

Maternal Interleukin-17 and Disease Activity Influence Pregnancy Outcomes in Women with Psoriatic Arthritis and Ankylosing Spondylitis

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Abstract

Objective: We aimed in this study to evaluate the impact of maternal interleukin -17A and the activity of the illness on pregnancy outcomes in Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients. **Methods:** This prospective cohort research was carried out on 48 Psoriatic arthritis and ankylosing spondylitis pregnant women attending the inpatient and outpatient clinics of Rheumatology & Rehabilitation and Obstetrics & Gynecology Departments, Faculty of Medicine, Zagazig university hospitals in Egypt and Yanbu National Hospital in KSA and 30 apparently healthy age- and sex-matched pregnant women between January 1, 2018, and December 31, 2019. **Results:** The study group patients have higher risk of preterm labour (32-36 weeks' gestation) (aRR 1.80, 95% CI 0.79–4.17), oligohydramnios (aRR 3.15, 95% CI 1.26-8.42), Caesarean delivery (aRR 1.57, 95% CI 1.41-2.68), and delivering infants small for gestational age (aRR 7.04, 95% CI 2.36-12.42). There was significant difference between the control group and the study groups regarding the level IL-17A. **Conclusion:** A lot of females with PsA and AS have uninhibited pregnancy as regards adverse events, but in comparison with normal pregnancies particularly with high IL-17A during third trimester we noticed a growing risk of preterm labour, oligohydramnios and caesarean section.

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Abstract

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Methods: This prospective cohort research was carried out on 48 Psoriatic arthritis and ankylosing spondylitis pregnant women attending the inpatient and outpatient clinics of Rheumatology & Rehabilitation and Obstetrics & Gynecology Departments, Faculty of Medicine, Zagazig university hospitals in Egypt and Yanbu National Hospital in KSA and 30 apparently healthy age- and sex-matched pregnant women between January 1,2018, and December 31, 2019.

Results: The study group patients have higher risk of preterm labour (32-36 weeks' gestation) (aRR 1.80, 95% CI 0.79–4.17), oligohydramnios (aRR 3.15, 95% CI 1.26-8.42), Caesarean delivery (aRR 1.57, 95% CI 1.41-2.68), and delivering infants small for gestational age (aRR 7.04, 95% CI 2.36-12.42). There was significant difference between the control group and the study groups regarding the level IL-17A.

Conclusion: A lot of females with PsA and AS have uninhibited pregnancy as regards adverse events, but in comparison with normal pregnancies particularly with high IL-17A during third trimester we noticed a growing risk of preterm labour, oligohydramnios and caesarean section.

KEYWORD: psoriatic arthritis; ankylosing spondylitis; Maternal interleukin-17; pregnancy outcomes

INTRODUCTION

Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are chronic inflammatory disorder that affect males and females at younger ages than other rheumatic diseases. Women with PsA and AS usually have normal pregnancy outcomes, although high disease activity during pregnancy may rise the adverse pregnancy outcomes, according to 2004-2018 data from the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease Project.(1)

Psoriatic arthritis is a chronic inflammatory arthritis coming with skin psoriasis. The onset of age is during the childbearing period. Psoriatic arthritis typically has varied joint and skin forms and variable degrees of severity. The clinic image is heterogeneous and symmetrical oligo or polyarthritis, axial manifestations, and enthesitis/dactylitis can be involved. Psoriatic arthritis is one of a linked set of diseases called spondyloarthritis.(2)

Ankylosing spondylitis disease characterized by pain and reduced axial bones flexibility and peripheral arthritic, extra-articular symptoms or enthesitis, all of which can lead to limitation of activity, disability, or poor life quality. Other inflammatory disorders such as psoriasis and IBD may be linked with AS. Management involves physiotherapy and medication with non-steroidal antiinflammatory medicines (NSAIDs), inhibitors

of tumour necrosis factor (TNF) and disease-modifying antirheumatic drugs (DMARDs). All of these variables can lead to poor results of pregnancy for women with AS.(3)

Although the pathogenesis is not well understood, many reports indicated that immune responses mediated by interleukin 17A (IL-17A) play a significant role in both diseases. The substantial clinical effectiveness seen in IL-17A inhibitors in the treatment of SpA and PsA is best demonstrated. However, there are many defects in understanding about the effect of IL-17A in pathophysiology of spondylarthritis, such as cellularity and its particular involvement in distinct disease processes such as enthesitis, bone erosion, and development of the bone, and in certain additional symptoms of spondyloarthritis, explanation for the uneven effect of the IL-17A inhibition was identified.

