Maternal Psoriasis Magnitude The Risk Of Pregnancy Complications In Women: A Systematic Review And Meta-Analysis

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Abstract

Psoriasis is a chronic inflammatory disease with significant physical and psychological distress. As there are conflicting data from published literatures on the relationship between psoriasis and pregnancy. We hypothesized that the dysregulation of the immune system in psoriasis, will result in negative impact regarding to fetomaternal morbidity and mortality. Therefore, objective of this systematic review and meta-analysis is to assess the effect of maternal psoriasis and adverse pregnancy outcomes. We searched PubMed, Web of Science, SCOPUS, and Cochrane Library for published articles from January 1980 to December 2020. Total 1592 citations and identified studies examining outcomes of pregnancies complicated by psoriasis. Seventeen studies were included with a total of 44,249 pregnancies in women with psoriasis and 47,807,880 pregnancies in women without the disease. Random-effect models were used to generate pool odds ratios. We found a higher odd of pregnancy-related complication in women with psoriasis compared with non-disease controls; 1.47 for pregnancy-related hypertension (9 studies; 95%CI 1.16–1.87), 1.70 for gestational diabetes (7 studies; 95%CI 1.34–2.15), 1.28 for preterm (10 studies; 95%CI 1.14–1.44), and 1.35 for cesarean section (10 studies; 95%CI 1.22–1.50). The results of this meta-analysis confirm that psoriasis is a risk factor for pregnancy-related hypertension, gestational diabetes, and preterm labor.

Introduction

Psoriasis is a chronic inflammatory mediated disorder that results from a polygenic predisposition combined with environmental triggers such as infections, trauma, and medications[1]. The pathophysiology of psoriasis involves various type of cells and cytokines in the immune response. Dysregulation of immune system together with interplay between immune cells and mediators provides a significant role in the pathogenesis of the disease. Inflammatory cytokines such as IL-17. IFN gamma, TNF alpha and IL-22 secreted from T helper cells are keys to chronicity of the disease, amplification of inflammatory cascades, and keratinocytes activation[2].

Psoriasis affects about 3 percent of world population including women. While the peak age of psoriasis is observed before the age of 40 years which considered childbearing age, there are still conflicting scientific evidences regarding to the impact of maternal psoriasis and pregnancy complications[3]. Pregnancy is associated with Th2 mediated phenomenon and various upregulation of several cytokines and cytokine-modulating molecules activity. Moreover, regulatory T-cells and decreased Th17 response associated with successful pregnancy outcome. In addition, immune mediated disease such as systemic lupus erythematosus and inflammatory bowel disease were proved to be associated with pregnancy complications[4,5]. Therefore, giving further linking for the understanding of potential impact on pregnancy outcomes on Th17-mediated autoimmune disorders such as psoriasis.

To date there are only handful of research on the effect of maternal psoriasis. Bobotsis et al. conducted a systematic review including nine studies. However, they did not assess the statistical analysis to evaluate the fetomaternal impact of the condition [6]. Despite the high prevenance in the general population,

especially in women of childbearing age the knowledge concerning the influence of pregnancy on psoriasis is necessary for in terms of counseling and management. Therefore, to provide evidence-based practical information for both physicians and patients, we conducted a systematic review and meta-analysis of maternal psoriasis and adverse pregnancy outcomes.

Results

Identification and characteristics of studies.

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

Table 1
Characteristic of the included studies

1st Author	Year of Publication	Study design	Number of pregnancies in women with psoriasis	Number of pregnancies 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 research were cohort studies and four had a prospective design. No randomized controlled trials were available. Three articles included exclusively women with psoriatic arthritis [7–9]. One article reported the odds of adverse pregnancy outcomes separately between psoriasis and psoriatic arthritis [10]. 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.

As quality assessment for risk of bias, one study was rated six stars, four studies were rated seven stars, six studies were rated eight, and six studies were rated nine stars according to the Newcastle-Ottawa Scale (NOS) [11].

Pregnancy related hypertension and gestational diabetes

Nine of the 17 studies reported on the incidence of pregnancy related hypertension in 26 679 patients with psoriasis versus 5 399 671 controls. Patients with psoriasis were more likely to have high blood pressure than controls (OR 1.47; 95% CI 1.16 to 1.87; P=0.001) (Figure 2). Analysis of gestational hypertension in psoriasis patients versus controls (OR 1.37; 95% CI 1.14 to 1.64; p = 0.0008) and preeclampsia in patients versus controls (OR 1.44; 95% CI 1.01 to 2.04; p = 0.04) also showed significant differences between the two groups (Figure 2).

Seven studies reported on the incidence of gestational diabetes in patients with psoriasis and in controls. A significant increase was seen in the incidence of gestational diabetes in psoriasis patients versus controls (OR 1.7 0; 95% CI 1.34 to 2.15; p<0.0001) (Figure 2).

