Case Report

Citation: Casather DM, Kaluarachchi DP & Atapattu H, et al., 2021. Fetal bradycardia due to congenital heart blocks: a study of three cases with review literature. Sri Lanka Journal of Medicine, 30(1), pp 142-150

DOI: <http://doi.org/10.4038/sljm.v30i1.283>

Foetal bradycardia due to congenital heart blocks: A study of three cases with review literature

¹Casather DM, ²Kaluarachchi DP, ³Atapattu H & ⁴Dias TD¹Obstetrics and Gynaecology Unit, Colombo North Teaching Hospital, Ragama, Sri Lanka²Obstetrics and Gynaecology Unit, Colombo North Teaching Hospital, Ragama, Sri Lanka³Obstetrics and Gynaecology unit, De Soysa Maternity Hospital for Women, Colombo, Sri Lanka⁴University Obstetrics and Gynaecology unit, Colombo North Teaching Hospital, Ragama, Sri Lanka

Correspondence: D.M.Casather
Acting Obstetrician and Gynaecologist.
Obstetrics and Gynaecology Unit, Colombo
North Teaching Hospital, Ragama, Sri Lanka.
Email: dilanmalinda7@yahoo.com

<https://orcid.org/0000-0003-1704-0001>

Abstract

Congenital heart block (CHB) is a cardiac disease with an overall prevalence of approximately 1:20000 live births. Structural heart defects, congenital malformations of the cardiac conduction system, maternal connective tissue disorders and fetal myocarditis are the main entities that can cause CHBs. Here we report three cases of congenital heart blocks due to three different pathologies and their outcomes. In the first case, we could not detect a structural pathology for congenital heart block; however, in second and third cases there were significant structural cardiac defects that could contribute to the fetal bradycardia. Prenatal management of fetal arrhythmia may improve the outcome of an affected fetus or neonate. Precise and timely prenatal diagnosis is critical for the selection of the appropriate prenatal treatments. However, there are many limitations in managing CHB even today and more useful strategies need to be investigated.

Keywords: *Fetal bradycardia, congenital heart block, fetal arrhythmia*

INTRODUCTION

Congenital heart block (CHB) is a rare cardiac disease with an overall prevalence of 1:20000 live births [1]. The perinatal mortality of congenital heart block is about 20% to 30%, and around 60% of children who are born alive with congenital heart block need a permanent pacemaker in early childhood [2]. Among the 80% of patients with CHB associated with structural heart diseases, complete atrioventricular septal defect is the

commonest structural anomaly that causes cardiac blocks [3]. Left atrial isomerism, conotruncal abnormalities and Tetralogy of Fallot are other structural defects that can cause CHB. Fetal bradycardia is diagnosed when the fetal ventricular rate is slower than 100 beats per minute and accounts for roughly 5% of all fetal arrhythmias [4]. In addition to structural defects of the heart, independent CHB can occur as a result of

congenital malformation of the conduction system of the heart, channelopathies such as Long QT syndrome, maternal connective tissue disorders and fetal myocarditis. Maternal Sjogren syndrome with positive antibodies (anti-SSA/Ro-SSB/La antibodies) is the main connective tissue disorder that causes CHB.

The prognosis of the heart blocks depends on the presence or absence of structural abnormalities of the heart, type and severity of the cardiac malformation [5]. Fetuses with heart blocks due to structural malformations generally have poor prognosis compare to the isolated heart blocks [5]. CHB are usually well tolerated in-utero during the third trimester unless the ventricular rate is extremely slow or there is significant valve regurgitation. Perinatal mortality may reach 85% in those associated with structural heart disease. However, heart failure and fetal death can occur in isolated heart block as well [6]. Early identification of fetal bradycardia warrants multidisciplinary prenatal counseling, prenatal interventions, decisions on early delivery, optimal management of labour proved to improve the prognosis of the baby.