Registered studies in Norway cohorts have shown lower fertility in women with chronic arthritis in general as well as in bad birth outcomes as intrauterine growth retardation, preterm labour and Caesarean delivery..(4)

The majority of Ankylosing spondylitis patients in 6 weeks to 6 months after birth, developed an exacerbation of this condition. Limited researches are carried out in prenatal and neonatal AS patients with relatively small number of patients. Østensen et al. showed that AS illness did not negatively influence pregnancy outcomes.(5)

Overall, RA research reveal elevated risks of preterm birth, small-for-gestational-age (SGA), pre-eclampsia and caesarean deliveries from an overall perspective of chronic arthritis and pregnancy results. (6) AS studies and pregnancy outcomes are sparse however the latest Swedish case-control research indicated that preterm birth and caesarean delivery chances had been elevated. (7) They reported an increase in the adjusted odds ratios (aOR) for gestational hypertension, pre-eclampsia and caesarean delivery for the sub-analysis containing PsA pregnancy. (8)

We aimed in this study to evaluate the impact of maternal interleukin -17A and the activity of the illness on pregnancy outcomes in AS and PsA patients.

Ethical approval considerations:

All patients enrolled in this study had an informed consent before joining our study and all had the rights to take away from the study without any interruption of their treatment plan and rights. At the onset of study, Approval was obtained from department of Rheumatology, Zagazig university

All personal data of our enrolled patients were preserved and kept away from data retrieving personnel.

SUBJECTS AND METHODS

This prospective cohort study involved 48 Psoriatic arthritis and ankylosing spondylitis pregnant women attending the inpatient and outpatient clinics of Rheumatology & Rehabilitation and Obstetrics & Gynecology Departments, Faculty of Medicine, Zagazig university hospitals in Egypt and 30 apparently healthy age- and sex-matched pregnant women between January 1,2018, and December 31, 2019.

All patients enrolled in this study had an informed consent before joining our study and all had the rights to take away from the study without any interruption of their treatment plan and rights. All personal data of our enrolled patients were preserved and kept away from data retrieving personnel.

The study group patients diagnosed using modified New York criteria for ankylosing spondylitis and classification for psoriatic arthritis (CASPAR) criteria.

Information has been gathered in advance preconception (3 months to 1 year), throughout the 1st trimester (8-12 weeks), 2nd trimester (16-24 weeks) and 3rd trimester (28- 34 weeks of pregnancy).

All pregnant women who consented to participate were subjected to:

- Complete medical history, medication exposures during pregnancy, obstetric history including maternal age, expected date of delivery, gravity, parity, gestational age at enrollment and at labour, pregnancy by ICSI, and previous preterm delivery or intrauterine growth retardation., family history,

pre-conception body mass index (BMI), and socioeconomic status. Medication included start and end dates, indications, variations in dose and frequency, use of caffeine, nutritional supplements, folic acid intakes, infections, or antenatal investigation or other medical intervention. Any woman with other autoimmune diseases or other chronic disease was excluded from the study.

- General and local musculoskeletal examination
- Laboratory investigations

The erythrocyte sedimentation rate (ESR) done by the Westergren method, C-reactive protein (CRP) level done by latex agglutination test, and estimation of HLA B27 (ELISA Kit) done by collection of blood samples and were stored at -20degC until tested for human HLA B27 using Sunlong Biotech kit, China (catalog number: SL1056Hu).

IL-17A ELISA assay: It is an enzyme-linked immunosorbent assay for the quantitative detection of human IL-17A. The kit was supplied from IBL International GmbH (Flughafenstr. 52A, 22335 Hamburg, Germany).

Disease activity Using patient-reported assessments, including the Health Assessment Questionnaire (HAQ) on a scale from 0-3, as well as pain score and patient global disease activity assessment on a scale from 0-100, the study group was evaluated at the same obstetric evaluation time points (preconceptional, first trimester, and third trimester). Next, the total pain score was divided by 10 for a range of 0-10, and the patient global assessment was done the same way. Cumulative Routine Assessment of Patient Index Data 3 (RAPID3) had three markers of disease activity and each marker was put together to yield a RAPID3 score ranging from 1 to 30, with active disease defined as RAPID3 score ≥ 7 (10). Active disease was defined as a HAQ score greater than 0.5.

Measures of pregnancy outcomes :

Premature birth (delivery before 37 weeks of gestation), small for gestational age (SGA—fetal weight is projected to be smaller than the 10th percentile for the child’s gestational age and sex), and delivery methods (vaginal or cesarean).

Inclusion criteria involved a singleton pregnancy aged ≥ 18 years, with diagnosis of AS or PsA for at least 6 months, without major fetal anomalies, known chromosomal abnormalities or other autoimmune diseases, and gestational age of 28–40 weeks. Patients with history of preterm labour or any medical disorder were excluded from study.

