

# Pregnancy outcomes with Primary Sjogren's syndrome among Chinese women: a retrospective cohort study

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## Research article

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# Abstract

Background Data on pregnancy outcomes in Primary Sjogren's syndrome (pSS) women are scarce, and results have been conflicting. The aim of our study is to analyze the adverse pregnancy outcome in patients with pSS.

Methods This was a retrospective cohort study conducted at a tertiary medical center located in Chengdu, Sichuan, China, from May 2013 to November 2018. The relevant medical records of all pregnant women were retrospectively reviewed. Logistic regression analyses were performed to compute crude odds ratios (crude OR) with 95% confidence intervals (CI) for maternal and fetal outcomes. Adjusted odds ratios (aOR) were estimated by logistic regression adjusted for confounders.

Results Women with pSS had a significantly higher incidence of pre-eclampsia (aOR 11.49, 95% CI 1.65-79.98), PPRM (aOR 5.09, 95% CI 1.14-22.63). Compared to general population, pregnant women with pSS were at increased risks of fetal loss (aOR 15.06, 95%CI 1.19 to 191.11), and a higher risk of fetal growth restriction (aOR 15.69, 95%CI 1.61 to 153.33), preterm birth (aOR 5.52, 95%CI 1.83 to 16.65), a cesarean section (aOR 6.53, 95%CI 3.18 to 13.42) and a neonatal intensive care unit admission (aOR 12.86, 95%CI 1.88 to 87.82) after adjusting for confounding factors. The rate of congenital heart block in the pSS group was 4.7%.

Conclusions Pregnant women with pSS were at increased risk of having adverse pregnancy outcomes. Women with pSS require prenatal counseling to explain the risks involved and well control of pSS condition before conception and a close antenatal monitoring should be performed by both rheumatologists and obstetricians.

## Background

Sjögren syndrome (SS) is an autoimmune disease that can present either alone, as in primary Sjögren syndrome (pSS), or in association with an underlying connective tissue disease, most commonly systemic lupus erythematosus (SLE) or rheumatoid arthritis (secondary Sjögren syndrome).[1] The clinical presentation of SS extends from dryness of the main mucosal surfaces to systemic involvement (extraglandular manifestations).[2] pSS is the second most common autoimmune disease that has an estimated prevalence ranging from 0.1% to 4.8% in different population, with a female to male ratio reaching 9:1[3]. pSS affects predominantly middle-aged women, characterized by the presence of anti-SSA/Ro antibodies, anti-SSB/La antibodies. Affected women are likely to experience more complicated pregnancies than women without the disease.[4, 5] These antibodies cross the placenta from 12 weeks of gestation, which mediate the tissue damage and are responsible for complications in pregnancies of women with pSS.[6] However, reports on pregnancy outcomes beyond congenital atrioventricular block(AV block) are rare in pSS. It may be related to the fact that pSS does not usually become clinically apparent until the fourth decade of life. Nowadays the incidence of pregnancy with pSS is visible due to the late marriage age and the Two-Child policy in China. However, pregnancy outcomes in women with

pSS have not been extensively studied. The objective of our study is to analyze the adverse pregnancy outcome in patients with pSS in a Chinese cohort.

## Methods

Our study was retrospectively conducted in the department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, People's Republic of China, which is a level-three, referral, mother-children medical center in southwest China from May 2013 to November 2018. pSS was diagnosed according to the American European Consensus Criteria for pSS.[7] All pregnant with pSS were evaluated by an experienced obstetrician and by a rheumatologist at least monthly. Reference participants were selected from women who were not diagnosed with pSS, matched with the study group by date of admission (five references were selected for every woman with pSS). Women with multiple pregnancies were excluded. All participants received regular, routine antenatal care in West China Second University Hospital, Sichuan University. Data were reviewed from electronic databases. Demographic characteristics of the participants including maternal age at pregnancy, region, body mass index (BMI), family history of pSS, way of conception, history of spontaneous abortion, and clinical comorbidities were recorded. Comorbidities included a diagnosis of hypertension or diabetes before pregnancy. For the pSS cohort, we collected the relevant data including the history of pSS, pre-gestational pSS status(the active stage, the remission stage, and the initial onset), pSS clinical manifestations, the laboratory tests and medications.

