

## Original article

# Pregnancy and fetal outcome in women with primary Sjögren's syndrome compared with women in the general population: a nested case–control study

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## Abstract

**Objective.** To study pregnancy and fetal outcome in women with primary SS (pSS) compared with women in the general population.

**Methods.** In a nested case–control setting, variables related to pregnancy and fetal outcomes were compared. Cases ( $n=16$ ) were identified through registry linkage (Malmö pSS registry and a database entailing information of all pregnancies and deliveries in Malmö from 1990 through 2006). For each pregnancy with pSS, the following five deliveries from the same registry were chosen as controls ( $n=80$ ).

**Results.** All cases fulfilled the American European Consensus Criteria for pSS and were positive for ANA and anti-SSA antibodies. Date of diagnosis was before pregnancy in 10 women and after delivery in 6. Mean age at delivery was significantly higher in women with pSS (33.6 years) vs controls (29.8 years). While pregnancy duration did not differ, mean birthweight was significantly lower in offspring of pSS mothers (3010 g) vs babies of control mothers (3458 g). Normal partus in contrast to vacuum extraction or Caesarean section was significantly more frequent in healthy women than in pSS women (83 vs 56%). Other pregnancy outcomes such as parity, miscarriages and Apgar score did not differ. There were no significant differences between women with a pSS diagnosis before or after the index pregnancy. Only one of the included pregnancies was complicated by intrauterine AV block.

**Conclusion.** Pregnancy occurs later in life in pSS women. Mothers with pSS give birth to offspring with lower birthweight and less commonly have normal partus.

**Key words:** Primary Sjögren's syndrome, Pregnancy, Fetal outcome, Nested case–control study.

## Introduction

Primary SS (pSS) is the second most common autoimmune disease after RA, with a prevalence of ~0.3–0.6% [1], when defined strictly according to the American European Consensus Criteria (AECC) [2] and a female: male ratio of 9:1. Uncomfortable symptoms (dry mouth

and eyes, gastrointestinal and urogenital discomfort) [3], reduced health-related quality of life [4], disabling fatigue [5] and increased risk of and death due to non-Hodgkin's lymphoma [6, 7] make pSS a bothersome condition for both patients and physicians. Secondary SS, in contrast, co-exists with other autoimmune diseases such as RA and SLE [8].

Although the incidence estimates are uncertain, it is well known that the disease often starts in the fourth or fifth decade of life; thus, the majority of pSS patients are post-menopausal. In a cross-sectional analysis of our female pSS patients, only 13% were  $\leq 45$  years. At diagnosis, only 29% were  $\leq 45$  years and 13% were  $\leq 35$  years of age (own unpublished registry data). However, pSS can occur in all age groups, including children.

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Pregnancy complications due to the occurrence of anti-Ro/SSA and anti-La/SSB autoantibodies in the maternal serum are well recognized as neonatal lupus and congenital heart block (CHB) [9]. The incidence of neonatal lupus in an offspring of a mother with anti-Ro/SSA antibodies is estimated at 1–2% [10], but may be as high as >20% if the mother has given birth to a child with neonatal lupus or CHB before [11].

Reports on pregnancy outcomes beyond neonatal lupus and congenital AV block are rare in pSS in contrast to the situation in SLE and APS. Pregnancy outcome in pSS has not been extensively studied, but has in general not been considered to be associated with impaired fetal outcome [12], although two studies have reported an increased rate of spontaneous abortion and fetal loss in pregnancies before SS diagnosis [13, 14]. The only study up to now applying the most recent and widely accepted classification criteria for pSS [2] could not reveal significant differences in pregnancies in pSS before diagnosis compared with controls [15]. The aim of the present study was to study the impact of pSS on fetal and pregnancy outcome compared with pregnancy outcomes in the general population by linking two registries covering the broad majority of pSS patients and all deliveries in Malmö since 1990.

