A systematic review and meta-analysis of maternal psoriasis and preterm labor

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Abstract

Psoriasis is an inflammatory mediated skin disease with significant physical and psychological distress. As there are conflicting data from published literature on the association between psoriasis and pregnancy; therefore, the researchers hypothesized that the dysregulation of the immune system in psoriasis will result in a negative impact regarding fetomaternal morbidity and mortality. The primary objective of this systematic review and meta-analysis is to assess the effect of maternal psoriasis and preterm labor. The researchers searched Web of Science, PubMed, Cochrane Central Register of Controlled Trials, and SCOPUS for published articles between January 1980 and December 2020, including reference lists of relevant studies. All 1592 citations were reviewed and identified studies examining adverse pregnancy outcomes associated with psoriasis. Seventeen studies were included with a total of 44,249 pregnancies with psoriasis and 47,807,880 pregnancies without the disease. Random-effect models were used to create pool odds ratios. For women with psoriasis, a higher odd of preterm labor was founded compared with non-disease controls (10 studies: OR 1.28, 95%CI 1.14-1.44). The results of this study confirmed that psoriasis is a risk factor for preterm labor.

Keywords: *Psoriasis, Psoriatic arthritis, Preterm labor, Pregnancy outcome, Pregnancy complication, Fetal risk*

1. Introduction

Psoriasis is an inflammatory mediated genetic disease, expressing in the skin or joints or both in millions of people worldwide. It's a chronic, debilitating problem that can cause distress physically and psychologically. The prevalence of psoriasis ranges from 0.09% to 5.1%, which can vary in different ethnic backgrounds (Michalek, Loring, & John, 2017). Psoriasis is characterized by symmetrically distributed, well-demarcated, erythematous, and scaly plaques. The scale is typically silvery in color, except in the intertriginous area where the lesions often have no scale due to the moist environment. The most commonly affected sites are the scalp, elbows, and knees, but any part of the body integument can also be involved.

The psoriasis pathophysiology involves both innate and adaptive immune systems. Several studies have supported the evidence of interactions between dendritic cells, T cells, keratinocytes, and cytokines that contribute to the inflammatory process in psoriatic lesions. Innate immune cells, particularly plasmacytoid dendritic cells, activated by antigenic stimuli, produce pro-inflammatory cytokines including interferon-alpha that activate the migration of myeloid dendritic cells. Interleukin-23, a cytokine produced from myeloid dendritic cells, induces the activation and differentiation of T cells. The activated T cells produce various inflammatory cytokine, especially IL-17, which stimulate keratinocyte proliferation and inflammatory process that lead to the formation of psoriatic plaque (Greb, 2016).

About half of the patients with psoriasis are women, and the peak age of onset is observed before the age of 40 years, which is considered the reproductive age (Gudjonsson & Elder, 2007). Besides, hypertension, obesity, depression, diabetes mellitus, and other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease were found to be associated with adverse pregnancy and birth outcomes in most psoriasis patients (Bae et al., 2012). However, some contrary data are available from previous studies on the impact of psoriasis on pregnancy outcomes. In 2016, Bobotsis et al. conducted a systematic review including nine observational studies and clinical trials. In three out of four showed a

statistically significant increase in the risk of pregnancy negative outcome, including spontaneous cesarean delivery, low birth weight, abortion, and preterm labor. However, those outcomes were inconsistent across studies, and there was no concrete evidence of a consistently increased risk of adverse pregnancy outcomes for women with psoriasis (Bobotsis, Gulliver, Monaghan, Lynde, & Fleming, 2016).

2. Objectives

To evaluate the association of maternal psoriasis and preterm labor compared with non-disease control.

3. Materials and Methods

Eligibility criteria

All published observational studies (cross-sectional, case-control, and cohort), clinical trials, and abstracts were included. Others such as case reports, review articles, case series, and observational studies with no control group were excluded. The language was restricted to English. The researchers included studies on pregnant women that have been diagnosed with psoriasis and/or psoriatic arthritis. There was no restriction on age, ethnicity, profession, and socioeconomic status.