Maternal outcomes included gestational hypertension, pre-eclampsia (PE), gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP), postpartum hemorrhage (PPH), premature rupture of membranes (PROM), including term PROM ( $\geq 37$  weeks), preterm PROM (PPROM,  $< 37$  weeks). Fetal outcomes were fetal loss, fetal growth restriction (FGR), congenital heart block (CHB) (diagnosis of CHB confirmed by fetal echocardiography; AV block diagnosed in utero, at birth or within the neonatal period), [8] very preterm birth ( $28^{+0} - 31^{+6}$  weeks), moderate to late preterm birth ( $32^{+0} - 36^{+6}$  weeks), mode of childbirth (cesarean section or vaginal birth), neonatal intensive care unit (NICU), birthweight and gestational days.

Statistical analysis was performed using SPSS V23.0. Continuous variables were presented as mean  $\pm$  standard deviation, median, or range and analyzed using Student's t-test. Categorical variables were presented as frequencies or percentages and analyzed using the  $\chi^2$  test or Fisher's exact probability test. Logistic regression analyses were conducted to compute crude odds ratios (crude OR) with 95% confidence intervals (CI) for adverse pregnancy outcomes. Potential confounding factors, including maternal age, BMI, in vitro fertilization (IVF), a history of spontaneous abortion, region, nulliparity, and comorbidities were adjusted and new results were presented as adjusted ORs with 95% CIs. Statistical significance was considered  $P < 0.05$ .

## Results

64 pregnant women with pSS (cases) and 320 pregnant without pSS (references) from May 2013 to November 2018 were included. The characteristics of the population are described in Table 1. Mean ages, BMI, nulliparity, and clinical comorbidities did not differ between the two groups. However, way of conception, history of spontaneous abortion and region were significantly different between cases and references. The median duration of pSS history was 2.5(range 0.2–10.6) years in pSS group. Only 2% of pregnant women with pSS were in the active age and 10% of women were first diagnosed with pSS during pregnancy. In pSS group, 43.8% were anti-SSA positive and 18.8% were anti-SSB positive. (Table 1).

Compared to the general population, women with pSS had a significantly higher incidence of pre-eclampsia (aOR 11.49, 95% CI 1.65–79.98), PPRM (aOR 5.09, 95% CI 1.14–22.63). However, we did not observe a difference in PROM (aOR 1.10, 95% CI 0.54–2.23), GDM (aOR 0.62, 95% CI 0.24–1.61), gestational hypertension (0% versus 0.6%), and PPH (0% versus 1.3%) between the two groups. Interestingly, the rate of ICP was lower in women with pSS than references (aOR 4.61, 95% CI 1.41–15.02). Twelve pSS patients(18.8%) flared up during pregnancy (Table 2).

Women with pSS were at increased risk of fetal loss (aOR 15.06, 95% CI 1.19–191.11), FGR (aOR 15.69, 95%CI 1.61–153.33), preterm birth (aOR 5.52, 95% CI 1.83–16.65), moderate to late preterm birth (aOR 4.56, 95% CI 1.39 –14.99), cesarean section (aOR 6.53, 95%CI 3.18–13.42), neonatal genders (aOR 1.93, 95% CI 1.02–3.63), and NICU admission for neonates (aOR 12.86, 95% CI 1.88–87.82). Furthermore, we found lower neonatal birthweights ( $2847.3\pm 682.5\text{g}$ ) and gestational days ( $264.8\pm 19.5\text{days}$ ) in pSS group (both  $p<0.05$ ). Congenital heart block (CHB) was diagnosed in 3 and 0, respectively, of the case group and the reference group. No significant differences were found regarding congenital malformations, low Apgar scores between the two groups (Table 3).

Medications of the pSS patients during pregnancy mainly included six kinds of medicines at the following frequencies: hydroxychloroquine (71.9%), glucocorticoids (62.5%), low-dose aspirin (17.2%), low-molecular-weight-heparin (LMWH) (7.8%), intravenous immunoglobulins(1.6%) and platelet transfusion (1.6%)(Table 4).

## Discussion

Our study showed that pregnant women with pSS had poorer pregnancy outcomes compared to a general obstetric population. They were at increased risk of pre-eclampsia, PPRM, elective cesarean sections, and their fetuses/infants were at increased risk of FGR, fetal loss, preterm births, CHB, and admission to NICU.