## Materials and methods

### Patients and controls

The present study is designed as a nested case-control registry linkage study. The Malmö SS registry was established in 1984 as an approved research registry covering the majority of clinically symptomatic pSS cases in Malmö and additionally a number of cases from the surrounding regions. All patients, independently of disease severity, were followed prospectively at intervals of 6 months to 2 years. Clinical, laboratory and histological data were collected. After 2002, all SS diagnoses were re-evaluated according to the AECC criteria for pSS [2] and only patients fulfilling the AECC criteria are included in this study.

All deliveries since 1990 at the only delivery department in Malmö have been continuously included in a prospective database and research registry. The Malmö SS registry and the Malmö delivery registry were linked using the unique Swedish personal identification number and all pregnancies in patients with pSS between 1990 and 2006 were included, as long as delivery occurred at Malmö University Hospital irrespective of whether they received their pSS diagnosis before or after pregnancy. Since this study was considered as a normal follow-up of health-care production and quality, there was no reason for applying to the Swedish research ethics committee.

Sixteen deliveries occurred in 14 pSS patients. For each delivery in a pSS patient, the next five deliveries from the general population in the registry were selected as control deliveries ( $n = 80$  deliveries). The study period was from January 1990 through December 2006. The following information was extracted from the delivery register: date of

delivery, numbers of parity and miscarriages, pregnancy duration, birth-length, birthweight, expected birthweight, artery and venous pH, Apgar score at 5 min and way of delivery (normal delivery, vacuum extraction delivery or Caesarean section and if any delivery induction). From the Malmö Sjögren's registry: autoantibody profile, disease duration and age were collected for all pSS cases. Premature birth was considered as birth before gestational Week 37 + 0. Low birthweight (LBW) was defined as birthweight <2500 g. Birthweight deviation was birthweight in relation to expected weight for the gestational age [(expected weight–newborn weight)/expected weight], presented as percentage. Severe fetal outcome is defined as a sum of the following: death (before or after delivery, Apgar score 0, 5 min after delivery), severe fetal distress (umbilical cord blood pH < 7, Apgar score < 4).

### Statistical methods

Mann–Whitney U-test and chi-squared test were used to compare pSS patients with a clinically diagnosed disease and their offspring with those in a pre-diagnostic state and their offspring. Conditional logistic regression analyses were used to compare cases and controls taking the matched design of the study into account. Statistical significance was set at  $P < 0.05$ .

## Results

### Demographic data

Mean age at delivery was significantly ( $P = 0.004$ ) higher for the pSS patients than for controls [33.6 (range 29–37) and 29.8 (range 24–35) years, respectively] (Table 1). Ten deliveries occurred in women with pSS diagnosis before pregnancy (mean disease duration 2.9 years), whereas in six deliveries pSS was not yet diagnosed (mean delay of diagnosis 5.7 years). ANA and Ro/SSA antibodies were present in all the cases at the time point of SS diagnosis. Anti-La/SSB and RF were present in 70 and 60% of those with pSS before pregnancy and 67 and 83% of those with pSS after pregnancy. Among the patients with pregnancy preceding diagnosis of pSS, retrospective analysis of saved serum samples revealed the presence of autoantibodies to Ro and La in all but two mothers, who were seronegative for Ro and La during pregnancy. These two pregnancies were completely uncomplicated. The number of parity and miscarriage was not significantly different either between cases and controls or between the two case groups (Table 2).

### Pregnancy outcome

Mean pregnancy duration was 277 days for controls vs 272 days for Sjögren's patients ( $P = 0.4$ ). Normal delivery in contrast to instrumental and Caesarean section was significantly more common in controls than pSS cases ( $P = 0.02$ ). Generally, pregnancy outcome did not differ between patients with a pSS diagnosis before or after the index pregnancy (Table 2).

