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Insights into maternal and neonatal anti-Ro/SSA antibodies: implications on pregnancy and neonatal health

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Introduction: The presence of anti-Ro/SSA antibodies is associated with an increased risk of adverse maternal and neonatal outcomes in patients with autoimmune rheumatic diseases. We evaluated the rate of adverse maternal and neonatal outcomes in a cohort of pregnant women with positive anti-Ro/SSA antibodies in Qatar and explored the significance of neonatal anti-Ro/SSA antibodies.

Methods: This retrospective observational study was conducted at the largest tertiary institute in Qatar between July 2016 and January 2021. The study included pregnant women with confirmed anti-Ro/SSA positivity who were consistently followed to evaluate maternal and fetal complications.

Results: One-hundred-thirty-two pregnancies from 79 women were included in the analysis. Anti-Ro/SSA positivity was observed in all pregnancies, whereas anti-LA/SSB positivity only in 23.5% of pregnancies. Of the 132 pregnancies, 99 (75%), 27 (20%), and 6 (4.6%) resulted in live birth, miscarriage, and intrauterine fetal demise (IUID), respectively. Among the 99 live births, serology testing for anti-Ro/SSA was performed on 84 neonates, of which only 45 were positive. Neonates born to mothers with primary SS and rheumatoid arthritis (RA) had higher median antibody titers (240 IU/ml) than those born to mothers with systemic lupus erythematosus (SLE) (89.5 IU/ml). The rheumatic diseases (SS, RA, or SLE) showed no significant correlation with adverse pregnancy and fetal outcomes. Congenital heart block (CHB) was recorded in only two infants (2%), and one infant had neonatal lupus (1%). Interestingly, CHB was only observed in previously asymptomatic women who were subsequently diagnosed with SS. Most women (85.9%) were treated with hydroxychloroquine throughout pregnancy. These women had lower rates of miscarriage and neither of their infants presented with CHB.

Conclusion: Miscarriage is the most common adverse outcome reported in this cohort. The incidence of CHB was among asymptomatic carriers only. Nevertheless, hydroxychloroquine use seems to lower the vulnerability to these adverse events. However, these findings need to be validated in larger controlled cohorts. This study is one of few to report results on neonatal anti-Ro/SSA antibody testing.

KEYWORDS

anti-RO/SSA positivity, neonatal lupus, Sjögren's syndrome, rheumatoid arthritis, congenital heart block, lupus

Abbreviations

SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; IUID, intrauterine fetal death; RA, rheumatoid arthritis; CHB, congenital heart block; NICU, neonatal intensive care unit; APL, antiphospholipid.

1 Introduction

Antibodies targeting specific cellular proteins in human connective tissues are valuable diagnostic and prognostic markers of numerous autoimmune diseases (1). However, antibodies do not cause direct harm. A classic example of autoantibodies playing a direct role in disease pathogenesis is the anti-Ro/SSA antibodies (2). Although these antibodies are prevalent in the general population, they are not capable of causing disease in most healthy individuals. Their significance becomes evident during pregnancy, as they can cross the placenta and potentially affect the fetal heart (3) and other tissues such as the skin, liver, and hematopoietic system (4).

These antibodies are associated with the development of congenital heart block (CHB) and neonatal lupus syndrome, while these conditions are both rare and transient (2, 5). Early detection of these complications can aid in the management of first- and second-degree heart blocks. Regular surveillance of the fetal heart rate is considered the standard of care in specialized medical centers. In cases of a complete heart block, a high risk of intrauterine fetal demise (IUID) and neonatal death exists. Dexamethasone and intravenous immunoglobulin (IVIG) are among the drugs commonly used in the management of these complications (6, 7). Consequently, these fetuses are often delivered prematurely, while the placement of permanent pacemakers is required to ensure adequate cardiac function (8, 9).

Hydroxychloroquine is commonly used to treat autoimmune diseases. Many studies support its benefits in preventing CHB recurrence in infants of women positive for anti-Ro/SSA antibody. However, there is not yet enough evidence for the use of hydroxychloroquine as a primary prevention of CHB (5).