Clinical signs of CHB are evident during late second trimester, between 22 to 24 weeks of gestation. Fetal bradycardia is often found during routine fetal heart rate monitoring or prenatal obstetric ultrasound examination. Doppler echocardiogram is a useful tool for diagnosing fetal bradycardia [7]. Doppler echocardiogram can demonstrate the atrio-ventricular coordination during ventricular contractions and assess the severity of the heart block. In addition to the fetal bradycardia, CHB may present with features of non-immune hydrops, which represent severe fatal cardiac decompensation due to congestive cardiac failure especially in the presence of severe congenital heart diseases. CHB is sometimes considered as a progressive disease and 3rd-degree heart block appears to be irreversible [8].

The importance of early identification and management of fetal bradycardia has been emphasized in the last few decades. However, efficacy of prenatal treatment for fetal atrio-ventricular blocks is limited. There is limited guidance for the treatment of in utero CHB apart from anecdotal reports. Combination therapy may reverse the 2nd degree CHB but hardly any third-

degree CHB. Maternal therapy for the prevention of heart failure and postnatal implantation of the pacemaker may have value in the management of the congenital heart blocks. Here we present three cases of heart blocks diagnosed in prenatal life, with the associations and the outcome of these patients.

CASE 01

A healthy asymptomatic 31-year-old gravida was referred to a tertiary care obstetric unit at 28 weeks of gestation following an incidental finding of fetal bradycardia on routine obstetric examination. There was no history of autoimmune diseases such as Systemic Lupus Erythematosus or Sjogren syndrome. On obstetric examination, symphysio-fundal height was compatible with the period of gestation and ultrasound findings of fetal biometry and umbilical artery Doppler studies were also normal. However, fetal bradycardia of 80 bpm was noted. There were no features of hydrops and liquor volume was within the normal range. She was negative for antinuclear antibody, double-stranded DNA, Anti Ro and Anti-La antibodies. She was referred to paediatric cardiologist for further evaluation of the cardiac condition. She underwent echocardiogram at 28 weeks and 5 days in gestation and found to have cardiac rhythm abnormality with higher atrial rate than the ventricular rate (atrial rate 100bpm and ventricular rate 76 bpm). However, there were no significant structural cardiac defects. The cardiologist's plan was to manage the patient conservatively with close fetal monitoring until up to the delivery. She had a serial ultrasound scan in two-week intervals, and the fetal growth and Doppler studies were normal. She had another fetal echocardiogram at 32 weeks of gestation and there was no new finding apart from fetal bradycardia.

She underwent planned caesarean section following dexamethasone at 36 weeks of gestation due to breech presentation. The male newborn weighing 2.1 kg (Apgar 10¹, 10⁵, 10¹⁰) was treated since birth with high flow oxygen for mild respiratory distress syndrome. Respiratory distress was improved by 36 hours following delivery. The newborn underwent echocardiogram at day 2 which revealed a complete heart block with a ventricular escape rhythm (atrial rate 140bpm,

ventricular rate 80bpm). In addition, there was moderate patent ductus arteriosus and small Ostium secundum atrial septal defects. The baby was referred to the consultant cardiac electrophysiologist for further evaluation. Since the baby had good ventricular rate and adequate cardiac output, acute interventions were not needed. The baby was followed up at 28 days following delivery and had an adequate weight gain (3.2 Kg), and was asymptomatic. Currently the baby is followed up at cardiology and electrophysiology clinics.

CASE 2

A 33-year-old mother of two children in her third pregnancy at 32 weeks of gestation was referred to the tertiary care assessment following the detection of fetal structural abnormality of the heart at routine obstetric ultrasound scan. Her previous pregnancies were uncomplicated, having healthy two children at 7 and 3 years of ages. She had normal blood sugar level during the pre-pregnancy period and her oral glucose tolerance test done at twelve-week of gestation was abnormal. She had been put on oral hypoglycaemic drugs since then and her glycaemic control was reasonably well throughout the pregnancy. There was no history of maternal autoimmune diseases such as Systemic Lupus Erythematosus or Sjogren syndrome. Fetal biometry assessed by obstetric ultrasound scan showed small for gestational age fetus. However, amniotic fluid index and fetal Doppler studies were normal except fetal bradycardia. The patient was referred to the paediatric cardiologist for a fetal echocardiogram. Several structural abnormalities of the hearts were detected, which includes A-V canal defect, congenitally corrected transposition of greater arteries, large inlet ventricular septal defect and moderate pulmonary stenosis. There was cardiac rhythm abnormality with higher atrial rate than the ventricular rate (atrial rate 140bpm and ventricular rate 80bpm). The plan was to repeat the echocardiogram following delivery. She had dexamethasone at 33 weeks of gestation as the fetal growth was static. At 34 weeks and 3 days in gestation, she had an emergency caesarean section due to abnormal umbilical artery Doppler study. A male baby with a birth weight of 1.9 kg was delivered with good condition and Apgar was

