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SYSTEMATIC REVIEW

Exposure to biologic therapy before and during pregnancy in patients with psoriasis: Systematic review and meta-analysis

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Abstract

Biologicals have transformed the management of severe disease phenotypes in psoriasis and are often prescribed in women of childbearing age. However, information on safety of biologicals in pregnancy are lacking. We conducted a systematic review and meta-analysis aimed to describe the characteristics and pregnancy outcomes in women with psoriasis exposed to biologics within 3 months before or during pregnancy, and to estimate the pooled prevalence of spontaneous, elective and total abortions, and congenital malformations in their newborns. Bibliographic searches were performed in the PubMed, Embase, Scopus and Web of Science databases up to 14 April 2022. No restrictions on sample size or publication date were applied. Review performance complied with PRISMA guidelines, and two reviewers assessed randomized controlled trials and nonrandomized studies reporting pregnancy outcomes in women exposed to biologics indicated for psoriasis during the pre-gestational and/or gestational period. Studies focusing on rheumatologic or gastroenterological immune-mediated inflammatory diseases were excluded. Regardless of data heterogeneity, a random-effects model was used to pool prevalence estimates. We included 51 observational studies, involving 739 pregnancies exposed to approved biologics for psoriasis. Administration was mostly (70.4%) limited to the first trimester, and the most common drug was ustekinumab (36.0%). The estimated prevalence of miscarriage was 15.3% (95% confidence interval [CI] 12.7–18.0) and elective abortions, 10.8% (95% CI 7.7–14.3). Congenital malformations occurred in about 3.0% (95% CI 1.6–4.8) of live births exposed to biologics during pregnancy. Altogether, exposure to biologics for psoriasis during pregnancy and/or conception does not seem to be associated with an increased risk of miscarriage/abortion or congenital malformations, showing similar rates to the general population. These results suggest that biologic drugs are safe and pose an acceptable risk to the foetuses/neonates.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disease (IMID) affecting 1%–3% of the world population.[1] Prevalence is similar in men and women, and the disease usually debuts before the age of 40.[2] Many of these women of childbearing age will require biologic therapy for disease control, so it is important to understand the potential impact of biologics on conception and pregnancy.

Psoriasis has an unpredictable course during pregnancy and postpartum. The course of psoriasis can fluctuate throughout pregnancy as hormone levels change, and up to 23% of psoriatic women may experience flares or intense disease activity.[3] The pathophysiology is characterized by cytokine and chemokine dysfunction, especially elevated

tumour necrosis factor (TNF)-alpha, which may increase the risk of preterm delivery, intrauterine growth restriction, and miscarriage.[4,5] Thus, treatment with the optimal regimen is essential for the mother and the child. Specific treatment with biologics should control these adverse events by blocking the central proinflammatory cytokine pathways in the immunopathogenesis of the disease.

However, decisions about initiating or continuing biologic therapy in pregnancy remain complex due to limited knowledge on safety. As pregnant women are excluded from prospective controlled clinical trials for ethical reasons, available safety information is limited to case reports of accidental exposures in clinical trials, some retrospective case series, observational patient registries, and the extrapolation of results from other IMIDs, such as rheumatoid arthritis or inflammatory bowel disease.[6] This results in significant uncertainty at the level of clinical decision making when adequately treated women with good therapeutic response on biologicals become pregnant. Therefore, treatment is often stopped because of the lack of safety data.

This study was conceived to address this evidence gap, with the aim of characterizing pregnancy outcomes and estimating the prevalence of spontaneous, elective, and total abortions and congenital malformations in women with psoriasis exposed to biologics in the preconception period or during gestation.

MATERIALS AND METHODS

Study design

Systematic literature review and meta-analysis of prevalence, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[7,8] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022321300).

Selection criteria

Published or forthcoming papers written in English, Spanish or Italian that met the following (PICOS) inclusion criteria were eligible.

- Population: patients with psoriasis who were pregnant or planning to conceive.
- Intervention: exposure to biologics indicated for treating psoriasis in the 3 months before or any time during pregnancy.
- Comparator: —
- Results: pregnancy outcomes.
- Study design: randomized controlled trials and non-randomized studies, specifically cohort studies, case–control studies, case series, case report studies and patient registries.
- Population size: no restrictions on sample size.

We excluded experimental studies with animal models, narrative reviews, systematic reviews, meta-analyses, studies focusing on rheumatic or gastroenterological IMIDs, articles with incomplete data on neonatal impact, studies administering the biologic agent during the postpartum period or to the father, and articles with the same population as another included study (in this situation the most recent article was included). No restrictions by date of publication were applied.

Data sources and search strategy

A systematic bibliographic search was carried out in MEDLINE (PubMed), Embase, Scopus and Web of Science, from database inception to 14 April 2022. The search terms consisted of medical subject headings (MeSH), using a combination of the key terms extracted from the research question. Search strategy reported in the Table S1. Two authors (VSG and RHQ) independently searched for the articles and exported the results to Mendeley software (Elsevier). We searched conference abstracts and presentations for additional references. Furthermore, the bibliographies of all selected records and of relevant systematic reviews and meta-analyses were handsearched to identify additional records.

Study selection

Search results were de-duplicated, and two researchers (VSG and IBR) independently screened the title and the abstract to classify records as relevant/irrelevant. For potentially relevant articles, the full text was retrieved and assessed in duplicate against the selection criteria; differences were resolved by consensus.

Variables and data extraction

The principal investigator (VSG) extracted and summarized the following data from included studies using an Excel spreadsheet; the last author (IBR) subsequently reviewed the data for quality control. If additional information or clarification was needed about a study, we contacted the authors of the relevant article.

- Exposure variables: biologics administered to women with psoriasis during pregnancy or in the 3 months prior to conception.
- Primary outcome variables: pregnancy outcomes, including live births, miscarriages, elective abortions, unspecified abortions; and congenital malformations (structural or functional abnormalities present at birth in live births). Congenital malformations causing miscarriages were considered miscarriages.

- Secondary outcome variables: small for gestational age (birthweight <10th centile for gestation and sex) and live-birth outcomes, including preterm birth (defined before 37 weeks of gestation), low birthweight (defined as <2.5 kg), neonatal complications [neonatal respiratory distress, neonatal interventricular haemorrhage, neonatal necrotizing enterocolitis, neonatal sepsis, admission to the neonatal intensive care unit], information on child morbidity, and long-term growth and development. Prevalence estimates for live-birth outcomes were calculated using the number of live-born infants as the denominator.
- Other variables
  - Characteristics of included studies: first author, journal and year of publication, country, language, study design, and sample size.
  - Baseline maternal characteristics: age of patients at conception and at psoriasis onset, family history of psoriasis, type of psoriasis (plaque/guttate/paradoxical/erythrodermic/pustular/generalized pustular psoriasis/impetigo herpetiformis), comorbidities, tobacco use (past or current), history of abortions, mean body mass index, mean exposure interval to the biologic (measured in weeks of gestation and calculated considering the date of the last dose and the date of last menstruation), trimester(s) of pregnancy when exposure occurred, systemic treatments for psoriasis before pregnancy, classic systemic treatments for psoriasis during pregnancy.

Assessment of risk of bias

Two reviewers (VSG and IBR) independently assessed the methodological quality of the studies included in the meta-analysis using the Quality Assessment Tool for Case Series Studies of the National Heart, Lung and Blood Institute (NHLBI) (Table S2).[9] Disagreements were resolved by consensus.

Analysis of results and meta-analysis

SPSS statistical software (version 25.0, IBM Corp) was used to analyse study data. Descriptive statistics are expressed as absolute and relative frequencies. Quantitative variables are described using mean or median and standard deviation (SD) or interquartile range, as appropriate. Normality was tested using the Kolmogorov–Smirnov test (results of $p < 0.05$ were considered to indicate a non-parametric distribution). A narrative synthesis of the individual results of the included studies was performed using text and a table (Table 1).

Analysis of variance (ANOVA) was used to compare means in more than two independent groups. p values under 0.05 were considered statistically significant.

To pool prevalence data on abortions (elective, spontaneous and total) and congenital malformations relative to the total number of pregnancies exposed to biologics indicated for psoriasis, a meta-analysis of prevalence was carried out using Statsdirect Statistical software v. 3.3.5.