Other obstetric complications such as pre-eclampsia, miscarriage, and preterm labor are frequently observed in patients with autoimmune diseases. Limited data is available regarding the association between these complications and anti-Ro/SSA positivity (5, 10). However, advancements in treatment strategies in the field of rheumatology allow many women with autoimmune diseases to conceive (11).

Research on obstetric and fetal complications in patients with anti-Ro/SSA positivity is of interest in optimizing patient care and improving pregnancy outcomes. However, current evidence regarding this subject is scarce. To address this knowledge gap, we aimed to describe the obstetric and fetal complications in patients with anti-Ro/SSA positivity in relation to their underlying diseases and anti-rheumatic medications in a cohort of pregnant women from Qatar.

2 Materials and methods

2.1 Study design and participants

This national, observational, retrospective study included pregnant women who were followed-up at a specialized pregnancy and rheumatic disease clinic using a standardized approach and management, located at the Hamad Medical

Corporation, the largest tertiary institute in Qatar. Pregnancy and rheumatic disease clinics have been well established at Hamad General Hospital since 2005 and are jointly managed by rheumatology experts in collaboration with high-risk obstetric and fetal medicine clinics.

To mitigate potential selection bias inherent in retrospective studies, the patients list was reviewed between July 2016 and January 2021, and each consecutive patient was screened for eligibility. The inclusion criterion for the study was any pregnant woman with anti-Ro/SSA positivity and those who were actively monitored at the pregnancy and rheumatic disease clinic and had documented pregnancy and neonatal outcomes. Pregnant women with anti-Ro/SSA positivity diagnosed according to the American College of Rheumatology classification criteria were categorized based on their underlying disease as SS, SLE, or RA. Notably, if the same woman had more than one pregnancy within the specified period, each pregnancy was considered as a separate case.

2.2 Sample size

The cohort size was based on the number of pregnancies identified during the study period, because the presence of anti-Ro/SSA during pregnancy is rare in the general population. The total number of pregnancies included in this study was 132, which is consistent with the numbers typically reported in other specialized centers worldwide during the same time period. As this study was retrospective and exploratory in nature, it aimed to generate a hypothesis; thus, formal sample size calculation was not implemented.

2.3 Data collection

Retrospective data were collected from the electronic records of pregnant women who visited the clinic between July 2016 and December 2021. Baseline characteristics such as patients' demographics, underlying rheumatic disease type, pregnancy complications, medication during pregnancy, and autoimmune serology profiles, including anti-Ro/SSA and anti LA/SSB titer, were obtained. The outcome measures included maternal, fetal and neonatal outcomes and correlation between antibody titers and medication during pregnancy. Maternal adverse events included pre-eclampsia (new-onset hypertension with systolic and/or diastolic blood pressure greater than or equal to 140 mmHg and 90 mmHg, respectively, after 20 weeks of gestation with proteinuria and/or end-organ dysfunction), eclampsia (defined as new-onset generalized tonic-clonic seizures in a woman with pre-eclampsia), and gestational diabetes (impaired glucose tolerance test after 20 weeks of gestation). Fetal outcomes included live birth, IUID (IUID that occurs at or greater than 20 weeks of gestation or at a birth weight greater than or equal to 350 g), miscarriage (spontaneous pregnancy loss at any time from conception until 24 weeks of gestation), preterm delivery (delivery of a live birth before 37 weeks of gestation), term delivery (labor of a live birth at or after

37 weeks of gestation), and low birth weight (birth weight less than 2.5 kg). Neonatal morbidities included any illness requiring treatment, intervention, or monitoring during the neonatal period. Particular attention was paid to CHB and neonatal lupus (NL).

2.4 Statistical analysis

Continuous and categorical data were analyzed using descriptive statistics, including frequencies and percentages. The Shapiro-Wilk test was used to assess data normality. Sub-group comparisons were conducted with a type-I error risk of 5%. The student's *t*-test was used for normally distributed variables, whereas the Wilcoxon/Mann-Whitney test was used for non-normally distributed quantitative variables. For categorical variables, the chi-square test or Fisher's exact test was used. The results were analyzed using the STATA 13 software (Stata Statistical Software: Release 13. College Station, TX: StataCorp LLC.), and a two-tailed *p*-value of <0.05 was considered statistically significant.