8, 9 and 9 at first, fifth and tenth minutes respectively. The baby had poor oxygen saturation since birth and it was around 75% with 1.5 l/min nasal prong Oxygen. Fetal heart rate was maintained around 80bpm and the baby developed severe respiratory distress about one hour following birth, which leads to cardio-respiratory arrest 2 hours following birth. Parents did not consent for postmortem examination. In the postnatal follow-up, mother was referred to a physician as she needs long term management of diabetes to maintain normoglycaemia. She is currently being regularly monitored with regard to diabetes in the medical department. She was emphasized the importance of the proper control of diabetes and pre-pregnancy counseling before the next pregnancy.

CASE 3

A 23-year-old healthy primigravida, who had an uncomplicated early antenatal period, was reviewed at 20 weeks of gestation for anomaly scan. There was a moderate-sized ventricular septal defect and she was referred for specialist assessment with fetal echocardiogram. The fetal echocardiogram confirmed the large perimembranous ventricular septal defect and 2:1 atrio-ventricular block (atrial rate 140bpm and ventricular rate 85bpm). Fetal biometry was normal and there were no features of fetal hydrops to suggest cardiac compromise. Oral glucose tolerance test done at 28 weeks of gestation was normal and there was no history of maternal autoimmune diseases such as Systemic Lupus Erythematosus or Sjogren syndrome. Fetal growth and Doppler studies had been normal throughout the pregnancy. She went into spontaneous onset of labour at 38 weeks of gestation and delivered a male baby vaginally. She was provided close fetal monitoring during labour. The baby was 3.4kg and delivered in good condition. The Apgar was 8, 9 and 9 at first, fifth and tenth minutes respectively. The baby was discharged by the neonatology team at postnatal day 3 following an evaluation by the paediatric cardiology team. Baby is currently being followed up in the cardiology clinic with the plan of future ventricular septal defect closure and planning to make a referral for electrophysiology opinion regarding heart block depending on the cardiac status.

Figure 1: Neonatal echocardiogram at day 14, showing complete heart block

(a)

(b)

(c)

(d)

Figure 2: Two-dimensional fetal echocardiogram at 32 weeks of gestation. Showing, A-V canal defect, congenitally corrected transposition of greater arteries and large ventricular septal defect.

DISCUSSION

Congenital heart block is a type of cardiac arrhythmias. It may manifest as an isolated rhythm abnormality or in combination with structural cardiac disease. The Isolated fetal heart block may be caused either by congenital malformation of the conduction system following fetal myocarditis or due to specific maternal connective tissue disorder. The complete heart block is the commonest type of heart blocks that can be seen among the newborn. Overall incidence of Congenital heart block (CHB) is 1:15000 to 1:22000, and that of complete heart block is around 1:20000 to 1:25000 newborns. The prognosis of fetuses with complete heart block is profoundly affected by the underlying aetiology and associated findings [1].

CHB associated with structural heart diseases is commonly seen in atrioventricular septal defect, heterotaxy syndrome, congenitally corrected transposition of the great arteries, atrial and ventricular septal defects, and in tetralogy of Fallot. Heterotaxy syndrome is a rare congenital heart defect characterized by abnormality of embryonic symmetry resulting in cardiac, visceral and vascular abnormalities. Heterotaxy syndrome with left isomerism is associated with polysplenia and heart blocks. The higher incidence of complete heart block in left atrial isomerism appears to be due to hypoplasia of the sinoatrial node and/or abnormal atrioventricular node development [9]. The commonest conotruncal anomaly that can cause heart block is the congenitally corrected transposition of the great arteries (CcTGA). It is a very rare cardiac defect with atrioventricular and ventriculoarterial discordance. A ventricular septal defect and varying degrees of outflow tract obstructions may coexist with this condition. In these patients, the atrioventricular conduction tissue has a long and extremely vulnerable course which is more prone to disruption. Atrial and ventricular septal defects, Tetralogy of Fallot are other structural defects that can interrupt the conduction pathway and cause heart block.

