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ORIGINAL RESEARCH

Pregnancy Outcomes in Patients with Primary Sjögren's Syndrome Undergoing Assisted Reproductive Therapy: A Multi-center Retrospective Study

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ABSTRACT

Introduction: The aim of this work was to investigate the pregnancy outcomes in infertile patients with primary Sjögren's syndrome (pSS) undergoing assisted reproductive therapy (ART).

Methods: A multi-center retrospective study was performed in pregnant women with pSS and ART from five tertiary hospitals from Guangdong Province from 2013 to 2022. Natural planned pregnancy in pSS and healthy people undergoing ART were selected as controls. Pregnancy outcomes were collected from medical records and compared among groups.

Results: Twenty-four pregnancies in pSS with ART, 70 natural planned pregnancies in pSS, and 96 pregnancies in healthy people with ART were analyzed. More than half of the pSS mothers undergoing ART have a past history of adverse pregnancy and spontaneous abortion was the most common (10/24, 41.7%). Primary infertility (25.0%) and recurrent spontaneous abortion (16.7%) were the leading causes of infertility in pSS. The major maternal adverse pregnancy outcome (APO) in pSS patients with ART was premature delivery (11/24, 45.8%), likely attributed to twin gestation (4/11, 36.4%) and fetal distress (3/11, 27.3%). Twenty-seven live infants were born from 22 successful deliveries. The live birth rate was 93.1% (27/29). The average delivery time was 36.1 ± 3.3 weeks of

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gestation. The average birthweight was 2434.4 ± 722.1 g, compared with 2844.9 g in natural planned pregnancy in pSS, and 3072.1 g from healthy mothers with ART ($P < 0.001$). Seven (25.9%) low-birthweight (LBW) infants were born, and the incidence was comparable to the other two groups (22.2% in natural pregnancy, 13.0% in healthy people, $P = 0.09$). No infants developed congenital heart block (CHB). ***Conclusions***: ART is an effective method for infertility in patients with pSS. Premature delivery is the leading maternal APOs. The incidence of fetal APOs does not increase, while birthweight is lower in offspring from pSS mothers with ART.

Keywords: Primary Sjögren's syndrome; Assisted reproductive therapy; Pregnancy; Outcome; Premature delivery

Key Summary Points

Why carry out this study?

Immune disturbance affects fertility negatively in patients with primary Sjögren's syndrome (pSS), especially in those of reproductive age.

The application of assisted reproductive therapy (ART) in pSS is still in its early stage and pregnancy outcomes remain to be determined.

What was learned from the study?

ART is safe and effective in infertile patients with pSS without increasing the risk of disease flares or fetal loss.

Premature delivery (45.8%) and low-birthweight (LBW) infants (22.2%) are the most common adverse pregnancy outcomes.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a common autoimmune disease involving the exocrine glands as well as extraglandular organs. pSS tends to occur in people in their fourth or fifth decades, while approximated 14% of the diagnosis is made before age 35 years [1]. Along with the tendency of delaying marriage, pregnancy has become one of the most concerning problems in pSS.

The immune disturbance in pSS may interfere fertility. Although far from being understood, various auto-antibodies including antinuclear antibodies (ANA) and anti-Sjögren's syndrome A (SSA) are found in peritoneal fluid and sera of infertile endometriosis women [2]. A pathological shift from Th2 to Th1 cells in pSS impairs embryo implantation and a skew towards Th2 response at the feto–maternal interface may aid successful pregnancy in patients with unexplained recurrent miscarriages [3, 4]. Besides, women with pSS report long menstrual cycles in a questionnaire survey, which is associated with infertility [5].

Reproductive health in pSS remains focused predominantly on fetal complication such as cardiac conduction abnormalities. Infertility receives little attention however. Assisted reproductive therapy (ART) has been successfully carried out in patients with stable systemic lupus erythematosus (SLE) [6]. The safety is assured by friendly ovarian stimulation, single embryo transfer, and anti-thrombotic prophylaxis if necessary [7, 8]. Generally, ART is considered safe among people with other quiescent rheumatic diseases such as rheumatoid arthritis (RA) and vasculitis [9]. Much remains to be explored regarding the success rate, pregnancy outcomes, and treatment strategy during pregnancy in the manipulation of ART in pSS. Herein, we conducted a multi-center retrospective study aiming to investigate the efficacy as well as safety of ART in patients with pSS.