We observed differences in region and spontaneous abortion between the two groups. Also, our study suggested that patients with pSS had a higher risk of PE (6.3% versus 0.6%) and PPRM (6.3% versus 1.9%). Explanations for PE are manifold, but often can be attributed to inadequate trophoblast invasion of the spiral arteries with a subsequent defective establishment of maternal-fetal vascularization. In addition, maternal proinflammatory status as well as endothelial dysfunction also seem to mediate

placental insufficiency. Of note, we noticed a significantly lower rate of ICP in women with pSS than in the controls (10.9% vs 39.4%). None of the previous studies reported the same result. Further studies of larger populations should be conducted.

Our results indicate that pSS is a significant risk factor for fetal loss. This finding was consistent with several previous studies. [11–13]CHB is the most severe fetal complication and supposedly occurs due to the damage of the atrioventricular node by anti-SSA or anti-SSB antibodies, or both. The reported prevalence of CHB in the offspring of an anti-SSA-positive woman is 1% to 2%. The recurrence rate in a patient with anti-SSA or anti-SSB antibodies positive, who has a previous child affected, is approximately ten times higher.[14–16] Our study confirmed this finding and we found the rate of CHB in the pSS group was 4.7%.

The incidence of preterm delivery was significantly higher in women with pSS than the references in several previous studies.[10, 17–20] Our study is in accordance with these results, and the risk of preterm birth was also fourfold higher in moderate to late preterm subgroups of women with pSS.

Our study showed an increased rate of FGR in pSS patients compared with the expect for the general women. In previous studies, the mean neonatal birthweight and the mean neonatal birthweight percentile were significantly lower in the offspring of women with pSS in comparison to controls.[10, 21] In the present study, we observed the mean neonatal birthweight of women with pSS was significantly lower ( $2847.3 \pm 682.5$  g VS.  $3283.3 \pm 406.8$  g) than the references. This may be related to a pathologic FGR and is not influenced by the timing of the delivery.[10] Immunological disturbances in patients with pSS could be responsible for the decrease in the neonatal birthweight through placental insufficiency.[10, 19]

A previous study confirmed that no significant difference was found regarding way of delivery.[22] However, our study indicated a high rate of cesarean section (cases vs references: 37.5% vs 15.0%), consistent with a previous study.[18] This might be related to an increased risk of severe fetal outcomes and pregnancy complications in pSS pregnancies resulting from an increased risk of preeclampsia and FGR. Furthermore, in order to prevent complications related to pSS during vaginal delivery, some patients with pSS may tend to undergo an elective cesarean.

A higher NICU admission rate can be found in pSS group. It can be interpreted in several ways. The most obvious explanation for the results might be pSS, causing FGR, PPRM, CHB and prematurity. Congenital malformations also lead to NICU admission. In our study, three live births with congenital malformations, including two congenital hydronephrosis, and one congenital intestinal obstruction, occurred in the pSS group.

The outcome of pregnancies in women with pSS can be good with use of a multidisciplinary management by both an obstetrician and a rheumatologist. In our study, hydroxychloroquine(HCQ) and steroids were the most common medications used by patients with pSS. Ballester, C., et al. reported that HCQ may play a role in preventing preterm birth and low birth weight of women with pSS.[19] Furthermore, they are proven to decrease the incidence of congenital heart block in neonates caused by anti-SSA/Ro

antibodies, anti-SSB/La antibodies.[23] Of note, steroids also can be used to reduce the antibody-mediated inflammatory damage of nodal tissue. Low-dose aspirin and prophylactic LMWH are recommended in women at high risk of preeclampsia. [24]

This is the first study to evaluate pregnancy outcomes for pSS women in a Chinese cohort. What's more, we have adjusted many important confounding factors when estimating the impact of pSS on adverse pregnancy outcomes. However, our study had several weaknesses that qualified our findings. The major limitation of our study may relate to the numbers of patients and retrospective designs. In addition, our study participants had undergone therapy that might influence our results. Finally, the dataset only included Chinese pregnancy in a single center. Our findings may not be generalizable to populations and larger prospective studies are needed to confirm our findings.