Forest plots were used to graphically represent the pooled prevalence (95% confidence intervals [CI]) of abortions and congenital malformations relative to the total number of pregnancies exposed to any biologic for psoriasis. The Stuart-Ord method (inverse double arcsine square root) was used to calculate the 95% coefficient intervals and create the forest plots.

Heterogeneity was assessed using the I^2 (95% CI) and Q statistic. I^2 values over 50% were considered indicative of heterogeneity. The random-effects model was applied regardless, as substantial between-study heterogeneity was expected.

Publication bias was assessed graphically using a funnel plot and statistically using Egger's regression test ($p < 0.10$ was considered to indicate statistically significant publication bias).

RESULTS

Results of the search

The searches yielded 856 records, 234 full-text articles were retrieved to assess eligibility, and 51 publications meeting inclusion criteria were included (Figure 1).[7]

Characteristics of included studies

Table S3 describes the characteristics of included studies. Most (58.8%) were published in 2018–2022 and used retrospective designs (84.3%), especially case reports (45.1%) and case series (29.4%). Studies mainly assessed ustekinumab (28.8%), infliximab (19.2%), and adalimumab (13.7%). None studied pregnancy outcomes following exposure to brodalumab, risankizumab or bimekizumab.

Six studies were rated as good quality; 26, fair quality; and 19, poor quality (Table S2). Table 1 summarizes the details on psoriatic disease, biologic drugs, exposure interval, and pregnancy outcomes in included studies.

Clinical characteristics of patients

Table S4 describes maternal characteristics in 713 patients with psoriasis exposed to biologics during pregnancy or the preconception period. Women had a mean age of 30.3 years (SD 5.6; range 19–44). The most frequent comorbidities were past or current smoking (29.5%), psoriatic arthritis (16.0%), psychiatric disorders (13.5%), hypertension (6.8%), and diabetes (4.3%). The predominant type of psoriasis was plaque psoriasis (96.7%), with an average of 2.2 systemic treatments prior to pregnancy, especially methotrexate (27.7%) and cyclosporine (24.1%).

TABLE 1 Characteristics of included studies and main pregnancy outcomes reported in women with psoriasis exposed to biologic therapy during pregnancy.

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Borrego 2010[65]	Case report	1 pregnancy in 1 woman/40 years	ETA	4 weeks 1st trimester	Plaque and PsA	Previous: acitretin, CsA, MTX During pregnancy: heliotherapy, topical steroids	Psoriasis exacerbation LGA Prolonged labor C-section Macrosomia Live birth	1 (100)/0 (0)
Kimball 2020[66]	Data from clinical trials	24 pregnancies in 24 women/19–40 years	GUS	105.9 ± 70.5 weeks ($n = 21$) 1st trimester ($n = 24$)	Plaque, PP and PsA	N/A	Live births ($n = 7/12$) Miscarriages ($n = 2/12$)[a] Elective abortions ($n = 2/12$) Unspecified abortions ($n = 1/12$)	7/12 (58.3)/5/12 (41.7)
Geldhof 2020[67]	Registry	41 pregnancies	UST	N/A	Psoriasis/PsA	N/A	Live births ($n = 30/37$) Congenital malformations ($n = 1/37$) Miscarriages ($n = 7/37$)	30/37 (81.1)/7/37 (18.9)
Echeverría-García 2017[68]	Case series	9 pregnancies in 7 women/21–41 years	ETA ($n = 5$) ADA ($n = 3$) UST ($n = 1$)	4 weeks ($n = 6$) 5 weeks ($n = 1$) 2 weeks ($n = 1$) 6 weeks ($n = 1$) 1st trimester ($n = 8$) 1st and 2nd trimester ($n = 1$)	Psoriasis	During pregnancy: systemic steroids ($n = 2$), CsA ($n = 2$), AZA ($n = 1$)	Psoriasis exacerbation ($n = 1$) SDRN ($n = 1$)[b] PROM ($n = 1$)[b] Elective abortion ($n = 1$)[c] Live births ($n = 8$)	8 (88.9)/1 (11.1)

Boggs 2020[29]	Case series	14 pregnancies (1 twin pregnancy) in 8 women/26–39 years	ADA ($n = 9$)
			UST ($n = 1$)
			ETA ($n = 1$)
			SEC ($n = 2$)
			IFX ($n = 1$)
				Continuation of biologic therapy ($n = 7$)
				Discontinuation of biologic therapy ($n = 7$)
					Psoriasis and PsA ($n = 5$);
					psoriasis ($n = 1$);
					psoriasis, PsA and HS ($n = 1$);
					psoriasis and Crohn's induced by TNFi ($n = 1$)
						Previous: N/A
						During pregnancy: phototherapy ($n = 3$), CsA ($n = 1$), topical steroids ($n = 2$)
							Gestational diabetes ($n = 2$)
							Placenta previa ($n = 1$)
							Severe psoriatic flares, with mean PASI of 18 points ($n = 6$)
							Elective C-section ($n = 4$)
							Induction ($n = 4$)
							Admission in neonatal ICU ($n = 1$)[d]
							Live births ($n = 12$)
							Miscarriages ($n = 3$)[e]
								12 (80)/3 (20)

Mugheddu 2019[69]	Case report	3 pregnancies in 1 woman/38 years	ADA ($n = 1$) UST ($n = 2$)	8 weeks ($n = 1$) 6 weeks ($n = 1$) Weeks not reported ($n = 1$) 1st trimester ($n = 3$)	Plaque	Previous: CsA, phototherapy, MTX Subsequent: none	Postpartum psoriasis flare ($n = 3$)[f] Premature ($n = 3$)[b] LBW ($n = 1$)[b] Health live births ($n = 3$)	3 (100)/0 (0)
Accortt 2015[11]	Retrospective registry	51 pregnancies and 51 live births	ETA	N/A	Psoriasis	N/A	LBW ($n = 6$) Prematurity ($n = 8$) Congenital malformations ($n = 1$)	-

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Adachi 2016[70]	Case report	1 pregnancy in 1 woman/18 years	IFX	2nd and 3rd trimester due to severe flare of psoriasis	GPP	Previous: CsA, etretinate During pregnancy: systemic steroids	Psoriasis exacerbation PROM Fetal infection[b] Emergency C-section Live birth	1 (100)/0 (0)
Lambiase 2022[71]	Case series	4 pregnancies in 4 women; 1 neonate exposed only during lactation/29–43 years	CZP	1st trimester ($n=2$) 1st and 2nd trimester ($n=1$) Throughout pregnancy ($n=1$) Only during lactation ($n=1$) Discontinuation of biologic therapy ($n=2$)	Plaque ($n=3$) Plaque and PsA ($n=2$)	Previous: ETA ($n=1$)	Psoriasis exacerbation ($n=1$) Healthy live births ($n=3$) Still pregnant ($n=1$) No adverse events during lactation ($n=1$)	2/2 (100)/0 (0)
Offiah 2014[10]	Case report	1 pregnancy in 1 woman/N/A	IFX	Throughout pregnancy and 6 months before conception	Psoriasis and PsA	N/A	PROM Prematurity Emergency C-section Collodion baby[b,g] Live birth	1 (100)/0 (0)
Russo 2021[72]	Case series	4 pregnancies in 4 women/N/A	ADA ($n=2$) UST ($n=1$) GUS ($n=1$)	Discontinuation of treatment as soon as pregnancy was discovered ($n=4$)	Psoriasis	N/A	Healthy live births ($n=4$) No prematurity, abortions, or congenital anomalies	4 (100)/0 (0)
Daham 2020[73]	Case report	1 pregnancy in 1 woman/24 years	ADA	Continuation of biologic therapy	Plaque	During pregnancy: topical steroids	Psoriasis exacerbation Fetal acrania[h] Medical abortion	0 (0)/1 (100)
Mizutani 2020[74]	Case report	1 pregnancy in 1 woman/31 years	IFX and CZP	IFX: 22 weeks CER: 14 weeks	GPP	Previous: cyclosporine, topical therapies, prednisolone During pregnancy: prednisolone	Psoriasis exacerbation LBW[b]	1 (100)/0 (0)
Azulay-Abulafia 2019[75]	Retrospective cohort	32 pregnancies (1 twin pregnancy) in 30 women/N/A	N/A	N/A	Psoriasis/PsA	N/A	Miscarriage of one twin pregnancy due to infectious chorioamnionitis ($n=1$) Prematurity ($n=8$) C-section ($n=23$) SGA ($n=3$) Congenital malformations ($n=3$)[i]	31 (93.9)/2 (6.1)