Preterm birth and psoriasis

Ten studies reported on the incidence of preterm births in infants born to patients with psoriasis versus controls (Figure 3). Maternal psoriasis was associated with prematurity compared to non-disease controls (OR 1.28; 95% CI 1.14 to 1.44; p<0.0001). Subgroup analysis demonstrated significant association between psoriatic arthritis and preterm birth, while severity of the disease showed no relation with prematurity (Figure 3).

Mode of delivery in pregnant women with psoriasis

Ten of the 17 studies reported on the cesarean section rates in psoriasis mothers and in non-disease controls (Figure 4). Analysis showed a significantly higher rate of cesarean section among mothers with psoriasis than in controls (OR 1.35; 95% CI 1.22 to 1.50; p<0.00001). The risk of cesarean section was statistically significant in those with psoriatic arthritis compared to controls (OR 1.86; 95% CI 1.41 to 2.47; p<0.0001). However, there were no significant correlation regarding to severity of psoriasis on mode of delivery (Figure 4).

Pregnancy related factors that not significantly associated with psoriasis

Maternal psoriasis was not associated with postpartum hemorrhage (OR 0.89; 95% CI 0.79 to 1.00; *p*=0.05), spontaneous abortion (OR 0.98; 95% CI 0.68 to 1.40; *p*=0.91), stillbirth (OR 1.10; 95% CI 0.79 to 1.51; *p*=0.57), fetal death (OR 1.11; 95% CI 0.84 to 1.47; *p*=0.47), low birth weight (OR 1.06; 95% CI 0.85 to 1.33; *p*=0.60), small for gestational age (OR 1.11; 95% CI 0.97 to 1.26; *p*=0.14), large for gestational age (OR 1.32; 95% CI 0.98 to 1.77; *p*=0.06), and congenital anomalies (OR 1.06; 95% CI 1.00 to 1.12; *p*=0.05).

Sensitivity analysis

Higher quality study (>= 8 stars)

Analysis of the high quality studies showed statistical differences between patients with psoriasis and non-disease control in four outcomes. An increase in the risk of pregnancy related hypertension (OR 1.66; 95% CI 1.32 to 2.09; $p < 0.0001$), gestational diabetes (OR 1.68; 95% CI 1.34 to 2.10; $p < 0.00001$), preterm birth (OR 1.36; 95% CI 1.16 to 1.60; $p = 0.0002$), and the mode of delivery as cesarean section (OR 1.40; 95% CI 1.19 to 1.65; $p < 0.0001$) was demonstrated for psoriasis group.

As for those statistically insignificant outcomes, after deducting lower quality studies, there were still no associations between psoriasis and postpartum hemorrhage, spontaneous abortion, stillbirth, fetal death, low birth weight, small for gestational age, large for gestational age, and congenital anomalies.

Studies reporting on >= 1000 patients

Analysis of the studies that included >= 1000 patients with psoriasis showed that the result was consistent with the overall results and the analysis of later studies. Significant differences were observed in the risk of pregnancy related hypertension (OR 1.54; 95% CI 1.15 to 2.07; $p = 0.004$), gestational diabetes (OR 1.70; 95% CI 1.24 to 2.34; p = 0.001), preterm birth (OR 1.17; 95% CI 1.07 to 1.28; $p = 0.0003$), and the mode of delivery as cesarean section (OR 1.23; 95% CI 1.12 to 1.35; $p < 0.0001$) in patient with psoriasis. No significant association for the risk of stillbirth (OR 1.07; 95% CI 0.66 to 1.75; $p = 0.77$), fetal death (OR 1.07; 95% CI 0.82 to 1.40; $p = 0.62$), low birth weight (OR 1.11; 95% CI 0.99 to 1.25; $p = 0.07$), small for gestational age (OR 1.10; 95% CI 0.94 to 1.28; $p = 0.07$), and congenital anomalies (OR 1.06; 95% CI 1.00 to 1.12; $p = 0.05$).

Publication bias

According to our results, the majority of studies showed possible heterogenicity. Figure 5 shows the funnel plot of included studies for this meta-analysis on the incidence of pregnancy-related hypertension, gestational diabetes, prematurity, and cesarean section. The graphs shows the incidence from each studies as odd ratios (OR) on the horizontal axis and the standard error (SE) on the vertical axis. Some studies line outside the 95% CI limits. Thus, there were possible publication bias among these studies.

Discussion

This meta-analysis of seventeen studies includes 44,249 women with psoriasis and over 47 million controls confirms that psoriasis could be considered as a risk factor for pregnancy-related hypertension, gestational diabetes, preterm birth, and cesarean section.