2.5 Ethical considerations

This study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice and the laws and regulations of the Ministry of Public Health, Qatar. The study was approved by the Institutional Review Board of the Medical Research Centre at Hamad General Hospital (MRC 01- 21-130). Due to its retrospective nature, the study was exempted from obtaining informed consent.

3 Results

3.1 Characteristics of the participants

One-hundred-thirty-two pregnancies from 79 women were included in the analysis. The median age at disease diagnosis was 29 years, whereas the median age at pregnancy was 32 years in the selected cohort (Table 1). In this study, participants had a maximum of four pregnancies (an average of two pregnancies following disease diagnosis). Given that Anti-Ro/SSA positivity was a requirement for inclusion, in all 132 pregnancies results were positive. However, LA-positivity was observed only in 31 (23.5%) pregnant women. In the selected samples, the median Ro/SSA antibody titer was 240 IU/ml, ranging from 9.4 to 282 IU/ml, and the median LA antibody titer was 84 IU/ml, ranging from 9.7 to 320 IU/ml). Among the included women, 64 (48.5%) had primary SS, 11 (8.3%) RA, and 57 (43.1%) SLE. Overall, 68% of the participants were from Arab nations and 32% were from other nations in Europe, America, and Asia. There were 15 maternal adverse events, including pre-eclampsia/eclampsia (4.6%) and gestational diabetes (6.9%). A significant proportion of women received folic acid during pregnancy (93.8%), followed by hydroxychloroquine (85.9%), and vitamin D

Table 1 Baseline characteristics of pregnant women with anti-Ro/SSA antibody positivity.

	Median	Range
Age at disease diagnosis (years)	29	22–51
Age at pregnancy (years)	32	17–48
Number of pregnancies after disease diagnosis	2	0–4
anti-Ro/SSA antibody titer among pregnant women (<i>n</i> = 100)	240	9.4–282
La-antibody titer among pregnant women (<i>n</i> = 21)	84	9.7–320
	<i>n</i>	%
anti-Ro/SSA positive pregnancies	132	100
LA-positive pregnancies	31	23.48
APL antibodies	25	18.94
Type of rheumatic disease		
Primary Sjögren's syndrome	64	48.48
Rheumatoid arthritis	11	8.33
Systemic lupus erythematosus	57	43.18
Nationality		
Arab	90	68.18
Others	42	31.82
Maternal complications		
Pre-eclampsia/eclampsia	6	4.65
Gestational diabetes	9	6.98
Medications during pregnancy		
Folic acid	120	93.8
Hydroxychloroquine	110	85.9
Vitamin D	105	82.0
Low dose acetylsalicylic acid	78	60.9
Enoxaparin sodium	30	23.4
Steroid	15	11.7
Azathioprine	11	8.6
Sulfasalazine	6	4.7

APL, antiphospholipid.