**TABLE 1** Demographic data for cases and controls (*n* = number of deliveries)

	Controls ( <i>n</i> = 80)	All SS deliveries ( <i>n</i> = 16)	<i>P</i> -value	SS diagnosis		<i>P</i> -value
				Before pregnancy ( <i>n</i> = 10)	After pregnancy ( <i>n</i> = 6)	
Age at delivery, mean (s.d.), years	29.8 (5.5)	33.6 (4.2)	0.004	35.2 (4.4)	31.0 (2.31)	0.042
Age at diagnosis, mean (s.d.), years		33.9 (5.7)		32.3 (6.0)	36.7 (4.0)	0.041
Disease duration at delivery, mean (s.d.), years				2.9 (2.5)	−5.7 (5.0)	
ANA, <i>n</i> (%)		16 (100)		10 (100)	6 (100)	
Ro/SSA autoantibodies, <i>n</i> (%)		16 (100)		10 (100)	6 (100)	
La/SSB autoantibodies, <i>n</i> (%)		11 (69)		7 (70)	4 (67)	
IgM-RF, <i>n</i> (%)		11 (69)		6 (60)	5 (83)	

**TABLE 2** Pregnancy outcome for cases and controls (*n* = number of deliveries)

	Controls ( <i>n</i> = 80)	SS ( <i>n</i> = 16)	<i>P</i> -value	SS diagnosis		<i>P</i> -value
				Before pregnancy ( <i>n</i> = 10)	After pregnancy ( <i>n</i> = 6)	
Para, mean (s.d.)	0.59 (0.91)	0.50 (0.63)	0.910	0.40 (0.7)	0.67 (0.5)	0.433
Para, <i>n</i> (%)			0.799			0.159
0	49 (61)	9 (56)		7 (70)	2 (33)	
1	21 (26)	6 (38)		2 (20)	4 (67)	
2	5 (6)	1 (6)		1 (10)	0	
>2	5 (6)	0		0	0	
Miscarriage, mean (s.d.)	0.54 (0.97)	0.56 (0.96)	0.926	0.40 (0.7)	0.83 (0.3)	0.403
Miscarriage, <i>n</i> (%)			0.348			0.391
0	51 (63)	11 (69)		7 (70)	4 (67)	
1	22 (28)	2 (13)		2 (20)	0	
2	4 (5)	2 (13)		1 (10)	1 (17)	
>2	3 (4)	1 (6)		0	1 (17)	
Pregnancy duration, mean (s.d.), days	277.3 (13.8)	271.8 (22.1)	0.417	267.0 (25.9)	279.8 (11.1)	0.274
Normal partus, <i>n</i> (%)	66 (83)	9 (56)	0.020	5 (50)	4 (67)	0.515
Caesarean section, <i>n</i> (%)	10 (12)	5 (31)	0.123	4 (40)	1 (17)	0.330
Vacuum extraction, <i>n</i> (%)	4 (5)	2 (13)	0.258	1 (10)	1 (17)	0.697

### Fetal outcome

Seventy-two (90%) deliveries ended at term in the controls vs 14 (87%) in the cases (NS). Premature birth occurred in 8 (10%) of the controls vs 2 (13%) of the cases (NS) (Table 3). Birthweight differed significantly between cases and controls ( $P = 0.025$ ). Newborn of women with pSS were characterized with greater birthweight deviation as compared with controls (−11.4 vs −1.3%,  $P = 0.007$ ), and 25% of these babies were small-for-gestational age (SGA) as compared with 7.5% in controls ( $P = 0.04$ ). Of the four SGA fetuses there was one intrauterine death (weight deviation −47%), one had pH umbilical artery 6.96 and was delivered by vacuum extraction, and two were delivered by Caesarean section. Mean birthweight for pSS patients' babies was 3010 vs 3458 g in controls. All babies born prematurely and with LBW among the cases were found in the group of pSS patients

diagnosed before pregnancy. The Apgar score between the cases and controls and between the case groups did not differ significantly. Only one case of intrauterine AV block II occurred and was treated with high-dose dexamethasone (published in detail elsewhere [16]).

