Correlation of Maternal Autoantibodies with Fetal Congenital Heart Block

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About the Author

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Abstract

Background Autoimmune fetal congenital heart block (CHB) is the most severe manifestation of neonatal lupus, and it is seen when maternal autoimmune antibodies cross the placenta and damage the AV node of the fetus. CHB is mainly associated with maternal SLE with anti-Ro/SSA- and anti-La/SSB-positive status, and incidence of CHB increases when both the antibodies are present. This study was conducted to know the incidence of fetal CHB in

patients of SLE who had ANA, anti-Ro/SSA and anti-La/SSB positivity.

Methods A prospective study was conducted in a tertiary-care teaching hospital of Indian Armed Forces between Jan 2012 to Sep 2014 where 13 cases of SLE were studied. All these patients were tested for ANA, anti-Ro/SSA and anti-La/SSB antibodies and fetal heart abnormalities. Fetuses with CHB were treated with steroids.

Results Incidence of SLE was 0.14 %, 92 % of SLE patients were positive for ANA, and 46 % had anti-Ro/SSA- and anti-La/SSB-positive status. Two fetuses had congenital heart block, and one fetus required pacemaker placement 5 months after delivery.

Conclusion All the fetal congenital heart blocks are associated with maternal anti-Ro/SSA and anti-La/SSB and ANA antibodies. Treatment by steroids may improve the outcome in early stages of fetal CHB, and delivery with follow-up should be planned in a tertiary-care center where pacemaker placement facility is available.

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Introduction

About 4–5 % of the population is affected by an autoimmune disease [1], and in general, the autoimmune disease incidence is higher in females compared to men. SLE may be diagnosed at any age, but it is common among women that SLE has its onset during the child-bearing years [2] and which indicates a close hormonal association. Pregnancy among the anti-SSA/Ro-SSB/La-positive women is commonly associated with different kinds of complications such as renal involvement, proteinuria and preterm delivery [3]. Studies indicate that regardless of symptomatic condition, lupus increases the fetal, neonatal and maternal risk during pregnancy. Even in inactive SLE, there is still an increased risk of complications during pregnancy [3]. Other studies, however, do not show further complications besides CHB development of anti-SSA/Ro antibodies affecting the pregnancy outcomes [4]. Congenital autoimmune atrioventricular (AV) block is usually seen in association with autoimmune antibodies in mother that cross the placenta and damage the AV node of fetus. The incidence of CHB is 2 % in cases of maternal anti-Ro/SSA antibody positivity, 3 % when both anti-Ro/SSA and anti-La-SSB are positive. The risk of recurrence is 9 times higher in the subsequent pregnancies [5]. Complete congenital fetal heart block related to maternal anti-Ro/SSA autoantibodies typically develops between 20 and 24 weeks of gestation. CHB with a structurally normal heart is frequently associated with maternal autoantibodies to Ro/SSA and La/SSB. A mosaic of maternal, fetal and possibly environmental factors might be involved in inducing CHB, but also the combination of such factors might be the way to induce the onset of CHB [5]. A study was conducted to know the incidence of fetal CHB in patients of SLE who had ANA, anti-Ro/SSA and anti-La/SSB positivity.

Materials and Methods

This study was a prospective observational study of women attending antenatal OPD at a tertiary-care teaching hospital of armed forces, India, over a period of 33 months starting from Jan 2012 till Sep 2014. The local ethics committee approved the study protocol. Pregnant women previously diagnosed as a case of SLE or diagnosed during the present pregnancy were included in the study. All these pregnancies were followed up till 6 months post-delivery. After diagnosis of SLE, all the mothers underwent blood test for

ANA (if not done earlier), anti-Ro/SSA and anti-Ro/SSB. All the fetuses underwent first or second trimester aneuploidy screening, anomaly scan at 18–20 weeks period of gestation and fetal echocardiography at 18–22 weeks period of gestation. If the pregnant woman presented late in pregnancy or late detection of SLE, aneuploidy screen was not done. Pregnant mother was treated during antenatal period with dexamethasone (4 mg/day) after detection of fetal congenital heart block (as per PRIDE study [6]), and all her previous medications (if any) were continued throughout during pregnancy. Period of gestation (POG) was confirmed by dates and correlated with ultrasonography (USG). In case of unsure dates, ultrasonography-expected date of delivery (USG-EDD) of first trimester was taken to calculate POG.

Data have been collected regarding the following aspects:

1. Socio-demographic data;
2. Maternal characteristics in current pregnancy;
3. Indication of delivery;
4. Mode of delivery;
5. Apgar score and neonatal outcome.