Ultrasound biometry measurements such as the biparietal diameter (PBD), head circumference (HC), abdominal circumference (AC), and femur length (FL) were taken on each fetus. Hadlock’s formula gives the estimated fetal weight (EFW). William’s tables were used to get the overall EFW percentile. The tables determine the birth weight percentile by gestational age and sex, and they are from a large population-based study with a sample size large enough to calculate the percentile in question. (9,10)

Statistical analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. The data collected were tabulated and analyzed by SPSS (statistical package for social science) version 25 (IBM, Armonk, NY, USA) on IBM compatible computer. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean $\pm$ SD

The following tests were used: Chi-square test (χ^2) and Fisher Exact test, Independent samples Student t-test, Mann-Whitney U Test , Adjusted risk ratio computed using Poisson regression with robust standard errors.

A P-value of < 0.05 was considered statistically significant & < 0.001 for high significant result.

RESULTS

The maternal age mean $\pm$ SD was 30.21 ± 2.13 , 33.42 ± 5.11 , and 31.34 ± 3.15 weeks in the control, Psoriatic Arthritis, and Ankylosing Spondylitis groups respectively. BMI (kg/m²) mean $\pm$ SD was 23.25 ± 4.17 , 38.21 ± 3.15 , and 24.81 ± 5.13 respectively. The maternal weight gain (kg) mean $\pm$ SD was 23.25 ± 4.17 , 38.21 ± 3.15 , and 24.81 ± 5.13 respectively. The socioeconomic score N (%) was 25 (83.3%), 24 (92.3%), and 20 (90.9%) respectively. There was statistically significant rising in the Psoriatic Arthritis patients than healthy group as regard to age, BMI and Socioeconomic Score (table 1).

As regards parity, primigravida N (%), and multigravida N (%), they were statistically significant higher in the Ankylosing Spondylitis group 17 (77.2) and 14 (63.6) than the control group 14 (46.6) and 9 (30). Abortions N (%) were statistically significant lower in the Psoriatic Arthritis group 2 (7.6%) than the control group 5 (16.7%). Regarding history of Preterm labor N (%), Gestational Diabetes N (%) and Preeclampsia N (%) there was no significant difference between the control group and the Psoriatic Arthritis, and the Ankylosing Spondylitis groups (table 2).

Disease duration (year) mean $\pm$ SD was 5.32 ± 5.61 , and 6.37 ± 4.15 in the Psoriatic Arthritis, and Ankylosing Spondylitis groups respectively. Also, HLA B27 positive testing was higher in PsA than AS group. The disease was active according to Routine Assessment Patient Index Data with 3 measures in 10 (38.5%) and 9 (41%) and according to Health Assessment Questionnaire the disease was active in 4 (15.4%) and 6 (27.2%) in the PsA, and AS groups respectively. As regards the medications usage distribution, it was in the Psoriatic Arthritis group 21 (80.7%) were using Biologic DMARDs, 3 (11.5%) DMARDs and 10 (38.4%) NSAIDs, while in the Ankylosing Spondylitis group, it was 18(81.8%) were using Biologic DMARDs, 6 (27.2%) DMARDs and 8 (36.3%) NSAIDs (table 3).

There was significant difference between the control group and the Psoriatic Arthritis, and the Ankylosing Spondylitis groups at preconception, 1st, 2nd and 3rd trimester regarding CRP and IL-17A (**Figure 1**) while there was no statistically significant difference between pre-conception, 1st, 2nd and 3rd trimester as regard to CRP and IL-17A (table 4).

Also, there was no significant difference between the control and study groups regarding RAPID 3 score and HAQ score (**Figure 2& 3**) at preconception, 1st, 2nd and 3rd trimester (table 4).

Comparing to healthy controls, the Women of study groups have higher risk of preterm labour (32-36 weeks' gestation) (aRR 1.80, 95% CI 0.79-4.17), oligohydramnios (aRR 3.15, 95% CI 1.26-8.42), Caesarean delivery (**Figure 4**) (aRR 1.57, 95% CI 1.41-2.68) and higher risk of SGA fetus (aRR 7.04, 95% CI 2.36-12.42) (table 5).

Table (1): Demographic data of studied groups

Table (2): Comparison between groups regarding obstetric history.

Table (3): History Comparison between study groups regarding disease duration, activity and medication

Table (4): Comparison between PsA and AS groups regarding laboratory investigations and disease activity at time points of study

Table (5): Comparison between groups regarding pregnancy outcome

Figure 1: Comparison between study and control groups regarding IL-17

Figure 2: RAPID 3 Score in study groups

Figure 3: HAQ Score in study groups

Figure 4: Comparison between study and control groups regarding Delivery

DISCUSSION

Main findings

This study conducted to estimate the birth outcome in pregnant women with AS and PsA and value of IL-17A assay. Our study showed that the use of CS was related with premature delivery of SGA and oligohydramnios to high levels of IL-17A in 3rd trimester, in pregnant with AS and PsA .