Search methods

To identify relevant studies, Web of Science, PubMed, SCOPUS, and the Cochrane Central Register of Controlled Trials (Cochrane Library) databases were used by 2 independent researchers to search comprehensively from their beginning to May 2020. The searched items were used as follows; psoriasis, pregnancy, and adverse outcome.

Selection of studies

The relevant studies obtained from the databases mentioned above were imported into literature management software Endnote version X7. After removing duplicates, both researchers independently evaluated the titles and abstracts of the studies and excluded the significantly unqualified literature. The full text of the remaining studies was carefully selected according to the inclusion criteria. The third reviewer stepped in and provided arbitration when different opinions failed to reach an agreement. The selection procedure is shown in a flow chart in line with PRISMA guidelines.

Data extraction and management

Two researchers independently undertook data extraction via a standardized data collection form. The information such as the first author, year of publication, study design, sample size, comparator group, study setting, outcome measured, methods for statistical data analysis, and publication characteristics were extracted and recorded. The researchers contacted those authors to request detailed information via e-mail if the data were unclear or missing. Any divergence on the data extraction was judged and discussed by the 2 reviewers. The third reviewer checked the final results of the data extraction and provided arbitration for further disagreements. The Newcastle-Ottawa Scale (NOS) was used for the assessment of the quality of nonrandomized studies, including case-control and cohort studies. Any discrepancies in the assessment of the risk of bias were resolved by discussion, and an arbiter will be consulted if it is necessary.

Data analysis

The measure of association of interest was based on the odds ratio (OR). To calculate unadjusted ORs for when ORs were not reported, 2 by 2 contingency tables were constructed. The random-effects models were used to estimate the pooled ORs, and 95 % confidence intervals (CIs) were obtained. The study heterogeneity was assessed using the Q test, and I^2 statistic. After grouping the studies by severity and the presence of psoriatic arthritis, the sensitivity analysis was performed for preterm birth.

All analyses were performed using Review Manager version 5.2 (The Nordic Center, The Cochrane Collection, Copenhagen) and Comprehensive Meta-Analysis version 2.2.064 (Biostat, Englewood, NJ).

4. Results and Discussion

Seventeen studies were included in our meta-analysis. The selection process was demonstrated in Figure 1 and the characteristic of the studies were mentioned in Table 1.