For socioeconomic status, monthly income was taken into consideration and divided in three groups namely low (Rs <15,000), middle (Rs 15,000–30,000) and high (Rs >30,000).

Result

A total number of deliveries were 9115 during the 33-month study period, and the incidence of SLE was 0.14 %. Twelve out of 13 SLE patients had ANA-positive status. Six patients had anti-Ro/SSA, and 05 patients had anti-La/SSB positivity. Among the anti-Ro/SSA- and anti-La/SSB-positive patients, only 02 had first-degree fetal congenital heart block (Table 2), and both the fetus had complete heart block with structurally normal heart, and one of them required permanent pacemaker placement at 5 months of age. Most of the mothers who had SLE was in their mid-twenties with average age of 25, and 61.5 % of them were pregnant for the first time. Most of them (77 %) belonged to middle socioeconomic status (Table 1).

Fetal congenital heart block was diagnosed in two fetuses at 34 and 24 weeks period of gestation, respectively. The fetus which was diagnosed CHB at 24 weeks of POG received antenatal corticosteroids in the form of tab dexamethasone 4 mg/day. Both the fetus had complete congenital heart block as detected by fetal echocardiography which was confirmed by neonatal echocardiography

Table 1 Maternal characteristics of SLE +ve patients

Patient No	Age	Socioeconomic status	Parity	Comorbidities	ANA	Anti-Ro/SSA	Anti-La/SSB	CHB diagnosed at POG	Antenatal corticosteroids	GA at delivery	Mode of delivery
1	24	Middle	1	–	+	+	+	34 weeks	Nil	35 weeks 6 days	VD
2	27	Middle	2	GDM	+	+	–	Nil	Nil	36 weeks 3 days	LSCS
3	22	Middle	1	Preeclampsia	+	–	–	Nil	Nil	38 weeks 4 days	LSCS
4	23	Middle	2	Gest Htn	+	+	+	24 weeks	Yes	35 weeks 3 days	LSCS
5	21	Low	1	–	–	–	–	Nil	Nil	37 weeks 5 days	VD
6	24	Middle	3	–	+	+	+	Nil	Nil	38 weeks	LSCS
7	28	Low	2	–	+	+	+	Nil	Nil	39 weeks 1 day	LSCS
8	31	Middle	1	Nephritis	+	–	–	Nil	Nil	36 weeks 2 days	VD
9	32	Middle	1	IVF-ET Preeclampsia	+	–	–	Nil	Nil	37 weeks 1 day	LSCS
10	26	Low	1	Preeclampsia	+	–	–	Nil	Nil	38 weeks 6 days	LSCS
11	24	Middle	1	–	+	–	–	Nil	Nil	36 weeks	VD
12	26	Middle	2	–	+	+	+	Nil	Nil	37 weeks 5 days	VD
13	25	Middle	1	GDM	+	–	–	Nil	Nil	38 weeks	VD

VD vaginal delivery, GDM gestational diabetes mellitus, GA gestational age

Table 2 Fetal-newborn features of SLE +ve mothers

Patient No	Sex	CHB diagnosed at POG	Lower fetal HR	GA at delivery	Birth weight	Apgar score	Age at pacemaker required	Features of block
1	F	34 weeks	76/min	35 weeks 6 days	2.3	8.9	5 months	Complete heart block
2	M	Nil	–	36 weeks 3 days	2.6	4.6	–	–
3	M	Nil	–	38 weeks 4 days	2.7	9.9	–	–
4	F	24 weeks	52/min	35 weeks 3 days	2.1	7.9	–	Complete heart block
5	F	Nil	–	37 weeks 5 days	3.2	7.9	–	–
6	M	Nil	–	38 weeks	2.75	7.9	–	–
7	M	Nil	–	39 weeks 1 day	3.5	7.9	–	–
8	M	Nil	–	36 weeks 2 days	2.45	7.9	–	–
9	F	Nil	–	37 weeks 1 day	2.1	7.9	–	–
10	F	Nil	–	38 weeks 6 days	2.4	7.9	–	–
11	M	Nil	–	36 weeks	2.6	7.9	–	–
12	M	Nil	–	37 weeks 5 days	2.9	7.9	–	–
13	F	Nil	–	38 weeks	3.6	7.9	–	–

after delivery. 62.5 % SLE mothers delivered beyond 37-week POG, and 53.8 % mothers underwent cesarean section.

Lowest heart rate was recorded for the fetuses who had CHB diagnosed at 34 weeks, and 24-week POG was 76 and 52/min, respectively (Table 2). Birth weight of all the babies were average for gestational age except for patient no 9, and this may be because of preeclampsia. Apgar score was within normal limits except for case no 2 as the mother underwent LSCS for non-reassuring fetal heart rate and the baby was on ventilator support for 7 days and recovered well.