(Continues)

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Chhabra 2019[25]	Case report	1 pregnancy in 1 woman/26 years	SEC	11 weeks during the 2nd and 3rd trimester	IH	During pregnancy: prednisolone, CsA	Psoriatic flare Oligohidramnios IUGR Intrauterine fetal death	0 (0)/1 (100)
Alsenaid 2016[12]	Case report	1 pregnancy in 1 woman/24 years	UST	14 weeks during 1st and 2nd trimesters	Plaque/IH	Previous: CsA	Prematurity Elective C-section Healthy live birth	1 (100)/0 (0)
Babuna 2020[14]	Case report	1 pregnancy in 1 woman/24 years	IFX	6 weeks during the 3rd trimester	IH	During pregnancy: CsA, systemic steroids	Psoriatic flare Elective C-section Healthy live birth	1 (100)/0 (0)
Egeberg 2020[30]	Data from clinical trials	50 pregnancies in 50 women/N/A	IXE	1st trimester ($n = 46$)	Psoriasis/PsA	N/A	Live births ($n = 24/44$) Miscarriages ($n = 9/44$) Elective abortions ($n = 11/44$) Preterm births ($n = 4/22$)	24/44 (54.5)/20/44 (44.5)
Megna 2019[26]	Case report	1 pregnancy in 1 woman/28 years	UST	10 weeks during 1st trimester	Psoriasis	Previous: CsA, MTX, ETA	Postpartum flare Healthy live birth	1 (100)/0 (0)
Gao 2018[22]	Case series	2 pregnancies in 2 women/21–31 years	IFX	Throughout pregnancy and lactation ($n = 1$) 1st trimester ($n = 1$)	Psoriasis ($n = 1$) Psoriasis/PsA ($n = 1$)	Previous: MTX ($n = 2$), acitretine ($n = 1$), ADA ($n = 1$) During pregnancy: prednisolone ($n = 1$), CsA ($n = 1$)	Healthy live births at term ($n = 2$)	2 (100)/0 (0)
Haycraft 2020[31]	Data from clinical trials	14 pregnancies in 14 women/21–37 years	TIL	9.13 weeks 1st trimester ($n = 7$) 2nd trimester ($n = 3$) N/A ($n = 4$) Discontinuación ($n = 14$)	Psoriasis ($n = 13$) Psoriasis/PsA ($n = 1$)	N/A	Miscarriages ($n = 2$) Elective abortions ($n = 4$) Preterm ($n = 1$)[b] Transient jaundice ($n = 1$) Healthy live births ($n = 8$)[b]	8 (57.1)/6 (42.9)
Vu 2018[23]	Case series	6 pregnancies in 6 women/N/A	UST	N/A	Plaque	N/A	Live births at term ($n = 6$)	6 (100)/0 (0)
Griffin 2021[35]	Case series	2 pregnancies in 2 women/38–39 years	SEC	Continuation of biologic therapy ($n = 1$) Discontinuation of biologic therapy ($n = 1$)	Psoriasis/PsA ($n = 2$)	N/A	Miscarriages ($n = 2$)[j]	0 (0)/2 (100)
Nardin 2018[24]	Case report	1 pregnancy in 1 woman/45 years	SEC	6 weeks during 1st trimester	Plaque	Previous: MTX, ETA, ADA, IFX	Miscarriage ($n = 1$)[k]	0 (0)/1 (100)

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Carman 2017[76]	Retrospective cohort	81 pregnancies in 81 women/31.8 years	ETA	N/A	Psoriasis	Previous: MTX (*n* = 4)	Healthy live births (*n* = 61) Miscarriages (*n* = 13) Elective abortion (*n* = 7) LBW (*n* = 6) Prematurity (*n* = 8) Congenital malformations (*n* = 1)	61 (75.3)/20 (37.04)
Dessinioti 2011[16]	Case report	1 pregnancy in 1 woman/34 years	ADA	5 weeks during 1st trimester	Psoriasis	N/A	Healthy live birth at term LBW Elective C-section	1 (100)/0 (0)
Rocha 2015[19]	Case report	1 pregnancy in 1 woman/25 years	UST	6 weeks during 1st trimester	Psoriasis	Previous: topical steroids, UVB, PUVA, MTX, CsA	Psoriatic flare Live birth at term	1 (100)/0 (0)
Schaufelberg 2014[77]	Data from clinical trials	29 pregnancies in 29 women/21–44 years	UST	72 ± 61 weeks Discontinuation of biologic therapy (*n* = 29)	Psoriasis	N/A	Healthy live births (*n* = 14/26)[b] Miscarriages (*n* = 5/26) Elective abortions (*n* = 7/26) Neonatal jaundice (*n* = 2)	14/26 (53.85)/12/26 (46.15)
Yurkon 2014[78]	Registries	59 pregnancies (1 twin pregnancy) in 59 women/31 years	IFX	Throughout pregnancy (*n* = 4)	Psoriasis (*n* = 36) PsA (*n* = 19) Psoriasis and PsA (*n* = 4)	N/A	Healthy live births (*n* = 43) Congenital malformations (*n* = 4)[l] Miscarriages (*n* = 5)[m] Elective abortions (*n* = 11)	43 (72.88)/16 (27.11)
Kimball 2021[54]	Registries	168 pregnancies/N/A	UST (*n* = 70) IFX (*n* = 14) Others (*n* = 84)[n]	N/A	Psoriasis	N/A	Live births (*n* = 131) Congenital malformations (*n* = 1) Adverse neonatal event (*n* = 7) Healthy life births (*n* = 122) Neonatal death (*n* = 1) Prolonged hospital stay (*n* = 15) Elective abortion (*n* = 9) Miscarriage (*n* = 28)	131 (77.98)/37 (22.02)
Naureckas 2016[79]	Registries	87 pregnancies/31 years	UST	During 1st trimester (*n* = 37) Throughout pregnancy (*n* = 16)	Psoriasis (*n* = 86) PsA (*n* = 1) Psoriasis and PsA (*n* = 1)	N/A	Live births (*n* = 57) Congenital malformations (*n* = 1) Prematurity (*n* = 3) Elective abortions (*n* = 14) Miscarriages (*n* = 16)	57 (65.52)/30 (34.48)

(Continues)

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Kawai 2019[27]	Registries	5 pregnancies in 5 patients/N/A	ADA	3rd trimester ($n=2$) 8 weeks ($n=1$) N/A ($n=2$)	Psoriasis	N/A	Live births ($n=4$) Miscarriage ($n=1$)	4 (80)/1 (20)
Allen 2022[80]	Retrospective cohort	4 pregnancies in 4 women/N/A	N/A	N/A	Psoriasis/PsA	N/A	Psoriatic flare ($n=1$) Maternal infection ($n=1$)[o] Hypertensive disorder ($n=1$) Live births ($n=4$) C-section ($n=2$) LBW ($n=1$) Prematurity ($n=1$) Admission in neonatal ICU ($n=1$)	4 (100)/0 (0)
Fierens 2016[20]	Case report	1 pregnancy in 1 woman/32 years	UST	16 weeks during 1st and 2nd trimester	Psoriasis	Previous: MTX, CsA and PUVA During pregnancy: topical steroids and UVB	Psoriatic flare Healthy live birth at term	1 (100)/0 (0)
Odorici 2019[44]	Case series	14 pregnancies in 12 women/26–37 years	SEC ($n=2$) IFX ($n=3$) IFX and CER ($n=1$) UST ($n=6$) ETA ($n=1$) ADA ($n=1$)	3 weeks ($n=1$) 4 weeks ($n=2$) 6 weeks ($n=5$) 5 weeks ($n=3$) 8 weeks ($n=1$) 11 weeks ($n=1$) Throughout pregnancy ($n=1$) 7.93 weeks	Psoriasis	During pregnancy: switch from IFX to CER ($n=1$)	Psoriatic flare ($n=9$) Healthy live births ($n=10$) Still pregnant ($n=1$) Miscarriages ($n=1$) Elective abortions ($n=2$) C-section ($n=1$)	10 (76.92)/3 (23.08)
Galluzzo 2019[28]	Case series	4 pregnancies (1 twin pregnancy) in 3 women/36–40 years	UST	1st trimester ($n=3$) 16 weeks ($n=1$) Discontinuation of biologic therapy ($n=4$)	Psoriasis	Previous: PUVA ($n=2$), CsA ($n=2$), ETA ($n=2$), IFX ($n=1$), EFA ($n=2$)	Psoriatic flare ($n=1$) Healthy live births ($n=5$)	5 (100)/0 (0)
Gallo 2022[81]	Case report	1 pregnancy in 1 woman/39 years	SEC	20 weeks	Plaque	Previous: topical therapies, MTX, CsA, UVB, IFX.	Healthy live birth Preterm	1 (100)/0 (0)
Fotiadou 2012[17]	Case report	1 pregnancy in 1 woman/35 years	UST	10 weeks	Psoriasis	Previous: topical steroids, CsA	Miscarriage	0 (0)/1 (100)
Galli-Novak 2016[13]	Case report	1 pregnancy in 1 woman/28 years	UST	33 weeks	Paradoxical psoriasis and Crohn's	Previous: IFX, ADA	Healthy live birth at term	1 (100)/0 (0)