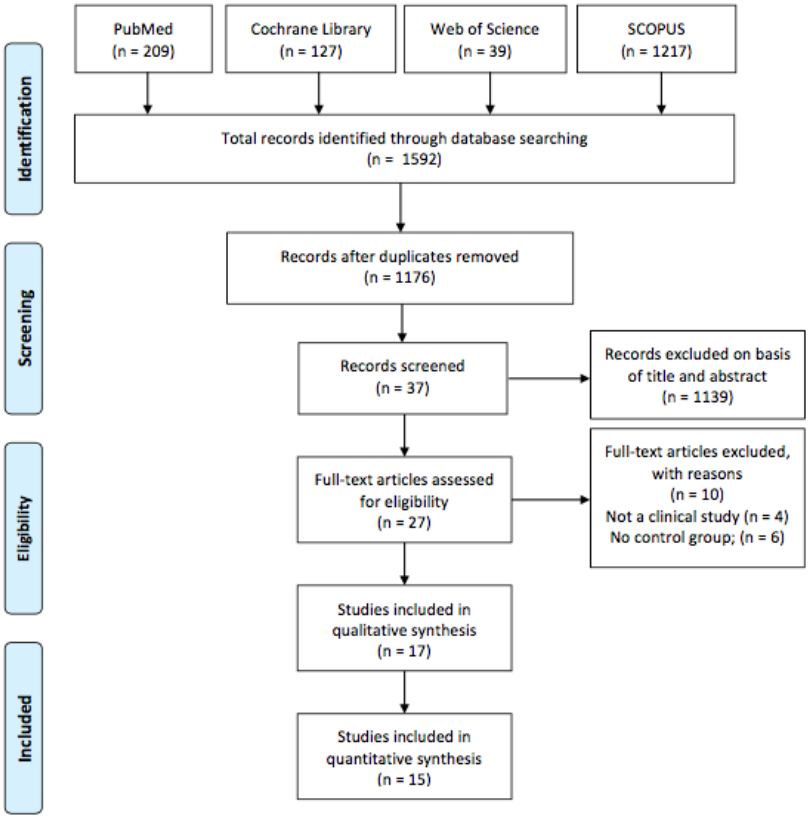

Figure 1 PRISMA Flow diagram

Table 1 Characteristic of the included studies

1st Author	Year of Publication	Study design	Number of pregnancy in women with psoriasis	Number of pregnancy in women without psoriasis	Study setting	Publication characteristic
Bandoli	2017	Prospective cohort	330	1730	United States	Full paper
Bandoli	2020	Retrospective cohort	1255	2962633	United States	Full paper
Ben-David	2008	Retrospective cohort	145	860	Israel	Abstract paper
Boddeda	2018	Retrospective cohort	11204	42306444	United States	Abstract paper
Broms	2018	Prospective cohort	8097	943846	Denmark, Sweden	Full paper
Carman	2017	Retrospective cohort	1430	405	United States	Full paper
Cohen-Barak	2011	Retrospective cohort	68	237	Israel	Full paper
Gulliver	2015	Retrospective cohort	615	2444	Canada	Full paper
Harder	2014	Retrospective cohort	2553	85139	Denmark	Full paper
Lambe	2020	Retrospective cohort	15975	1448542	Sweden	Full paper
Lima	2012	Retrospective cohort	162	501	United States	Full paper
Park	2019	Retrospective cohort	23772	118860	Korea	Abstract paper
Polachek	2019	Retrospective cohort	151	189	Canada	Full paper
Remaeus	2019	Retrospective cohort	541	40944	Sweden	Full paper
Seeger	2007	Prospective cohort	305	2592	United States	Full paper
Smith	2020	Prospective cohort	117	171	United States	Full paper
Yang	2011	Retrospective cohort	1463	11704	Taiwan	Full paper

All of the included papers were cohort studies, and four had a prospective design (G. Bandoli & Chambers, 2017; Gretchen Bandoli et al., 2020; Ben-David, Sheiner, Hallak, & Levy, 2008; Boddeda, Harrison, Kishore, & Majithia, 2018; Bröms et al., 2018; Carman, Accortt, Anthony, Iles, & Enger, 2017; Cohen-Barak, Nachum, Rozenman, & Ziv, 2011; Gulliver, Morrissey, Randell, Gulliver, & Macdonald, 2015; Harder, Andersen, Kamper-Jørgensen, & Skov, 2014; Lambe, Bergstrom, Johansson, & Weibull, 2020; Lima, Janakiraman, Hughes, & Kimball, 2012; Park et al., 2019; Polachek, Li, Polachek, Chandran, & Gladman, 2017; Remaeus, Stephansson, Johansson, Granath, & Hellgren, 2019; Seeger, Lanza, West, Fernandez, & Rivero, 2007; Smith et al., 2017; Yang, Chen, Chen, & Lin, 2011). No randomized controlled trials were available. Three articles included exclusively women with psoriatic arthritis (Polachek et al., 2017; Remaeus et al., 2019; Smith et al., 2017). One article reported the odds of adverse pregnancy outcomes separately between psoriasis and psoriatic arthritis (Bröms et al., 2018). The analyses were carried out on a total of 44,249 pregnancies in women with psoriasis and 47,807,880 pregnancies in women without the disease. The

quality assessment score for a cohort study using the Newcastle-Ottawa scale resulted in overall quality scores ranging from 6-9. Two studies reported outcomes as adjusted ORs without providing further information (Lima et al., 2012; Park et al., 2019), thus the researchers cannot use data from these two studies to calculate in our meta-analysis.

