REVIEW ARTICLE

Safety of Dupilumab Therapy for Atopic Dermatitis during Pregnancy: A Systematic Review and Meta-analysis

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Atopic dermatitis (AD) is the most common skin condition among pregnant women. However, there is limited information on the safety of biologicals during pregnancy. A systematic review and meta-analysis was conducted following the PRISMA guidelines to evaluate the effects of exposure to biologicals during pregnancy and/or preconception in women with AD, and to estimate the pooled prevalence of spontaneous abortions and congenital malformations in their newborns. MEDLINE, Embase, Scopus, and Web of Science to 31 May 2024 were searched to identify randomized controlled trials and non-randomized studies. To test the robustness of our findings, sensitivity analyses were performed. Fifteen observational studies involving 115 pregnant women with a mean age of 33.46 years (standard deviation [SD] 3.02 were included). All studies evaluated dupilumab. The mean duration of exposure to dupilumab during pregnancy was 27.52 weeks (SD 11.16). The weighted prevalence of spontaneous abortions was 18.9% (95% confidence interval 5.3 to 38.2). There were no reports of congenital malformations. The sensitivity analyses showed no significant differences in weighted prevalences. In conclusion, the current scientific evidence suggests that dupilumab is probably safe during pregnancy and preconception in women with AD, with no significant increase in the risk of miscarriage or congenital malformations compared to the general population. However, the results of this review are inconclusive due to the limited number of large, well-designed clinical studies.

Key words: atopic dermatitis; biological therapy; pregnancy; spontaneous abortion; congenital abnormalities.

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SIGNIFICANCE

This study was undertaken to evaluate whether use of biological therapy for atopic dermatitis in pregnant women increases the risk of spontaneous abortion and congenital malformations. The studies included in the meta-analysis do not show that exposure to dupilumab for atopic dermatitis during pregnancy and/or preconception increases the risk of spontaneous abortion and congenital malformations, so may pose an acceptable risk for pregnant women and their foetuses/newborns. These findings may facilitate clinical decision-making for women with a good therapeutic response to dupilumab who become pregnant or are planning to conceive, or for pregnant women who require biological therapy to control atopic dermatitis.

Atopic dermatitis (AD) is the most common skin condition among pregnant women. It accounts for around 50% of all dermatoses of pregnancy and usually develops in the second or third trimester (1, 2). During pregnancy, immune system deviation towards T helper 2 (Th2) response helps ensure tolerance of the foetus and reduces the risk of spontaneous abortion (3, 4). Unfortunately, as AD is a Th2-driven disease, women with AD are at increased risk of experiencing flares during pregnancy (3). Untreated AD can lead to serious complications for the mother and foetus, including eczema herpeticum, premature rupture of membranes (PROM), and neonatal staphylococcal septicaemia, in addition to reduced quality of life and increased anxiety for the mother (5, 6).

To treat moderate-to-severe AD during pregnancy, the European Task Force on Atopic Dermatitis recommends systematic corticosteroids, cyclosporine, and azathioprine (4, 7–9). Currently, 2 biological drugs are approved for moderate-to-severe AD: dupilumab (approved in 2017), a monoclonal antibody that blocks the IL-4 and IL-13 signalling pathways; and tralokinumab (approved in 2021), an anti-IL-13 antibody. However, current guidelines advise against biological therapy during pregnancy owing to a lack of clinical data on the potential risks (4, 7–10). Most current evidence on the safety of biologicals during pregnancy comes from studies of women with inflammatory bowel disease (IBD) and rheumatic diseases.

In view of the high prevalence of AD in women of childbearing age, it is crucial to determine the safety of biological therapy during pregnancy and breastfeeding to optimize maternal and neonatal outcomes (11). We carried out a systematic review and meta-analysis to evaluate the current evidence on the impact of exposure to biologicals in women with AD during pregnancy and preconception.

MATERIALS AND METHODS

Study design

We conducted a systematic review and prevalence meta-analysis following the Preferred Reporting Items for Systematic Reviews

and Meta-Analysis (PRISMA) guidelines (12, 13). Our protocol was prospectively registered in the international prospective register of systematic reviews (PROSPERO; CRD42023457685).

Inclusion criteria

We selected studies that were published or pending publication; written in English, Spanish, or Italian; and that met the following inclusion criteria (PICOS):

- Population: women with a diagnosis of AD who were pregnant or planning to conceive.
- Intervention: exposure to biological drugs approved for the treatment of AD in the 3 months before pregnancy (preconception period) or during pregnancy (any trimester).
- Comparison: not applicable.
- Outcomes: pregnancy, foetal and neonatal outcomes.
- Study type: randomized controlled trials and non-randomized studies (cohort studies, case-control studies, case series, clinical case studies, and patient registries).

Our exclusion criteria were as follows:

- Design: reviews (narrative or systematic) and animal studies.
- Population: atopic diseases or immune-mediated inflammatory skin diseases other than AD.
- Outcomes: articles with incomplete data on foetal impact.
- Intervention: exposure to biological during the postpartum period only, or paternal exposure to biological.

If we found more than 1 article reporting results of the same population, we included the most recent article. We applied no restrictions related to sample size or publication date.

Sources of information and search strategy

We searched the databases PubMed, Embase, Scopus, and Web of Science to 31 May 2024. The search strategy was based on a combination of Medical Subject Headings (MeSH) terms extracted from our research question. Table SI shows the search strategy for each database. Two authors (VSG and IBR) performed the searches independently and archived the references using the reference management software Mendeley (Elsevier). We reviewed conference abstracts and presentations and manually checked the reference lists of all selected articles and relevant systematic reviews to identify additional citations.

Study selection

After removing duplicates, 2 review authors (VSG and IBR) independently screened the title and abstract of each reference and excluded those that were clearly irrelevant. They then retrieved the full text of all potentially relevant records and assessed them against our eligibility criteria. We resolved any disagreements by consensus.

Variables and data extraction

The first author (VSG) extracted data from the included studies to an Excel spreadsheet (Microsoft Corp, Redmond, WA, USA). The senior author (IBR) then revised all extracted data. We contacted study authors to request further information or clarifications where necessary. Table SII lists the variables collected from each study.

Risk of bias assessment

Two review authors (VSG and IBR) assessed the methodological quality of the included studies independently and in duplicate using the Cochrane tool Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I; Table SIII) (14). We resolved any disagreements by consensus.

