, Petri M. Management of pregnancy in systemic lupus erythematosus. Nat Rev Rheumatol 2012;8:710-8. doi: 10.1038/nrrheum.2012.133.
45. Riega-Torres JC, Villarreal-Gonzalez AJ, Ceceñas-Falcon LÁ, Salas-Alanis JC. Sjögren's syndrome (SS), a review of the subject and saliva as a diagnostic method. Gac Med Mex 2016;152:371-80.
46. Huang M, Ida H, Kamachi M, Iwanaga N, Izumi Y, Tanaka F, *et al.* Detection of apoptosis-specific autoantibodies directed against granzyme B-induced cleavage fragments of the SS-B (La) autoantigen in sera from patients with primary sjögren's syndrome. Clin Exp Immunol 2005;142:148-54. doi: 10.1111/j.1365-2249.2005.02888.x.
47. Stojan G, Baer AN. Flares of systemic lupus erythematosus during pregnancy and the puerperium: Prevention, diagnosis and management. Expert Rev Clin Immunol 2012;8:439-53. doi: 10.1586/eci.12.36.
48. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, *et al.* Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76-82. doi: 10.1161/CIRCULATIONAHA.111.089268.
49. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, *et al.* ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American college of cardiology/American heart association task force on practice guidelines (Writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices): Developed in collaboration with the American association for thoracic surgery and society of thoracic surgeons. Circulation 2008;117:e350-408. doi: 10.1016/j.jacc.2008.02.032.
50. Li YN, Ma H, Zhou L, Zhang J, Guo LP, Li SQ, *et al.* Autoimmune hepatitis-related cirrhosis: Clinical features and effectiveness of immunosuppressive treatment in Chinese patients. Chin Med J 2016;129:2434-40. doi: 10.4103/0366-6999.191760.
51. Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity. J Autoimmun 2012;39:249-52. doi: 10.1016/j.jaut.2012.07.011.
52. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261:412-7. doi: 10.1111/j.1365-2796.2007.01809.x.