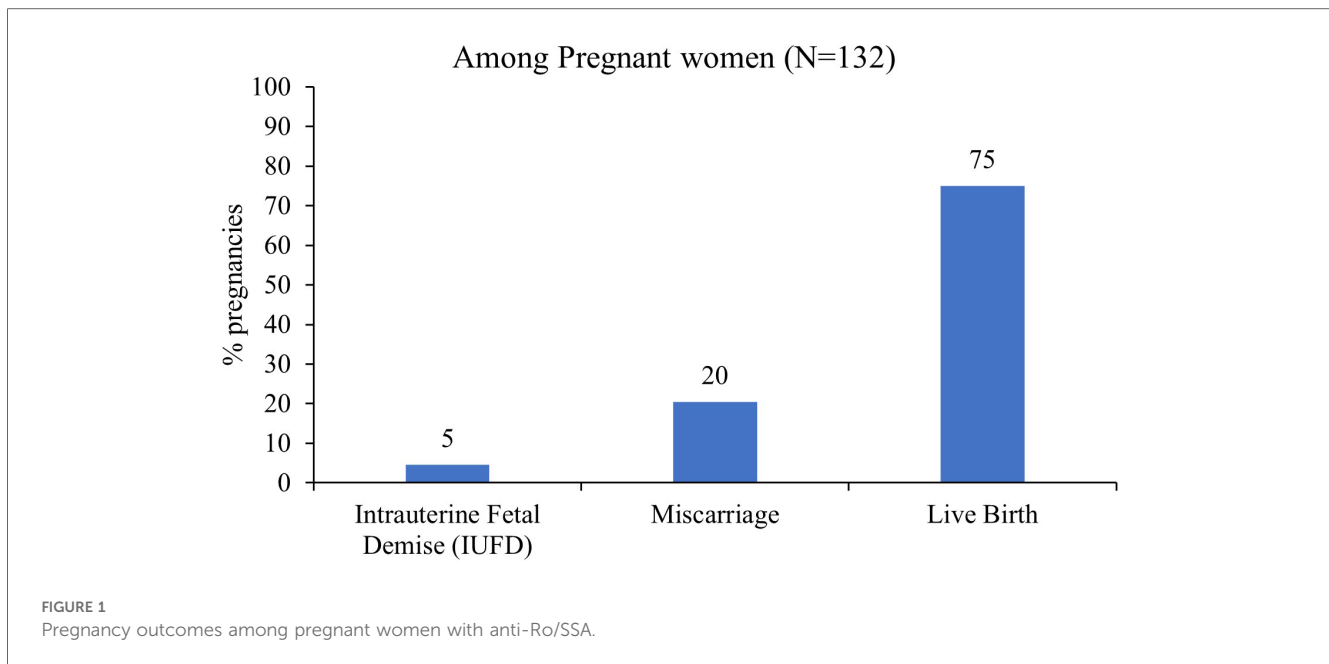
(82.0%). Of the 132 pregnancies, 99 (75%) resulted in live births, 27 (20%) ended in miscarriages, and 6 (4.6%) resulted in IUFD (Figure 1).

3.2 Fetal outcomes and neonatal morbidity

Of the 99 live births, 82 (75%) were full term and 17 (16.5%) preterm births (Table 2). Among the live births, 56 (56.7%) were delivered vaginally, 35 (35.1%) were via cesarean section, and 8 (8.3%) required assisted delivery. Most babies had a birth weight of 2.5 kg or above, with only 12 babies (12.4%) classified as low birth weight (<2.5 kg). A total of 23 pregnancies presented at least one neonatal morbidity. Among these cases, three (3.1%) had fetal distress, one (1%) infection, 12 (12.4%) jaundice, and four (4.1%) congenital anomalies. Additionally, two live births developed CHB and one had neonatal lupus.

Eleven infants required admission to the neonatal intensive care unit (NICU): two for hypoglycemia, three for respiratory distress syndrome, two for sepsis, and two for CHB.

A total of 45 newborns were tested positive for anti-Ro/SSA antibodies. The anti-Ro/SSA titers in newborns ranged from 10 to 240 IU/ml (median, 240 IU/ml; Table 3). When examining



the neonates' anti-Ro/SSA titers based on the mothers' underlying diseases, we found that neonates born to mothers with primary SS and RA had a higher median titer of 240 IU/ml) than those born to mothers with SLE (89.5 IU/ml)).

3.3 Case presentation of congenital heart block and neonatal lupus

CHB was diagnosed in two neonates of two previously asymptomatic mothers who were found to have an anti-Ro/SSA titer >240 IU/ml) upon investigation of abnormal fetal heart rate (at 26 weeks of gestation). Subsequently, both mothers were diagnosed with primary SS during the first year of postpartum follow-up.

The first woman, who also had gestational diabetes, delivered a fetus weighing 3 kg with a complete heart block via assisted delivery at 37 weeks. In addition to hydroxychloroquine administration at 26 weeks of gestation, no additional treatment was provided during pregnancy. The neonate required NICU admission for 4 days. Although bradycardia persisted throughout infancy, permanent pacemaker insertion was not required. Unfortunately, the anti-Ro/SSA antibody testing was not performed at birth.