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Gao 2016[21]	Case report	1 pregnancy in 1 woman/32 years	IFX	Single dose of IFX	GPP	During pregnancy: prednisone, CsA	Psoriatic flare Healthy live birth	1 (100)/0 (0)
Liu 2020[32]	Case report	1 pregnancy in 1 woman/37 years	SEC	13 weeks during the 3rd trimester	GPP	Previous: topical steroids	Psoriatic flare Healthy live birth C-section	1 (100)/0 (0)
Beksac 2021[36]	Case report	1 pregnancy in 1 woman/22 years	IFX	2 weeks during the 3rd trimester	GPP	Previous: topical steroids, MTX, CsA During pregnancy: methylprednisolone	Psoriatic flare (psoriatic erythroderma) Postpartum flare IUGR C-section Transient jaundice Healthy live birth	1 (100)/0 (0)
Puig 2010[15]	Case report	1 pregnancy in 1 woman/28 years	IFX	Throughout pregnancy	Plaque	Previous: topical steroids, CsA	Urinary tract infection C-section Healthy live birth	1 (100)/0 (0)
Esposito 2021[37]	Case series	2 pregnancies in 1 woman/34 years	CZP	14 weeks during the 3rd trimester 37 weeks ($n=1$)	Plaque	Previous: CsA, MTX, ETA, ADA During pregnancy: topical and oral steroids	Psoriatic flare ($n=1$) Healthy live births at term ($n=2$) Elective C-section ($n=2$)	2 (100)/0 (0)
Andrulonis 2012[18]	Case report	1 pregnancy in 1 woman/22 years	UST	6 weeks during 1st trimester and 11 weeks during the 3rd trimester	Pustular psoriasis/ PsA	Previous: topical therapies, CsA, acitretin, alefacept, phototherapy, ETA, MTX, IFX During pregnancy: topical therapies	Psoriatic flare (psoriatic erythroderma) Healthy live birth at term	1 (100)/0 (0)
Carter 2006[82]	Case report	1 pregnancy in 1 woman/28 years	ETA	Throughout pregnancy	Psoriasis/PsA	-	Live birth at term Congenital anomaly[p]	1 (100)/0 (0)
Tanaka 2020[33]	Case report	1 pregnancy in 1 woman/22 years	ETA	8 weeks	Plaque and GPP	During pregnancy: MTX (8 weeks), topical therapies, systemic steroids	Psoriatic flare (GPP) Healthy live birth at term	1 (100)/0 (0)
Babuna 2020[34]	Case series	9 pregnancies in 6 women/24–40 years	IFX ($n=3$) ADA ($n=2$) ETA ($n=1$) UST ($n=2$) SEC ($n=1$)	30 months (range: 6 weeks to 50 months) 1st trimester ($n=6$) 3rd trimester ($n=3$)	Plaque ($n=2$) Plaque/PsA ($n=3$) IH ($n=1$)	N/A	Psoriatic flare (IH) ($n=3$) Elective C-section ($n=6$) Elective abortion ($n=1$) Tubal ectopic pregnancy ($n=1$)[q] Healthy live births at term ($n=7$)	7 (77.78)/2 (22.22)

(Continues)

TABLE 1 (Continued)

1st author, year	Study design	*N* pregnancies and patients exposed/mean age or range	Biologic therapy	Exposure interval or time of last dose of biologic therapy	Type of psoriasis	Anti-psoriasis treatments before or during pregnancy (other than biologics)	Pregnancy or neonatal outcomes	Live births (%)/ Total abortions (%)
Lund 2017[83]	Case series	10 pregnancies in 7 women/21–44 years	IFX ($n=4$) UST ($n=4$) ADA ($n=2$)	3 months prior to conception ($n=1$) 1st trimester ($n=4$) Throughout pregnancy ($n=5$)	Psoriasis	Previous: topical therapies ($n=7$), UVB ($n=2$), PUVA ($n=1$), heliotherapy ($n=1$), MTX ($n=6$), CsA ($n=3$), ETA ($n=1$), UST ($n=4$), ADA ($n=2$), IFX ($n=1$)	Gestational diabetes ($n=1$) C-section ($n=1$) Manually removed placenta ($n=1$) Healthy live births ($n=9$) Still pregnant ($n=1$)	9 (100)/0 (0)
Watson 2019[84]	Case series	10 pregnancies in 7 women/19–39 years	UST ($n=10$)	1st trimester ($n=9$) 2nd trimester ($n=1$)	Psoriasis	N/A	Gestational diabetes ($n=2$) Miscarriage ($n=2$) IUGR ($n=1$) Oligohidramnios ($n=1$) Instrumental delivery ($n=1$) Elective C-section ($n=3$) C-section ($n=1$) Healthy live births ($n=8$) Prematurity ($n=1$)	8 (80)/2 (20)
Sheeran 2014[85]	Case series	2 pregnancies in 2 women/21–34 years	UST ($n=2$)	4 weeks ($n=1$) 2 weeks ($n=1$) 1st trimester ($n=2$)	Psoriasis	Previous: ETA ($n=1$)	Psoriatic flare ($n=1$) Healthy live births at term ($n=2$)	2 (100)/0 (0)

Abbreviations: ADA, adalimumab; CsA, cyclosporin A; CZP, certolizumab pegol; DM, diabetes mellitus; ETA, etanercept; GPP, generalized pustular psoriasis; GUS, guselkumab; HS, hidradenitis suppurativa; ICU, intensive care unit; IFX, infliximab; IH, impetigo herpetiformis or pustular psoriasis of pregnancy; IUGR, intrauterine growth restriction; IXE, ixekizumab; LBW, low birth weight; LGA, large for gestational age; MTX, methotrexate; N/A, not available; NRDS, neonatal respiratory distress syndrome; PASI, Í Psoriasis Area Severity Index; PP, palmoplantar psoriasis; PROM, premature rupture of membranes; PsA, psoriatic arthritis; PUVA, psoralen and ultraviolet A; SEC, secukinumab; SGA, small for gestational age; TIL, tildrakizumab; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; UVB, ultraviolet B.

[a]One miscarriage in a 38-year-old woman with a history of 2 elective abortions. In the other case, there were no risk factors reported.

[b]No fetal or neonatal anomalies were observed.

[c]The elective abortion was in a patient exposed to etanercept for 4 weeks, who already had a child with Down's syndrome.

[d]Admitted to the neonatal ICU for 4 days, with good recovery.

[e]One miscarriage in a 39-year-old woman receiving UST for psoriasis and PsA. Of note, she had a previous normal preganancy with no biologics. Another miscarriage occurred at 13 weeks and was diagnosed shortly thereafter with nephrotic syndrome associated with streptococcus. The last miscarriage occurred in a 31-year-old woman with severe psoriasis/PsA, who was unable to conceive without biologic therapy despite two IVF attempts. 22 weeks later, continuing with ADA treatment, she became pregnant again and had a healthy son, suggesting that active disease might have affected the ability to conceive.

[f]The mother started on UST while breastfeeding her third child due to a severe psoriatic flare, without complications for the baby.

[g]The collodion membrane was completely detached and the skin normalized in 2 months. The skin had a normal appearance at 1 year of age.

[h]The patient stated that she had not been taking folic acid before or during her pregnancy and that she was married to her first cousin.