Several studies suggested the role of IL-17 in correlation with the pregnancy-related hypertension, gestational diabetes, and prematurity. During normal pregnancy, the down-regulation of Th17 lymphocytes and the increase expression of regulatory T cells have been observed [12,13]. As for pregnant women with preeclampsia, there are supporting evidence of Th17 lymphocytes expansion which leads to fetomaternal inflammatory response and increase in level of IL-17 [14–16]. Interleukin 17 secreted from Th17 cells leads to increase the maternal systolic blood pressure and results in hypertension[15]. According to an animal model, the administration of IL-17 resulted in significant increase of mean arterial blood pressure in pregnant rats compared to the non-pregnant ones [17]. Similar observations were notated in pregnancy women with hypertensive diseases may be more susceptible to future cardiovascular diseases. Therefore, presence of psoriasis in women may share common risk factors for pregnancy induced gestational hypertension and preeclampsia.

The level of maternal IL-17 is also increasing in gestational diabetes patients compared with healthy controls which suggested the role of IL-17 in the pathogenesis of gestational diabetes. One study reported the positive correlation between IL-17 level in maternal serum and insulin resistance [18]. Moreover, previous studies also support that IL-17 can promotes higher levels of inflammatory cytokines which can leads to preterm delivery. The researchers found higher levels of inflammatory cytokines including IL-17, IL-8, and tumor necrosis factor (TNF) alpha in preterm neonates than in term cases [19]. This may also contribute to newborn with low birth weight in women with psoriasis, especially in those suffering from severe conditions. A better understanding of the prevalence of gestational diabetes, and hypertension among psoriasis women with reproductive potential can help minimize birth complications like preterm delivery.

We also found a significant association between psoriatic arthritis and preterm birth. In contrast, there were no correlation regarding to the severity of psoriasis and preterm birth. Several studies about inflammatory mediated arthritis disease such as rheumatoid arthritis reported an association of the disease and prematurity [20]. But since the inflammatory cascade of rheumatoid arthritis and psoriasis take different pathway, therefore further studies are recommended to explore the relation between psoriatic arthritis and preterm birth.

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 [2,21]. Many studies found statistically significant differences in serum IL-17 level in psoriasis patients comparing to healthy controls [21,22].

Our result from this meta-analysis can be explained by the increase level of IL-17 in psoriatic mothers which influence the pregnancy-related complications such as gestational hypertension, preeclampsia,

gestational diabetes, and preterm labor. Our hypothesized model (Fig. 6) showing that the imbalanced of TH17/Treg and the increase level of IL-17 may connect to pregnancy morbidities and endocrine dysregulations.

However, for the mode of delivery, due to various indication of the cesarean section, we can only report that the incidence of the procedure was significantly higher in women with psoriasis. There was no significant association between maternal psoriasis and either, postpartum hemorrhage, spontaneous abortion, stillbirth, fetal death, premature ruptured of membrane, low birth weight, small for gestational age, large for gestational age and fetal anomaly.

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 psoriasis in pregnancy condition which cannot be randomized. The statistical analysis shows reporting bias possibly due to selective reporting of the outcomes. Therefore, the results should be considered carefully due to heterogeneity among studies that also stands in the choice of different severity of the disease in the included papers.

Conclusion

While some autoimmune diseases have been shown to affect pregnancy outcomes, such relationship has not been well exhibited in psoriasis. Our meta-analysis found an increased risk of pregnancy-related hypertension, gestational diabetes, preterm labor and cesarean section among women with psoriasis compared with non-disease controls. To the best of our knowledge these associations are the result of the largest meta-analysis so far available. We hypothesized that the correlation between these outcomes and psoriasis might be due to the expression of IL-17, however future prospective studies are necessary to understand the association of the disease and pregnancy complications.

Recommendations

Preconception counseling offers an opportunity to address patient concerns regarding potential risks and to encourage delay of conception until clinical remission is established. Early consultation with feto-maternal specialists, dermatologists, and rheumatologists (as indicated) is recommended to plan appropriate pregnancy management and mode of delivery. Further studies should focus on determining which women with psoriasis are at highest risk of adverse outcomes so that those with varying disease severity may be accurately counseled and undergo appropriate antepartum maternal and fetal surveillance. With careful planning and close monitoring, the risk of adverse pregnancy outcomes for women with psoriasis may be minimized.

Methods

Study registration

The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number, CRD42020208708, Oct 11, 2020) basing on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines on 10th Sep 2020.

Identification of studies and data extraction.

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 search items were used as follows: psoriasis, pregnancy, and adverse outcome. The relevant studies were imported into literature management software Endnote version X7. After removing duplicates, both researchers were independently evaluated the titles and abstracts of the studies and exclude 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 provide arbitration, when different opinions failed to reach an agreement. The selection procedure is shown in a flow chart in line with PRISMA guidelines.

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. Language was restricted to English. We included studies on pregnant women that have been diagnosed as psoriasis and/or psoriatic arthritis. There was no restriction on age, ethnicity, profession, and socioeconomic status.

