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Association between maternal dupilumab exposure and pregnancy outcomes in patients with moderate-to-severe atopic dermatitis: A nationwide retrospective cohort study

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Abstract

Importance: There is limited comparative epidemiological evidence on outcomes associated with dupilumab exposure during pregnancy; monitoring pregnancy outcomes in large populations is required.

Objective: To investigate the potential association between exposure to dupilumab in pregnant women with atopic dermatitis and any adverse pregnancy, neonatal, congenital, and post-partum outcomes.

Design: Multicenter retrospective cohort study using electronic health records and/or specific datasets of the participating sites.

Setting: 19 Italian tertiary referral hospitals.

Participants: Childbearing women were eligible if aged 18-49 years and carried out the pregnancy between October 1st, 2018 and September 1st, 2022.

Exposure: The exposed cohort included patients with moderate-to-severe atopic dermatitis who received at least 1 dose of dupilumab, administered at standard dosage within 8 weeks prior to conception and/or at any time during pregnancy; all pregnant patients who did not meet the criteria for exposure were defined as unexposed.

Main Outcomes and Measure: Primary outcome was defined as the presence of any adverse pregnancy, congenital, neonatal or post-partum events.

Results: We retrospectively screened records of 5062 patients receiving dupilumab regardless of age and gender, identifying 951 female AD patients of childbearing age, 29 of whom had been exposed to the drug during pregnancy (3.05%). The median duration of dupilumab treatment prior to conception was 22.5 weeks (range: 3-118). The 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 immediately discontinued in all cases once pregnancy status was reported. The comparison of the study cohort and the control group found no significant drug-associated risk for adverse pregnancy, congenital, neonatal, or post-partum outcomes. The absence of a statistically significant effect of exposure on the event was confirmed by bivariate analysis and multivariate analysis adjusted for other confounding factors.

Conclusion and relevance: This cohort of pregnant patients exposed to dupilumab adds to the existing evidence concerning the safety of biologic agents in pregnancy. No safety issues were identified regarding the primary outcomes assessed. In clinical practice, these data provide reassurance in case of dupilumab exposure during the first trimester. However, the continuous use of dupilumab throughout pregnancy warrants further research.

Introduction

Dupilumab is an IgG4 human monoclonal antibody directed against the common interleukin (IL)-4 receptor alpha (IL-4Rα) subunit of both the IL-4 and the IL-13, key drivers of type 2 inflammation. The drug is the first biological being licensed for atopic dermatitis (AD)[1,2]. In pregnancy, AD frequently has a deleterious course and may relevantly impact quality of life[3]. Although there is no specific concern regarding the potential risk secondary to dupilumab exposure in pregnancy, current recommendations suggest the use of other systemic drugs in pregnant women with AD, whilst dupilumab should be reserved for special circumstances in light of the little evidence available[4-6].

This study sought to address this knowledge gap by investigating the potential association between exposure to dupilumab in pregnant women with AD and any adverse pregnancy, congenital, neonatal and post-partum outcomes.

Methods

Study Design and Patient Population

We performed a multicenter, retrospective, cohort study across 19 Italian tertiary referral hospitals. Childbearing women were eligible if aged 18-49 years and if they got pregnant and carried out the pregnancy between October 1st, 2018 and September 1st, 2022. The exposed cohort consisted of patients with moderate-to-severe AD who received at least one dose of dupilumab administered at standard dosage within 8 weeks prior to conception and at any time during pregnancy. All pregnant patients who did not meet the criteria for exposure were defined as unexposed. Patients were enrolled from each center through a retrospective review of both electronic health records and/or specific datasets. The Institutional Review Board approved the study protocol (n. 003370), and patient informed consent was waived owing to the retrospective nature of the study and the use of deidentified data. Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were followed[7].

Data collection

Data including maternal demographics, medical history, AD severity, pregnancy outcomes, and live-births characteristics were collected (Table 1). Information was collected at different timepoints: at each pregnancy trimester, at delivery or pregnancy termination, at 40 days the post-partum period; offspring outcomes data were retrieved up to the study end cut-off date. The primary outcome was defined as the presence of any adverse pregnancy, congenital, neonatal or post-partum events, as summarized in Table 2. The occurrence of adverse events in the offspring was also evaluated. For each exposed patient we assessed whether dupilumab was discontinued, as well as the duration of its exposure, AD severity, and its impact on quality of life assessed by means of Dermatology Life Quality Index. Furthermore, in both patient cohorts, the topical and/or systemic medications taken during pregnancy were assessed. (Supplementary Table 1).