[i]Three cases of congenital malformations in preterm infants were observed, two of them with spontaneous resolution: benign external hydrocephalus and patent foramen ovale.

[j]One woman presented with post-strectococcal glomerulonephritis, which could have contributed to the loss of the fetus.

[k]The woman had undergone hysteroscopic tubal sterilization with the Essure device.

[l]Polydactyly ($n=1$), hypospadias ($n=1$); concomitant treatment with MTX, large omphalocele containing liver ($n=1$) and congenital lesser metatarsus varus ($n=1$).

[m]One miscarriage occurred in a woman treated concomitantly with azathioprine.

[n]Predominantly etanercept and adalimumab, but also includes secukinumab, risankizumab, alefacept, efalizumab, tildrakizumab, brodalumab, ixekizumab, and guselkumab.

[o]Included chorioamnionitis, endometritis, surgical site infection, intra-abdominal abscess, and pyelonephritis.

[p]Born with tracheal atresia and tracheoesophageal fistula, oesophageal atresia, imperforate anus, patent foramen ovale, hypospadias and T12 vertebral anomaly. The newborn was diagnosed with VATER syndrome (V: vertebral abnormalities; A: anal abnormalities; T: tracheal problems; E: oesophageal problems; R: radius or renal defects), with no renal or extremity abnormalities. Amniocentesis had previously revealed a 46XY chromosome analysis.

[q]The tubal pregnancy was successfully diagnosed and terminated at 8 weeks of gestation by endoscopic curettage.

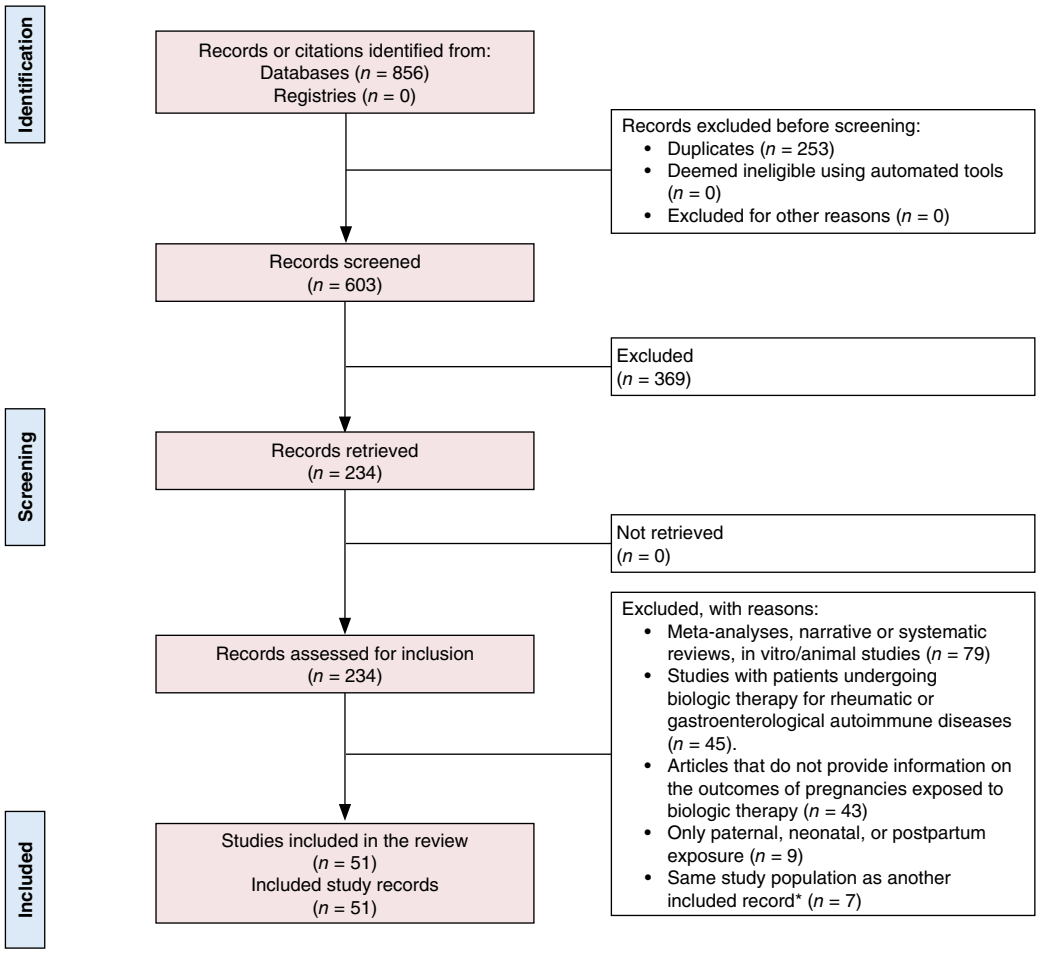

FIGURE 1 PRISMA flow chart for study selection.

Characteristics of pregnancies

Table 2 presents the characteristics of the pregnancies in included patients; 739 pregnancies were exposed to biologics indicated for psoriasis, especially ustekinumab (35.9%), etanercept (19.3%), infliximab (12.7%), and ixekizumab (5.9%). No biologic was specified in 16.2% of the pregnancies (Figure S1). No study reported the concomitant use of systemic teratogenic anti-psoriatic treatments. In most pregnancies (70.4%), exposure was limited to the first trimester, and treatment was suspended in 77.6% of pregnancies. The mean duration of exposure was 16.8 weeks (SD 15.2).

Pregnancy and live-birth outcomes

Table 3 presents primary and secondary outcomes. All articles, except one,[11] reported on miscarriage and live-births, but the other outcomes of small for gestational age, preterm birth, congenital malformation, low birthweight, neonatal outcomes, and long-term growth and development were not consistently stated in all articles.

In total, 517 live births, 100 spontaneous abortions and 71 elective abortions have been reported in 689 pregnancies with known outcomes exposed to biologics in women with psoriasis. 36 observational studies reported on 283 live births and 42 preterm deliveries. 24 observational studies reported the presence or absence of congenital malformations in their live births, out of the known 492 live births were 14 congenital malformations. Long-term outcomes of the offspring have been described in 42 neonates, all of them with completely normal growth.

Pregnancy outcomes according to biologic

Table 4 and Figure S2 present pregnancy outcomes according to the type of biologic prescribed. There were no statistically significant differences between baseline maternal characteristics or discontinuation of biologic therapy and duration of exposure between the different classes of biologics (Figure S3). Likewise, there was no association between exposure to different biologic therapies and pregnancy outcomes (live birth rates, miscarriages, or congenital malformations).

TABLE 2 Characteristics of pregnancies exposed to biologic therapy indicated for treatment of psoriasis.

Variables	Frequency, *n* (%)
N pregnancies exposed to biologics	739 (100)
Biologics used during pregnancy (*n* = 740)[a]	
Ustekinumab	266 (35.9)
Etanercept	143 (19.3)
Infliximab	94 (12.7)
Ixekizumab	44 (5.9)
Adalimumab	27 (3.6)
Tildrakizumab	14 (1.9)
Guselkumab	13 (1.8)
Secukinumab	11 (1.5)
Certolizumab	8 (1.1)
Brodalumab	0 (0)
Risankizumab	0 (0)
Bimekizumab	0 (0)
Unspecified biologic	120 (16.2)
Classical concomitant treatments during pregnancy (*n* = 53)	
Systemic corticosteroids	10 (18.9)
Cyclosporine	6 (11.3)
Phototherapy	5 (9.4)
Azathioprine	1 (1.9)
Trimester of exposure (*n* = 226)	
3 months prior to conception	1 (0.4)
1st trimester	159 (70.4)
2nd trimester	0 (0)
3rd trimester	9 (4.0)
1st and 2nd trimester	10 (4.4)
2nd and 3rd trimester	2 (0.9)
1st and 3rd trimester	1 (0.4)
Throughout pregnancy	44 (19.5)
Discontinuation of biologic therapy (*n* = 393)	305 (77.6)
Exposure interval during pregnancy in weeks, mean (SD) (*n* = 103)	16.8 (15.2)

Abbreviations: CZP, certolizumab pegol; IFX, infliximab; SD, standard deviation.
[a]There is one pregnancy[74] exposed to IFX and CZP that computes in both biological therapies.

However, there were significant differences in the frequency of elective abortions, with women exposed to tildrakizumab (28.6%) and ixekizumab (25.0%) choosing to terminate the pregnancy more often.