The second woman, who had an additional comorbidity of hypothyroidism, received betamethasone and hydroxychloroquine following the diagnosis of congenital heart block in her neonate at 26 weeks of gestation. Despite treatment, the complete heart block in the fetus was not reversed. She delivered via cesarean section at 38 weeks of age and the newborn weighed 2.8 kg. The neonate was admitted to the NICU for 1 week and required permanent pacemaker insertion. The infant tested positive for Ro antibodies with a neonatal anti-Ro/SSA titer of 240 IU/ml). Interestingly, each of these

mothers had another pregnancy documented during the study period, and, while on hydroxychloroquine, they delivered healthy babies without a CHB. Furthermore, another newborn was diagnosed with neonatal lupus, while the sole manifestation was a skin rash without organ involvement. The rash resolved spontaneously. In this case, the mother of the baby was diagnosed with primary SS and presented an anti-Ro/SSA titer of 240 IU/ml). The delivery mode was a cesarean section, and the neonate weighed 3.5 kg. The newborn infant was tested positive for anti-Ro/SSA antibodies, with a titer of 240 IU/ml). The mother received hydroxychloroquine throughout pregnancy, while the neonate was not admitted to the NICU.

3.4 Adverse obstetric outcomes and neonatal morbidity in different disease subgroups

The adverse outcomes, delivery characteristics, and neonatal morbidity were compared between mothers diagnosed with SLE, RA, and SS (Table 4). The analysis did not reveal any significant association between the mother's primary disease and pregnancy outcomes, including IUFD, miscarriage, live births as well as pregnancy-related complications, mode of delivery, neonatal birth weight, and neonatal morbidity. However, a significant association was found between the type of maternal disease and the neonates who were tested positive for anti-Ro/SSA antibodies. The incidence of preterm birth, lower birth weight, neonatal morbidity, and admission to the NICU after birth was higher among neonates with a positive anti-Ro/SSA serology than among those in which Ro/SSA antibodies were not detected (Table 5). However, this association was not statistically significant.

Table 2 Obstetric outcomes and neonatal morbidity among pregnant women with anti-Ro/SSA antibody positivity.

	<i>n</i>	%
Term of delivery		
Full term	82	82.83
Preterm ^a	17	17.17
Mode of delivery		
Normal spontaneous vaginal delivery	56	56.57
Caesarean section	35	35.35
Assisted delivery	8	8.08
Birth weight		
Birth weight of >2.5 kg	87	87.88
Low birth weight ^b	12	12.12
Pregnancies with at least one neonatal morbidity		
None	76	76.77
At least one	23	23.23
Type of neonatal morbidity		
Fetal distress	3	3.03
Infection	1	1.01
Jaundice	12	12.12
Congenital heart block	2	2.04
Congenital anomalies	4	4.21
Neonatal lupus	1	1.04
NICU admission	11	11.11
Reasons for NICU admission		
Not admitted	88	88.89
Hypoglycemia	2	2.02
Respiratory distress syndrome	3	3.03
Prematurity	1	1.01
Sepsis	2	2.02
Congenital heart block	2	2.02
No reason defined	1	1.01
Neonates positive for anti-Ro/SSA serology		
Negative	39	39.39
Positive	45	45.45
Not performed	15	15.15
Total	99	

^aBorn before 37 weeks of gestation.

^bLow birth weight: birth weight of <2.5 kg NICU: neonatal intensive care unit.

3.5 Adverse obstetric outcomes and morbidities in different treatment subgroups

Pregnancy outcomes were also examined based on the medications prescribed for the mothers during pregnancy (Table 6). The study found no correlation between sulfasalazine, azathioprine, steroids, and enoxaparin sodium use and any pregnancy outcome. However, significantly lower miscarriage rates ($p < 0.05$) were observed in patients who received hydroxychloroquine (11.8%), low-dose acetylsalicylic acid (10.3%), vitamin D (8.6%), or folic acid (13.3%) than in those who did not receive any treatment. The results of the multivariate logistic regression analysis, which aimed to identify the risk factors for miscarriage (Table 7), indicated that women in which hydroxychloroquine (OR = 0.11) or Vitamin D (OR = 0.07) was administered exhibited significantly reduced odds of miscarriage.

