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ORIGINAL ARTICLE

Outcome of pregnancy in women with psoriatic arthritis compared to healthy controls

Ari Polachek[1,2] · Inbal Polachek Shlomi[3,4] · Karen Spitzer[5] · Daniel Pereira[6] · Justine Yang Ye[6] · Vinod Chandran[7,8] · Carl A. Laskin[9] · Dafna D. Gladman[7,10]

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Abstract

Objectives The mean age at onset of psoriatic arthritis (PsA) ranges between the 4th–6th decades of life. However, little is known about fertility and pregnancy outcome in PsA patients. The aim of this study was to examine whether fertility and pregnancy outcome of PsA patients are different from healthy controls and to evaluate PsA and psoriasis disease activity perception during pregnancy and the year postpartum.

Methods A questionnaire-based study, including demographic, fertility, pregnancy outcome, and disease activity questions, was conducted in PsA patients and healthy controls. The inclusion criterion was diagnosis of PsA before at least 1 pregnancy. Descriptive statistics are provided. *T* tests and Pearson chi-square tests were used to analyze the differences between continuous and categorical variables, respectively.

Results The 74 PsA patients and 74 healthy controls were not significantly different in most of the demographic variables. The mean number of pregnancies, children, and infertility diagnosis were not significantly different between the groups. The pregnancy outcomes in the PsA group ($n = 151$) and in the control group ($n = 189$) were similar in: live birth (76% vs. 76%, $P = 0.3$), vaginal delivery (48% vs. 51%, $P = 0.6$), gestation age (38.5 vs. 38.3, $P = 0.3$), weight at birth (3.4 kg vs. 3.4 kg, $P = 0.5$), low rate of maternal and fetal complications, and the duration and rate of breastfeeding. Most (58%) patients reported favorable joint activity during pregnancy and 50% reported worsening during the 1st postpartum year.

Conclusions PsA patients do not have more infertility or worse pregnancy outcomes compared to healthy controls.

Keywords Birth · Conception · Gestation · Pregnancy · Psoriasis · Spondyloarthritis

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✉ Dafna D. Gladman
dafna.gladman@utoronto.ca

[1] Toronto Western Hospital, Centre for Prognosis Studies in the Rheumatic Diseases, University of Toronto, Toronto, Ontario, Canada

[2] Department of Rheumatology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Reproductive life Stages Program, Women's College Hospital, Toronto, Ontario, Canada

[4] Beer Yaakov- Ness Ziona Mental Health Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[5] TRIO Fertility, University of Toronto, Toronto, Ontario, Canada

[6] Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Disease, Toronto Western Hospital, Toronto, Ontario, Canada

[7] Centre for Prognosis Studies in the Rheumatic Diseases, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada

[8] Departments of Medicine and Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

[9] Departments of Medicine (Rheumatology) and Obstetrics and Gynecology (REI), TRIO Fertility, University of Toronto, Toronto, Ontario, Canada

[10] Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Disease, Toronto Western Hospital, 399 Bathurst Street 1E-410B, Toronto, Ontario M5T 2S8, Canada

Introduction

Psoriasis is an inflammatory skin disease affecting 2–3% of the general population [1]. Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease affecting up to a third of psoriasis patients [2]. PsA is a heterogeneous disease involving articular and extra-articular locations [3]. The articular involvement includes synovial and extra-synovial structures [4].

The distribution of PsA between the genders appears to be equal [5, 6]. The mean age at onset of PsA ranges between the 4th–6th decades of life [5, 7]. Accordingly, many female patients suffer with PsA during their reproductive years, potentially impacting their childbearing potential.

Overall, there is a paucity of data regarding pregnancy-related issues in PsA and the existing studies tried to examine the influence of pregnancy on the joint disease and not the impact of the disease on pregnancy. A few studies in pregnant PsA patients showed that the joint activity ranged between a tendency toward improvement to high rate of remission during pregnancy followed by a postpartum flare [8–10]. The pregnancy outcome in these studies was good with a high percentage of live births. However, additional information regarding the fetal and maternal pregnancy course, delivery, and postpartum period is scarce. Furthermore, there is no specific study concerned with fertility in women with PsA.