METHODS

Patients and Data Collection

A multi-center retrospective study was performed. Consecutive infertile patients with pSS undergoing ART followed up in five tertiary hospitals from Guangzhou (i.e., the First Affiliated Hospital of Sun Yat-sen University, Guangzhou First People's Hospital, the Third Affiliated Hospital of Guangzhou Medical University, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Nanfang Hospital of Southern Medical University) from January 2013 to October 2022 were included. Only women with established pSS prior to pregnancy were included. pSS was diagnosed according to the criteria proposed by the American-European Consensus Group (AECC). [10] Both Schirmer's test and labial gland biopsy were performed, in addition to auto-antibodies, in all patients to confirm diagnosis of pSS. Patients diagnosed with SS secondary to other connective tissue diseases such as SLE, or diagnosed with undifferentiated connective tissue disease were excluded. Patients with past head and neck radiation treatment, hepatitis C virus infection, acquired immunodeficiency disease (AIDS), lymphoma, sarcoidosis, graft-versus-host disease, and using anticholinergic medications were excluded. All natural planned pregnancies in patients with pSS during the same period were enrolled as controls. Healthy women undergoing ART were selected as controls. For each pregnancy in a patient with pSS and ART, the next four pregnant women having no medical disorders known at the time of pregnancy were selected as healthy controls. Obstetric history, ART procedure, obstetrical complications, laboratory tests, medical treatments, and outcome of pregnancies were extracted from the electronic medical records and reviewed by two independent rheumatologists (D.C. and Z.Z.).

ART Procedure

Patients with established pSS meeting the following criteria were eligible for ART: (1) stable disease (defined as EULAR Sjögren's syndrome disease activity index (ESSDAI) < 5) [11, 12] for at least a year without major organ dysfunction such as pulmonary hypertension, heart failure, and kidney insufficiency, (2) incapacity to fulfill pregnancy for more than 1 year of sexual intercourse without contraceptive measures, (3) oral prednisone ≤ 10 mg per day, (4) discontinuation of teratogenic immunosuppressants including cyclophosphomide, methotrexate, and mycophenolate mofetil for at least 6 months, (5) for those who were taking leflunomide, wash-out therapy was administered. All the patients were evaluated and followed up by a multidisciplinary team with rheumatologists, obstetricians, and pediatricians.

ART procedure included ovarian stimulation, oocyte retrieval, fertilization-embryo transfer via in vitro fertilization-embryo transfer (IVF-ET), intracytoplasmic sperm injection (ICSI), or intrauterine insemination (IUI). Preimplantation genetic testing (PGT) encompassed preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) [13]. Clinical pregnancy rate was defined as patients detected with fetal heartbeat divided by the total number of patients.

Ovulation Induction (OI) and Controlled Ovarian Stimulation (COS)

OI/COS was tailored by obstetricians according to the ovarian function of the patients. Long protocol: Gonadotropin-releasing hormone (GnRH) agonist was given in the midluteal phase. Individualized injection with recombinant follicle-stimulating hormone (FSH) was prescribed 14 days after according to the sex hormone levels and obstetric ultrasound findings. Ultralong protocol: GnRH agonist was prescribed on day 2 of the menstrual period and repeated for 1–3 cycles. Gonadotropin (Gn) was given 28 days after the last injection of GnRH for ovarian stimulation. Antagonist protocol: Exogenous Gn was administered on day 2 of the menstrual period, followed by antagonist 4 days later to prevent early ovulation. Other unconventional protocols included modified natural

cycle with a small amount of Gn, mini-dose protocol with a small dose of Gn in patient with declined ovarian reserves.

Definition

Natural planned pregnancy in patients with pSS was defined as patients conceiving babies naturally fulfilling the following criteria: (1) ESSDAI < 5 for at least 6 months prior to conception, (2) dose of oral prednisone ≤ 10 mg per day, (3) absence of major organ dysfunction, (4) discontinuation of teratogenic immunosuppressants for at least 6 months.

Disease flare during pregnancy was defined as re-occurrence of extraglandular manifestations associated with pSS including cutaneous lesions, inflamed arthritis, myositis, hemocytopenia, central and peripheral neuropathy, interstitial lung disease, and nephropathy. Patients presenting neurological symptoms and kidney impairment secondary to preeclampsia/eclampsia, low back pain caused by the sacroiliac joints loosening in normal pregnancy, or non-hemolytic anemia that is pregnancy-related were not considered disease flares.

Infertility

Primary infertility was defined as a couple that has been incapable of conceiving a pregnancy after at least 1 year of attempting through unprotected intercourse. Secondary infertility is defined as the inability to conceive or carry a pregnancy to term after having successfully delivered a child.

Pregnancy Trimesters

Pregnancy trimesters were categorized as follows: the first trimester (up to the 13th week of gestation), the second trimester (from the 14th to the 26th week of gestation), and the third trimester (starting from the 27th week of gestation).