Data analysis and synthesis methods

To analyse the extracted data, we used SPSS version 25.0 (IBM Corp, Armonk, NY, USA). We presented the results as absolute and relative frequencies in tables and graphs. For quantitative data, we calculated means with standard deviations (SDs) or medians with interquartile ranges (IQRs). The choice of measure depended on normality of distribution, which we tested using the Kolmogorov–Smirnov test (where *p*-values below 0.05 represented non-normal distribution). We also provided a narrative synthesis of the individual outcomes in the Results section and **Table I**.

To combine data on the number of live births, spontaneous abortions, and newborns with congenital malformations relative to the total number of pregnancies exposed to biological therapy, we performed a prevalence meta-analysis using the statistical software StatsDirect v. 3.3.5 (Merseyside, UK; https://www.statsdirect.co.uk/) and applying the Stuart-Ord method (inverse double arcsine square root). We pooled the results of studies that included more than 1 pregnant woman, excluding isolated clinical case reports. We then performed a sensitivity analysis including all studies, to check whether this modified the pooled result (15, 16).

We used forest plots to display the individual and pooled prevalences (with 95% confidence intervals [CIs]).

To evaluate statistical heterogeneity between the studies, we used the I^2 statistic and Q test. We considered I^2 values above 50% representative of heterogeneity. Because we expected to find substantial heterogeneity, we used the random-effects model for all meta-analyses.

To explore the possibility of publication bias/small study effects, we created funnel plots and performed Egger's regression test, considering a *p*-value below 0.10 indicative of statistically significant publication bias.

RESULTS

Results of the search

Our search strategies returned 1,541 references. After the screening process, we included 15 eligible publications in our systematic review (**Fig. 1**) (11, 17–30).

Characteristics of the included studies

Table SIV presents a descriptive analysis of the characteristics of the included studies. The biological evaluated in all studies was dupilumab. We found no studies on exposure to tralokinumab.

The overall methodological quality of the studies was low (Table SIII).

Table I presents the participant characteristics, intervals of exposure to biological therapy, concomitant systemic treatments used before and/or during pregnancy, and pregnancy outcomes reported in each included study.

Clinical characteristics of participants

Table II presents the characteristics of the study participants.

Characteristics of the pregnancies

There were 115 pregnancies exposed to dupilumab. No studies reported concomitant use of teratogenic treatments during pregnancy.

Table I. Characteristics of included studies and main pregnancy outcomes reported in women with atopic dermatitis exposed to biological therapy during pregnancy

1st author, year	Study design	Pregnancies and women exposed/mean age	Dosage, frequency[a]	Exposure interval or time of last dose of biological therapy	Classic systemic treatments for AD before or during pregnancy	Pregnancy, foetal, or neonatal outcomes	Live births (%); abortions (%)
EMA 2017 (17)	PV database from 1 phase 2b and 3 phase 3 studies	23 pregnancies in 23 women (1 twin pregnancy)/NR	300 mg every 2 weeks	NR	NR	Live births ($n=8$) Twin pregnancy ($n=1$) Elective abortion ($n=2$) Spontaneous abortion ($n=6$)[b] Ongoing pregnancy ($n=5$) Participants lost to follow-up ($n=3$)	8/16 (50); 8/16 (50)
Mian 2020 (18)	Case report	1 pregnancy in 1 woman/28 years	300 mg every 2 weeks	From week 24 to week 37 of pregnancy and during breastfeeding. The woman decided to stop breastfeeding shortly after the birth	Before pregnancy: SCS, phototherapy During pregnancy: SCS	Gestational hypertension Gestational diabetes AD exacerbation during pregnancy SGA LBW Live term birth Postpartum AD flare	1 (100); 0 (0)
Kage 2020 (19)	Case report	1 pregnancy in 1 woman/35 years	300 mg every 2 weeks	During preconception until week 2 of pregnancy, from week 20 to week 40 of pregnancy, and during breastfeeding	Before pregnancy: SCS, phototherapy, CsA	AD exacerbation during pregnancy (due to discontinuation of dupilumab) Live term birth without complications	1 (100); 0 (0)
Kage 2021 (20)	Case report	1 pregnancy in 1 woman/36 years	300 mg every 2 weeks	During preconception, whole pregnancy, and breastfeeding	Before pregnancy: SCS, phototherapy, CsA	Live term birth without complications	1 (100); 0 (0)
Lobo 2021 (21)	Case report	1 pregnancy in 1 woman/36 years	300 mg every 3 weeks (dose reduction due to ocular AEs)	During preconception until 24 weeks of pregnancy The woman decided not to breastfeed while receiving dupilumab	Before pregnancy: SCS, UVB phototherapy, MTX, CsA During pregnancy: oral antibiotics and UVB phototherapy	Gestational diabetes AD exacerbation during pregnancy (due to discontinuation of dupilumab) Live term birth without complications	1 (100); 0 (0)
Gracia-Darder 2021 (22)	Case report	1 pregnancy in 1 woman/28 years	300 mg every 2 weeks	During preconception and throughout pregnancy The woman decided not to breastfeed while receiving dupilumab	Before pregnancy: CsA, SCS, IVIg, oral antibiotics During pregnancy: IVIg every 14 days	Live birth without complications	1 (100); 0 (0)
Costley 2021 (23)	Case report	1 pregnancy in 1 woman/NR	300 mg every 2 weeks	During preconception, throughout pregnancy, and during breastfeeding	Before pregnancy: CsA, phototherapy	Live term birth without complications	1 (100); 0 (0)
Khamisy-Farah 2021 (24)	Global PV database. (VigiBaseTM)	36 pregnancies, puerperium and perinatal adverse drug reactions/NR	300 mg every 2 weeks	NR	NR	Unspecified abortion ($n=2$) Spontaneous abortion ($n=21$) Ectopic pregnancy ($n=1$) Heterotopic pregnancy ($n=1$) Pre-eclampsia ($n=1$) PROM ($n=1$) Neonatal jaundice ($n=1$) Other adverse drug reactions during pregnancy, puerperium, and perinatal period ($n=8$)[c]	—
Akhtar 2022 (25)	Case report	1 pregnancy in 1 woman/33 years	300 mg every 2 weeks	From 12 weeks before pregnancy to week 36 of pregnancy, with temporary discontinuation between week 27 and week 29 Self-discontinuation of dupilumab at 36 weeks and during the postpartum period	Before pregnancy: SCS, CsA, MTX, phototherapy, and antibiotics against staphylococcal infection	AD exacerbation during pregnancy (due to discontinuation of dupilumab between week 27 and 29) IUGR LBW Emergency Caesarean delivery (breech position) Live term birth	1 (100); 0 (0)
Kojanova 2022 (26)	Multicentric database (BIOREP registry)	4 pregnancies in 4 women/NR	300 mg every 2 weeks	Discontinuation ($n=4$)	NR	Ruptured ectopic pregnancy ($n=1$) Spontaneous abortion ($n=1$)	2 (50); 2 (50)
Escolà 2023 (11)	Multicentre case series	11 pregnancies (1 twin pregnancy) in 11 women/34 years 2 neonates exposed only during breastfeeding in 2 women (excluded)	300 mg every 2 weeks	Mean time of exposure to dupilumab during pregnancy was 6.8 (SD 2.9) months Conception ($n=9$) 1st trimester ($n=2$) 1st and 2nd trimester ($n=1$) 2nd and 3rd trimester ($n=1$) 1st, 2nd, and 3rd trimester ($n=2$) Throughout pregnancy ($n=5$) During breastfeeding ($n=7$)	Before pregnancy: CsA ($n=10$), MTX ($n=1$), AZA ($n=1$), phototherapy ($n=2$), SCS ($n=11$), IVIg ($n=2$), MMF ($n=1$), apremilast ($n=1$), ustekinumab ($n=1$)	LBW ($n=2$)[d] Elective Caesarean delivery ($n=2$)[d] Premature ($n=2$)[d] Twin pregnancy ($n=1$)[d] Instrumental delivery ($n=1$) Term births, without complications during delivery and with newborns of normal weight ($n=10$)	12 (100); 0 (0)
Alvarenga 2023 (30)	Case report	1 pregnancy in 1 woman/37 years	300 mg every 2 weeks	During preconception, throughout pregnancy, and during breastfeeding	Before pregnancy: SCS, CsA, phototherapy	Live term birth without complications	1 (100); 0 (0)