Statistical analysis

Descriptive analyses were performed and stratified with respect to the exposure of interest and an appropriate bivariate test was used to describe the association between each variable and exposure: in particular, Kruskal-Wallis, Chi-squared, and Wald tests were used for continuous, categorical, and primary outcome variables respectively. As a final step of analysis, a multiple logistic regression model was performed to correct the initial estimate of the Wald test for the effect of other variables and confounders, and hence assess more precisely the association between adverse events in pregnancy and dupilumab exposure: the covariates for the model were chosen primarily based on

clinical criteria and later through a stepwise selection algorithm. All tests were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed with SAS®, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Data analysis was conducted from 15th January 2023 to 15th February 2023.

Results

Patients' characteristics

At the cut-off date for this analysis, we retrospectively screened records of 5062 patients receiving dupilumab regardless of age and gender, identifying 951 female AD patients of childbearing age, 29 of whom had been exposed to the drug during pregnancy (3.05%). Only one patient was excluded due to her ongoing pregnancy status. The mean duration of dupilumab treatment prior to conception was 22.5 weeks (range: 3-118). All the documented pregnancies were unplanned, and the drug was immediately discontinued in all cases. The median time of exposure to the drug was 6 weeks (range: 2-24). The effects of discontinuing dupilumab during pregnancy AD are illustrated in Figure 1a. As for baseline and demographics characteristics, no statistically significant differences were documented.

Pregnancy outcomes

The primary outcome of the logistic regression was first analyzed through a bivariate analysis: we detected an OR of 2.10 (0.89 - 4.94) in accordance with the higher event rate in the exposed cohort (0.54 *vs* 0.35), albeit without reaching statistical significance (p-value: 0.0896). Dupilumab exposure was one of the variables retained in the regression logistic model by applying the stepwise selection algorithm, but the associated estimate again was not statistically significant (OR: 3.842; 95% CI: 0.962-15.343) (Supplementary Table 2). At the bivariate level, we further investigated the association between dupilumab administration and each of the four event categories selected as primary outcome. No congenital abnormalities were observed in the cohort of exposed patients, whereas the event rates associated to the exposed patients were slightly higher for pregnancy (0.32 *vs* 0.29), neonatal (0.29 *vs* 0.23), and post-partum (0.07 *vs* 0.03) complications (Figure 1b-e); in particular, the highest OR was associated with the latter event (OR: 2.31; 95% CI: 0.37-14.55). As for the primary outcome, however, none of the previously reported differences were statistically significant.

Discussion

The primary reason for this study was to contribute to the debate concerning the safety of dupilumab when used during the first trimester of pregnancy by providing real-life data relating to the routine use of the drug in Italy. The treatment was stopped in all cases as soon as the women reported that they were pregnant, which reflects the physicians' attitude to the use of dupilumab during pregnancy in a large and representative sample of our country. The relatively small proportion of women who became pregnant during the treatment was probably secondary to the common habit to discontinue the drug before planning parenthood, due to the potential harmful effects to the fetus. As expected, drug discontinuation worsened the severity of AD in the majority of cases, consequently leading to a poorer quality of life of the patients. Overall, our findings are in line with previously published reports of pregnant women with AD exposed to dupilumab and animal studies, which showed no fetal abnormalities or impacts on fertility[3,8-14].

Limitations

Study limitations include the retrospective design and the relatively small population of pregnant women exposed to dupilumab. Nonetheless, our study investigates one of the largest patients' samples reported to date. It is well known that human immunoglobin G crosses the placental barrier in a linear fashion as the pregnancy progresses, with the greatest transfer of IgG in the third trimester[15]. The difficulty of evaluating such effects is an intrinsic limitation of our data, as the drug was discontinued earlier. Finally, the unexposed group data were derived from a gynecological setting, potentially entailing a higher degree of accuracy and a reduced recall bias.

Conclusions

This cohort of pregnant patients exposed to dupilumab adds to the existing evidence concerning the safety of biologic agents in pregnancy. No safety issues were identified regarding the primary outcomes assessed. In clinical practice, these data provide reassurance in case of dupilumab exposure during the first trimester. However, the continuous use of dupilumab throughout pregnancy warrants further research.