Pooled prevalence

Table 5 shows the main findings of the meta-analysis on the prevalence of spontaneous, elective, and total abortions and congenital malformations relative to total pregnancies exposed to biologics.

Five studies were excluded from the meta-analysis on abortions due to lack of data.[10–14] Pooled data from the rest showed a prevalence of miscarriage of 15.3% (95% CI 12.7–18.0), with low heterogeneity ($I^2 = 0\%$, 95% CI 0–31.2; Figure 2); elective abortions, 10.8% (95% CI 7.7–14.3; $I^2 = 23.7\%$; 95% CI 0–46.9; Figure S5), and of total abortions, 23.7% (95% CI 18.8–29.0; $I^2 = 36.5\%$, 95% CI 2.3–55.2; Figure S6). The funnel plots showed no asymmetry (Figure S4A–C), findings corroborated by Egger's test ($p = 0.98$, $p = 0.38$, $p = 0.99$, respectively).

Twenty-seven articles were excluded from the meta-analysis on congenital malformations due to lack of data.[10–13,15–37] Pooled prevalence was 3.0% (95% CI 1.6–4.8; Figure 3). Although heterogeneity was low ($I^2 = 10.5\%$; 95% CI 0–45.8), the funnel plot showed asymmetry (Figure S4D), and Egger's test yielded significant results ($p = 0.074$).

DISCUSSION

This systematic review pooled available evidence and evaluated the impact of biologic drugs on pregnancy outcomes in women with psoriasis. To our knowledge, this is the first meta-analysis that specifically studies such effects. The literature has only a few systematic reviews[38–41] that synthesize pregnancy outcomes in women taking biologics for various conditions, but these are not limited to psoriasis. However, including women with different pathologies could limit the extrapolation of results to women with psoriasis, since many biologics used in rheumatic or gastroenterological IMIDs (e.g., golimumab, abatacept, or rituximab) are not authorized for psoriasis or are used with different protocols for each indication.[4,42–46] Furthermore, the characteristics, comorbidities and idiosyncrasies of the different inflammatory diseases are different.

This dearth of information often leads to the discontinuation of biologics during preconception and pregnancy, favouring disease exacerbations.[47,48] Thus, there is a strong demand for scientific evidence, which explains the recently intense research interest: not only have most included studies (58.8%) been published since 2018, they feature in high-impact scientific journals.

Our meta-analysis involved 739 pregnancies, reported in 51 studies, mostly case reports (45.1%) and case series (29.4%), with none reporting on newer anti-psoriatic biologics like brodalumab, risankizumab or bimekizumab. This omission underlines the remaining gaps in the current body of evidence.

Research shows that both specialists and patients feel they lack the knowledge and skills needed to manage IMIDs during the childbearing age. A 2021 study[49] reported on interviews of dermatologists and rheumatologists regarding the management of chronic inflammatory disease before, during, and after pregnancy. Professionals perceived a lack of competence for advising patients about pregnancy and family planning; a preference to leave pregnancy-related discussions to obstetricians and/or gynaecologists; and a

TABLE 3 Summary of primary and secondary outcomes in pregnancies exposed to biologic therapy for psoriasis.

Outcomes	No. of participants (studies)	Observations
Pregnancy outcomes[a]		
Live births	517/689 (50 observational studies)	All articles, except one,[11] reported on miscarriage and live-births.[b] One study[66] did not report the reason for one miscarriage.
Spontaneous abortions	100/689 (50 observational studies)	
Elective abortions	71/689 (50 observational studies)	
Small for gestational age	5/63 (8 observational studies)	The lower rate might be due to reporting bias of successful pregnancies in the included studies.
Live-birth outcomes		
Congenital malformations	14/492 (24 observational studies)	The congenital malformations reported were not grouped by any specific system or organ. Please, consult Table 1 for details.
Preterm birth	42/283 (36 observational studies)	The higher rate of preterm birth compared to the general population has been suggested in different studies in the psoriasis population. However, the actual relationship between psoriasis and preterm birth remains unclear.
Low birthweight	16/163 (19 observational studies)	Furthermore, 14 observational studies, that involved 47 neonates, reported their birth weight (mean 3.12 kg, SD 0.51).
Neonatal outcomes	2 (2 observational studies)	Neonatal complications have been only described in two offsprings: One infant with neonatal respiratory distress.[68] One neonate required admission to the neonatal intensive care unit for 4 days, and recovered well without issue.[29]
Long-term growth and development	42 (12 observational studies)	12 observational studies, that involved 42 neonates, reported on long-term outcomes and physiological development of the offspring. Studies describe 42 healthy children with completely normal growth.

Abbreviations: CZP, certolizumab pegol; ETA, etanercept; IFX, infliximab; Kg, kilograms; SD, standard deviation.

[a]There is one pregnancy[74] exposed to IFX and CZP that counts as two pregnancy outcomes.

[b]The study by Accortt et al.[11] only reported congenital malformations in 51 live births exposed to ETA.

tendency to consider that all biologics are strictly contraindicated during pregnancy. Likewise, the results of a survey[50] focused on managing women with psoriasis showed that only 28% of dermatologists were familiar with the existing recommendations regarding psoriasis treatment during pregnancy, and only 21% considered them appropriate.

Nonetheless, another qualitative study[51] reported the concerns of patients with cutaneous and joint IMIDs regarding family planning and pregnancy. Up to 24% of respondents reported that their disease influenced the number of children they finally decided to have; among their most frequent concerns were possible flares and the effects of treatments on the fetus.

In contrast, our results show that the prevalence of miscarriages and congenital malformations in newborns exposed to biologics during pregnancy are similar to those in the general population (estimated at 10%–20% and 2%–5.5%, respectively).[52,53] These results are consistent with the PSOLAR multicenter observational registry study, which evaluated pregnancy outcomes in women with psoriasis who received biologics during pregnancy or the prenatal period. That study showed that the rates of miscarriage, neonatal problems, and congenital malformations were similar to those in the general US population.[54]

Regarding other live birth outcomes, preterm births rates were higher than rates reported in the general European population (5%–9%) and PSOLAR (9.1%).[54,55] The higher rate of preterm birth compared to the general population has been suggested in different studies in the psoriasis population.[4,5] However, the actual relationship between psoriasis and preterm birth remains unclear.[56] Further studies are needed to clarify whether there is an increased risk of preterm delivery due to exposure to biologic drugs or due to the disease itself.

The literature contains conflicting results. A 2018 meta-analysis[38] evaluated the safety of biologics with TNF inhibitors at conception and/or pregnancy in women with IMIDs (including psoriasis), showing an increased risk of congenital malformations and premature delivery compared to controls. However, results were not always statistically significant or adjusted for confounders. Another meta-analysis from 2021 revealed that exposure to anti-TNF-α agents during pregnancy increased the risk of preterm birth, low birth weight, and infections in the newborns of women with IMIDs compared to disease-matched controls.[40]

On the other hand, a 2020 systematic review[39] considered the results of each biologic individually in pregnant women with IMIDs, reporting rates of miscarriages and congenital malformations comparable to the general population. Similarly, a meta-analysis of observational studies with adjusted ORs did not reveal an increase in congenital malformations in pregnant women with IMIDs taking versus not taking biologics, suggesting that disease activity or other confounders are behind the adverse events, not the biologic therapy.[41] Similarly, Tsao et al.[41] showed that underlying conditions are important confounders in pregnancy

TABLE 4 Pregnancy outcomes according to biologic therapy exposure.