Continued

Table I (Continued). Characteristics of included studies and main pregnancy outcomes reported in women with atopic dermatitis exposed to biological therapy during pregnancy

1st author, year	Study design	Pregnancies and women exposed/mean age	Dosage, frequency[a]	Exposure interval or time of last dose of biological therapy	Classic systemic treatments for AD before or during pregnancy	Pregnancy, foetal, or neonatal outcomes	Live births (%); abortions (%)
Avallone 2024 (27)	Multicentre retrospective cohort study	28 pregnancies in 28 women/32.4 years (range 19–45)	300 mg every 2 weeks	Median time of exposure to the drug during pregnancy was 6 weeks (range 2–24) All the documented pregnancies were unplanned, and the drug was discontinued in all cases once pregnancy status was reported	Before pregnancy: CsA (*n* = 27) During pregnancy: prednisone (*n* = 2)	Gestational diabetes (*n* = 1) AD recurrence (*n* = 13) Poor control of AD (*n* = 1) Postpartum haemorrhage (*n* = 1) Oligohydramnios (*n* = 2) Miscarriage (*n* = 5) Prematurity (*n* = 7) Respiratory distress (*n* = 1) Pulmonary hypertension (*n* = 1) Postpartum depression (*n* = 1) Idiopathic anaphylaxis (*n* = 1) AD in offspring (*n* = 2) Solitary cutaneous mastocytoma in offspring (*n* = 1)	23 (82.1); 5 (17.9)
Hong 2024 (28)	Case series	4 pregnancies in 4 women/34 years (range: 29–39)	300 mg every 2 weeks	Preconception (*n* = 4) 2nd trimester (*n* = 3) 3rd trimester (*n* = 1)	Before pregnancy: CsA (n = 3), SCS (n = 3), MTX (n = 1)	Mild aggravation of AD symptoms (*n* = 1) Facial erythema (*n* = 1) Live term births without complications	4 (100); 0 (0)
Di Lernia 2024 (29)	Case report	1 pregnancy in 1 woman/35 years	300 mg every 2 weeks	During preconception, pregnancy (discontinued for 2 weeks), and breastfeeding	Before pregnancy: SCS, CsA	Mild aggravation of AD symptoms (due to discontinuation of dupilumab)	1 (100); 0 (0)

[a]The biological drug was dupilumab in all studies. [b]Of the 6 women with spontaneous abortion, 2 had 1 or more factors known to increase the risk of spontaneous abortion (elevated parathyroid hormone, clotting disorders, and a history of infertility). [c]Includes exposure to the drug during pregnancy. [d]One was a twin pregnancy that required a Caesarean delivery, with 2 premature babies (week 35) with low weight (1.5 kg and 2.0 kg) but with adequate development and weight gain.
AD: atopic dermatitis; AE: adverse effect; AZA: azathioprine; CsA: cyclosporine A; IVIg: intravenous immunoglobulin; IUGR: intrauterine growth restriction; LBW: low birthweight; MMF: mycophenolate mofetil; MTX: methotrexate; NR: not reported; PROM: premature rupture of membranes; PV: pharmacovigilance; SCS: systemic corticosteroids; SD: standard deviation; SGA: small for gestational age; UVB: ultraviolet B.