Maternal Adverse Pregnancy Outcome (APOs)

Pregnancy-induced hypertension (PIH): included gestational hypertension, pre-eclampsia, and eclampsia. Pre-eclampsia was established as a new onset of hypertension with or without proteinuria after the 20th week of gestation in a previously normotensive woman. Eclampsia was defined as the occurrence of one or more generalized, tonic–clonic convulsions unrelated to other medical conditions in women with hypertensive disorder of pregnancy [14]. Gestational diabetes mellitus (GDM): the onset or first recognition of diabetes occurred during pregnancy [15]. Fetal loss included spontaneous abortion, therapeutic abortion (artificial termination of pregnancy due to the exacerbation of pSS or obstetric complications), intrauterine fetal death (death of a fetus after 20 weeks of gestation), and neonatal death (death of a live infant within 28 days after birth). Premature delivery: birth under 37 weeks gestational age, with further classification into early (< 34 weeks) and late ($> = 34$ weeks) preterm births. Preterm premature rupture of membranes (PPROM): the spontaneous rupture of membranes during pregnancy before the 37th week of gestation.

Fetal APOs

Fetal growth restriction (FGR) was diagnosed with birth weight below the 10th percentile of the Chinese population according to gestational week at delivery and fetal gender. Fetal distress: fetus hypoxia and acidosis which endangers the health of the fetus. Low-birth-weight (LBW): infant with birth weight < 2500 g. Very-low-birth-weight (VLBW): infant with birth weight < 1500 g.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 (SPSS Inc, Chicago, IL, USA). Normally distributed data were presented as mean $\pm$ standard deviation (SD), and non-normally distributed variables were expressed as median

(interquartile range, IQR). Categorical variables were presented as frequency and percentage. Comparison among groups was evaluated with Pearson's chi-square test or Fisher's exact test if one or more of the cells have $exp_i < 5$ for categorical variables. One-way ANOVA was applied in the comparison among three groups for continuous variables with normal distribution. Between-group comparison was evaluated using Student's t test for continuous variables with normal distribution, and Mann–Whitney U test for continuous variables with non-normal distribution. A two-tailed P value < 0.05 was considered statistically significant.

Ethics Approval

Ethics committee of the above five centers approved the research. Informed consent was obtained from the participants. This work was conducted according to the provisions of the Declaration of Helsinki.

RESULTS

Demographic Data

We identified 32 patients with pSS undergoing ART from five centers. Five of them were excluded because pSS was diagnosed after pregnancy. Three patients were excluded for SS secondary to SLE. Finally, 24 successful cycles out of 51 ART cycles in 24 patients were analyzed. Clinical pregnancy rate was 47.1% (24/51). The mean age at conception was 34.3 ± 5.2 years. The mean body mass index (BMI) at pregnancy was 25.0 ± 3.7 kg/m^2. The median (IQR) disease course was 12 (11.5, 24.3) months. Six patients (25.0%) were pluripara. Half of them (13/24, 54.2%) had past histories of adverse obstetric outcomes. Spontaneous abortion was the most common (10/24, 41.7%) (Table 1).

Ten patients were taking prednisone prior to ART for the reasons of arthritis ($n = 4$), rash ($n = 2$), thrombocytopenia ($n = 3$), and leukopenia ($n = 1$). Seven patients continued to take prednisone during pregnancy. Cyclosporin A (CsA) was given to two patients with thrombocytopenia prior to ART, and one of them continued the therapy during pregnancy. The majority of patients with pSS undergoing ART (20/24, 83.3%) were taking hydroxychloroquine (HCQ) during pregnancy.

Manipulation of ART

Underlying causes for infertility in pSS are shown in Table 2. Primary infertility accounted for 25.0% (6/24), followed by recurrent spontaneous abortion (4/24, 16.7%), and obstruction of fallopian tubes (2/24, 8.3%).

Baseline reproductive function evaluated at day 3 of menstrual cycle in patients with pSS prior to ART was evaluated by obstetricians. The median (IQR) level of follicle-stimulating hormone (FSH) was 7.2 (6.0, 9.4) IU/l. The median (IQR) level of luteinizing hormone (LH) was 4.6 (3.8, 6.7) IU/l. The median (IQR) level of estrogen was 43.4 (36.0, 52.4) pg/ml. The median (IQR) level of anti-Müllerian hormone (AMH) was 2.0 (1.0, 3.1) ng/ml.

OI/COS was performed in 20 (87.0%) pregnancies, including long protocol (8/24, 33.3%), mini-dose protocol (4/24, 16.7%), modified natural cycle (4/24, 16.7%), antagonist protocol (3/24, 12.5%), and ultralong protocol (1/24, 4.2%). IVF was performed in 22 (91.7%) pregnancies, and ICSI in 1 (4.2%). One patient (4.2%) received PGT due to parental thalassemia. Neither ovarian hyperstimulation syndrome (OHSS) nor thrombotic event was observed.