Risk of bias assessment.

The Newcastle-Ottawa Scale (NOS) was used for assessment of the quality of nonrandomized studies, including case-control and cohort studies [11]. Any discrepancies in the assessment of risk of bias were resolved by discussion and an arbiter will be consulted if it is necessary.

Data extraction.

Two researchers independently undertook data extraction via a standardized data collection form. The information such as 1st author, year of publication, study design, sample size, comparator group, study setting, outcome measured, methodology for statistical data analysis, and publication characteristic were extracted and recorded. We contacted the authors to request detailed information via e-mail, if the data were unclear or missing. Any divergence on data extraction were judged and discussed by the 2 reviewers. The third reviewer checked the final results of the data extraction and provide arbitration for further disagreements.

Statistical analysis.

The measure of association of interest was based on odd ratio (OR). In order 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. Study

heterogeneity was assessed using Q test, and I2 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).

Declarations

Competing Interests

The authors declare no competing interests.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its Additional information.

Acknowlegements

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Author contributions

Rosalyn Kupwiwat: conception, investigation, data curation, formal analysis, writing the original draft of the manuscript.

Poonnapa Deewongkij: conception, data curation and critical review

Dhammika Leshan Wannigama: conception, data curation, formal analysis, supervision, critical review and editing of the manuscript.

Cameron Hurst: conception, supervision, critical review and editing of the manuscript.

Panlop Chakkavitthumrong: conception, funding acquisition, supervision, critical review and editing of the manuscript.

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Figures

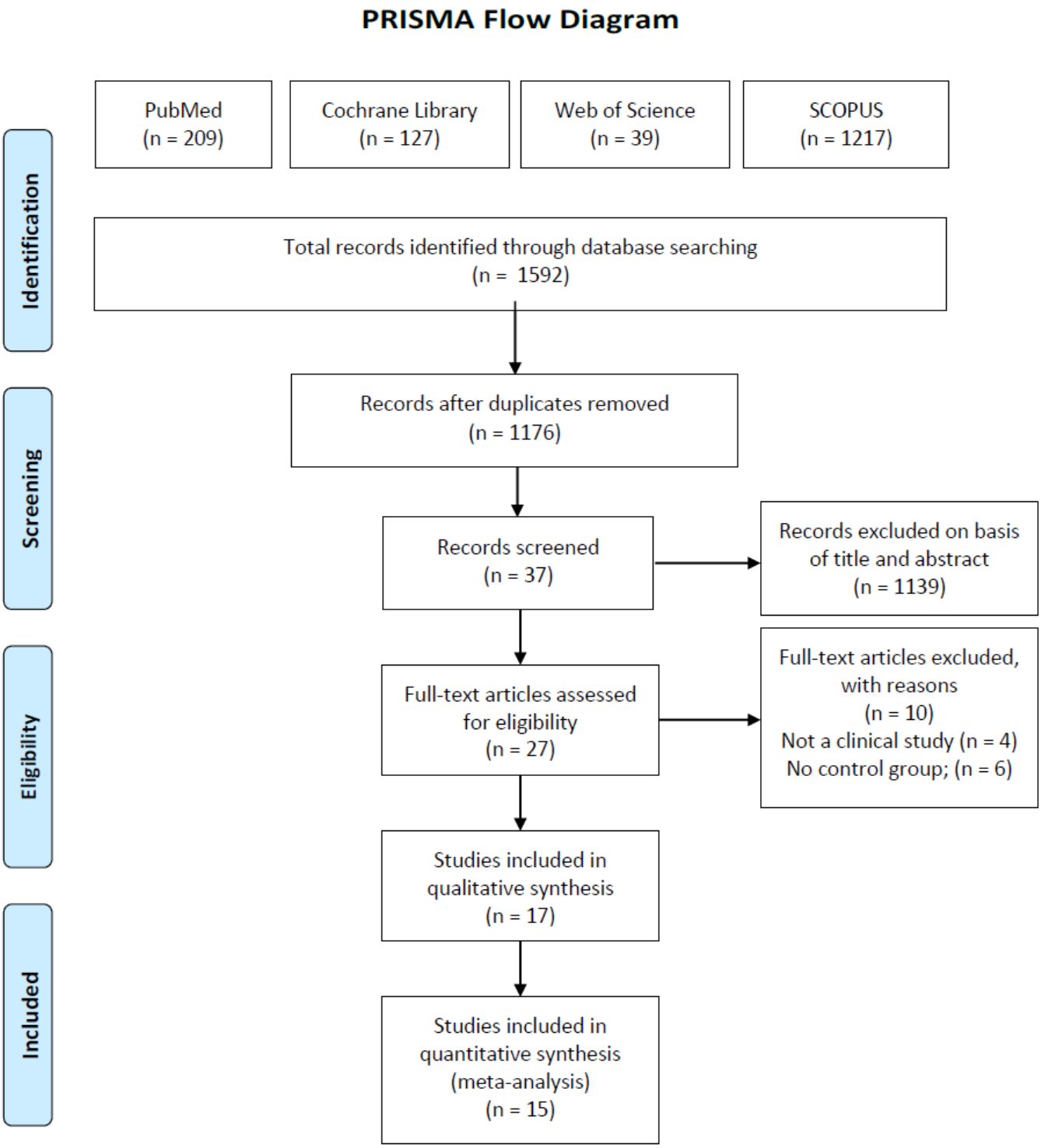
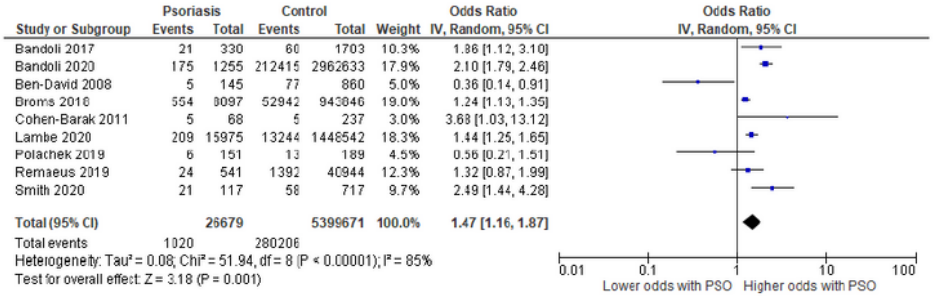