Hence, the aims of the study were (1) to examine whether fertility and pregnancy outcome of PsA patients are different from healthy controls, and (2) to evaluate PsA patients' perception of skin and joint disease activity during pregnancy and the 1st year postpartum.

Methods

Setting

The University of Toronto PsA cohort was established in 1978. Patients are included in the cohort if they are diagnosed with PsA. Among these patients, 98% fulfill the CASPAR criteria [4]. The clinic is a tertiary medical center affiliated with the University of Toronto. In addition, it serves as a primary and secondary medical center in downtown Toronto. Hence, patients range from those in complete remission to those with severe manifestations. According to the PAIR (PsA assessment in rheumatology) study, the patients in the clinic are similar to other PsA patients across Canada [11].

At each visit, patients undergo complete assessment by a rheumatologist, including complete history, physical examination (with emphasis on peripheral and axial musculoskeletal features), laboratory, and radiographic assessment. The collected information is stored in a computerized database. The database was used to identify pregnancy history.

Patient selection

PsA patients The patients in this study included 74 PsA women who were followed in the clinic. A questionnaire was given to those who were diagnosed with PsA prior to at least 1 pregnancy. Figure 1 describes the flowchart of patient selection. Of the 249 PsA patients that completed the questionnaire, 51 did not have pregnancy history due to lack of partner (34 patients), did not want children (10 patients), or because of disease (PsA/psoriasis) concerns (7 patients). Four patients failed to conceive: 2 due their own problems (1 of them had it before she was diagnosed with PsA) and 2 due to partner problems. These 4 did not have a history of pregnancy and hence they did not fulfill the inclusion criteria.

Controls The control population included 74 healthy women from Toronto who had at least 1 pregnancy. This group included the patients' friends and patients attending the family health clinic in the Toronto Western Hospital who did not have any chronic disease.

The study was approved by the University Health Network Research Ethics Board and an informed consent was obtained from patients and controls.

Outcomes

A questionnaire was completed by the PsA patients and the controls during 2016. The time frame of the pregnancies was from 1978 with two thirds occurring after 2000. Medical terms (for example, eclampsia, preeclampsia, peri-, and neonatal death) were explained in the questionnaire. The questionnaire included:

1. Demographics—age, ethnic origin (Caucasians, Indian, Chinese, south-eastern Asian, Philippine, middle-eastern), marital status (married, common law, single, divorced, widowed, separated), level of education (high school incomplete, high school graduate, college, university), employment status (employed, retired, home maker, looking for work, disabled, sick leave, student), and number of pregnancies and of children.
2. Fertility status—a physician diagnosis of a fertility problem; failure to conceive within 12 months of unprotected intercourse, use of fertility medication; undergoing intrauterine insemination (IUI) or in vitro fertilization (IVF), or other fertility treatment.
3. Pregnancy course and outcome—the number of abortions and miscarriages, pregnancy outcome (live birth, stillbirth, elective termination, spontaneous miscarriage, therapeutic, ectopic pregnancy); weeks of gestation at completion of the pregnancy; the method of conception (spontaneous or fertility treatment), maternal complication during pregnancy (none, preeclampsia, eclampsia,