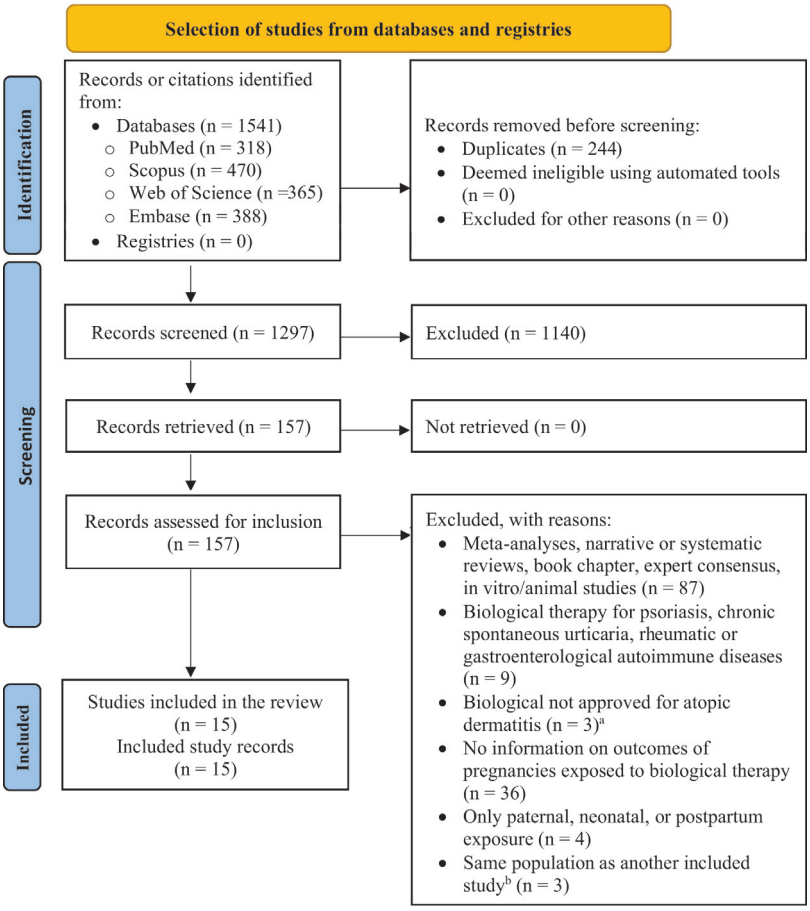

Fig. 1. PRISMA flowchart illustrating the study selection process (12). [a]Omalizumab (*n* = 2) (71,72) and rituximab (*n* = 1) (73). [b]In these situations, the most recent article was included in the review.

Table II. Clinical characteristics of women with atopic dermatitis who were exposed to biological therapy during pregnancy

Maternal clinical characteristics	*n* (%)[a]
Number of pregnant women	115 (100)
Mean age in years (SD) (*n* = 51)	33.46 (3.02)
Age range	19–45
Age at AD diagnosis, mean (SD) (*n* = 18)	1.63 (1.77)
Comorbidities	
Asthma (*n* = 18)	14 (77.8)
Rhinitis (*n* = 18)	14 (77.8)
Conjunctivitis (*n* = 18)	11 (61.1)
Food allergy (*n* = 18)	4 (22.2)
Obesity (*n* = 45)	6 (13.3)
Mental health disorders (*n* = 18)[b]	2 (11.1)
Gastrointestinal diseases (*n* = 18)[b]	2 (11.1)
Smoking (past or current) (*n* = 39)	3 (7.7)
Cancer (*n* = 18)[b]	1 (5.6)
Endocrine diseases (*n* = 46)[b]	2 (4.4)
Allergic contact dermatitis (*n* = 18)	0 (0)
Hives (*n* = 18)	0 (0)
Hypertension (*n* = 18)	0 (0)
Diabetes mellitus (*n* = 18)	0 (0)
Dyslipidaemia (*n* = 18)	0 (0)
Liver disease (*n* = 18)	0 (0)
Cardiovascular diseases (v = 18)	0 (0)
Kidney disease (*n* = 18)	0 (0)
Neurological diseases (*n* = 18)	0 (0)
Others (*n* = 51)[b]	14 (27.5)
Previous abortions (*n* = 42)	2 (4.8)
Age at initiation of dupilumab, mean (SD) (*n* = 8)	32.4 (3.54)
Severity score before initiation of dupilumab, mean (SD)	
EASI (*n* = 17)	36.3 (18.72)
SCORAD (*n* = 4)	55 (4.89)
IGA (*n* = 4)	4 (0)
BSA (*n* = 3)	61 (34.22)
DLQI (*n* = 2)	24 (5.66)
Systemic treatments prior to pregnancy	
Cyclosporine (*n* = 52)	48 (92.3)
Systemic corticosteroids (*n* = 24)	22 (91.7)
Phototherapy (*n* = 24)	9 (37.5)
Methotrexate (*n* = 24)	4 (16.7)
Intravenous immunoglobulin (*n* = 24)	3 (12.5)
Azathioprine (*n* = 24)	1 (4.2)
Mycophenolate mofetil (*n* = 24)	1 (4.2)
Apremilast (*n* = 24)	1 (4.2)
Ustekinumab (*n* = 24)	1 (4.2)
Previous treatments, mean (SD) (*n* = 24)	2.77 (0.78)

[a]Unless otherwise specified. [b]Mental health disorders: anxiety (*n* = 2); gastrointestinal diseases: ulcerative colitis (*n* = 2); endocrine diseases: hyperparathyroidism (*n* = 1), thyroid disease (*n* = 1); cancers: anaplastic lymphoma (*n* = 1); others: gynaecological diseases (*n* = 11), autoimmune disease (*n* = 1), blood clotting disorder (*n* = 1), and hyperimmunoglobulin E syndrome (*n* = 1).
AD: atopic dermatitis; BSA: body surface area; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation.

More than one-third of women with available data (9/24; 37.5%) continued using dupilumab throughout their pregnancy. Biological therapy was discontinued at some point during pregnancy in 78.6% of pregnant women (44/56). The mean duration of exposure to dupilumab during pregnancy in the 52 women with available data was 27.52 (SD 11.16) weeks (**Table III**).

The main maternal complication was AD exacerbation during pregnancy (36.5%), followed by gestational diabetes (5.8%). The type of delivery was vaginal in 17 of the 20 women with available data (**Table IV**).

Pregnancy and live birth outcomes

Table V summarises the results for our primary and secondary outcomes. Fourteen studies (all except Khamisy-Farah et al. [24]) recorded data on spontaneous abortions and live births, but reporting was less consistent across studies for other outcomes, such as small for gestational age (SGA), premature birth, congenital malformations, low birthweight (LBW), neonatal complications, and long-term growth and development. Among the 73 women with known results, there were 58 live births, 13 spontaneous abortions, and 2 elective abortions.