Figure 1

PRISMA Flow diagram

a)



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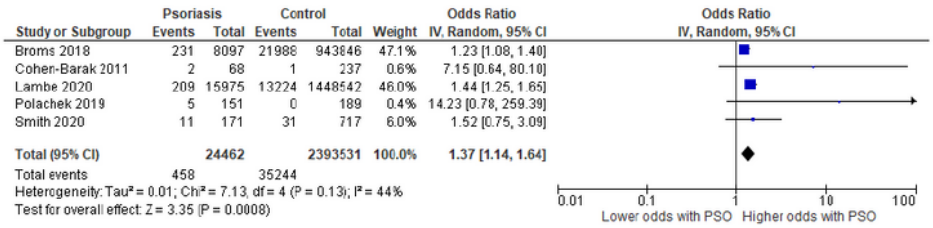

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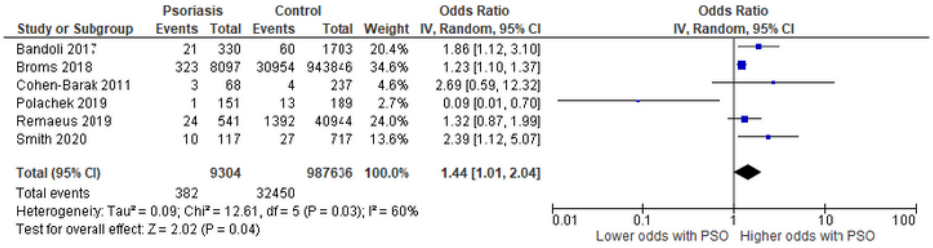

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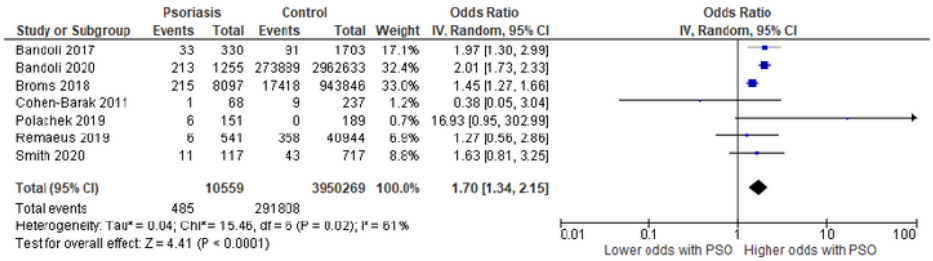
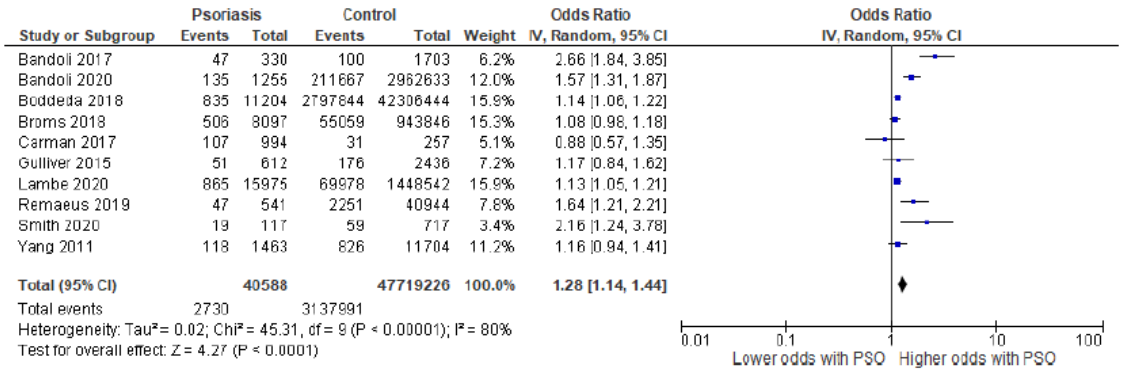