	Biologic therapy during pregnancy, *n*/*N* total reported (%)[a]											
	IFX (*N* = 94)	**ADA (*N* = 27)**	**ETA (*N* = 143)**	**CZP (*N* = 8)**	**UST (*N* = 266)**	**SEC (*N* = 11)**	**IXE (N = 44)**	**GUS (*N* = 13)**	**TIL (*N* = 14)**	**Unspecified (*N* = 120)**	**All biologics (*N* = 740)**	***p* value[b]**
Baseline maternal characteristics												
Age in years, mean (SD)	28.31 (4.9)	31.25 (4.6)	31 (5.5)	33.75 (3.1)	30.4 (4.5)	36.13 (6.0)	N/A	30 (–)	28 (6.33)	30.9 (4.8)	30.34 (5.6)	0.09
Age range	18–35	21–40	25–41	29–43	19–44	27–39	N/A	19–40	21–37	N/A	19–44	-
Age at psoriasis diagnosis, mean (SD)	13.5 (8.3)	15.5 (16.3)	18.5 (10.6)	13 (10)	17.29 (6.7)	11.67 (9.7)	N/A	N/A	N/A	N/A	15.98 (7.6)	0.7
Discontinuation of biologic therapy (*n* = 393)	63/78 (80.8)	17/27 (63.0)	10/11 (90.9)	3/8 (37.5)	136/189 (72.0)	5/9 (55.6)	44/44 (100)	13/13 (100)	14/14 (100)	N/A	305/393 (77.6)	0.1
Exposure interval during pregnancy in weeks, mean (SD)	23 (17.9)	9 (6.3)	11.8 (14.2)	29 (8.7)	16.85 (18.5)	11 (6.0)	N/A	N/A	9.2 (3.58)	N/A	16.76 (15.2)	0.36
Pregnancy outcomes												
Live births	76/94 (80.9)	23/27 (85.2)	71/92 (77.2)	8/8 (100)	197/266 (74.1)	5/11 (45.5)	24/44 (54.5)	8/13 (61.5)	8/14 (57.1)	97/120 (80.8)	517/689 (75)	0.11
Miscarriage	6/94 (6.4)	2/27 (7.4)	13/92 (14.1)	0/8 (0)	42/266 (15.8)	6/11 (54.5)	9/44 (20.5)	2/13 (15.4)	2/14 (14.3)	18/120 (15.0)	100/689 (14.5)	0.15
Elective abortion	12/94 (12.8)	2/27 (7.4)	8/92 (8.7)	0/8 (0)	27/266 (10.2)	0/11 (0)	11/44 (25.0)	2/13 (15.4)	4/14 (28.6)	5/120 (4.2)	71/689 (10.3)	0.04*
Unspecified abortions	0/94 (0)	0/27 (0)	0/92 (0)	0/8 (0)	0/266 (0)	0/11 (0)	0/44 (0)	1/13 (7.7)	0/14 (0)	0/120 (0)	1/689 (0.2)	0.00*
Congenital malformations[c]	4/67 (6)	1/11 (9.1)	3/120 (2.5)[d]	0/6 (0)	3/180 (1.7)	0/4 (0)	N/A	0/8 (0)	N/A	3/96 (3.1)	14/492 (2.9)	0.73

Abbreviations: ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; N/A, not available; SD, standard deviation; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.

[a]2 events in twin pregnancies. There is one pregnancy[74] exposed to IFX and CZP that computes in both biological therapies.

[b]ANOVA.

[c]Congenital malformations relative to total live births, except in cases in which a congenital malformation caused the abortion.

[d]There is one study[11] that only report congenital malformations in 51 live births exposed to ETA.

*Statistically significant result.

TABLE 5 Summary of main findings.

Weighted prevalence of pregnancy outcomes	Weighted prevalence (random-effects: 95% CI)	I^2 (95% CI)	Egger's test (95% CI)	*p* value
Spontaneous abortions	15.3% (12.7, 18.02)	0% (0, 31.2)	0.01 (−0.7, 0.67)	0.98
Elective abortions	10.8% (7.7, 14.3)	23.7% (0, 46.9)	0.21 (−0.26, 0.68)	0.38
Total abortions	23.7% (18.8, 29.0)	36.5% (2.3, 55.2)	−0.001 (−0.87, 0.86)	0.99
Congenital malformations in live births	3.0% (1.6, 4.8)	10.5% (0, 45.8)	0.58 (−0.06, 1.22)	0.074*

Note: Meta-analysis of prevalence of spontaneous and elective abortions and congenital malformations in pregnancies exposed to biologic therapy.

Abbreviations: CI, confidence interval; I^2, heterogeneity.

*Statistically significant result.

outcomes. Results should be adjusted for obesity, dyslipidemia, depression, diabetes, and hypertension—all comorbidities associated with psoriasis.

Our study provides detailed information on baseline maternal characteristics, as reported by included studies. The most frequent comorbidity was tobacco use (29.5%), which is associated with other adverse pregnancy outcomes like preterm delivery.[57] Other conditions included psoriatic arthritis, psychiatric diseases (mainly anxiety and depression) and metabolic syndrome, all commonly associated with psoriasis and comparable with the clinical characteristics of the cohort from the PSOLAR registry.[54] Concordantly, Bandoli et al.[57] reported that women with psoriasis were more likely to be obese, smoke, and have depression prior to pregnancy than women without psoriasis.

In general, the greatest teratogenic risk occurs during the first trimester of gestation, when IgG transport across the placenta is limited.[58] Fetal IgG blood levels in the umbilical vein do not exceed maternal levels until the third trimester (around the 22nd gestational week), when active placental transport increases rapidly, facilitated by neonatal Fc receptors on the syncytiotrophoblast.[59] Thus, exposure to biologic agents in late pregnancy is associated with elevated cord blood drug levels and may result in therapeutic fetal levels of monoclonal antibodies.[59,60] However, our study shows that most fetal exposure (72.4%) occurs exclusively during the first trimester. This fact could limit the generalizability of the results, as data on fetal complications in pregnancies exposed to biologics during the last trimesters are scarce.

Although the transfer of IgG antibodies begins in the second trimester by binding to placental Fc receptors, not all monoclonal antibodies have the same affinity for binding to these receptors. IgG1 (adalimumab, infliximab, secukinumab, ustekinumab, guselkumab, risankizumab, tildrakizumab, and bimekizumab) is considered the most easily transported subtype, followed by IgG4 (ixekizumab), IgG3, and IgG2 (brodalumab).[58] Exceptions include etanercept, a fusion protein with low affinity, and certolizumab pegol, a pegylated human IgG1 monoclonal antibody with reduced or no placental transfer due to the absence of an Fc receptor.[60–62]

In our study, pregnancy outcomes were comparable across different classes of biologics, despite the different mechanisms of action and placental transport. There were significant differences only in the frequency of elective abortions in women exposed to tildrakizumab (28.6%) and ixekizumab (25%). For both drugs, all pregnancy outcomes came from accidental pregnancies that occurred during clinical trials,[30,31] so results could be explained by the greater propensity for clinical trials to report this information due to the unknown effects of an experimental drug. Moreover, clinical trials generally require participants of childbearing age to use birth control, which may bias the results towards including patients who prefer not to become pregnant and would choose to terminate the pregnancy anyway. In any case, there is no feasible way to prevent this potential bias towards elective termination in clinical trial settings.

Another consideration is the potentially altered immune response or immunosuppression in newborns of patients who continue treatment with biologics in late pregnancy, particularly in the third trimester.[39,63] The Centers for Disease Control and Prevention (CDC) recommends not administering live attenuated vaccines to full-term infants exposed to biologics during gestation until at least 6 months of age, as fatal outcomes are not unheard of, for example, a case of disseminated BCG infection in a newborn whose mother had been treated with infliximab for Crohn's disease.[64] Neonatal complications have been only described in two offsprings and only 12 observational studies reported long-term outcomes of the offspring. Therefore, studies reporting long-term adverse effects (such as neonatal infections) in children exposed to biologic therapies during pregnancy are needed.

Limitations of our meta-analysis include heterogeneous definitions of outcomes between studies. In addition, only a few studies performed long-term follow-up in newborns, so relevant late adverse events, such as neonatal infection, may have been missed. Likewise, the funnel plot for the meta-analysis of congenital malformations shows a publication bias, corroborated by Egger's test, suggesting the existence of small, unpublished studies with negative results. Thus, the incidence of congenital malformations could be overestimated. Moreover, data were amenable to a meta-analysis of prevalence but precluded any estimation of the strength of association. Additionally, few studies compared pregnancy outcomes with controls, and those that did not match for disease or adjust the results for confounders. Therefore, the effect attributed to biologics could be confounded by the effects arising from concomitant diseases in the intervention group, increasing the risk of reporting and selection bias. Finally, studies were generally small, and none involved pregnant patients with psoriasis on brodalumab, risankizumab or bimekizumab.