In heterotaxy syndrome, there is a progression of the second-degree to third-degree heart block due to disruption of the atrioventricular conduction

system by fibrous tissue. The progression of second-degree AV-block in to complete heart block in utero has been described in CcTGA. In contrast, the progression from sinus cardiac rhythm to heart block in left atrial isomerism may have been detected but is certainly not commonly recognized.

Immune-mediated inflammation of the myocardial tissues and conduction system of the fetus due to trans-placental passage of maternal antibodies is another cause of CHB. In the absence of structural abnormalities, maternal transfer of antibodies against SSA/Ro (Sjögren's-syndrome-related antigen A autoantibodies) and SSB/La (Sjögren's-syndrome-related antigen B autoantibodies) produce approximately 80% congenital heart block. However, only 2 % of the seropositive mothers for SSA/Ro and/or SSB/La have newborns with congenital heart block. The gestational age for identification of fetal heart block due to SSA/SSB antibodies is around 23 to 25 weeks of gestation. This is the period where transplacental IgG transfer to the fetus is initiated. It has been suggested that SSA/SSB antibodies, damage the fetal cardiac conduction system to produce congenital heart blocks.

The intrauterine complications associated with congenital heart block are fetal cardiomyopathy, heart failure, development of hydrops, and ultimately intra-uterine fetal deaths. Although it has been suggested that isolated CHB is a generally benign condition, 20% of the affected children die due to the complications.

Reviewing the literature on isolated complete heart block, we found that heart rate below 55 beats/ min in early pregnancy is associated with a greater likelihood of the poor outcome. The likelihood of requiring early pacemaker insertion, however, cannot be predicted confidently by the prenatal fetal heart rate. The prognosis of complete heart block is worsened by the presence of hydrops, a ventricular rate of <60 beats/min and by the presence of associated structural cardiac anomalies. Fetuses with isolated heart block have a better prognosis, but the outcomes are lethal once hydrops develops [10].

If fetal arrhythmias assessed prenatally by echocardiographic and Doppler ultrasound techniques, AV block frequently identified during the fetal period. Fetal bradycardia can also be detected at abdominal auscultation and cardiotocography (CTG) which can be confirmed by an echocardiography. Despite recent developments in the field of fetal magnetocardiography and electrocardiography, fetal echocardiographic ultrasound techniques remain the leading modality for prenatal diagnosis of CHBs.

Efficacy of prenatal treatment for fetal bradycardia due to heart block is limited compared with treatment for fetal tachycardia. Beta receptor stimulants and steroids have been reported to be satisfactory transplacental treatments for fetal heart block, especially first and second degrees. Beta receptor stimulants, such as salbutamol, Ritodrine, and Terbutaline may efficiently increase the ventricular rate and reverse hydrops in some fetuses. Dose and duration of administration time may be adjusted according to fetal cardiac assessment and maternal side effects.

Initial studies have demonstrated the potential benefits of transplacental steroids with or without beta-receptor agonists [11]. This benefit ranges from the resolution of disease to first degree or sinus rhythm [12], to regression of features of hydrops complicating CHB [13].

Considering the transplacental steroids that can be used to treat CHB, placental 11 β -hydroxysteroid dehydrogenase complexes inactivates maternal non-fluorinated corticosteroids such as prednisolone, but not fluorinated corticosteroids. Hence, Dexamethasone and Betamethasone are available to the fetus in active form [14]. Besides, non-fluorinated prednisolone present in the fetal circulation is in inactive form due to the immaturity of fetal hepatic functions [15]. Transplacental steroids are effective in modulating immunological reactions and subsequent inflammation and fibrosis [16].

