Pregnancy Outcome in Inflammatory Arthropathies — Are Population Database Studies the Right Tool?

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) belong to the inflammatory arthropathies (IA) group. These diseases differ from one another in their underlying mechanisms, clinical phenotype, extraarticular manifestations, and in the ways they are treated. Accordingly, they are classified into different groups, such as RA versus spondyloarthropathies (SpA) including PsA and AS^{1,2}.

However, despite these differences, IA share a similar period of onset, during the third to the sixth decades of life^{3,4,5}. Accordingly, many female patients with IA are in their childbearing years and the interplay between the inflammatory arthritic disease and pregnancy is a matter of concern. To date, most of the information in this field derives from studies conducted in patients with RA, and unfortunately the gestational data regarding those who have other types of IA are scarce^{6,7,8}.

In the current issue of *The Journal*, Keeling, *et al*⁹ addressed a very important topic of pregnancy course and outcome among patients with IA by comparing patients with RA, SpA, and healthy controls (HC) using population-based administrative data from Alberta, Canada.

The study results showed that patients with RA were at higher risk than patients with SpA and HC of experiencing hypertensive disorder during pregnancy, preterm deliveries, and cesarean deliveries. They were also more likely to give birth to small for gestational age (SGA) babies, and to deliver babies with lower birth weight compared to patients with SpA and to HC. Further multivariate analyses confirmed the association with hypertensive disorder and SGA. These findings are in line with several previous studies in patients with RA that showed similar pregnancy outcomes^{6,7,8}.

The main contribution of this study is the gestational information about pregnancy outcomes in patients with SpA, a topic that has been examined in only a few studies^{10,11,12}. Contrary to the RA group, the patients with SpA in the current study had similar pregnancy courses and outcomes compared

to HC, including hypertensive disorders, SGA, preterm deliveries, and cesarean deliveries. The only significant finding was higher induction rates in the SpA group. These results are similar to a recent small, retrospective study from Toronto that did not find significant differences in maternal or neonatal outcomes between patients with PsA and matched controls¹⁰. In contrast, 3 studies suggested that SpA is associated with several adverse pregnancy outcomes^{10,11,12}. A study that used data from a large prospective North American pregnancy registry found a higher risk of preterm deliveries and labors, oligohydramnios, and cesarean deliveries in patients with PsA and more infants who needed intensive care hospitalizations in patients with AS compared to HC¹¹. Another study, from Sweden, using a nationwide population-based administrative dataset, found that patients with AS were more likely to experience more emergency and elective cesarean deliveries and preterm births, and to deliver SGA babies¹². Finally, a large population-based study that used large and detailed national health registries from Sweden and Denmark found more gestational diabetes, hypertension, and cesarean deliveries among patients with psoriasis and PsA compared to controls¹³.

These wide variations across the studies could result from many factors, including differences in study populations, case definitions, health systems, and study designs. The authors of the current study used a population-based administrative database as their data source. This source has several clear advantages, including the substantially large number of cases and controls (308,989 HC, 631 RA, and 2461 SpA patients) and the lack of selection bias, because the participants arrived from different ethnic groups and regions in the province. Further, the patients were managed in different medical centers and likely represented a wide variety of disease severities. These factors increase the generalizability of the results, in contrast to single-center studies and studies using patient registries. Finally, the study includes several

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detailed gestational, birth, and peripartum outcomes. All of these ensured a solid base for various analyses.

However, there are several important limitations caused by this study's reliance on administrative data. The lack of information about relevant confounders such as obesity, smoking, and education level might have influenced the investigated outcomes. Obese pregnant women are more likely to experience pregnancy and perinatal complications, and these adverse outcomes are amplified with the level of obesity¹⁴. Smoking during pregnancy is a risk factor for several outcomes including preeclampsia, miscarriage, stillbirth, low birth weight, and preterm birth¹⁵. Finally, education level may have an influence on the awareness of the significance of a healthy pregnancy, and accordingly could correlate with the degree of care during this period. It is expected that the inclusion of these confounders in the analysis would have resulted in weakening of significant associations between the disease and adverse pregnancy outcomes. However, these associations were demonstrated mainly in the RA and not in the SpA group and hence the lack of inclusion of these confounders could have a significant effect on the results of the RA but not of the SpA group.