Table 1: Baseline and demographic characteristics

	Unexposed (N=93)	Exposed (N=28)	Total (N=121)	P-value
Age				0.1332[2]
N	91	28	119	
Mean (SD)	33.6 (3.84)	32.4 (7.46)	33.4 (4.92)	
Median	33	30	33	
Range	26.0-45.0	19.0-45.0	19.0-45.0	
Dupilumab exposure prior to conception (n weeks)				-
N	-	28	-	
Mean (SD)	-	36.8 (37.97)	-	
Median	-	22.5	-	
Range	-	3.0-118.0	-	
Total number of weeks in pregnancy during dupilumab				-
N	93	28	121	
Mean (SD)	-	6.4 (4.21)	-	
Median	-	6	-	
Range	-	2.0-24.0	-	
Duration of gestation (n weeks)				0.2974[2]
N	90	28	118	
Mean (SD)	33.3 (12.45)	32.8 (11.69)	33.2 (12.23)	
Median	39	38	39	
Range	5.0-45.0	6.0-44.0	5.0-45.0	
Age of the offspring at the study end date (n months)				-
N	93	21	114	
Mean (SD)	44 (-)	16.4 (9.21)	38.9 (-)	
Median	-	16	-	
Range	3.0-26.0	1.0-36.0	1.0-26.0	
Infant's weight at birth (kg)				0.5373[2]
N	75	19	94	
Mean (SD)	3.1 (0.43)	3.3 (0.37)	3.2 (0.42)	
Median	3.2	3.2	3.2	
Range	1.7-3.9	2.8-4.2	1.7-4.2	
Race n (%)				0.1282[3]
Asian	1 (1.1%)	1 (3.6%)	2 (1.7%)	
Caucasian	90 (98.9%)	26 (92.9%)	116 (97.5%)	
Black	0 (0.0%)	1 (3.6%)	1 (0.8%)	
Missing	2	0	2	
Maternal body mass index n (%)				0.0032[2]
Underweight	2 (2.2%)	0 (0.0%)	2 (1.6%)	

Normal weight	77 (82.8%)	21 (75%)	98 (81%)	
Overweight	12 (12.9%)	1 (3.6%)	13 (10.7%)	
Obese (class I)	0 (0%)	5 (17.8%)	5 (4.1%)	
Missing	2	1	3	
Smoke in the month prior to conception or in pregnancy n (%)				0.8940[3]
No	79 (86.8%)	18 (85.7%)	97 (86.6%)	
Yes	12 (13.2%)	3 (14.3%)	15 (13.4%)	
Missing	2	7	9	
Alcohol intake during the first trimester or in pregnancy n (%)**				0.0076[3]
No	91 (100.0%)	24 (92.3%)	115 (98.3%)	
Yes	0 (0.0%)	2 (7.7%)	2 (1.7%)	
Missing	2	2	4	
Work involving night shifts during the period of conception and gestation n (%)				0.0037[3]
No	66 (72.5%)	24 (100.0%)	90 (78.3%)	
Yes	25 (27.5%)	0 (0.0%)	25 (21.7%)	
Missing	2	4	6	
Exposure to pesticides in the first three months of pregnancy? n(%)				0.0553[3]
No	91 (100.0%)	24 (96.0%)	115 (99.1%)	
Yes	0 (0.0%)	1 (4.0%)	1 (0.9%)	
Missing	2	3	5	
Previous cyclosporine therapy n(%)				<.0001[3]
No	91 (100.0%)	1 (3.6%)	92 (77.3%)	
Yes	0 (0.0%)	27 (96.4%)	27 (22.7%)	
Missing	2	0	2	
Patient's partner aged 40 years old n(%)				0.5510[3]
No	67 (73.6%)	19 (67.9%)	86 (72.3%)	
Yes	24 (26.4%)	9 (32.1%)	33 (27.7%)	
Missing	2	0	2	
Poliabortivity n (%)				0.0831[3]
No	83 (98.8%)	25 (92.6%)	108 (97.3%)	
Yes	1 (1.2%)	2 (7.4%)	3 (2.7%)	
Missing	9	1	10	
Parity n (%)				0.0667[3]
nulliparous	61 (67.0%)	12 (42.9%)	73 (61.3%)	
pluriparous	8 (8.8%)	5 (17.9%)	13 (10.9%)	
primiparous	22 (24.2%)	11 (39.3%)	33 (27.7%)	
Missing	2	0	2	
Concomitant gynecological diseases n (%)				0.0139[3]
No	77 (82.8%)	17 (60.7%)	94 (77.7%)	
Yes	16 (17.2%)	11 (39.3%)	27 (22.3%)	
Concomitant thyroid diseases n (%)				0.0459[3]
No	73 (80.2%)	26 (96.3%)	99 (83.9%)	