Figure 2

a) Meta-analysis of the odds of pregnancy-related hypertension in women with psoriasis compared to non-disease controls b) Subgroup analysis of the odds of gestational hypertension in women with psoriasis compared to non-disease controls c) Subgroup analysis of the odds of preeclampsia in women with psoriasis compared to non-disease controls d) Meta-analysis of the odds of gestational diabetes in women with psoriasis compared to non-disease controls

a)



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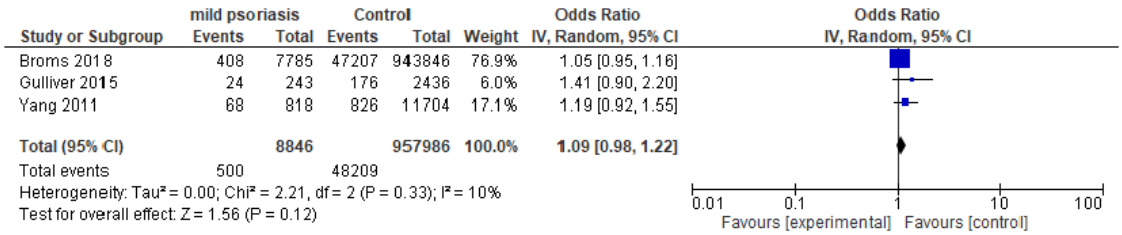

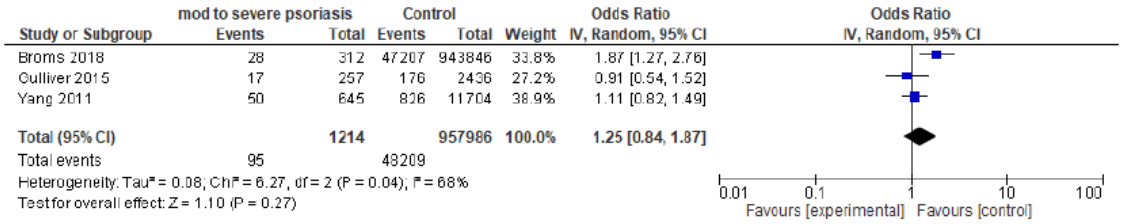

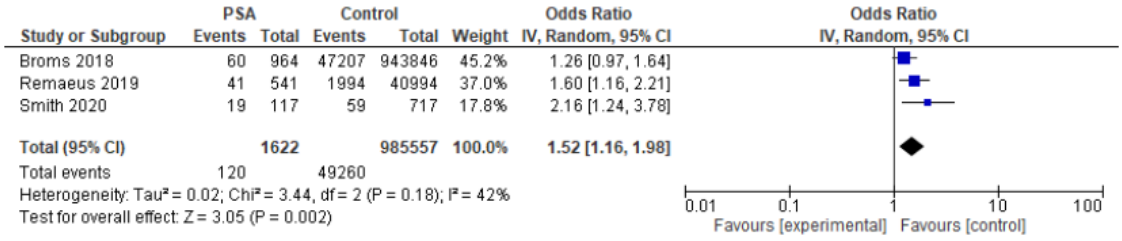

Figure 3

a) Meta-analysis of the odds of preterm labor in women with psoriasis compared to non-disease controls
b) Subgroup analysis of the odds of preterm labor by disease severity and psoriatic arthritis in women with psoriasis compared to non-disease controls