Several reports have demonstrated that transplacental administration of steroid such as Betamethasone is ineffective for AV block caused by the anti-SSA antibody [17]. The degree of AV block

is improved if steroid administered immediately after the onset of AV block. However, most mothers have not been diagnosed with the disease at the onset of fetal AV block. Another concern of starting steroid is the relatively low (3–7.5%) incidence of fetuses developing AV block in mothers with seropositive SSA. Since steroid therapy has adverse effects on the fetus and the mother, prophylaxis steroid therapy for all mothers who are positive for SSA antibody may not be acceptable. Prophylaxis steroid therapy can be considered in high-risk cases in which there is a previous child with AV heart block.

CHB secondary to maternal immunological disorders are likely to be related to immune response in the form of inflammation and fibrosis, which subsequently damages conduction fibers and myocardium. Therefore, early detection of AV block and early administration of steroids may be the most accepted method [18]. However, there are reports with sudden onset of complete AV block in fetuses without first- or second-degree AV block, even with close cardiac monitoring with frequent fetal echocardiography.

Some studies have shown improvement in the degree of AV block spontaneously without any steroid therapy. Hence, the effect of steroid therapy for AV block remains uncertain. Armia M. et.al. reported that fluorinated steroids is not greater than no treatment for CHB, except downgrading of CHB following the commencement of the treatment. In addition, they raised concerns on fetal growth restriction, oligohydramnios and neurodevelopmental delays with a high dose and/ or prolonged use of fluorinated corticosteroids. Gestational diabetes mellitus and hypertension are common maternal complications associated with prenatal steroid administration [19].

Maternal autoantibodies may affect not only the AV node and conduction system but also fetal myocardium and can cause myocarditis. Administration of steroids may also be effective for treating myocarditis, and it may improve cardiac function of the fetus [20].

Due to its side effects and limited benefits of transplacental steroids, combined therapy has

been attempted. Intravenous immunoglobulin and plasmapheresis have been used to decrease autoantibodies in maternal circulation to treat CHB in mothers with autoimmune diseases. Although there were possible benefits, intravenous immunoglobulin and/or plasmapheresis either did not reverse the progression to complete heart block or did not produce long term satisfactory results [21]. Hence, administration of maternal terbutaline, Dexamethasone and plasmapheresis in combination has been used in situations when the fetal demise is imminent.

An antimalarial agent Hydroxychloroquine probably affects the inflammatory process as well as fibrosis of cardiac tissue. Even with satisfactory results, the use of Hydroxychloroquine limited due to the probable visual and hearing adverse effects [22]. Combined therapy with corticosteroids and Hydroxychloroquine has been described; however, their beneficial effect can be attained when they are used within a strict window period. Hence, there is a place for large prospective studies to comprehensively evaluate the efficacy of different drug combinations [23].

Aslam E et. al. and Yang CH et. al. investigated the combination therapy with immunosuppressive medications such as cyclophosphamide and azathioprine in pregnant women with Sjogren syndrome with good results. However, their evidence was limited to case reports [24] [25]. Regarding fetal pacing therapy, percutaneous transapical in utero fetal cardiac pacing has been attempted as a fetal heart support. However, with currently available technique and instruments, it appears to be associated with high risk, as fetal demise occurred after the procedure in a high proportion of studies cases [26].

In patients with reduced cardiac function in the prenatal period, the postnatal circulatory management is challenging even after inserting a pacemaker. Hence, delivery before the development of reduced cardiac function is recommended. However, too early delivery increases the risk of prematurity associated neonatal complications.

In-utero injuries to the conduction system can be continued even after clearance of maternal

antibodies from the neonatal circulation. In neonates with CHB, if the baby is free of symptoms, a pacemaker is not required. Pacemaker implantation itself can be harmful to neonates. Indications for placement of pacemakers in children include, average heart rate <50 beats/min, associated with episodes of junctional exit block or a flat junctional response to exercise, prolonged QT interval and wide QRS complexes [27].

CONCLUSION

The prognosis of the congenital heart block depends on the presence or absence of structural heart diseases and the type and severity of the cardiac malformation. In general, fetuses with CHB and associated heart disease have a poorer prognosis than those with isolated complete heart block. Prenatal management of fetal arrhythmia may improve the outcome of an affected fetus. Precise and timely prenatal diagnosis is critical for the selection of the appropriate prenatal treatments. However, there are many limitations in managing fetal bradycardia even today and more useful strategies need to be investigated.