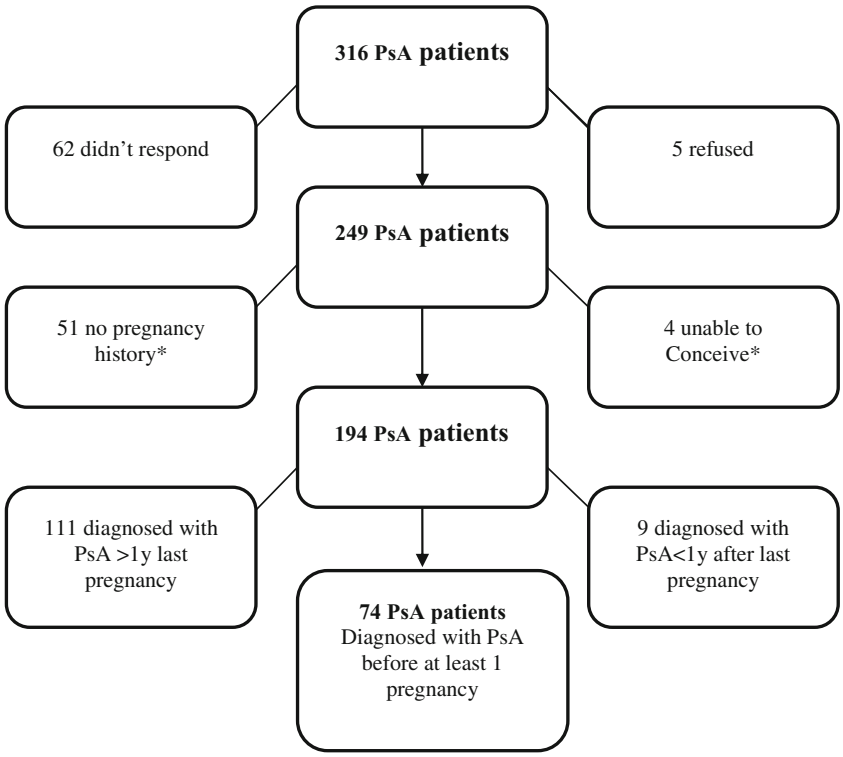

Fig. 1 Flowchart of PsA patient's selection

pregnancy-induced high blood pressure, hemorrhage, gestational diabetes, placental insufficiency or infarction), medication during pregnancy, method of delivery (vaginal, planned cesarean, emergency cesarean, assisted delivery), fetal complications (none, perinatal death, neonatal death, congenital malformations, neonatal intensive care unit admission).

4. Disease activity questions for both psoriasis and PsA at 3 time points: prior to conception, during pregnancy, and during the 1st year postpartum. The participants were asked whether the disease was active, improving, the same level or worsening.

Statistical analyses

Descriptive statistics were used to compare the women with PsA and the healthy controls with respect to demographics, fertility, and pregnancy course, and to evaluate the influence of pregnancy on PsA activity. For each individual pregnancy, the time of onset of PsA is also identified and grouped into 151 cases for "Pregnancy after PsA diagnosis" and 38 cases for "Pregnancy before PsA diagnosis," then compared with the same descriptive statistics. Medication intake during each pregnancy was investigated in the 151 pregnancies after the diagnosis of PsA. Fifty pregnancies on medication related to PsA were compared with 101 pregnancies without any medication related to PsA. Continuous variables were reported as mean (± standard deviation [SD]) and analyzed using a *t* test. Categorical variables were reported in frequency (%) and compared by Pearson chi-square test, with non-normally distributed variables reported as median (min, max) and compared using Wilcoxon rank sum non-parametric test. *P* value < 0.05 was set as the threshold of rejecting a null hypothesis.

The use of medication and disease activity during pregnancy were reported as number of counts in each level with respected percentages (%).

SAS (version 9.3; SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Demographics

The PsA group included 74 patients with a mean (± SD) age of PsA onset of 24.9 years (6.4). The healthy controls group included 74 participants. The overall number of pregnancies was 189 in the PsA group and 193 in the controls. However, after restricting the PsA pregnancies to those which occurred after the diagnosis of PsA, the final number was 151. The mean (± SD) PsA disease duration up to the pregnancies was 9.8 (7.1) years.

The groups were not significantly different in their mean age, marital status, ethnicity, level of education, and the mean number of total pregnancies and children (Table 1). The only difference was a higher employment rate in the control group (88% vs. 57%, $P < 0.001$).

Fertility assessment

Several fertility parameters were compared between the PsA patients and healthy controls, including a diagnosis of infertility by a physician, failure to conceive within 1 year of unprotected intercourse, and the use of fertility medications or procedures (IUI, IVF). However, there were no significant differences between the groups (Table 2). In addition, the rate of polycystic ovary syndrome was similar.

Pregnancy course and outcome in the PsA patients and healthy controls

Fetal complications were uncommon in both groups (Table 3). The dominant mode of delivery was vaginal in both groups. Maternal complications were also uncommon; however, there was a statistical difference ($P = 0.001$) due to a higher frequency of preeclampsia and bleeding in the control group. Pregnancy outcome in both groups was similar resulting in healthy neonates delivered at term with an average weight of 3.4 kg. Finally, there were no significant differences in the frequency and duration of breastfeeding.