Yes	18 (19.8%)	1 (3.7%)	19 (16.1%)	
Missing	2	1	3	
Concomitant autoimmune diseases n (%)				0.4464[3]
No	84 (92.3%)	27 (96.4%)	111 (93.3%)	
Yes	7 (7.7%)	1 (3.6%)	8 (6.7%)	
Missing	2	0	2	
Adverse pregnancy/neonatal/congenital/post-partum events in previous pregnancies n (%)*				0.0004[3]
No	45 (54.2%)	24 (92.3%)	69 (63.3%)	
Yes	38 (45.8%)	2 (7.7%)	40 (36.7%)	
Missing	10	2	12	

[1]Type-3 Wald p-value; [2]Kruskal-Wallis p-value; [3]Chi-Square p-value;

*These events are defined as following: spontaneous abortion = pregnancy loss within 20 weeks' gestation; stillbirth= pregnancy loss later than 20 weeks' gestation; preterm birth = gestational age of less than 37 weeks; small for gestational age= below the 10th percentile of the gestational-age-specific birth weight; low birth weight = <2500g)

** At least three alcoholic beverages per week

Table 2: Events and outcomes

	Unexposed (N=93)	**Exposed (N=28)**	**Total (N=121)**	**P-value**
Events Summaries				
Primary outcomes				
Events/N	33/93	15/28	48/121	
Event Rate (95% CI)	0.35 (0.26 - 0.45)	0.54 (0.35 - 0.72)	0.40 (0.31 - 0.48)	
Odds Ratio* (95% CI)	Reference	2.10 (0.89 - 4.94)		0.0896[2]
Adjusted Odds Ratio (95% CI)**	Reference	3.842 (0.962-15.343)		0.0568[2]
Pregnancy outcomes				
Events/N	27/93	9/28	36/121	
Event Rate (95% CI)	0.29 (0.20 - 0.38)	0.32 (0.15 - 0.49)	0.30 (0.22 - 0.38)	
Odds Ratio* (95% CI)	Reference	1.16 (0.47 - 2.88)		0.7524[2]
Neonatal outcomes				
Events/N	21/93	8/28	29/121	
Event Rate (95% CI)	0.23 (0.14 - 0.31)	0.29 (0.12 - 0.45)	0.24 (0.16 - 0.32)	
Odds Ratio* (95% CI)	Reference	1.37 (0.53 - 3.56)		0.5160[2]
Congenital anomalies				0.1613[1]
No	70 (93.3%)	28 (100.0%)	98 (95.1%)	
Yes	5 (6.7%)	0 (0.0%)	5 (4.9%)	
Missing	18	0	18	
Post-partum outcomes				
Events/N	3/93	2/28	5/121	
Event Rate (95% CI)	0.03 (0.00 - 0.07)	0.07 (0.00 - 0.17)	0.04 (0.01 - 0.08)	
Odds Ratio* (95% CI)	Reference	2.31 (0.37 - 14.55)		0.3734[2]