Table 3 Neonatal anti-Ro/SSA titers.

	Neonates' anti-Ro/SSA titer (IU/ml) (N = 45)	
	Median	Range
Type of mother's disease		
Systemic lupus erythematosus	89.5	10–240
Rheumatoid arthritis	240	25–240
Primary Sjogren's syndrome	240	17–240
Birth weight		
Birth weight >2.5 kg	214.5	17–240
Low birth weight (lbw)	240	10–240
Admitted to NICU after birth		
No	240	10–240
Yes	214.5	109–240
Type of neonatal morbidity		
None	233.5	10–240
Fetal distress	189	189–189
Infection	NA	NA
Jaundice	135	17–240
Congenital heart block	240	240–240
Congenital anomalies	240	240–240
Neonatal lupus	240	240–240
Total	240	10–240

4 Discussion

We aimed to provide a comprehensive analysis of the profile of pregnant women who were tested positive for anti-Ro/SSA antibodies and investigated the outcomes of their pregnancies. By describing the specific characteristics of this group, this study aimed to shed light on the potential implications and effects of anti-Ro/SSA antibodies during pregnancy. Additionally, this study examined the various pregnancy outcomes experienced by these women, offering valuable insights into the associated risks and challenges they may face during gestation. We aimed to demonstrate the existence of a relationship between anti-Ro/SSA antibodies and pregnancy outcomes; thus, affecting, potentially, future treatment approaches in this unique population.

Anti-Ro/SSA is a specific type of antinuclear antibody often associated with various conditions, including primary SS, SLE, and RA (12). In this study cohort, most women with anti-Ro/SSA antibodies had primary SS, followed by those with SLE.

Autoimmune diseases influence pregnancy outcomes, increasing the risk of miscarriages and premature labor (13, 14). These effects may be attributed to the potential impact of therapy on the fetus and the passage of autoantibodies through the placenta (15, 16). Consistent with findings of other studies, in the present study, we observed that of the total pregnancies, 20% and 5% resulted in miscarriage and IUFD, respectively, while 17% of 99 live births were preterm newborns. The rate of prematurity in this study is comparable with that reported in previous studies, suggesting that patients with autoimmune diseases have an increased risk of preterm birth (17, 18). Moreover, 12% of the newborn in this cohort had low birth weights, whereas this percentage was higher among those born to

Table 4 Association between the type of rheumatic disease among pregnant women and pregnancy outcomes, complications, and neonatal morbidities.

	Primary Sjögren's syndrome <i>n</i> (%) 34 (45)	Rheumatoid arthritis <i>n</i> (%) 7.5 (10)	Systemic lupus erythematosus <i>n</i> (%) 33.3 (44)	<i>p</i> -value
Pregnancy complications				
None	38 (82.6)	10 (100)	41 (87.2)	0.339
At least one	8 (17.4)	0 (0)	6 (12.8)	
Fetal outcome				
Intrauterine fetal demise (IUFD)	2 (3.1)	1 (9.1)	3 (5.3)	0.206
Miscarriage	17 (26.6)	0 (0)	10 (17.5)	
Live birth	45 (70.3)	10 (90.9)	44 (77.2)	
Term of delivery				
Full term	36 (80)	9 (90)	37 (84.1)	0.798
Preterm	9 (20)	1 (10)	7 (15.9)	
Mode of delivery				
Normal spontaneous vaginal delivery	24 (53.3)	7 (70)	25 (56.8)	0.308
Caesarean section	18 (40)	1 (10)	16 (36.4)	
Assisted delivery	3 (6.7)	2 (20)	3 (6.8)	
Birth weight				
Birth weight >2.5 kg	40 (88.9)	10 (100)	37 (84.1)	0.397
Low birth weight (lbw)	5 (11.1)	0 (0)	7 (15.9)	
Neonates positive for anti-Ro/SSA serology				
No	24 (60.0)	7 (70)	8 (23.5)	0.049
Yes	16 (40.0)	3 (30)	26 (76.5)	
Admitted in NICU after birth				
No	41 (91.1)	10 (100)	37 (84.1)	0.371
Yes	4 (8.9)	0 (0)	7 (15.9)	
Any neonatal morbidity				
No	31 (68.9)	9 (90)	37 (84.1)	0.176
Yes	14 (31.1)	1 (10)	7 (15.9)	