Pregnancy course and outcome before and after PsA diagnosis

A comparison of pregnancies occurring before and after the diagnosis of PsA was undertaken to determine whether developing PsA changed the pregnancy course and outcome. In the group of pregnancies occurring before PsA diagnosis, the mean (± standard deviation) duration between PsA diagnosis and pregnancy was 4.4 (3.7) years. There were no significant differences in the pregnancy course and outcome measures regardless of the timing of the onset of PsA (Table 1 supplemental data).

Medications during pregnancy

Anti-inflammatory drugs were used in 50 (33.1%) pregnancies. The dominant medications during pregnancy were NSAIDs (20.5%). Permitted disease modifying antirheumatic drugs (DMARDs) included Salazopyrine, Azathioprine, and hydroxychloroquine, and were used by 8.6% of the patients. Methotrexate was used in 4 pregnancies, all of which ended spontaneously in the 1st trimester. Biologic medications (TNFα inhibitors in 13 pregnancies and ustekinumab in 1 pregnancy) were used in 9.3% of the pregnancies.

The comparison of pregnancy course and outcome revealed that in most variables, there were no significant differences regardless of medication treatment (see Table 2, supplementary data). The only exception was the mode of delivery showing more vaginal deliveries in the group that used medications, while more planned cesarean sections in the group without medications ($P = 0.045$).

Disease perception

The majority (58%) of the PsA patients had the perception of favorable arthritis outcome (comprising no activity and improvement) during pregnancy, while 50% recalled worsening during the 1st postpartum year (Table 4). Half of the patients had the perception of favorable psoriasis activity, while 29% recalled worsening during the 1st postpartum year.

Discussion

Many women with PsA are in their childbearing years, and accordingly, pregnancy-related questions are asked frequently at the clinic [5, 7]. Unfortunately, there are only a few studies in PsA that addressed this issue [8–10]. The current study tried to provide valuable information by comparing PsA patients to healthy controls. Demographically, these groups were comparable since they were similar in most of the relevant parameters including age, marital status, ethnicity, level of education, and the total number of pregnancies and children. The findings of this study did not demonstrate substantial differences between the PsA patients and healthy controls in fertility status, pregnancy course, pregnancy outcome, or breastfeeding.

The measurement of fertility in patients with rheumatic diseases is complicated as many factors may impact the occurrence of conception including disease activity, pain, anxiety and depression, therapy, impaired sexual function, disease-related concerns, and personal desires [12]. A few studies in rheumatoid arthritis (RA) showed a tendency toward reduced fertility [13, 14]. A questionnaire-based study in ankylosing spondylitis (AS) did not demonstrate this impairment [15]. Similarly, the present study did not find a higher frequency of a diagnosis of infertility or the use of fertility treatments in PsA patients compared to the healthy controls. A population-based study from Norway included a group of patients with chronic inflammatory arthritis, among them, PsA patients showed interesting results [13]. The relative fertility rate of patients with chronic inflammatory arthritis was reduced compared to the general population, whereas the relative fertility rate adjusted for birth order was similar. A follow-up study from the same group did not find higher use of assisted reproductive technology compared to healthy controls [16]. However, the definition of inclusion of PsA and the number of PsA patients in both studies were not reported. In addition, the PsA group was analyzed as part of a group of chronic forms of arthritis and not separated as a distinct disease.

The present study did not demonstrate that having or developing PsA leads to a worse pregnancy course or pregnancy

Table 1 Demographics of PsA patients and healthy controls

Variable	PsA ($n = 74$)	Controls ($n = 74$)	P value
Age, mean (± SD)	46.5 (8.7)	46.1 (8.5)	0.8
Married, n (%)	55 (74)	52 (70)	0.58
Ethnicity, Caucasians, n (%)	60 (81)	58 (78)	0.68
Level of education, ≥ college, n (%)	54 (73)	61 (82)	0.17
Employment status, employed, n (%)	42 (57)	65 (88)	< 0.001
Total number of pregnancies, mean (± SD)	2.5 (1.2)	2.6 (1.1)	0.72
Total number of children, mean (± SD)	1.9 (0.9)	2 (0.8)	0.69
Boys, mean (± SD)	1 (0.9)	1.1 (0.9)	0.39
Girls, mean (± SD)	0.9 (0.9)	0.8 (0.8)	0.65
Miscarriages and abortions	0.6 (0.8)	0.6 (0.9)	0.66