Maternal Outcomes

Twenty-two (91.7%) pregnancies ended in successful delivery. Cesarean section was conducted in 14 pregnancies (58.3%). Maternal APOs are shown in Table 3. Premature delivery was a complication with the highest incidence (11/24, 45.8%). The incidence of GDM ranked second (3/24, 12.5%). Two fetal losses (8.3%) occurred due to spontaneous abortion (Table 4).

Table 1 Basic characteristics in patients with pSS and ART

	pSS		Healthy controls with ART (n = 96)	P value#
	ART (n = 24)	Natural planned pregnancy (n = 70)		
Basic characteristics				
Age, year, mean ± SD	34.3 ± 5.2	32.6 ± 4.0	34.0 ± 4.5	0.09
BMI, kg/m^2, mean ± SD	25.0 ± 3.7	22.9 ± 3.8	21.1 ± 2.5	< 0.001
ESSDAI, median (IQR)	0.5 (0, 3)	1.0 (0, 4)	–	0.56
Disease course, month, median (IQR)	12.0 (11.5, 24.3)	12.5 (0, 36.0)	–	0.85*
Pluripara, n (%)	6 (25.0)	37 (52.9)	31 (32.3)	0.01
Parity, mean ± SD	0.3 ± 0.6	0.7 ± 0.9	0.1 ± 0.4	< 0.001
Parity, n (%)				
0	18 (75.0)	33 (47.1)	65 (67.7)	0.01
1	5 (20.8)	32 (45.7)	21 (21.9)	0.002
2	1 (4.2)	4 (5.7)	6 (6.3)	> 0.99
> 2	0 (0)	1 (1.4)	4 (4.2)	0.37
History of adverse pregnancy				
Incidence rate, n (%)	13 (54.2)	28 (40.0)	35 (36.5)	0.29
Ectopic pregnancy, n (%)	4 (16.7)	1 (1.4)	9 (9.4)	0.04
Spontaneous abortion, n (%)	10 (41.7)	19 (27.1)	5 (5.2)	< 0.001
Missed abortion, n (%)	0 (0)	0 (0)	4 (4.2)	0.18
Recurrent miscarriage, n (%)	2 (8.3)	0 (0)	1 (1.0)	0.04
Embryo damage, n (%)	0 (0)	5 (7.1)	17 (17.7)	0.02
Fetal death, n (%)	1 (4.2)	1 (1.4)	2 (2.1)	> 0.99
Therapeutic abortion, n (%)	0 (0)	4 (5.7)	2 (2.1)	0.36
Premature delivery, n (%)	1 (4.2)	5 (7.1)	2 (2.1)	0.26
FGR, n (%)	0 (0)	0 (0)	1 (1.0)	> 0.99
Neonatal death, n (%)	1 (4.2)	1 (1.4)	0 (0)	0.24
Laboratory test				
ANA, n (%)	21 (87.5)	62 (88.6)	–	> 0.99*
Anti-SSA, n (%)	21 (87.5)	58 (82.9)	–	0.76*
Anti-SSB, n (%)	3 (12.5)	31 (44.3)	–	0.01*
CRP, median (IQR)	2.2 (1.2, 2.6)	2.5 (1.6, 4.1)	–	0.08

Table 1 continued

	pSS		Healthy controls with ART (n = 96)	P value#
	ART (n = 24)	Natural planned pregnancy (n = 70)		
IgG, median (IQR)	11.4 (10.4, 11.8)	11.1 (10, 12.7)	–	0.41
ESR, median (IQR)	16.5 (9, 24.3)	20 (12, 30)	–	0.08
Treatment during pregnancy				
Glucocorticoids, n (%)	7 (25.0)	19 (27.1)	–	0.85*
HCQ, n (%)	20 (83.3)	40 (57.1)	–	0.02*
CsA, n (%)	1 (4.2)	4 (5.7)	–	> 0.99*

ANA antinuclear antibodies, *ART* assisted reproductive therapy, *BMI* body mass index, *CRP* C-reactive protein, *CsA* cyclosporin A, *ESR* erythrocyte sedimentation rate, *ESSDAI* EULAR Sjögren's syndrome disease activity index, *FGR* fetal growth restriction, *HCQ* hydroxychloroquine, *IQR* interquartile range, *pSS* primary Sjögren's syndrome, *SD* standard deviation, *SSA* Sjögren's syndrome A, *SSB* Sjögren's syndrome B

*Comparison between ART and natural planned pregnancy in pSS

#Comparison among three groups

Causes for Premature Delivery

Preterm birth was primarily attributed to twin gestation (4/11, 36.4%) and fetal distress (3/11, 27.3%) (Table 5). The average delivery time of premature delivery was 33.5 ± 2.6 weeks of gestation in ART, including five patients (45.5%) with early premature delivery and six patients (54.5%) with late premature delivery. The average birthweight in preterm infants was 2124.5 ± 646.2 g.