Table III. Characteristics of pregnancies exposed to biological therapy indicated for treatment of atopic dermatitis

Variables	*n* (%)[a]
Pregnancies exposed to biologicals[b]	115 (100)
Biologicals used during pregnancy (*n* = 81)	
Dupilumab	115 (100)
Tralokinumab	0 (0)
Classic concomitant treatments during pregnancy (*n* = 51)	
Systemic corticosteroids (*n* = 24)	3 (5.9)
Phototherapy	1 (2)
Intravenous immunoglobulin	1 (2)
Cyclosporine	0 (0)
Azathioprine	0 (0)
Exposure 3 months before conception or previously (*n* = 24)	21 (87.5)
Trimester of exposure (*n* = 24)	
1st trimester	2 (8.3)
2nd trimester	3 (12.5)
3rd trimester	2 (8.3)
1st and 2nd trimester	2 (8.3)
2nd and 3rd trimester	1 (4.2)
1st and 3rd trimester	0 (0)
1st, 2nd, and 3rd trimester	5 (20.8)
Throughout pregnancy	9 (37.5)
Maintained during breastfeeding (*n* = 52)	15 (28.9)
Discontinuation of biological therapy (*n* = 56)	44 (78.6)
Exposure duration during pregnancy in weeks, mean (SD) (*n* = 52)	27.52 (11.16)

[a]Unless otherwise specified. [b]Twin pregnancies were counted as one event.
SD: standard deviation.

Weighted prevalence and sensitivity analysis

Table VI shows the main findings of our prevalence meta-analyses and sensitivity analyses for the outcomes of spontaneous abortion, live births, and congenital malformations.

Table IV. Prenatal and delivery complications in pregnancies exposed to biological therapy indicated for the treatment of atopic dermatitis

Variables[a]	*n* (%)
Maternal complications during pregnancy and postpartum period	
AD flare during pregnancy (*n* = 52)	19 (36.5)
Gestational diabetes (*n* = 52)	3 (5.8)
Twin pregnancy (*n* = 47)	2 (4.3)
Ectopic pregnancy (*n* = 57)	2 (3.5)
Postpartum AD flare (*n* = 52)	1 (1.9)
Gestational hypertension (*n* = 52)	1 (1.9)
Preeclampsia (*n* = 53)	1 (1.9)
Heterotopic pregnancy (*n* = 53)	1 (1.9)
Infectious complications (*n* = 52)	0 (0)
Eclampsia (*n* = 52)	0 (0)
Type of delivery (*n* = 20)	
Vaginal	17 (85)
Instrumental	1 (5.9)
Elective Caesarean	2 (10)
Emergency Caesarean	1 (5)

[a]Twin pregnancies were counted as one event.
AD: atopic dermatitis.

Table V. Summary of primary and secondary outcomes in pregnancies exposed to biological therapy for atopic dermatitis

Outcomes[a]	No. of participants (studies)	Observations
Pregnancy outcomes		
Live births	58/73 (14 studies)	All articles except one (24) reported spontaneous abortions and live births.[b] In addition, there were 5 ongoing pregnancies, 3 losses to follow-up, and 2 twin pregnancies
Spontaneous abortion	13/73 (14 studies)	
Elective abortion	2/73 (14 studies)	Only the pharmacovigilance report of the phase 2 and phase 3 clinical trials of dupilumab reported elective abortions (of which there were 2) (17). No articles focused on the frequency of elective abortions in women exposed to biologicals
SGA	4/44 (12 studies)	2 of the SGA foetuses were from a twin pregnancy
Live birth outcomes		
Congenital malformations	0/58 (14 studies)	—
Preterm birth	9/52 (11 studies)	2 of the premature newborns were from a twin pregnancy 11 observational studies, involving 42 newborns, reported gestational age at birth (mean 37.4 weeks, SD 2.26)
Low birthweight	4/44 (12 studies)	2 of the newborns with low birthweight were from a twin pregnancy with preterm delivery 10 observational studies, involving 32 neonates, reported birthweight (mean 2.93 kg, SD 0.56)
Neonatal complications	2/54 (12 studies)	There were 2 reported cases of neonatal complications: 1 case of neonatal jaundice (24) and 1 case of respiratory distress (27)
Long-term growth and development	42 (8 studies)	8 observational studies, involving 42 neonates, reported long-term outcomes and physiological development of the offspring. The studies described 42 healthy children with completely normal growth. The mean follow-up time was 46.4 week (SD 26.81)

[a]The newborns from the twin pregnancy were counted as 2 events. [b]The study by Khamisy-Farah et al. (24) reported only pregnancy, puerperium, and perinatal adverse drug reactions ($n=36$).
SD: standard deviation; SGA: small for gestational age.

We meta-analysed the results of studies that included more than 1 pregnant woman, excluding isolated clinical case reports (**Figs 2 and 3**). We were unable to include 1 study in the meta-analyses of spontaneous abortions and live births because it provided no usable data (24). We then performed a sensitivity analysis, including all studies, to check whether this resulted in any substantial change in the weighted prevalences (15, 16).

The results of the sensitivity analyses were similar to those of the main analyses. The weighted prevalence of spontaneous abortions reduced from 18.9% to 18.3% (**Fig. 4**), and the weighted prevalence of live births increased from 78.8% to 80.2% (**Fig. 5**). Between-study heterogeneity was low for both sensitivity analyses. The weighted prevalence of congenital malformations was 0% in the main analysis and the sensitivity analysis. We detected no funnel plot asymmetry (Fig. S1A–B), which we corroborated using Egger's test ($p=0.83$ for spontaneous abortions; $p=0.88$ for live births).

DISCUSSION

We performed a systematic review and prevalence meta-analysis to synthesize the available evidence on the impact of biological therapy during pregnancy in women with AD. To the best of our knowledge, ours is the first meta-analysis to estimate the weighted prevalence of spontaneous abortions in women with AD exposed to biological drugs during pregnancy, and the weighted prevalence of congenital malformations in their newborns. Our review included 15 observational studies in 115 women.

Although AD is one of the most common diseases among women of reproductive age, there is a lack of research on the pharmacokinetics and safety of biological therapy during pregnancy (31). Controlled clinical trials of biologicals exclude pregnant women for ethical reasons, and participants must have frequent pregnancy tests after the trial begins (32). For this reason, when women who use biological drugs become pregnant or plan to conceive, their treating physician has little evidence on which to base a clinical decision (32).

This scientific need explains the recent contributions to the literature on this topic: most of the studies included in our meta-analysis (93.3%) were published in the last 5 years in journals of high scientific impact. However, most publications were case reports or case series, with low methodological quality (33). In addition, we found no studies of pregnant women exposed to tralokinumab, which reveals a persisting gap in the current evidence.