The figures in the brackets represent the percentage. The percentages given here are column percentages. NICU, neonatal intensive care unit.

a mother with SLE, similar to that reported in the literature (5, 19). Maternal antibodies have been linked to mid-pregnancy miscarriages and may be associated with placental blood vessel thrombosis, although this association has not been confirmed

Table 5 Association between neonates' positivity for anti-Ro/SSA serology and term of delivery, birth weight, neonatal morbidities, and NICU admission.

	Neonates positive for anti-Ro/SSA serology		
	Negative <i>n</i> (%)	Positive <i>n</i> (%)	<i>p</i> -values
Term of delivery			
Full term	35 (89.74)	36 (80)	0.245
Preterm	4 (10.26)	9 (20)	
Birth weight			
Birth weight >2.5 kg	36 (92.31)	40 (88.89)	0.719
Low birth weight (lbw)	3 (7.69)	5 (11.11)	
Any neonatal morbidity			
No	30 (76.92)	34 (75.56)	0.99
Yes	9 (23.08)	11 (24.44)	
Admitted in NICU after birth			
No	37 (94.87)	39 (86.67)	0.275
Yes	2 (5.13)	6 (13.33)	

The figures in the brackets represent percentages. The percentages given here are column percentages NICU, neonatal intensive care unit.

definitively (20). Additionally, in 19% of all pregnancies, an overlap of anti-Ro/SSA and antiphospholipid (APL) antibodies was observed. APL antibody testing is routinely performed in patients with a history of miscarriage or in those with SLE. Although APL antibody positivity was not significantly associated with increased risk of miscarriage in this cohort, it may represent a confounding factor for the increased risk of pregnancy-related morbidity.

After the 12th week of pregnancy, anti-Ro/SSA autoantibodies can cross the placenta and damage the developing fetal tissue, leading to CHB and transient neonatal lupus (21). However, other genetic components may also contribute to the development of these conditions (21, 22). In this cohort, two neonates had CHB (2%) and one neonatal lupus (1%). The current findings indicated an incidence of 2% for CHB in neonates born to anti-Ro/SSA positive women, similar to that reported in previous studies in different settings (22, 23). Notably, CHB was only observed in previously asymptomatic women within this cohort, a trend that was also noted by Fredi et al. (24) in a recent study in which these women were referred to as asymptomatic carriers. Hydroxychloroquine, an antimalarial medication, is widely used during pregnancy because of its favorable safety profile. This drug reduces neonatal morbidity in women with SLE by significantly decreasing the rate of premature birth and intrauterine growth restriction (25). In this

Table 6 Association between pregnancy outcomes and medication use during pregnancy.

	Intrauterine fetal demise (IUID) <i>n</i> (%)	Miscarriage <i>n</i> (%)	Live birth <i>n</i> (%)	<i>p</i> -value
Steroids	1 (6.67)	1 (6.67)	13 (86.67)	0.404
Hydroxychloroquine	5 (4.55)	13 (11.82)	92 (83.64)	≤0.001
Enoxaparin	0 (0)	3 (10)	27 (90)	0.175
Sulfasalazine	0 (0)	0 (0)	6 (100)	0.697
Azathioprine	1 (9.09)	1 (9.09)	9 (81.82)	0.441
Low dose acetylsalicylic acid	4 (5.13)	8 (10.26)	66 (84.62)	0.016
Vitamin D	5 (4.76)	9 (8.57)	91 (86.67)	≤0.001
Folic acid	4.17 (5)	16 (13.33)	99 (82.5)	≤0.001

The figures in the brackets represent the percentage. The percentages given here are row percentages.

Table 7 Logistic regression analysis of associated risk factors for miscarriage among pregnant women with auto-immune disease.