## Conclusion

In this study, pSS significantly increased the risk of adverse pregnancy outcomes. Women with pSS require prenatal counseling to explain the risks involved and well control of pSS condition before conception. A close antenatal monitoring by both rheumatologists and obstetricians should be performed in pregnant women with pSS. More large studies are needed to investigate the mechanisms behind these findings in pSS pregnancies in the future.

## Abbreviations

ACA: anticardiolipin antibodies; ANA: antinuclear antibodies; aOR: adjusted odds ratios; aPL: antiphospholipid antibody; APS: antiphospholipid syndrome; AV block: atrioventricular block; BMI: body mass index;  $\beta$ 2GP1: anti- $\beta$ 2-glycoprotein 1; CHB: congenital heart block; CI: confidence intervals; FGR: fetal growth restriction; GDM: gestational diabetes mellitus; HCQ: Hydroxychloroquine; ICP: intrahepatic cholestasis of pregnancy; IVF: in vitro fertilization; LA: antibodies and lupus anticoagulant; LMWH: low-molecular-weight-heparin; NICU: neonatal intensive care unit; PE: pre-eclampsia; PPH: postpartum hemorrhage; PROM: premature rupture of membranes; pSS: primary Sjögren syndrome; SLE: systemic lupus erythematosus; SS: Sjögren syndrome

## Declarations

## Ethics approval and consent to participate

The Medical Ethical Committee granted a waiver for informed consent for this study. Approval to obtain clinical data from the database was received from the Office of the Medical Director of the hospital. All patient information remained confidential.

## Consent for publication

Not applicable.

## Availability of data and materials

The data that support the findings of this study are available, but restrictions apply to the availability of these data, which was used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Internal Review Board.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

JFX and DJC were responsible for the conception and design of the study. JFX and YT collected and analyzed the data. JFX drafted the initial manuscript. BP revised the manuscript. All authors read and approved the final version of the manuscript.

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Not applicable

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## Tables

<b>Variables</b>	<b>pSS cases</b>	<b>Non-pSS cases</b>	<b>P values</b>
	<b>(n=64)</b>	<b>(n=320)</b>	
<b>Characteristics</b>			
Age (Years)	32.0±4.3	30.3±4.1	0.12
BMI	20.8±2.5	20.8±2.4	0.98
Family history of pSS [frequency]	3(4.7%)	NA	NA
IVF (frequency)	9(14.1%)	9(2.8%)	0.00**
<b>History of spontaneous abortion (frequency)</b>			
0	31 [48.4%]	287 [89.7%]	0.00**
1	17 [26.6%]	20 [6.3%]	
≥2	16 [25.0%]	13 [4.1%]	
History of pSS	2.5(0.2-10.6)	NA	NA
<b>Region</b>			
City	47 [73.4%]	300 [93.8%]	0.00**
Rural	17 [26.6%]	20 [6.3%]	
Nulliparity	50 [78.1%]	227 [70.9%]	0.24
<b>Clinical comorbidities</b>			
Prepregnancy diabetes	0 [0%]	2 [0.6%]	NA
Prepregnancy hypertension	1 [1.56%]	0 [0%]	NA
<b>pSS clinical manifestation</b>			
APS	2(3.1%)	NA	
SLE	1(1.56%)	NA	
Nephritis	1(1.56%)	NA	
Hyperglobulinemia	1(1.56%)	NA	
Thrombocytopenic purpura	1(1.56%)	NA	
Leukopenia	1(1.56%)	NA	
<b>Pre-gestational pSS status</b>			
Remission stage	52(81.3%)	NA	
Active stage	2(3.1%)	NA	
Initial onset	10(15.6%)	NA	
<b>Laboratory test during pregnancy</b>			
SSA	28 [43.8%]	NA	
SSB	12 [18.8%]	NA	
ANA	33 [51.6%]	NA	
aPL	3 [4.7%]	NA	

\*\*P<0.01

ANA, anti-nucleus antibody; aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; BMI, body mass index; NA, not applicable; pSS, primary Sjogren's syndrome; SLE, systemic lupus erythematosus;