Ten studies reported the incidence of preterm labor. The result suggested that neonates born from women with psoriasis had a significantly higher risk of prematurity than those from non-psoriatic mothers. (Figure 2; OR 1.28, 95% CI 1.14-1.44; $I^2 = 80\%$; $P < 0.0001$) However, after sensitivity analyses, there was no significant correlation regarding the severity of psoriasis on prematurity. A difference in preterm birth ORs based on severity and extracutaneous involvement was revealed by sensitivity analyses. Those with psoriatic arthritis had a significant risk of preterm birth (Figure 3; OR 1.52, 95% CI 1.16-1.98; $I^2 = 42\%$; $P = 0.002$). The risks were statistically insignificant using analyses based on the severity of psoriasis. The analyses for other fetal complications such as spontaneous abortion, stillbirth, fetal death, premature rupture of membrane, low birth weight, small for gestational age, large for gestational age, and fetal anomaly were statistically insignificant between women with psoriasis and healthy women.

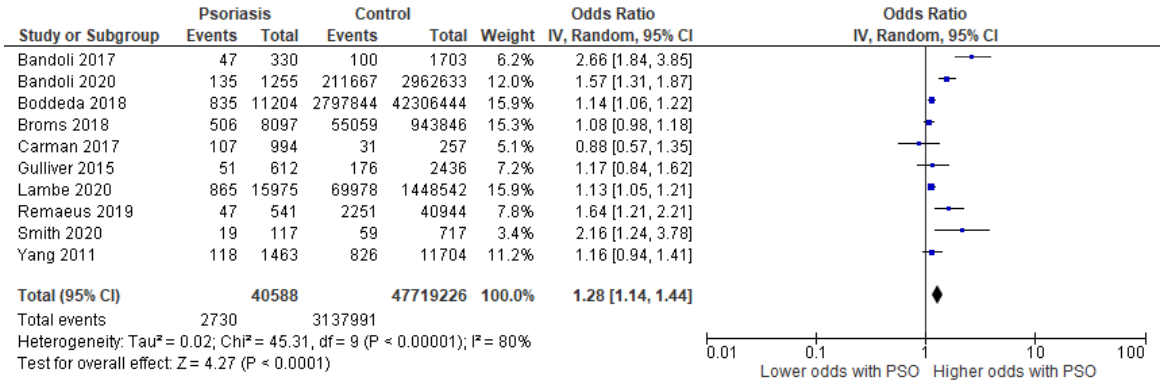

Figure 2 Meta-analysis of the odds of preterm labor in women with psoriasis compared to non-disease controls

Our meta-analysis confirmed that psoriasis could be considered a risk factor for preterm birth. To the best of our knowledge, these associations are the result of the largest meta-analysis so far available. Several studies suggested the role of IL-17 in correlation with the significant outcomes mentioned above. There is a deficit of regulatory T cells in pregnancy complicated by preeclampsia, which supports the expressions of Th17 lymphocytes and the induction of inflammatory response in the fetomaternal interface (Sasaki et al., 2007; Steinborn et al., 2008).

Another study conducted by Ito et al. examined the role of IL-17 in the pathogenesis of preterm delivery by studying the level of IL-17, IL-8, and tumor necrosis factor (TNF) alpha in amniotic fluid. The result showed higher levels of inflammatory cytokines in preterm cases than in term delivery cases. Those results indicated that IL-17 can promote inflammation at the fetomaternal interface in preterm delivery (Ito et al., 2010). To date, it has been confirmed that IL-17 plays a significant role in the pathogenesis and sustaining inflammation process in psoriasis. It influences the recruitment of inflammatory cells, enhances keratinocyte proliferation, and inhibits keratinocyte differentiation (Michalak-Stoma et al., 2020; Takahashi, Tsuji, Hashimoto, Ishida-Yamamoto, & Iizuka, 2010). Many studies found statistically significant differences in serum IL-17 level in psoriasis patients compared with healthy controls (Oliveira et al., 2015; Takahashi et al., 2010; Zaher, El-Komy, Hegazy, El Khashab, & Ahmed, 2013). Our result from this meta-analysis can be explained by the increased level of IL-17 in psoriatic mothers that influence the higher risk of preterm labor.