Fetal and Neonatal Outcomes

Twenty-seven live infants were born, including five pairs of twins. The live birth rate was 93.1% (27/29). The average delivery time was 36.1 ± 3.3 weeks of gestation. The average birth weight was 2434.4 ± 722.1 g. Fetal APOs are shown in Table 6. LBW infants accounted for 25.9% (7/27), including four VLBW (16.7%). Six LBW infants were born prematurely and three LBW infants were from twin gestation. No infant with either neonatal lupus or congenital heart block (CHB) was born.

Comparison Among pSS Patients Undergoing ART, Planned Pregnancy, and Healthy Controls

Basic Characteristics

The age of pregnancy (34.3 vs. 32.6 vs. 34.0 years, $P = 0.09$) was comparable among three groups, while pre-pregnant BMI (25.0 vs. 22.9 vs. 21.1 kg/m^2, $P < 0.001$) increased in pSS with ART. The incidence of past history of adverse pregnancy in three groups was similar (54.2% vs. 40.0% vs. 36.5%, $P = 0.29$). Previous spontaneous abortion was the most common in pSS groups (41.7% in ART, 27.1% in natural pregnancy), compared with only 5.2% in healthy controls ($P < 0.001$).

Causes for Infertility

Nearly half of the patients suffered from primary infertility (25.0%) or recurrent spontaneous abortion (16.7%) in pSS. Obstruction of fallopian tubes (30.2%), primary infertility (19.8%), and male factors (19.8%) appeared to be the leading causes in healthy population.

Table 2 Causes for infertility

	pSS (n = 24)	Healthy controls (n = 96)	P value
Causes for infertility			
Primary infertility, n (%)	6 (25.0)	19 (19.8)	0.57
Recurrent spontaneous abortion, n (%)	4 (16.7)	0 (0)	0.001
Obstruction of fallopian tubes, n (%)	2 (8.3)	29 (30.2)	0.04
PCOS, n (%)	1 (4.2)	2 (2.1)	> 0.99
Endometriosis, n (%)	1 (4.2)	2 (2.1)	> 0.99
Hereditary disease, n (%)	1 (4.2)	0 (0)	0.20
Cervical factors, n (%)	0 (0)	1 (1.0)	> 0.99
Scarred uterus, n (%)	0 (0)	9 (9.4)	0.20
Fetal chromosomal abnormalities, n (%)	0 (0)	3 (3.1)	0.61
Male factor, n (%)	2 (8.3)	19 (19.8)	0.24
Unexplained, n (%)	13 (54.2)	28 (29.2)	0.02
Procedure			
IVF-ET, n (%)	22 (91.7)	73 (76.0)	0.09
ICSI, n (%)	1 (4.2)	13 (13.5)	0.30
IUI, n (%)	0 (0)	4 (4.2)	0.58
PGT, n (%)	1 (4.2)	6 (6.3)	> 0.99

ART assisted reproductive therapy, *ICSI* intracytoplasmic sperm injection, *IUI* intrauterine insemination, *IVF-ET* in vitro fertilization-embryo transfer, *PCOS* polycystic ovary syndrome, *PDT* preimplantation genetic testing, *pSS* primary Sjögren's syndrome

Maternal Outcomes

Pre-eclampsia occurred in one (4.2%) pSS patient in ART, six (8.6%) pSS patients in planned pregnancy, and one (1.0%) healthy patient with ART (P = 0.04). One pSS patient (1.4%) in planned pregnancy developed eclampsia. The risk of GDM did not differ among the three groups (12.5% vs. 11.4% vs. 10.4%, $P > 0.99$). The rate of fetal loss was comparable (8.3% vs. 11.4% vs. 10.4%, P = 0.95). The Cesarean section rate remained high among the three groups (58.3% vs. 55.7% vs. 58.3%, P = 0.94). Patients with ART were more likely to deliver prematurely compared with planned pregnancy and healthy control (45.8% vs. 20.0% vs. 7.3%, $P < 0.001$). Placental abruption occurred in six (25.0%) and 16 (22.9%) patients from ART and natural pregnancy in pSS, respectively. No patient with ART had disease flare during pregnancy.