Strengths and limitations

The main limitation of study was the small size of study groups, and the factors strengthen the study, the prospective nature of study and use of inclusion and exclusion criteria with coding of the data collected for proper interpretation.

Interpretation

Sub-set studies show that these finding's processes are complicated, varied for different outcomes, including a more severe AS phenotype, higher co-morbidity, pre-eclampsia and/or unknown variables.

Our findings are consistent with previous chronic inflammatory disorders researches. Females with IBD and RA are at greater risk for both premature baby and SGA. (11)

Also, Wallenius *et al.* (12) was found the same results in primiparous women with chronic inflammatory arthritis with a higher risk for preterm and SGA deliveries, but not in their future delivery.

A new report was carried out by the OTIS group showed that corticosteroid usage and a high disease activity might contribute to an elevated risk for premature birth to RA. (13) The study in our hand shows that there could be comparable tendencies in PsA and AS as the active disease increased the risk of PsA preterm birth later in pregnancy and corticosteroid usage increased the risk of AS pre-term birth in the second trimester.

In the other side Broms *et al.* (14) revealed that women with PsA have not shown a higher risk of premature birth. Various exposure criteria or different demographic variables might explain this disparity, as the Broms *et al* trial is Danish/Swedish. The discrepancies might potentially be affected in the two distinct research groups by the distribution of parity. Preterm delivery is a complicated process, which does not entirely understand the underlying processes, risk factors, and causes.(15)

We also identified an elevated risk for C.S in PsA, not described by the activity of illness. It is unknown if patients, doctors or other medical indications have been responsible for the elevated risk. This result is consistent with other studies on PsA,(16) AS,(17) juvenile idiopathic arthritis(16) and inflammatory chronic arthritis (12).

We discovered an overall higher risk of C.S amongst females in our result, also a higher C.S over vaginal delivery, such as in spondyloarthritis, sacroiliitis and hip arthritis. We discovered that elevated illness activity in third trimester was linked to an elevated risk in this group for C.S, but it is uncertain how many such deliveries were elective versus emergency. Also, Jakobsson *et al* noticed an elevated risk of C.S amongst AS pregnant (20,21).

Co-morbidities including obesity could influence the risk of preterm birth and caesarean deliveries. However, after restricting the analysis to those without IBD, AS or RA, the findings remained substantially unchanged. An association between obesity, including the metabolic syndrome, and PsA is well established (22,23). In our study, a greater proportion of pregnancies with PsA were complicated by obesity than non-PsA pregnancies but the frequency of pre-pregnancy hypertension was low.

Our investigation showed that women with PsA had a higher risk of oligohydramnios, as well. While it is unclear how this works, it is possible that the medicine she is taking and other maternal variables and/or additional comorbidities not measured or accounted for could be to blame. There was no substantial effect on the newborn outcomes for AS and PsA.

In particular, IL-17A values were shown to be elevated in the 2nd and 3rd trimesters of pregnancy and to be substantially linked with unfavourable maternal and foetal outcomes. In certain cases, IL-17 has been

detected with conflicting findings in serum and in plasma samples from cases with preeclampsia. Additional studies of homeostasis between the production of the regulatory T cells by Foxp3 and CD4+ T cells produced by IL-17 might be crucial to the maternal tolerance of the semi-allogeneic foetus. Foxp3 also decreased and IL-17A elevated were related to maternal and foetal problems (24,25).

In conclusion the majority of females with PsA and AS had an unincidental pregnancy with regard to deleterious effects, however in comparison to normal pregnancies with high levels of IL-17A in 3rd trimester, we found an elevated risk of premature birth, oligohydramnios and caesarean delivery. In future research with indications for surgical deliveries and medically indicated premature delivery, PsA or AS knowledge and pregnancy will be further enhanced. Studies on the influence of the illness severity and IL-17A serum on pregnancy outcomes are also needed.

Conflict of interest

The authors of this manuscript declare no relevant conflicts of interest, and no relationships with any companies, whose products or services may be related to the subject matter of the article.

Data Availability

Data available on reasonable request

Compliance with ethical standards

A written consent was taken from all subjects. The protocol of study was approved by Institutional Review Board and ethical committee of Rheumatology & Rehabilitation Department, Faculty of Medicine -Zagazig University- Egypt.

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Author contributions:

E.F.G: study design, writing and share in gynecological work up of study

S.M.A : collect the study and control groups

H.M.A.: share in gynecological work up of study

H.E.S.: share in gynecological work up of study

R.M.A.: share in laboratory work up of study

D.S.A: collect the study and control groups and share in writing of study

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