In recent years, various international societies and organizations have highlighted the need to include pregnant and breastfeeding women in clinical trials and pharmacovigilance studies (31, 32, 34, 35). In addition,

Table VI. Summary of main findings: prevalence meta-analysis and sensitivity analysis of spontaneous abortions, live births, and congenital malformations in pregnancies exposed to biological therapy

Outcome	Weighted prevalence (95% CI)	I^2 (95% CI)	Egger's test (95% CI)	*p*-value
Main analysis				
Miscarriage	18.9% (5.3 to 38.2)	62.8% (0.0 to 83.8)	−0.13 (−1.34 to 1.09)	0.83
Live births	78.8% (55.3 to 95.0)	73.0% (0.0 to 87.2)	−2.76 (−9.53 to 4.00)	0.28
Congenital malformations	0% (—)		—	—
Sensitivity analysis				
Miscarriage	18.3% (10.7 to 27.5)	0.0% (0.0 to 47.4)	−0.13 (−1.34 to 1.09)	0.83
Live births	80.2% (68.7 to 89.6)	14.3% (0.0 to 54.7)	0.11 (−1.31 to 1.52)	0.88
Congenital malformations	0% (—)	—	—	—

CI: confidence interval; I^2: heterogeneity.

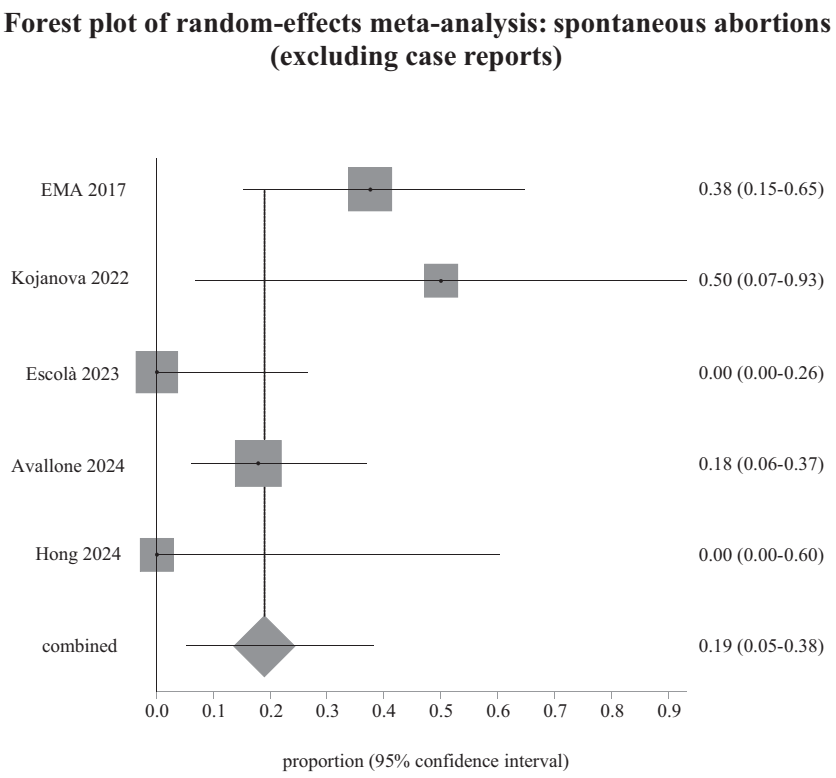

Fig. 2. Weighted prevalence of spontaneous abortions relative to the total number of pregnancies exposed to biological therapy, after excluding case reports. EMA: European Medicines Agency.

researchers have performed observational studies to help establish practical recommendations for pregnant and breastfeeding women (36). Regarding treatment for AD during pregnancy, there are 2 ongoing observational studies of dupilumab (NCT04173442 (37) and NCT03936335 (38)), both of which are currently recruiting; the estimated completion dates are in 2026 and 2027, respectively (31).

Maternal age and comorbidities are important risk factors for congenital abnormalities and other adverse

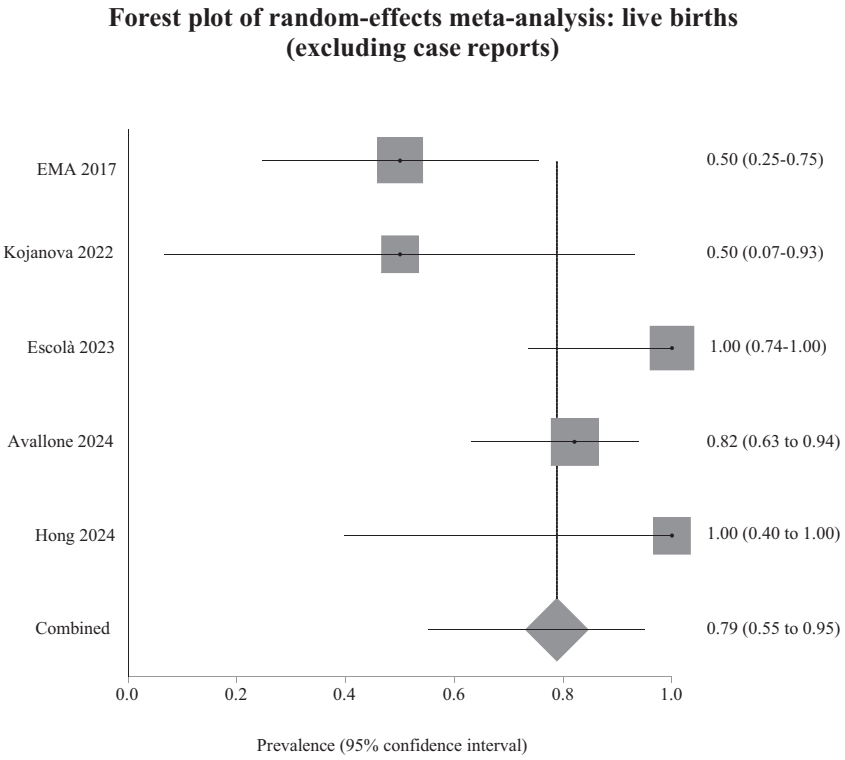

Fig. 3. Weighted prevalence of live births relative to the total number of pregnancies exposed to biological therapy, after excluding case reports. EMA: European Medicines Agency.