Abbreviations

CHB: Congenital Heart Block

bpm: beats per minute

ECHO: Echocardiogram

CcTGA: Congenitally corrected transposition of the great arteries

SSA/Ro: Sjögren's-syndrome-related antigen A autoantibodies

SSB/La: Sjögren's-syndrome-related antigen B autoantibodies

CTG: Cardiotocography

Author declaration**Acknowledgements**

We would like to thank all the patients who participated in this paper for their immense support throughout the study.

Author Contributions

First author DMC did the conception, design, and writing/editing of the paper, and he is responsible for the principal work of this paper. Authors DPK, HA and TDD contributed in editing of the paper. Each author agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Funding sources

We did not receive any funds for the study.

Availability of data and materials

Complete informed written consents were obtained from patients for the publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

Specific ethical board approval was not required for this study as we reported the case of three patients the same way we do for a case report. They received routine, standard clinical care.

Competing interests

Author certifies that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Clancy RM, Buyon JP. Autoimmune-associated congenital heart block: dissecting the cascade from immunologic insult to relentless fibrosis. *Anat Rec A Discov Mol Cell Evol Biol*. 2004; 280(2):1027-35. DOI: <https://doi.org/10.1002/ar.a.20072>.
2. Hon KL, Leung AK. Neonatal lupus erythematosus. *Autoimmune Dis*. 2012; 301274. DOI: <https://doi.org/10.1155/2012/301274>.
3. Gembruch U, Hansmann M, Redel DA, Bald R, Knöpfle G. Fetal complete heart block: antenatal diagnosis, significance and management. *Eur J ObstetGynecolReprod Biol*. 1989; 31(1):9-22. DOI: [https://doi.org/10.1016/0028-2243\(89\)90022-1](https://doi.org/10.1016/0028-2243(89)90022-1)
4. Lin MT, Hsieh FJ, Shyu MK, et al. Postnatal outcome of fetal bradycardia without significant cardiac abnormalities. *American Heart Journal*. 2004; 147(3):540-544. DOI: <https://doi.org/10.1016/j.ahj.2003.09.016>.
5. G R Hughes, Autoantibodies in lupus and its variants: experience in 1000 patients. *Br Med J (Clin Res Ed)*. 1984; 289(6441): 339-342. DOI: <https://doi.org/10.1136/bmj.289.6441.339>
6. Mchado M V, Tynan M J, Curry P V L, Allan L D, Br Heart J. Fetal complete heart block, 1988; 60:512-5. DOI: <https://doi.org/10.1136/hrt.60.6.512>
7. Mevorach D, Elchalal U, Rein AJ. Prevention of complete heart block in children of mothers with anti-SSA/Ro and anti-SSB/La autoantibodies: detection and treatment of first-degree atrioventricular block. *Curr Opin Rheumatol*. 2009; 21(5): 478-82. DOI: <https://doi.org/10.1097/BOR.0b013e32832ed817>.
8. Ruffatti A et. Al. A combination therapy protocol of plasmapheresis, intravenous immunoglobulins and betamethasone to treat anti-Ro/La-related congenital atrioventricular block. A case series and review of literature. *Autoimmun Rev*. 2013; 12(7):768-773. DOI: <https://doi.org/10.1016/j.autrev.2013.01.002>
9. Jaeggi ET, Nii M. Fetal brady- and tachyarrhythmias: new and accepted diagnostic and treatment methods. *Semin Fetal Neonatal Med*. 2005; 10(6):504-14. DOI: <https://doi.org/10.1016/j.siny.2005.08.003>
10. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. A single institution's experience of 30 years. *J Am Coll Cardiol*. 2002; 39(1):130-7. DOI: [https://doi.org/10.1016/s0735-1097\(01\)01697-7](https://doi.org/10.1016/s0735-1097(01)01697-7). PMID: 11755298.
11. Deborah M. et al, Prospective Evaluation of Fetuses With Autoimmune-Associated Congenital Heart Block Followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study, *The American Journal of Cardiology*. 2009; 103(8):1102-1106. DOI: <https://doi.org/10.1016/j.amjcard.2008.12.027>.
12. Copel JA, Buyon JP, Kleinman CS. Successful in utero therapy of fetal heart block. *Am J Obstet Gynecol*. 1995; 173(5):1384-90. DOI: [https://doi.org/10.1016/0002-9378\(95\)90621-5](https://doi.org/10.1016/0002-9378(95)90621-5). PMID: 7503173.
13. Buyon J, Waltuck J, Kleinman C, Copel J. In Utero identification and therapy of congenital heart block. *Lupus*. 1995; 4(2):116-121. DOI: <https://doi.org/10.1177/096120339500400207>
14. Quinkler M, Oelkers W, Diederich S. Clinical implications of glucocorticoid metabolism by 11beta-hydroxysteroid dehydrogenases in target tissues. *Eur J Endocrinol*. 2001; 144 (2): 87-97
15. Saxena A, Izmirly PM, Mendez B, Buyon JP, Friedman DM. Prevention and treatment in utero of autoimmune-associated congenital heart block. *Cardiol Rev*. 2014; 22(6):263-267. DOI: <https://dx.doi.org/10.1097%2FICRD.0000000000000026>
16. Cuneo BF et. al. A management strategy for fetal immune-mediated atrioventricular block. *J Matern Neonatal Med*. 2010; 23 (12):1400-1405 DOI: <https://doi.org/10.3109/14767051003728237>
17. Ciardulli A et. al. Maternal steroid therapy for fetuses with second-degree immune-mediated congenital atrioventricular block: a systematic review and meta-analysis. 2018; 97(7): 787-794. DOI: <https://doi.org/10.1111/aogs.13338>
18. Lindsey E, John M. Atrioventricular block during fetal life. 2015; 27 (3): 164-178. DOI: <https://doi.org/10.1016/j.jsha.2014.07.001>
19. Armia M. et. Al. Use of antenatal fluorinated corticosteroids in management of congenital heart block: Systematic review and meta-analysis, *European Journal of Obstetrics & Gynecology and Reproductive Biology*: X.