Risk factors	Odds ratio	<i>p</i> -value	95% CI
Primary Sjögren's syndrome	3.58	0.313	(0.30, 42.5)
Systemic lupus erythematosus	4.25	0.259	(0.34, 52.5)
APL antibodies	2.34	0.316	(0.44, 12.28)
Hypothyroidism	1.36	0.715	(0.26, 7.12)
Hydroxychloroquine	0.11	0.004	(0.02, 0.50)
Low dose acetylsalicylic acid	1.6	0.591	(0.28, 9.02)
Enoxaparin sodium	0.53	0.507	(0.08, 3.50)
Vitamin D	0.07	≤0.001	(0.01, 0.29)

study, women who received hydroxychloroquine had lower rates of miscarriage. Moreover, hydroxychloroquine is prescribed for secondary prevention of CHB in women with anti-Ro/SSA positivity (9). Although promising, its role in the primary prevention of CHB is yet to be defined. IVIG was proposed as a potential therapeutic agent in the management of second-degree congenital heart block, however its administration at replacement doses did not prevent the recurrence of CHB in mothers who had a previous child with CHB (6, 22). None of the cases in our study received IVIG. Treatment with dexamethasone may be beneficial in the early stages of fetal CHB but does not seem to improve established third-degree heart block (26).

Unfortunately, there is no universally accepted protocol for the prevention of CHB and the associated mortality. Katsafourou et al. suggested that women with autoimmune diseases should receive proper counseling, multidisciplinary surveillance, and individualized antenatal care (14). Therefore, it's recommended for these pregnancies to be managed with serial surveillance using fetal echocardiography between 16 and 18 weeks of gestation until week 26 (27).

Furthermore, vitamin D and folic acid supplementation were associated with improved birth outcomes.

When assessing all live births, 45% of the neonates were found seropositive for anti-Ro/SSA antibodies. The average anti-Ro/SSA titer in neonates was higher among those who were born to mothers with primary SS, had a low birth weight and required admission to the NICU. The presence of anti-Ro/SSA autoantibodies is a defining feature of neonatal lupus. Several clinical manifestations, such as CHB, cutaneous lupus, hepatobiliary disease, hematological manifestations, and central nervous system diseases, may occur in these infants (25). Zuppa et al. (28) suggested that neonates must be monitored

for 6–9 months, as 10% of the infants in their study had anti-Ro/SSA persistence in the blood even at 9 months. The highest incidence of hematological and hepatobiliary neonatal lupus features was observed at 3 months of age. However, available literature on anti-Ro/SSA antibody testing in neonates remains limited.

4.1 Limitations and strengths

Although not all associations mentioned in this study reached statistical significance, valuable insights into the risks associated with pregnancy and neonatal outcomes among women with anti-Ro/SSA positivity are provided. Furthermore, this is the first study to shed light on autoimmune diseases in pregnant women in this geographical region. It is also a rare report documenting anti-Ro/SSA titers in neonates. As the study was retrospective and exploratory in nature, formal sample size calculation and power analysis were not conducted. Therefore, the results should be perceived as laying the groundwork for more comprehensive future investigations in this area.

5 Conclusion

Although an elevated rate of miscarriages, cesarean delivery, and preterm birth was noted in this cohort of women with anti-Ro/SSA positivity, the study was not controlled to draw solid conclusions. It's important to consider other factors that may influence this outcome. Therefore, larger, controlled studies are required to validate this risk. Notably, hydroxychloroquine use was associated with a lower risk of miscarriage and no incidence of CHB. Finally, the significance of neonatal anti-Ro/SSA positivity remains unclear. In this study, the median titer was higher in neonates born to mothers with primary SS; however, further research is needed to explore the significance and potential implications of neonatal anti-Ro/SSA antibody testing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by this study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice and within the laws and regulations of the Ministry of Public Health, Qatar. The study was approved by the Institutional Review Board of the Medical Research Centre at Hamad General Hospital (MRC 01-21-130). Due to its retrospective nature, the study was exempt from obtaining informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this was a retrospective data obtained from the electronic health records and did not involve patient interaction.

Author contributions

SA: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ES: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. NH: Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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