outcome compared to either healthy population or to the same patients who underwent a pregnancy prior to the onset of PsA. The few studies in PsA that focused on disease activity during pregnancy reported on a high rate of live births [8–10, 17], without mentioning other pregnancy course and outcome variables. In a population-based study, Wallenius et al. compared the pregnancy course and outcome of a group of chronic inflammatory arthritis patients including RA, AS, undifferentiated arthritis, juvenile inflammatory arthritis, and PsA [16]. This study demonstrated a higher elective cesarean section (CS) in the entire patient group and also a lower birth weight, more preterm delivery, and more perinatal mortality in the first birth but not in the subsequent births. Again, the number of patients and the method of inclusion of the PsA patients was not mentioned and the PsA patients were not assessed separately. Furthermore, the authors mentioned that the AS group had the highest rate of CS which may be responsible for the higher rate of the entire group. Recently, a very large population-based study from Denmark and Sweden, including 964 births in 753 women with PsA, showed increased gestational hypertension, preeclampsia, and delivery by elective cesarean section [18]. The main strength of this study is its large size; however, the definition of PsA relied on the general ICD-10 code without a validation process that will ensure the inclusion of the right patients.

A third of the PsA patients used medications during pregnancy, with NSAIDs being the most common group. Recent EULAR guidelines recommended considering the use of TNFα inhibitors during pregnancy [19]. This is based on a few studies that did not show more maternal or fetal complications in patients that were given these drugs [19]. In the current study, less than 10% of the patients used biologic drugs. However, some pregnancies occurred before the era of biologic drugs, and hence, this percentage might be higher today. In addition, those patients that used pregnancy-safe medications (NSAIDs, permitted DMARDs, and biologic drugs) during pregnancy demonstrated no difference in pregnancy outcome compared to those that did not use such medications.

Arthritis activity in PsA was assessed only in a few small studies. Older studies showed a very high rate of remission (80%) during pregnancy followed with high rate of flare in the 1st postpartum year [9, 10]. A recent study showed that 58% had favorable arthritis outcome during pregnancy followed with 50% worsening during the 1st postpartum year [8]. Similarly, 58% of the PsA patients in the current study reported more favorable arthritis activity during pregnancy followed with 50% reporting on worsening in the 1st postpartum year. As opposed to these studies, Mouyis et al. showed worsening

Table 2 Fertility comparison between PsA patients and healthy controls

Variable, n (%)	PsA ($n = 74$)	Controls ($n = 74$)	P value
- Diagnosis of infertility by a physician			0.48
Participant	21 (28)	15 (20)	
Partner	1 (1)	0	
Both	1 (1)	1 (1)	
- Failure to conceive within 1 year of unprotected intercourse	18 (25)	11 (15)	0.14
- Intrauterine insemination (IUI) or in vitro fertilization (IVF)	11 (15)	5 (7)	0.11
- Fertility medication	4 (5)	1 (1)	0.17
- Polycystic ovary syndrome (PCOS)	4 (10)	5 (15)	0.51

Table 3 A comparison of pregnancy course and outcome between the PsA and controls