- 2019;4:1-12. DOI:
<http://dx.doi.org/10.1016/j.eurox.2019.1000722>
20. Maeni Y, Akiko H, Kanbe T, Hori D. Fetal arrhythmia: Prenatal diagnosis and perinatal management. *J.Obstet.Gynaecol.Res.* 2009; 35(4):623–629 DOI: <https://doi.org/10.1111/j.1447-0756.2009.01080.x>
 21. Zhou KY, Hua YM. Autoimmune-associated Congenital Heart Block: A New Insight in Fetal Life. *Chin Med J* 2017; 130: 2863-71. DOI: <https://dx.doi.org/10.4103%2F0366-6999.219160>
 22. Peter M, Izmirly 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(1): 76-82. DOI: <https://doi.org/10.1161/CIRCULATIONAHA.111.089268>
 23. Noble D, Anna E, Kuller, Jeffrey A, Rhee, Eleanor J. Controversies in the Management of Isolated Congenital Atrioventricular Block. *Obstetrical & Gynecological Survey.* 2015; 70 (8) 518-523. DOI: <https://doi.org/10.1097/OGX.0000000000000208>
 24. Aslan E, Tarim E, Kilicdag E, Simsek E. Sjögren's syndrome diagnosed in pregnancy: a case report. *The Journal of Reproductive Medicine.* 2005;50(1):67-70.
 25. Yang CH, Chen JY, Lee SC, Luo SF. Successful preventive treatment of congenital heart block during pregnancy in a woman with systemic lupus erythematosus and anti-Sjögren's syndrome A/Ro antibody. *J Microbiol Immunol Infect.* 2005; 38(5):365-9. PMID: 16211147.
 26. Jaeggi E, Öhman A. Fetal and Neonatal Arrhythmias. *ClinPerinatol.* 2016; 43(1):99-112. DOI: <https://doi.org/10.1016/j.clp.2015.11.007>. PMID: 26876124.
 27. Brooks P. Fetal manifestations of maternal anti-Ro and La antibodies - more than complete heart block. *Australas J Ultrasound Med.* 2015; 18(3):124-128. DOI: <https://doi.org/10.1002/j.2205-0140.2015.tb00212.x>