Causes for Premature Delivery

Premature delivery was mainly attributed to twin gestation in ART (4/11, 36.4%) and fetal distress in natural pregnancy (4/14, 28.6%) in pSS. The predominant cause for premature delivery in healthy people with ART was twin gestation (5/7, 71.4%).

Fetal and Neonatal Outcomes

In comparison with planned pregnancy and healthy controls, delivery time in ART was earlier (36.1 vs. 37.6 vs. 38.5 weeks, $P < 0.001$) and birthweight was lower (2434.4 vs. 2844.9 vs. 3072.1 g, $P < 0.001$). Apgar score at 1 min (9.7

Table 3 Maternal pregnancy outcomes

Maternal outcomes	pSS		Healthy controls with ART (n = 96)	P value[#]
	ART (n = 24)	Natural planned pregnancy (n = 70)		
GDM, n (%)	3 (12.5)	8 (11.4)	10 (10.4)	> 0.99
Gestational hypertension, n (%)	1 (4.2)	0 (0)	0 (0)	0.13
Pre-eclampsia, n (%)	1 (4.2)	6 (8.6)	1 (1.0)	0.04
Eclampsia, n (%)	0 (0)	1 (1.4)	0 (0)	0.50
Placental abruption, n (%)	6 (25.0)	16 (22.9)	0 (0)	< 0.001
Placenta previa, n (%)	2 (8.3)	3 (4.3)	4 (4.2)	0.79
Fetal loss, n (%)	2 (8.3)	8 (11.4)	10 (10.4)	0.95
Disease flares, n (%)	0 (0)	2 (2.9)	–	0.62*
Cesarean section, n (%)	14 (58.3)	39 (55.7)	56 (58.3)	0.94
Premature delivery, n (%)	11 (45.8)	14 (20.0)	7 (7.3)	< 0.001
Postpartum hemorrhage, n (%)	1 (4.2)	1 (1.4)	3 (3.1)	0.87

ART assisted reproductive therapy, *GDM* gestational diabetes mellitus, *pSS* primary Sjögren's syndrome
*Comparison between ART and natural planned pregnancy in pSS
[#]Comparison among three groups

vs. 9.6 vs. 10.0, P = 0.01) and 5 min (9.9 vs. 9.9 vs. 10.0, P = 0.09) were lower in pSS compared with healthy controls.

LBW was more frequent in patients with pSS and ART although no statistical significance was found (25.9% vs. 22.2% vs. 13.0%, P = 0.09). The incidence of fetal distress increased in infants from pSS mothers (14.8% vs. 12.9% vs. 0%, P = 0.002), while the incidence of FGR was comparable (3.7% vs. 6.5% vs. 3.3%, P = 0.64).

Neonatal complications including neonatal pathological jaundice (3.7% vs. 8.3% vs. 6.5%, P = 0.54) and neonatal respiratory distress syndrome (NRDS) (0% vs. 1.4% vs. 0%, P = 0.49) did not differ among the three groups.

DISCUSSION

In the current study, we reported the maternal and fetal outcomes in patients with pSS undergoing ART for the first time. Generally, pregnancy outcomes of ART in pSS are favorable. Most of the pregnancy ends up with live births. Premature delivery, especially early premature delivery, is the primary maternal APO. The incidence of fetal loss does not increase in pSS mothers with ART in comparison with natural pregnancy or healthy controls. Birthweight is lower in ART infants. No neonatal death, neonatal lupus, or infants with CHB were observed.

OI/COS has been a matter of concern for the increasing risk of OHSS, flare-ups, and thrombotic event in connective tissue disease such as SLE. None of the above complications was observed in our study, though. Different from SLE, high levels of estrogen and human chorionic gonadotropin are found to be protective factors for the development of pSS [16, 17]. Pregnancy outcomes in women with anti-SSA/SSB undergoing IVF are not affected by GnRH agonist or antagonist protocols [18]. Thus, patient-tailored OI/COS based on ovarian

Table 4 Causes for fetal loss

	pSS		Healthy controls with ART (n = 10)
	ART (n = 2)	Natural planned pregnancy (n = 8)	
Ectopic pregnancy, n (%)	0 (0)	1 (12.5)	0 (0)
Spontaneous abortion, n (%)	1 (50.0)	0 (0)	0 (0)
Inevitable abortion, n (%)	0 (0)	0 (0)	1 (10.0)
Missed abortion, n (%)	0 (0)	0 (0)	1 (10.0)
Fetal defect, n (%)	0 (0)	1 (12.5)	0 (0)
Embryo damage, n (%)	0 (0)	0 (0)	1 (10.0)
Fetal death, n (%)	0 (0)	2 (25.0)	6 (60.0)
Oligoamnios, n (%)	1 (50.0)	0 (0)	0 (0)
Intrauterine infection, n (%)	0 (0)	0 (0)	1 (10.0)
Disease flares, n (%)	0 (0)	2 (25.0)	–
Maternal comorbidities, n (%)	0 (0)	2 (25.0)	0 (0)

ART assisted reproductive therapy, *pSS* primary Sjögren's syndrome

function can be safely applied in patients with pSS.