Variable, *n* (%)	PsA (*n* = 74)	Controls (*n* = 74)	*P* value
Number of pregnancies	151	193	0.12
Maternal complications, *n* (%)			
None	124 (86)	161 (86)	0.001
Preeclampsia	1(1)	13 (7)	
Eclampsia	0	0	
Pregnancy induced HTN	5 (3)	0	
Hemorrhage	3 (2)	9 (5)	
Gestational diabetes	6 (4)	0	
Placental insufficiency	2 (1)	0	
Other (cholestasis, hyperemesis, hypothyroidism, low amniotic fluid)	3 (3)	2 (2)	
Fetal complications, *n* (%)			
None	113 (98)	130 (93)	0.31
Perinatal/neonatal death	0	0	
Congenital malformations	0	2 (2)	
NICU admission	2 (2)	5 (3)	
Jaundice	0	3 (2)	
Mode of delivery, *n* (%)			
Vaginal	73 (61)	99 (67)	0.1
Planned cesarean section	28 (24)	23 (15.5)	
Emergency cesarean section	14 (12)	23 (15.5)	
Assisted vaginal delivery	3 (3)	3 (2)	
Gestation week, mean (± SD)	38.5 (1.6)	38.3 (2.2)	0.29
Pregnancy outcome, *n* (%)			
Live birth	115 (76)	147 (76)	0.27
Still birth	1 (1)	1 (1)	
Spontaneous miscarriage	32 (21)	32 (17)	
Therapeutic abortion	1 (1)	5 (3)	
Choice abortion	2 (1)	8 (3)	
Gestation weight (kg), mean (± SD)	3.4 (0.4)	3.4 (0.6)	0.49
Breastfeeding, *n* (%)	95 (63)	133 (69)	0.24
Breastfeeding duration (months), mean (± SD)	8 (7.3)	9.7 (8.6)	0.12

(57%) of PsA activity during pregnancy [17]. However, it was a very small (only 14 pregnancies) retrospective study that did not elaborate when and how many times during pregnancy, PsA activity was monitored. Hormonal and immunological changes during pregnancy as well as HLA class disparity between mother and fetus may explain the beneficial effect of the pregnancy period on joint activity [20–22]. In contrast to this similarity, only 49% of the patients reported favorable skin activity during pregnancy. Previous studies showed a very high rate of favorable activity during this period [8, 14]. A possible explanation for this discrepancy may derive from the method of skin evaluation (PASI—Psoriasis Area Severity Index) which is complicated, relying on a formula that includes a few non-intuitive parameters (including size, erythema, induration, and desquamation), and not just pain or swelling as in the joint evaluation.

The present study identified 9 patients with PsA onset during the 1st year postpartum. Similarly, McHugh et al. reported on several psoriasis patients that developed PsA within 3 months after giving birth [23]. Thumboo et al. showed in an administrative study that pregnancy was protective for developing PsA [24]. However, 2 larger case control studies did not find any effect of pregnancy on the development of PsA [25, 26].

The main limitation of the study is its retrospective questionnaire design which may allow recall bias. However, previous studies in women who gave birth showed a good correlation between memory-based self-report and medical records in several pregnancy-related variables such as reproductive history, mode of delivery, medical procedures, gestational age at delivery, and breastfeeding [27–29]. Furthermore, Amissah et al. showed an association between increased education level and decreased recall bias [28], which may

Table 4 Disease perception during pregnancy and the 1st year postpartum

	n (%)
Arthritis activity	
Before pregnancy, active	128 (85)
During pregnancy	
No activity	46 (35)
Improvement	31 (23)
Same activity	36 (27)
Worsening	20 (15)
During the 1st year postpartum	
No activity	25 (19)
Improvement	8 (6)
Same activity	34 (25)
Worsening	68 (50)
Psoriasis activity	
Before pregnancy, active	113 (75)
During pregnancy	
No activity	48 (36)
Improvement	17 (13)
Same activity	63 (47)
Worsening	6 (4)
During the 1st year postpartum	
No activity	33 (24)
Improvement	5 (4)
Same activity	58 (43)
Worsening	39 (29)

correspond to the relatively high education level in the current study in both the patient and control groups (73% and 82% had ≥ college education, respectively). Another limitation is the lack of documented disease activity which may have an influence on fertility and pregnancy course and outcome. Unfortunately, the vast majority of the PsA participants did not visit the clinic during their pregnancies. This may be explained by better disease course during pregnancy and time constraints due to career and family demands as well as the need to be followed also by an obstetrician.

In conclusion, the current study did not find a worse pregnancy course and adverse outcome compared to a healthy population, suggesting that PsA does not have a deleterious effect on these parameters. PsA patients did not have a significantly higher incidence of a diagnosis of infertility or used more fertility procedures compared to the healthy population which may suggest that PsA does not affect fertility. Pregnancy may have a beneficial effect on joint activity since disease perception during pregnancy showed a tendency toward joint activity improvement. Further large prospective studies in PsA women who are in their childbearing age and planning pregnancy and in those who become pregnant are warranted.

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Compliance with ethical standards

Disclosures None.

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