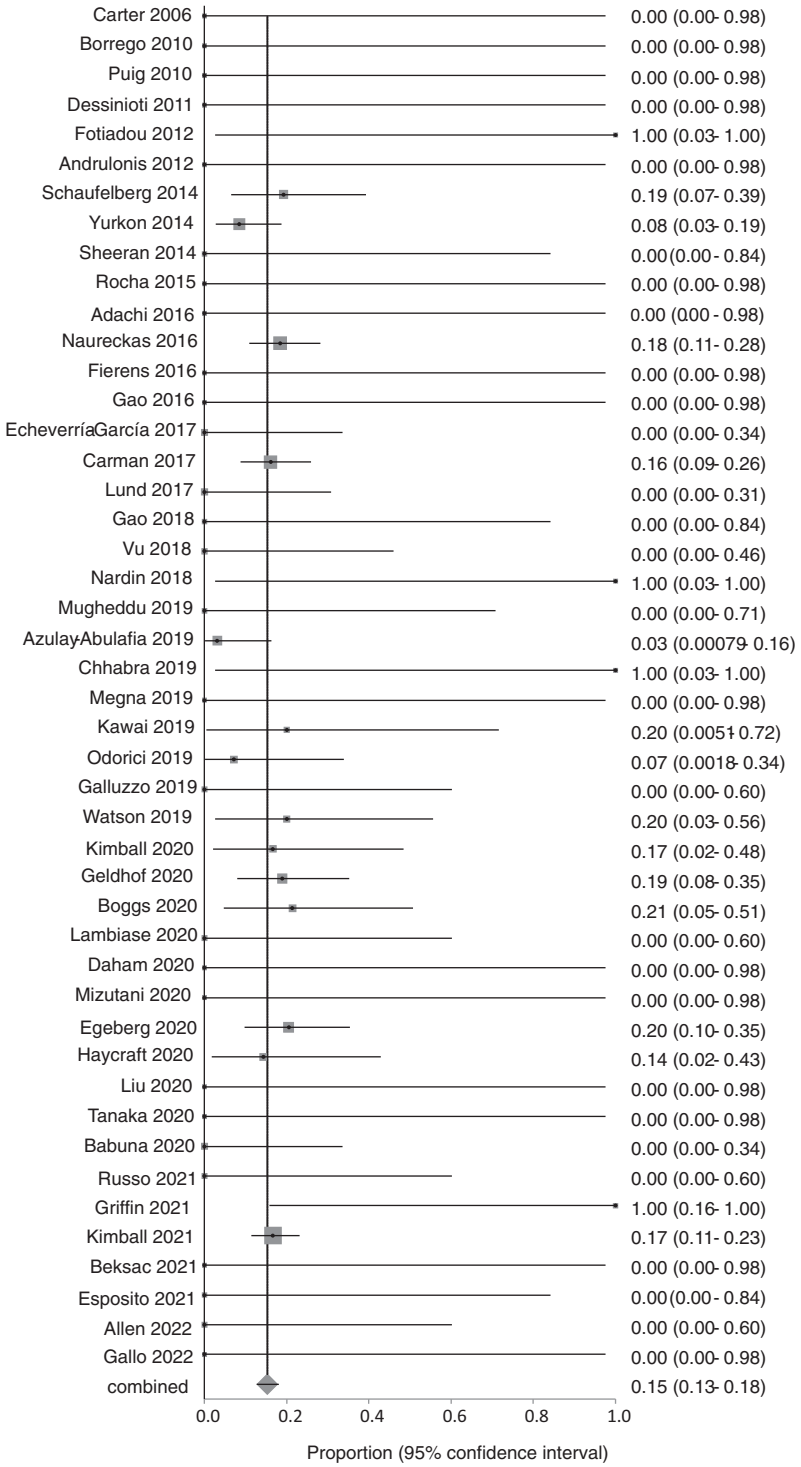

FIGURE 2 Weighted prevalence of miscarriages relative to total pregnancies exposed to biologic therapy.

In conclusion, exposure to biologics for treating psoriasis during pregnancy and/or conception appears to be unrelated to a higher risk of miscarriages or congenital malformations. These results are consistent regardless of the biologic therapy administered, suggesting the drugs are safe and pose an acceptable risk. However, we emphasize the apparent needs of research in this field. Further studies are still needed to determine the true indication for biologic therapy in pregnant patients with psoriasis and to fully characterize the association between psoriasis, treatment, and pregnancy outcomes. Addressing the clinical uncertainty will require large cohort studies with disease-matched controls, which adjust for

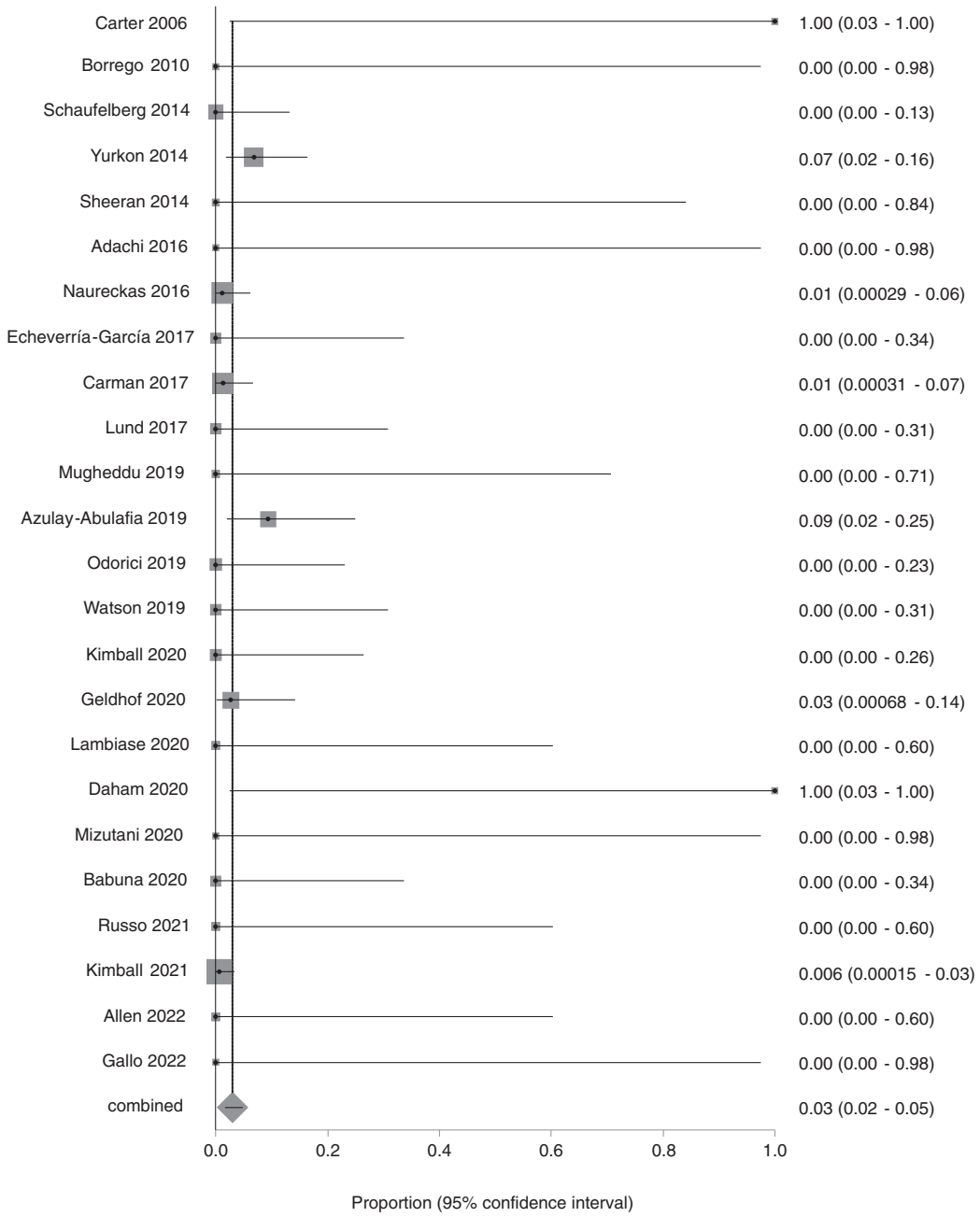

FIGURE 3 Weighted prevalence of congenital malformations in live births exposed to biologic therapy during pregnancy.

potential confounders such as disease activity, exposure interval, concomitant therapies, and maternal demographics. Psoriasis-specific pharmacovigilance registries also provide an opportunity to address this need, so physician and patient participation is strongly encouraged.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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