An increasing number of pSS patients undergoing ART experience a history of APOs (54.2%), and spontaneous abortion is the most frequent (41.7%). Even in pSS patients with natural pregnancy, the incidence of past spontaneous abortion is 27.1%, comparing with 17.7% in healthy controls. The inherent immune disorder of pSS contributes to the increasing risk. Endometrial glands are speculated to be involved in pSS and embryo implantation is affected by chronic inflammation, leading to endometrial dysfunction [19]. Anti-SSA and/or anti-SSB antibodies are related to poor outcomes in patients undergoing IVF-ET, such as reducing clinical pregnancy rate and take-home babies [18]. The presence of anti-SSA and/or anti-SSB antibodies promotes the differentiation from naïve T cells towards Th1 and Th17 cells, and pro-inflammatory cytokines secreted by the imbalanced Th1/Th2 and Th17/Treg cells, such as TNF-α, impair oocyte number and maturation [18].

The risk of fetal loss is not likely to increase in patients with pSS undergoing ART compared with natural pregnancy and healthy people (8.3% vs. 11.4% vs. 10.4%). However, the increased incidence of premature delivery is remarkable (45.8% vs. 20.0% vs. 7.3%). Premature delivery is the leading maternal APO in patients with pSS undergoing ART, similar to that in lupus patients undergoing ART (20–50%) [20]. The major causes include twin gestation, fetal distress, and PPROM. pSS patients with ART bear many risk factors for premature delivery. Advancing age continues to be the most remarkable factor associated with APOs such as preterm birth, LBW, PIH, and stillbirth [21, 22]. The onset of pSS is usually late, with only 29% ≤ 45 years and 13% ≤ 35 years of age at diagnosis [23]. The advanced conceiving age in pSS patients undergoing ART contributes to the risk of a preterm birth.

Table 5 Causes for premature delivery

	pSS		Healthy controls with ART (n = 7)
	ART (n = 11)	Natural planned pregnancy (n = 14)	
Twin gestation, n (%)	4 (36.4)	0 (0)	5 (71.4)
Fetal distress, n (%)	3 (27.3)	3 (21.4)	0 (0)
PPROM, n (%)	2 (18.2)	3 (21.4)	0 (0)
Spontaneous labor, n (%)	2 (18.2)	0 (0)	1 (14.3)
FGR, n (%)	0 (0)	1 (7.1)	0 (0)
Disease flares, n (%)	0 (0)	1 (7.1)	–
Maternal comorbidity, n (%)	0 (0)	1 (7.1)	0 (0)
Mirror syndrome, n (%)	0 (0)	0 (0)	1 (14.3)
Placenta previa, n (%)	0 (0)	1 (7.1)	0 (0)
Placental abruption, n (%)	0 (0)	2 (14.3)	0 (0)
Elective cesarean section, n (%)	0 (0)	1 (7.1)	0 (0)
Mixed factors, n (%)	0 (0)	1 (7.1)	0 (0)

ART assisted reproductive therapy, *FGR* fetal growth restriction, *PPROM* preterm premature rupture of membranes, *pSS* primary Sjögren's syndrome

Twin pregnancies experience increasing risk of premature delivery. In the general population, the average delivery time in twin pregnancies is 35.3 weeks of gestation [24]. In our study, one-third (36.4%) of the preterm births in pSS mothers with ART had twin gestation. Accordingly, practice guidelines overtly encourage more single-embryo transfers in ART [25].

In addition, ART pregnancies per se are at a higher risk of adverse perinatal outcomes such as premature delivery compared with natural pregnancies, even after adjusting for known confounding factors [26]. The increasing odds of premature delivery are reported to be 2.0 and 1.8, respectively, in comparison between 12,283 singleton infants from IVF and 1.9 million singleton infants from natural pregnancies [27]. Other contributors such as increasing weight is observed in our study since the average BMI increased in ART compared with natural pregnancies (25.0 vs. 22.9 kg/m^2) [28]. Apart from the traditional risk factors, intrinsic immunologic disorder in pSS may offer additional risk to premature delivery, since the incidence of premature delivery in healthy controls is lower than pSS despite more frequent twin gestation.