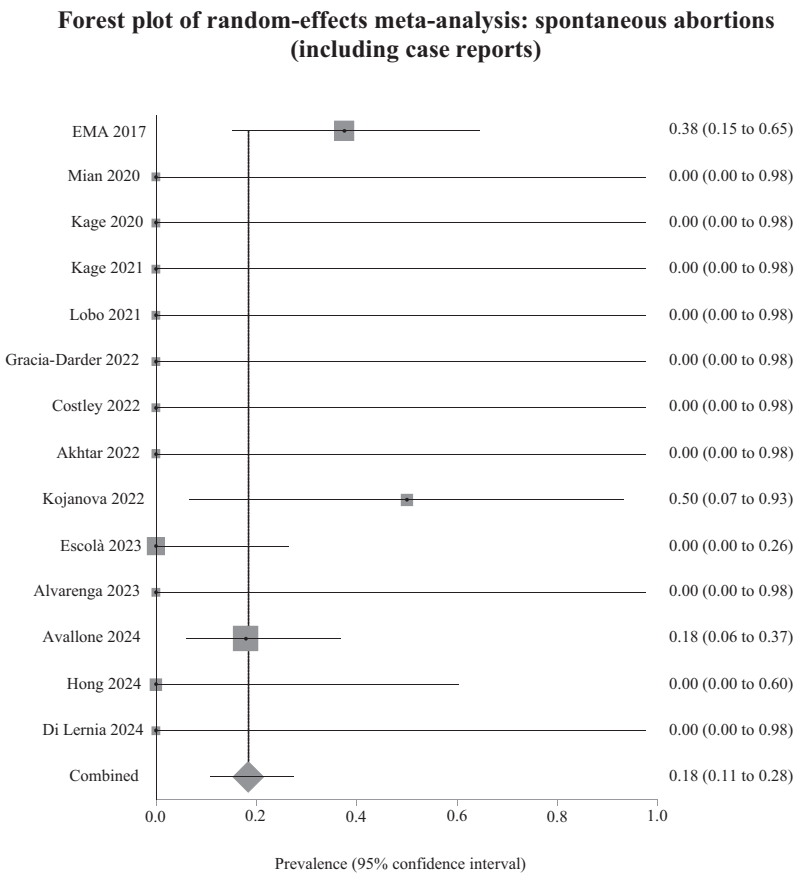

Fig. 4. Weighted prevalence of spontaneous abortions relative to total pregnancies exposed to biological therapy (including case reports). EMA: European Medicines Agency.

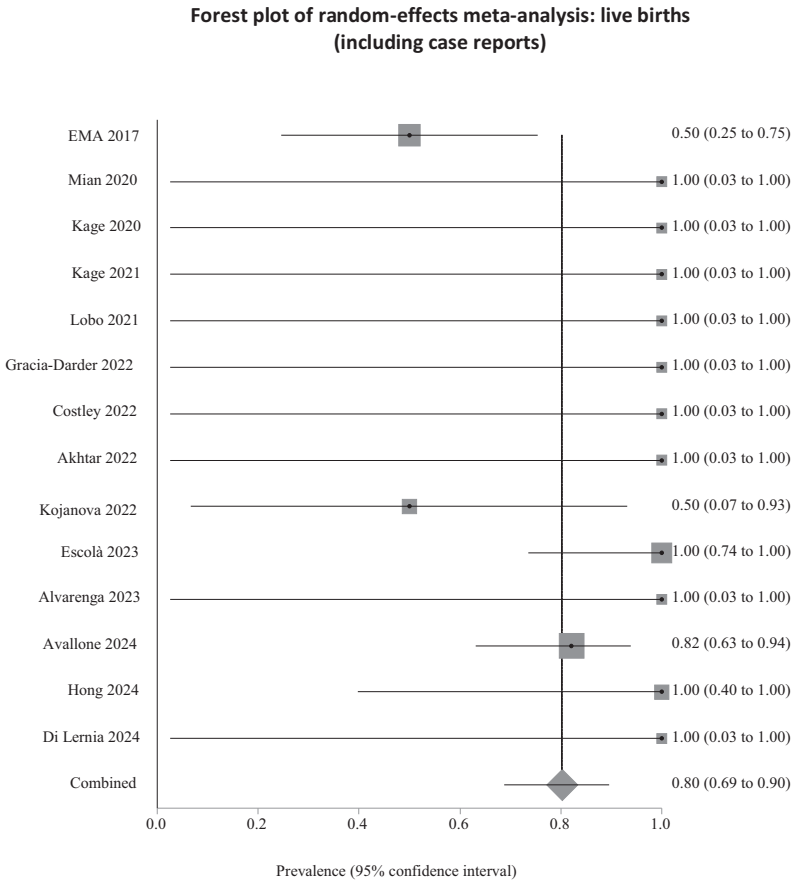

Fig. 5. Weighted prevalence of live births relative to total pregnancies exposed to biological therapy (including case reports). EMA: European Medicines Agency.

pregnancy events. The mean age in our review (33.46 years) was similar to that of the Xolair Pregnancy Registry (EXPECT) cohort (31 years) (36, 39). The main comorbidities in our population were other atopic diseases (asthma, conjunctivitis, and food allergies, all of which are commonly associated with AD). These results are comparable to the baseline clinical characteristics of the treatment groups in clinical trials of dupilumab performed in adults and adolescents with AD (40–43). The main non-allergic comorbidities in our population were mental health disorders, in line with previous research. Seeger and colleagues reported a greater consumption of psychotherapeutic drugs in pregnant women with psoriasis and AD than in the control group; this result may reflect an association between dermatitis flares during pregnancy and stress (44).

The women in our review had an average baseline Eczema Area and Severity Index (EASI) score of 36.3 (SD 18.7) and received dupilumab during pregnancy for 27.5 (SD 11.1) weeks. However, 78.6% of women with available data stopped using dupilumab at some point during pregnancy, and 36.5% had AD exacerbations during the pregnancy.

Although AD tends to worsen during pregnancy, 2 recent studies showed that many women discontinue use of topical and systemic medications once they are aware of their pregnancy, and gradually taper off over the 3 trimesters (45,46). Specifically, 1 study showed that the rates of dupilumab reduced from 2.0% before pregnancy to 0.7% during the first trimester and 0.3% during the second and third trimesters (46). This could reflect a tendency for women to endure more AD flares during pregnancy, combined with a more cautious and restrictive treatment approach (45).