### Medication and disease activity during pregnancy

We anticipate that patients without pSS diagnosis when pregnant did not have active systemic disease and no immunosuppressive treatment. Three out of 10 patients who became pregnant after pSS was diagnosed were on low-dose prednisolone (maximum 5 mg/day), whereas one patient had been treated with high-dose dexamethasone during pregnancy due to intrauterine fetal AV block II [16]. This patient was on ciclosporin as well due to severe interstitial lung disease. This case is one of the two with LBW and preterm delivery. Another patient on low-dose

**TABLE 3** Fetal outcome for cases and controls (*n* = number of deliveries)

Fetal outcome marker	Controls ( <i>n</i> = 80)	Sjögren's Syndrome ( <i>n</i> = 16)	<i>P</i> -value	Sjögren's Syndrome diagnosis		<i>P</i> -value
				Before pregnancy ( <i>n</i> = 10)	After pregnancy ( <i>n</i> = 6)	
Birth weight (g) (mean ± s.d.)	3458.0 ± 606.8	3010.0 ± 787.1	0.025	2840.5 ± 930.0	3292.5 ± 385.5	0.281
LBW, <i>n</i> (%)	5 (6)	2 (13)	0.380	2 (20)	0	0.242
Weight deviation	-1.3 ± 13.1	-11.4 ± 14.8	0.007			
SGA	6 (7.5)	4 (25)	0 = 0.04			
Full-term birth, <i>n</i> (%)	72 (90)	14 (87)	0.380	8 (80%)	6 (100%)	0.248
Premature birth, <i>n</i> (%)	8 (10)	2 (13)	0.765	2 (20)	0	0.248
Apgar, <sup>a</sup> <i>n</i> (%)			0.129			0.361
6-10	79 (99)	15 (94)		9 (90)	6 (100)	
2-5	1 (1)	0		0	0	
0	0	1 (6)		1 (10)	0	
CHB, <i>n</i> (%)	0	1 (6)	0.424	1 (10)	0	0.424

SGA = small-for-gestational-age. <sup>a</sup>Apgar score: determined at 5 min.

prednisolone was also on AZA due to chronic active hepatitis. Pregnancy was terminated at term by Caesarean section. The other 10 patients had neither prednisolone nor any other DMARDs during pregnancy. One stopped anti-malarials when pregnant. The other patient with LBW/stillbirth had had severe RP, but no other systemic disease symptoms before/during pregnancy and neither during the following uncomplicated pregnancy. In general, disease activity is difficult to assess in pSS and only very recently have assessment instruments become available [17, 18]. However, young-onset pSS is usually associated with more systemic disease complications and high concentrations of autoantibodies, which was the case in several of the patients in the present study [19].

## Discussion

Beyond intrauterine AV block and neonatal lupus syndrome, it is usually anticipated that pSS is not associated with unfavourable pregnancy outcome. The few studies investigating the topic are with one exception >10 years old [13-15, 20] and rely on older classification criteria for case definition. Therefore, we performed a registry linkage study including all available pSS pregnancies (*n* = 16) in our region between 1990 and 2006 matched with population-derived controls (*n* = 80) avoiding any selection bias as far as possible.

Our results confirm normal fertility expressed by parity and lack of excess numbers of fetal losses or preterm deliveries. However, maternal age at delivery is higher in pSS patients, birthweight in pSS offspring lower and delivery by Caesarean section or vacuum extraction more frequent than in the background population.

This increased risk of operative delivery in our study was supposedly due to an increased risk of fetal growth restriction in the pSS pregnancies resulting in increased risk of severe fetal outcome. It was not detected in the recent Norwegian study [15]. A recent publication on RA and birth outcomes demonstrated exactly the same