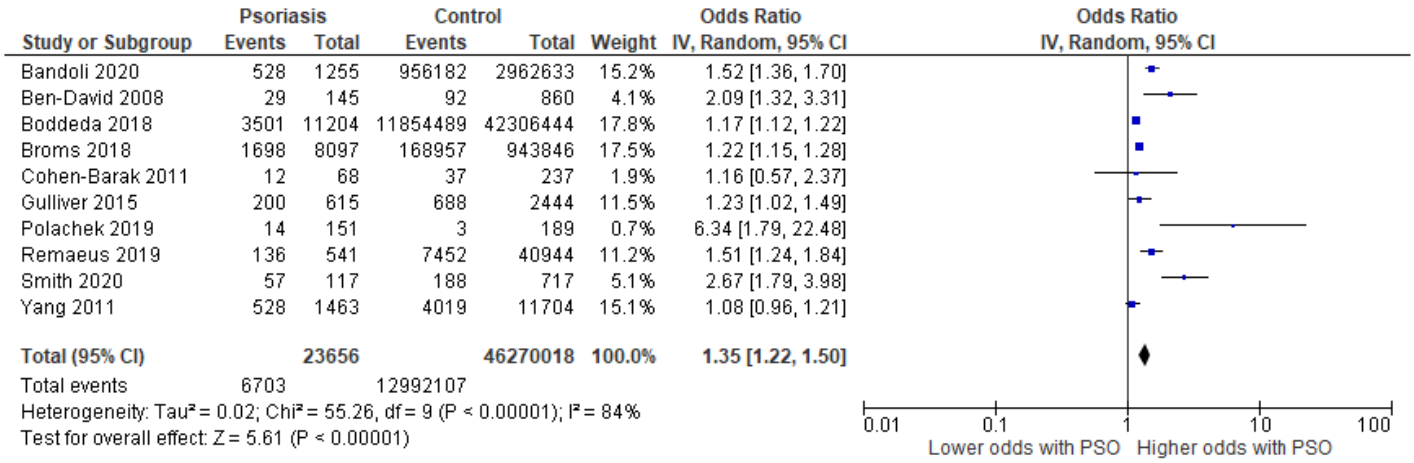

Figure 4

Meta-analysis of the odds of cesarean section in women with psoriasis compared to non-disease controls