During pregnancy, foetal exposure to biological drugs depends on the maternal IgG concentration. At term, foetal IgG can be 20% to 30% higher than maternal levels (47). Because IgG antibodies are large molecules (>100 kDa), placental IgG transfer depends on the neonatal Fc receptor (FcRn) in the syncytiotrophoblast, and the order of transport efficacy is IgG1, IgG4, IgG3, then IgG2. Both dupilumab and tralokinumab are IgG4 monoclonal antibodies (48). Although IgG4 is the second most transported IgG across the placenta, experts think there is no exposure during early embryogenesis owing to the absence of FcRn in the first trimester, meaning the risk of teratogenicity is low (48). In our review, as most women with available data used dupilumab for some period of time in all 3 trimesters, we consider their outcomes provide relevant safety evidence.

Regarding pregnancy outcomes, our meta-analysis shows that the weighted prevalence of spontaneous abortions and congenital malformations in newborns exposed to dupilumab during pregnancy did not differ from rates estimated in the general population, which are 11–22% for spontaneous abortion, and 2–5.5% for congenital malformations (49–51). In our review, among the 73 pregnancies with known results, the weighted prevalence of spontaneous abortions was 18.9% (18.3% with the case reports). There were no reports of congenital malformations in the live newborns.

The prevalence of spontaneous abortions in our study is very similar to the prevalence reported in women with AD. Seeger and colleagues observed a total prevalence of spontaneous abortions of 20.3% in the group of pregnant women with AD, and 19.3% in the group of pregnant women with psoriasis (44). In addition, they showed that the age-adjusted incidence rate of spontaneous abortions in women with AD were similar to that estimated for the control group and the psoriasis group (44, 52).

Animal studies of dupilumab have indicated no increased risk of malformation (17, 53, 54), and there is no evidence that dupilumab causes other pregnancy complications, such as preterm birth or spontaneous abortion. Nevertheless, dupilumab works by blocking Th2 immune response. Th2 cytokines play a role in the maintenance of pregnancy (3, 55, 56). In this sense, Piccinni and colleagues demonstrated reduced production of IL4 and IL10 by T cell clones generated in the placenta of women who had unexplained recurrent spontaneous abortions, compared with women who had elective abortions (57). Despite this, there is no explanation in the current literature for the improvement in AD after blockade of the Th2 response with dupilumab without an increase in gestational complications. Therefore, we cannot rule out that this contradictory lack of increase in the prevalence of spontaneous abortions in pregnant women exposed to dupilumab in our study may not be due to the fact that the total of 115 cases is too low to make a reliable statement.

Regarding the use of dupilumab for other indications, a European Medicines Agency assessment report on the extension of marketing authorization of dupilumab to treatment of asthma, published in 2019, presented a summary of the pregnancy outcomes of 1 phase 2b study and 2 phase 3 studies, concluding that the rate of spontaneous abortions was no higher than the general rate (53). However, comparing the 2 atopic diseases seems inappropriate, in view of the differences in foetal outcomes (36, 58–62).

Although the evidence is scarce, dupilumab appears to have no impact on human fertility (4). There is more evidence from animal studies, which also suggest no effect on fertility (17, 53, 54). However, in theory, dupilumab could be present in the seminal fluid of men who receive the drug (4). Bosma and colleagues presented a case series of 2 men and 2 women who conceived during or after dupilumab therapy and who experienced no complications related to their ability to conceive, the course of the pregnancy, or foetal outcomes (63). The two women stopped dupilumab before conceiving because of the planned pregnancy; both experienced aggravation of

AD symptoms (63). In our study, 21 women were receiving dupilumab in the preconception period, and there were no reported problems with conceiving.

In our review, there were no reported complications in the newborns of women who continued dupilumab therapy during breastfeeding. It is unknown whether dupilumab is excreted in breast milk or enters the newborn's bloodstream after ingestion (64). Since dupilumab is a large protein molecule, with high molecular weight, the amount present in breast milk is expected to be low, except during the first 3 days after birth, when the large spaces between the alveolar cells in the breast allow the passage of immunoglobulins. Furthermore, systemic absorption is improbable because the molecule is almost certainty destroyed in the infant's gastrointestinal tract (64–66).

Although no studies included in our review reported developmental abnormalities in the long term (growth, psychomotor development, infectious complications, or risk of atopy), several studies did not record these results or did not specify the follow-up time. The scientific community has yet to uncover the effects of exposure to dupilumab during pregnancy on the newborn's immune system. In 1 study of women with IBD, intrauterine exposure to tumour necrosis factor (TNF)-alpha showed no negative impact on long-term development of the children, compared with non-exposure in children born to mothers without IBD (67).

We found no published clinical data on the use of tralokinumab in pregnant or breastfeeding women. Tralokinumab is an IgG4 monoclonal antibody against IL-13, and should be transported across the placenta similarly to dupilumab. However, while animal studies of tralokinumab have shown no direct or indirect harmful effects, there are no clinical data in humans to support any conclusions (68, 69).

Our review has some limitations. First and foremost, 13 of the 15 studies we included were descriptive. The case series were at risk of selection bias because the clinician selected the cases, which may be atypical in clinical practice (70). Owing to the type of studies included, we were only able to perform prevalence meta-analyses, without effect estimates (risk ratio or odds ratio), which means our findings cannot show a causal relationship. However, we have summarized the available evidence in the absence of higher-quality studies, which can take several years to complete (15, 16, 70). Second, we found no studies of pregnant women exposed to tralokinumab. Third, there was substantial clinical heterogeneity among the studies due to inconsistent reporting of some outcomes of interest and a lack of standard definitions for the outcomes evaluated (or, in some cases, no definition at all). In addition, most studies had a limited or unclear follow-up period after birth, meaning they may have missed relevant late adverse events, such as neonatal infection.

In conclusion, our findings are relatively reassuring: data published in a small number of pregnancies suggest that dupilumab is probably safe during pregnancy and breastfeeding. Most studies found no significant increase in the risk of adverse maternal outcomes, pregnancy outcomes, or foetal outcomes. We are unable to draw any conclusions concerning tralokinumab due to lack of data, although we expect both biologicals behave similarly during pregnancy and breastfeeding due to their comparable pharmacology and molecular weight. The findings of this review are inconclusive owing to the limited number of large, well-designed clinical studies. There is a need for appropriate pharmacological trials in women of reproductive age (8).

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