difference between RA and controls [21]. It may partly be explained by physical or psychological preconditions (pain, fatigue and sicca problems) or maternal or fetal factors not formally registered in the birth registry. Also higher age at first delivery compared with controls was demonstrated in the RA study similar to our results in pSS [21]. According to an older study, women with RA experience a longer time to conception [22] than healthy women, when trying to become pregnant at the same age. This might be similar in pSS. The mechanism is unclear. However, the higher age of the mother was most pronounced in those having been diagnosed with pSS before pregnancy. Young women with pSS often have systemic and severe disease compared with pSS patients with later onset. In these young women, in concordance with the situation in SLE, reduction of disease activity is necessary before pregnancy. In some of the patients in the present study, this was certainly the reason for delayed pregnancy. Parity is not different and Skopouli *et al.* [20] could not detect statistically significant deviations from normal sexual behaviour in their study. Despite normal average gestational length, birthweight in offspring to pSS patients was significantly lower due to 13% (2 out of 16) of babies being born with birthweight <2500 g. These two children were born preterm. Thus, 2 (20%) out of 10 children of mothers with a diagnosis of pSS before pregnancy were born preterm, one with CHB and one as stillbirth. No abnormalities were found in pSS pregnancies before diagnosis. Niewold *et al.* [23] documented recently that Type I IFN activity was high in symptomatic in contrast to asymptomatic individuals with pSS or SLE having given birth to children with neonatal lupus. Possibly, the presence of severe pregnancy abnormality in post-diagnostic symptomatic women with pSS might be associated with Type 1 IFN up-regulation. The retrospective nested case-control design of our study does not allow comparison of IFN levels at the time of pregnancy. Intrauterine growth retardation is described in SLE pregnancies. SLE and pSS are

partly overlapping diseases and all of our patients are seropositive for SSA/SSB. Mechanisms resulting in placental insufficiency may be similar to SLE in some seropositive pSS patients. Also in the study by Julkunen *et al.* [14], birthweight of pSS offspring was lower than that of controls, but not as low as that of SLE patients.

We could not confirm a higher number of abortions (either spontaneous or medical) or fetal losses as seen in the Greek study from 1988 and in the publication from Finland 1995. This difference most probably is to be ascribed to the small numbers of pregnancies in all the studies. However, spontaneous or medical abortions occurring without following pregnancy resulting in delivery or stillbirth are not included due to the design of our study deriving information from the birth registry.

The main drawback of our study is the low number of deliveries. Despite linkage of the Malmö SS registry with the Malmö delivery registry, the number of available SS deliveries is as low as 16. As controls, five population-derived consecutive deliveries following the index delivery in a pSS patient were chosen. The usually late onset of pSS results in low numbers of pSS pregnancies, mirrored also by the lack of reliable epidemiological data regarding maternal/fetal outcome of pregnant patients with this autoimmune disease in the literature. The fact that pSS diagnosis is often made with several years of delay from symptom onset explains the fact that 6 out of 16 pregnancies had occurred before the patients were diagnosed with pSS. There was no statistically significant difference between pregnancy outcomes in SS patients with delivery before or after the diagnosis was made. Explanations for this could be both lack of statistical power to detect small differences or that the disease in fact in most cases does not influence pregnancy outcome to a high degree.

One strength of our study despite its limited size is the population-based approach with cases as well as controls representing the underlying population in the catchment area, which minimizes selection bias of cases and ensures representativeness of the controls. None of the previous studies has been truly population based. Another strength, with regard to the outcome variables related to pregnancy and delivery is the prospective registration in identical fashion in both cases and controls. A few studies that have evaluated the pregnancy and fetal outcome in patients with pSS (the early studies from Yoannina/Greece from 1988 [13] and 1994 [20]) used questionnaire and interview techniques, while Haga *et al.* [15] combined questionnaire and birth registry data in their study.

The present study is too small to investigate the possible mechanism leading to the lower number of normal delivery and lower birthweight in the cases. It is likely that it may be a result of immunological abnormalities, such as autoantibodies, B-cell, complement or IFN activation and inflammation. A multicentre prospective approach for detecting markers of unfavourable pregnancy outcome in pSS would probably be necessary for sufficient statistical power to disentangle these issues.

In conclusion, this study indicates that pregnancy occurs later in patients with pSS, they give birth to babies with lower birthweight and have a lower frequency of normal deliveries compared with controls. Larger studies are needed to investigate the mechanisms behind these findings in pSS pregnancies in more detail.

#### Rheumatology key messages

- Pregnancy occurs later in life in pSS.
- Mothers with pSS give birth to offspring of lower birthweight.
- Normal partus is less common in pSS patients than among healthy controls.

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