**Table 2 Maternal outcomes in patients with pSS and non-pSS**

Maternal outcomes	pSS	Non-pSS	Crude OR	aOR†
	(n=64) n(%)	(n=320) n(%)	(95%CI)	(95%CI)
Gestational hypertension	0(0)	2(0.6)	NA	NA
Pre-eclampsia	4(6.3)	2(0.6)	10.60(1.90-59.18)**	11.49(1.65-79.98)*
GDM	8(12.5)	41(12.8)	0.97(0.43-2.19)	0.62(0.24-1.61)
PROM	17(26.6)	76(23.8)	1.16(0.63-2.14)	1.10(0.54-2.23)
PPROM	4(6.3)	6(1.9)	5.34(1.50-19.02)*	5.09(1.14-22.63)*
Term PROM	10(15.6)	70(21.9)	0.89(0.46-1.74)	0.84(0.39-1.79)
ICP	7(10.9)	11(3.4)	3.45(1.28-9.27)*	4.61(1.41-15.02)*
PPH	0(0)	4(1.3)	NA	NA
SS flare	12(18.8)	NA	NA	NA

\*P&lt;0.05

\*\*P&lt;0.01

aOR†, adjusted ORs were calculated using a logistic regression analysis and were adjusted for maternal age, body mass index, region, nulliparity, history of spontaneous abortion, history of diabetes and history of hypertension.

GDM, gestational diabetes; ICP, intrahepatic cholestasis of pregnancy; IVF, in vitro fertilization; NA, not applicable; PPH, postpartum hemorrhage; PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes; pSS, primary Sjogren's syndrome; SLE, systemic lupus erythematosus; Term PROM, term premature rupture of membranes;

**Table 3 Fetal outcomes in patients with pSS and non-pSS**

Fetal outcomes	pSS	Non-pSS	Crude OR	aOR
	(n=64) n(%)	(n=320) n(%)	(95%CI)	(95%CI)
Fetal loss	3(4.7)	1(0.3)	15.69(1.61-153.33)*	15.06(1.19-191.11)*
Live birth	61(95.3)	319(99.7)	0.06(0.01-0.62)*	0.07(0.01-0.84)*
FGR	3(4.7)	1(0.3)	15.68(1.61-153.33)*	15.69(1.61-153.33)*
Preterm birth	10(16.4)	11(3.4)	5.20(2.11-12.84)**	5.52(1.83-16.65)**
Very preterm birth	2(3.1)	1(0.3)	10.29(0.92-115.24)	12.43(0.81-192.45)
Moderate to late preterm	9(14.1)	10(3.1)	4.43(1.68-11.71)**	4.56(1.39-14.99)*
Caesarean section	48(75.0)	88(27.5)	7.91(4.27-14.65)**	6.53(3.18-13.42)**
Elective caesarean	24(37.5)	48(15.0)	3.40(1.88-6.15)**	3.32(1.59-6.93)**
Emergency caesarean	24(37.5)	40(12.5)	4.20(2.29-7.69)**	3.05(1.48-6.26)**
Congenital malformation	3(4.7)	1(0.3)	1.68(0.17-16.39)	0.62(0.04-9.87)
CHB	3(4.7%)	0(0)	NA	NA
Neonatal gender(boys)	38(59.4%)	155(48.4%)	1.48(0.86-2.54)	1.93(1.02-3.63)*
Birth weight(kg)	2847.3±682.5	3283.3±406.8	NA	NA
Gestational days(d)	264.8±19.5	275.4±11.7	NA	NA
Apgar score at 1min	1(1.6%)	0(0%)	NA	NA
NICU	5(8.2%)	2(0.6%)	13.48(2.55-71.09)**	12.86(1.88-87.82)**

\*P&lt;0.05.

\*\*P<0.01.

aOR†, adjusted ORs were calculated using a logistic regression analysis and were adjusted for maternal age, body mass index, region, nulliparity, history of spontaneous abortion, history of diabetes and history of hypertension.

CHB, congenital heart block; FGR, fetal growth restriction; NA, not applicable; NICU, neonatal intensive care unit.  
pSS, primary Sjogren's syndrome

**Table 4 Medications used during pregnancy by women with pSS**

<b>Medications</b>	<b>pSS (n=64)</b>	<b>Frequency(%)</b>
Hydroxychloroquine	46	71.9
Glucocorticoids	40	62.5
Aspirin	11	17.2
Low molecule heparin	5	7.8
Intravenous immunoglobulins	1	1.6
Platelet transfusion	1	1.6

pSS, primary Sjogren's syndrome