Discussion

Most of the SLE cases are in women (90 %), and many of them detected first time during pregnancy. According to Clowse et al. [7], the incidence of SLE in pregnancy is 1:1250. The incidence of SLE in our study was higher as our institute received more referral cases due to a tertiary-care center. During pregnancy, SLE improves in 1/3rd women, worsen in 1/3rd, and it remains unchanged in the remaining third, and pregnancy outcomes are improved remarkably due to early detection and treatment. Most cases of CHB developed almost exclusively in fetuses of

women with anti-Ro and anti-La antibodies, but CHB is also found in fetuses with mothers negative of both the antibodies [8]. During pregnancy, the maternal autoantibodies cross the placenta and bind to cardiomyocytes, and the atrioventricular (AV) conduction system is disrupted by inflammation with subsequent fibrosis and calcification leading to a complete AV block. A life-threatening cardiomyopathy [9] may be present in 10–15 % cases. The most important risk factors for death in these patients are low birth weight, premature gestation, hydrops fetalis, endocardial fibroelastosis and diminished ventricular function.

The best screening test for SLE is identification of ANA. Anti-ds DNA is highly specific for SLE. ANA was found to be positive in 92 % patients of SLE in this study. Bramham et al. [10] reported that even in the presence of anti-Ro and anti-La antibodies, the incidence of myocarditis is only 2–3 % and increases to 20 % with a prior affected child. In our study, 2 fetuses had CHB diagnosed late in pregnancy, and in both the cases, mothers were found to be positive anti-Ro and anti-La antibodies. Seven of our cases were diagnosed case of SLE before pregnancy, and 6 of them were diagnosed first time during pregnancy, but anti-Ro and anti-La were carried out during the pregnancy. Two cases that had CHB referred to us after diagnosis of CHB, and both of them were diagnosed case of SLE before pregnancy. During pregnancy, the antibodies present in the maternal circulation can cross the placenta and affect the fetus. In addressing whether such cross-reactions have pathogenetic consequences, consideration must be given to the low frequency of CHB births among autoantibody-positive women. During pregnancy, these autoantibodies can be absorbed by the placenta which is rich in laminin. If the titer of antibodies exceeds the functional capacity of the placenta for absorption, they will be actively transported into the fetal circulation and could react with fetal cardiac laminin [11].

The substantial morbidity and mortality associated with CHB and the readily available technology for identification of CHB in utero have prompted the search of effective treatment. Maternal administration of intravenous immunoglobulin, corticosteroids, and plasma exchanges has not found to reduce the risk of CHB. PITCH study showed that IVIG at 400 mg/kg on a triweekly schedule from 12 to 24 weeks of gestation is ineffective as a prevention of CHB in pregnancies at risk of recurrence [12]. Regular and close monitoring for heart block and transplacental therapy with fluorinated steroids (dexamethasone) have shown satisfactory results at first evidence of heart block, and it is beneficial in first- and second-degree heart block, but once fetal third-degree block is detected, it is irreversible regardless of treatment [5]. One of our diagnosed case of CHB at 24-week POG had

dexamethasone therapy till delivery. Although maternal tolerability of dexamethasone in our patient was excellent, dexamethasone used throughout the pregnancy may be associated with infection, osteoporosis, osteonecrosis, diabetes, hypertension, premature rupture of membranes, preterm labor and preeclampsia with infection in the fetus, adrenal insufficiency of the fetus, intrauterine growth restriction (IUGR) and oligohydramnios [13]. Information on prenatal progression of the cardiac anomaly is important to plan perinatal management, as early pacemaker insertion may be required in some newborns. Temporary pacing can be achieved transcutaneously, transesophageally or transvenously. A permanent pacemaker placement is needed in most children with CHB. The medical care of CHB is currently focused on identifying the optimal timing of pacemaker therapy to ensure a positive outcome [14]. The fetus diagnosed to have CHB at 34-weeks POG required placement of pacemaker at 5th month of life, and the second newborn is still under follow-up.

Conclusion

In SLE patients, all the fetal congenital heart blocks are associated with maternal anti-Ro/SSA and anti-La/SSB and ANA antibodies. Treatment by steroids may improve the outcome in early stages of fetal CHB, and delivery with follow-up should be planned in a tertiary-care center where pacemaker placement facility is available.

Compliance with Ethical Standards

Conflict of interest Dey Madhusudan, Agarwal Raju and Nambula Vijaya declare that they have no conflict of interest.

Informed Consent Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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