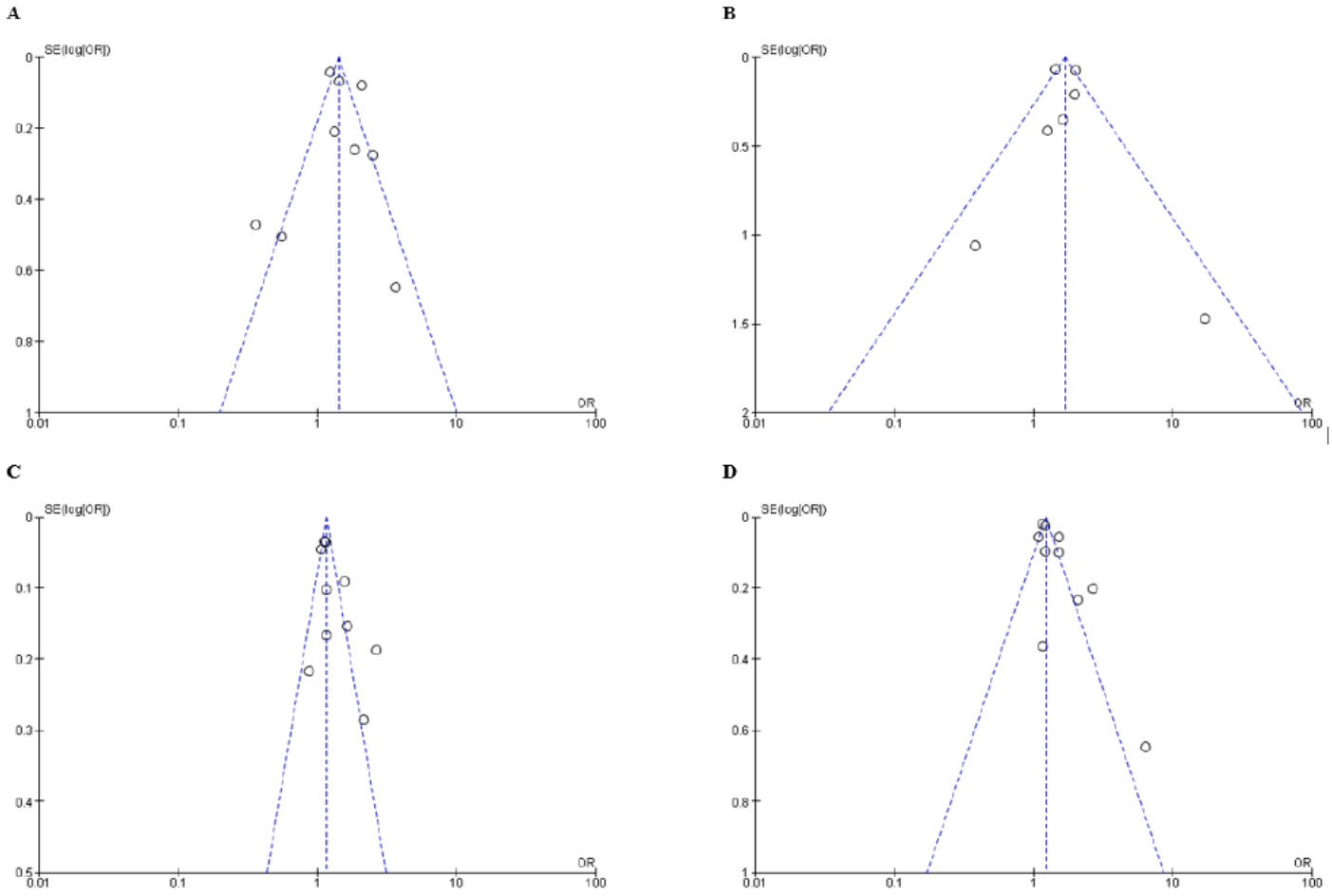

Figure 5

Funnel plot analysis of pregnancy-related a) hypertension, b) gestational diabetes, c) prematurity, and d) cesarean section in patients with psoriasis versus controls

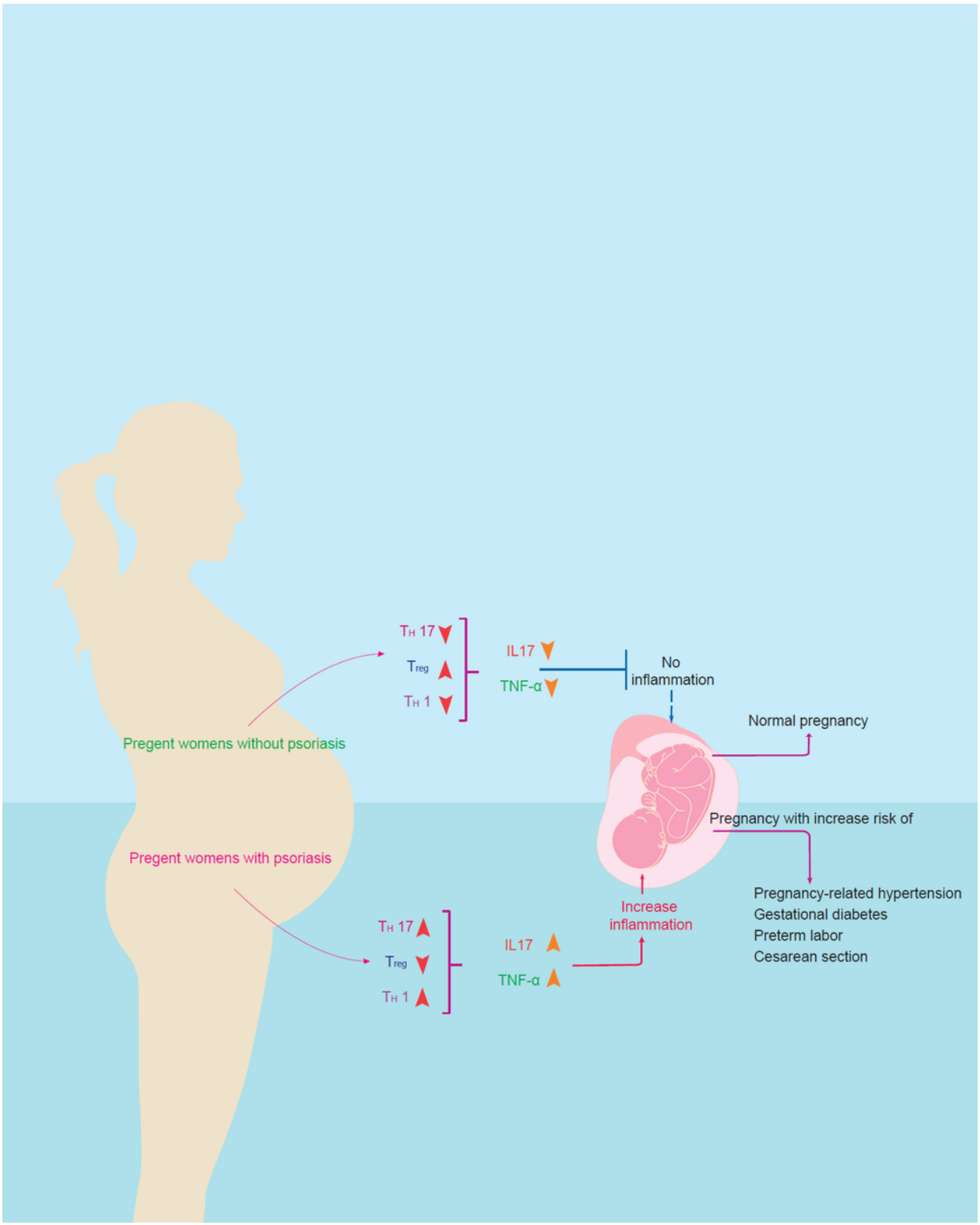

Figure 6

Hypothesized model showing that the imbalanced of TH17/Treg and the increase level of IL-17 may connect to pregnancy morbidities and endocrine dysregulations.