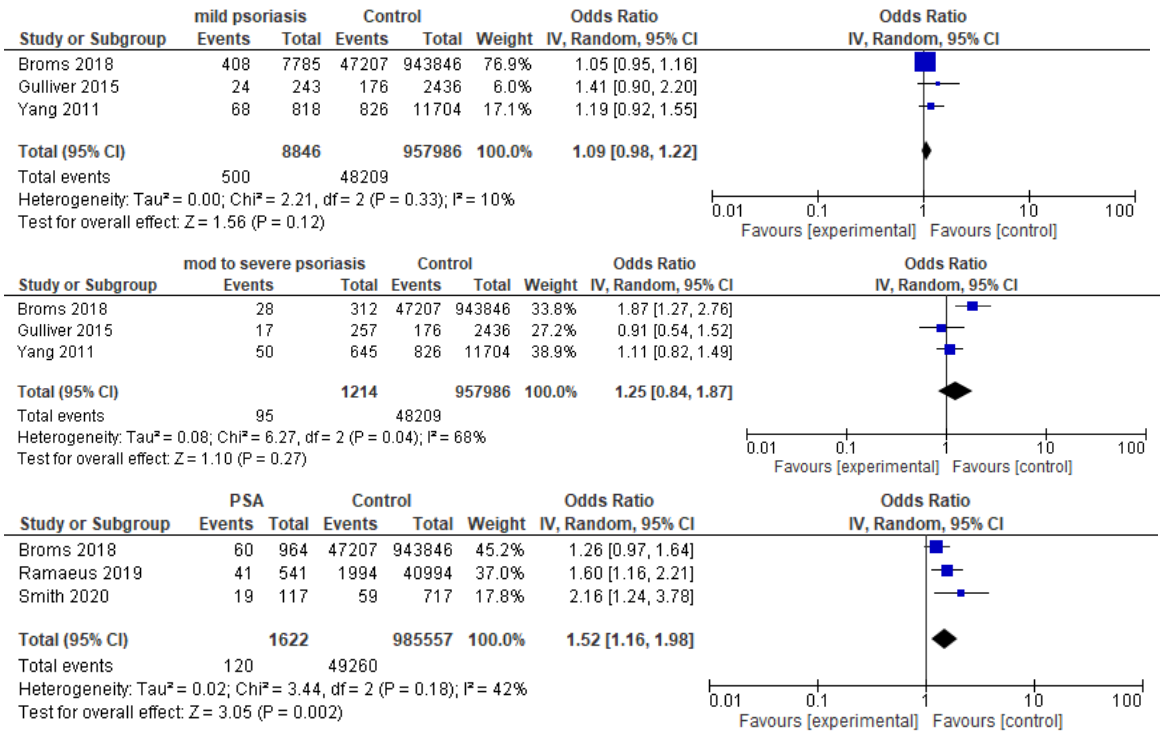

Figure 3 Sensitivity analysis of the odds of preterm labor by disease severity and psoriatic arthritis in women with psoriasis compared to non-disease controls

However, there was no significant association between maternal psoriasis and either spontaneous abortion, stillbirth, fetal death, premature rupture of membrane, small or large for gestational age, low birth weight, or fetal anomaly. The meta-analysis increases the power to detect existing associations compared with individual studies alone and was designed to include studies reporting the outcomes of interest while excluding those with a lack of methodological detailed, appropriate control group. Besides, the researchers established a strict methodology and a predefined review process. The main limitation of this study is the quality of the included studies, the studies were inevitably all observational studies as the exposure of interest is the disease itself and therefore cannot be randomized, and all but four studies were in a retrospective manner. Therefore, the statistical combination of data might have been subjected to bias related to selection and reporting. These results should be considered carefully due to heterogeneity among studies that also stand in the choice of different severity of the disease in the included papers.

5. Conclusion

Psoriasis is a chronic inflammatory disease with immunological complexity. The majority of patients experience disease onset in their adult years. For women, it often occurs during their childbearing age. While some autoimmune diseases have been shown to affect pregnancy outcomes, such a relationship has not been well exhibited in psoriasis. Our meta-analysis found an increased risk of preterm delivery among women with psoriasis compared with non-disease controls. The researchers hypothesized that the correlation between these outcomes and psoriasis might be due to the expression of IL-17, however, further studies are essential to understand the association of the disease and pregnancy complications.

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