Different from SLE, no patient with pSS and ART developed disease flare during pregnancy in our study. Only two cases of disease flare were observed in pSS patients with natural pregnancy. The incidence ranges from 13 to 15% in patients with SLE and ART, though [20, 29]. The opposite impact of estrogen on pSS and SLE could be one of the potential mechanisms [16].

Treatment diversities might have impacted the pregnancy outcomes. The main medications used during pregnancy were prednisone and HCQ. A low dose of prednisone is safe and tolerable in pregnant women without causing severe adverse pregnancy outcomes [30]. HCQ

Table 6 Fetal and neonatal pregnancy outcomes

Fetal outcomes	pSS		Healthy controls with ART (n = 92)	P value#
	ART (n = 27)	Natural planned pregnancy (n = 62)		
Time of delivery, week, mean ± SD	36.1 ± 3.3	37.6 ± 1.7	38.5 ± 1.6	< 0.001
Birthweight, g, mean ± SD	2434.4 ± 722.1	2844.9 ± 497.4	3072.1 ± 496.0	< 0.001
Twin, n (%)	5 (18.5)	0 (0)	6 (6.5)	0.004
Apgar score at 1 min, mean ± SD	9.7 ± 1.0	9.6 ± 1.3	10.0 ± 0.2	0.01
Apgar score at 5 min, mean ± SD	9.9 ± 0.5	9.9 ± 0.4	10.0 ± 0	0.09
LBW infants, n (%)	7 (25.9)	16 (22.2)	12 (13.0)	0.09
Fetal distress, n (%)	4 (14.8)	8 (12.9)	0 (0)	0.002
FGR, n (%)	1 (3.7)	4 (6.5)	3 (3.3)	0.64
Neonatal lupus, n (%)	0 (0)	3 (4.2)	–	0.55*
Neonatal pathological jaundice, n (%)	1 (3.7)	6 (8.3)	6 (6.5)	0.54
NRDS, n (%)	0 (0)	1 (1.4)	0 (0)	0.49

ART assisted reproductive therapy, *FGR* fetal growth restriction, *LBW* low birth weight, *NRDS* neonatal respiratory distress syndrome, *pSS* primary Sjögren's syndrome

*Comparison between ART and natural planned pregnancy in pSS

#Comparison among three groups

is recommended for continuous use during pregnancy in women with SLE, given good safety and benefits for reducing disease flares and thrombotic events [31]. Although the impact of HCQ in pregnant women with pSS is not clearly delineated, they might gain advantage due to the shared autoimmune background of pSS and SLE. Due to the limited participants in the current study, we are not able to study the association between HCQ and pregnancy outcomes in pSS. With the increasing application of ART in pSS women, we look forward to investigating the impact of HCQ on pregnancy outcomes in pSS.

The live birth rate in pSS patients with ART is assured (93.1%), and is comparable to that in the lupus population. In our center, the live birth rate in patients with SLE undergoing ART is 83.3% [6]. The number ranges from 50 to 85% in patients with SLE and/or antiphospholipid syndrome (APS) receiving ART from other series [32, 33]. Despite the high live birth rate in pSS patients with ART, adverse fetal outcomes are observed. The average birthweight is lower in infants from pSS mothers with ART (2434.4 vs. 2844.9 vs. 3072.1 g), so is the Apgar's score at 1 min (9.7 vs. 9.6 vs. 10.0). Our results suggest that adverse fetal complications in pSS patients with ART continue to exceed that in healthy population despite of high live birth rate.

Being the first study reporting pregnancy outcomes of ART in patients with pSS, our analysis has inherent limitations related to small sample size explained by the rarity of ART in patients with pSS. Some of the differences among three groups, such as the causes for premature delivery, were not submitted to statistical analysis due to the limited number of

cases. Conducting a larger study would strengthen and validate our findings in pSS and ART. Furthermore, our understanding of how the immune background of pSS affects pregnancy is still preliminary. In-depth scientific research is needed to reveal the underlying mechanisms.

ART is an effective method for infertility in patients with pSS with the feature of high conception age and frequent history of adverse pregnancy. Premature delivery, especially early premature delivery, is the major complication. Preterm infants are likely to develop adverse fetal outcomes. To reduce the incidence of premature delivery, weight control and single-embryo transfer might partially improve the pregnancy outcomes in pSS patients with ART, while the autoimmune nature of pSS might exert additional impact.

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

Declarations

Conflict of Interest. The authors declare no conflicts of interest. Peiyin Dai is now affiliated with Department of Rheumatology, Maoming People's Hospital.

Ethical Approval. Ethics committees of five centers approved the research (Supplementary table 1). Informed consent was obtained from the participants. This work was conducted according to the provisions of the Declaration of Helsinki.

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