Another important aspect to consider is the effect of disease activity on pregnancy outcomes. Several previous studies showed that the level of IA disease activity during pregnancy might play a role in gestational outcomes. In a nationwide prospective cohort study, Brouwer, *et al* found 28 miscarriages among 162 RA pregnancies¹⁶. Patients with a higher disease activity level (by 28-joint count Disease Activity Score) had a greater tendency toward miscarriages. Bharti, *et al* found that an increase in Health Assessment Questionnaire–Disability Index (HAQ-DI) was associated with an elevated risk for preterm delivery and SGA among 440 women with RA¹⁷. Smith, *et al* showed that an increased HAQ score was associated with preterm delivery in patients with PsA, and high Routine Assessment of Patient Index Data 3 score with cesarean delivery¹¹. Finally, Yang, *et al* demonstrated that severe psoriasis was associated with having low birth weight babies compared to mild psoriasis¹⁸. As expected by the design of the study that relied on administrative data, which does not include detailed information on disease activity measures, these analyses were not performed in the Keeling, *et al* study.

An important issue that may explain the discrepancy with other studies is related to the accuracy of case definition. Inclusion of patients with accurate diagnosis is a basic requirement for every study. Accurate diagnosis in general in medicine and particularly in rheumatology is a challenging task that relies on many factors such as the experience of the specialist. The diagnostic codes in this study were assigned by different physicians and not necessarily by rheumatologists. This may have resulted in misclassification of patients. International Classification of Diseases, 9th ed (ICD-9) and 10 were used as the tool for identification and classification

of the patients with IA. However, ICD-9 and 10 are coding methods and not exclusive rheumatologic classification criteria, which may explain how some patients received both a diagnosis of RA and one of SpA. The authors decided arbitrarily to include these patients in the RA group. The lack of additional information of the validity of the ICD codes in the current database limits the ability of the readers to estimate the level of misclassification.

In addition, Keeling, *et al*⁹ combined different types of SpA as well as patients with psoriasis in the SpA group. This heterogeneous group of different diseases may have resulted in the lack of association between SpA and adverse pregnancy outcomes. Psoriasis is an inflammatory skin disease affecting 2–3% of the population¹⁹. The prevalence of SpA ranges from 0.4% to 2% in the general population²⁰. This means that patients with psoriasis probably dominated the group of SpA in this study. Psoriasis severity ranges widely. The majority of patients tends to have a mild disease, while only about a third of patients have moderate to severe psoriasis, which tends to be associated with comorbidities²¹. Further, patients with psoriasis or PsA are not necessarily similar; only 20–30% of patients with psoriasis develop PsA²². A previous study comparing patients with psoriasis without arthritis to those with psoriasis and PsA found more comorbidities and combined systemic treatment such as biologic drugs in the PsA group²³. Given that in this study the investigators could not differentiate between psoriasis and PsA using ICD-9 codes, it is possible that patients with mild psoriasis without IA were a substantial part of the SpA group. Taken together, all of these may have led to better pregnancy outcomes in the SpA group.

Keeling, *et al* showed more adverse gestational outcomes in the RA but not in the SpA group compared to controls⁹. The way of establishing this conclusion is the heart of the matter. There is a genuine need for further large population-based studies that will address these issues. However, this requires a preliminary process of validation of patients' diagnoses, focusing on patients with IA, and inclusion of all the relevant confounders.

ARI POLACHEK, MD,
Department of Rheumatology,
Tel Aviv Sourasky Medical Center,
Sackler Faculty of Medicine,
Tel Aviv University,
Tel Aviv, Israel;

LIHI EDER, MD, PhD,
Department of Medicine,
University of Toronto,
Women's College Research Institute,
Women's College Hospital,
Toronto, Ontario, Canada.

Address correspondence to Dr. A. Polachek, Department of Rheumatology, Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, 6 Wizeman St., Tel Aviv 64239, Israel.
E-mail: arikpolachek@yahoo.com

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