Events details***			
Pregnancy outcomes			
Hypertension gravidarum	7 (7.5%)	0 (0%)	7 (5.8%)
Gestational diabetes	5 (5.4%)	1 (3.6%)	6 (5%)
Post-partum hemorrhage	4 (4.3%)	1 (3.6%)	5 (4.1%)
Oligohydramnios	2 (2.2%)	2 (7.1%)	4 (3.3%)
Pre-eclampsia	3 (3.2%)	0 (0%)	3 (2.5%)
Placenta previa	1 (1.1%)	0 (0%)	1 (0.8%)
Polydramnios	1 (1.1%)	0 (0%)	1 (0.8%)
Others	11 (11.8%)	5 (17.9%)	16 (13.2%)
Miscarriage	*2 (18.2%)*	*5 (100%)*	*7 (43.8%)*
Autoimmune hyperthyroidism only in pregnancy	*2 (18.2%)*	*0 (0%)*	*2 (18.2%)*
Preterm premature rupture of membranes	*2 (18.2%)*	*0 (0%)*	*2 (12.5%)*
Intracranial extra-axial meningioma with tumour-associated hemorrhage	*1 (9.1%)*	*0 (0%)*	*1 (6.3%)*
Hyperemesis gravidarum	*1 (9.1%)*	*0 (0%)*	*1 (6.3%)*
Cholestasis gravidarum	*1 (9.1%)*	*0 (0%)*	*1 (6.3%)*
Nonautoimmune hypothyroidism in pregnancy only	*1 (9.1%)*	*0 (0%)*	*1 (6.3%)*
Toxoplasmosis	*1 (9.1%)*	*0 (0%)*	*1 (6.3%)*
Neonatal outcomes			
Prematurity	10 (10.8%)	7 (25%)	17 (14%)
Respiratory distress	1 (1.1%)	1 (3.6%)	2 (1.7%)
Hyperbilirubinemia	12 (12.9%)	0 (0%)	12 (9.9%)
Other	2 (2.2%)	1 (3.6%)	5 (4.1%)
Pulmonary hypertension	*0 (0%)*	*1 (100%)*	*1 (20%)*
Episodes of apnea	*1 (50%)*	*0 (0%)*	*1 (20%)*
Intensive care unit observation for aspiration of amniotic fluid	*1 (50%)*	*0 (0%)*	*1 (20%)*
Post-partum outcomes			
New-onset hypertension	3 (3.2%)	0 (0%)	3 (2.5%)
Clostridium infection	1 (1.1%)	0 (0%)	1 (0.8%)
Post-partum depression	0 (0%)	1 (3.6%)	1 (0.8%)
Idiopathic anaphylaxis	0 (0%)	1 (3.6%)	1 (0.8%)
Congenital anomalies			
Ventricular septal defect	2 (2.2%)	0 (0%)	2 (1.7%)
Atrial septal defect	1 (1.1%)	0 (0%)	1 (0.8%)
Duane's syndrome	1 (1.1%)	0 (0%)	1 (0.8%)
Tetralogy of Fallot	1 (1.1%)	0 (0%)	1 (0.8%)
Offspring outcomes			
Atopic dermatitis	0 (0%)	2 (7.1%)	2 (1.7%)
Solitary cutaneous mastocytoma	0 (0%)	1 (3.5%)	1 (0.8%)
Bronchiolitis complicated by COVID-19	1 (1.1%)	0 (0%)	1 (0.8%)
Growth Hormone deficiency	1 (1.1%)	0 (0%)	1(0.8%)

[1]Chi-Square p-value; [2]Type-3 Wald p-value;

* OR is calculated considering as reference group unexposed patients

Table 1 supplementary: Drug exposure other than dupilumab during pregnancy

	Unexposed (N=93)	**Exposed (N=28)**	**Total (N=121)**
Topical medication applied during pregnancy, n (%)			
No	93 (100%)	13 (46.4%)	106 (87.6%)
Yes	0 (0%)	15 (53.6%)	15 (12.4%)
Duration of topical medication application (days)			
N	0	13	-
Mean (SD)	- (-)	38.4 (45.75)	- (-)
Median	-	28	-
Range	-, -	7.0, 183.0	-, -
Topical medication, n (%)			
Methylprednisolone aceponate	0 (0%)	7 (25%)	7 (25%)
Mometasone furoate	0 (0%)	3 (10.7%)	3 (10.7%)
Fusidic acid + betamethasone valerate	0 (0%)	2 (7.1%)	2 (7.1%)
Tacrolimus 0.1%	0 (0%)	2 (7.1%)	2 (7.1%)
Emollient cream	0 (0%)	1 (3.5%)	1 (3.5%)
Desoximetasone	0 (0%)	1 (3.5%)	1 (3.5%)
Fusidic acid	0 (0%)	1 (3.5%)	1 (3.5%)
Rifamycin	0 (0%)	1(3.5%)	1(3.5%)
Pregnancy trimester in which topical medication were applied, n (%)			
I	0 (0%)	4 (14.2%)	4 (3.3%)
II	0 (0%)	11 (39.2%)	11 (9.1%)
III	0 (0%)	8 (28.5%)	8 (6.6%)
Reason of topical medication application n (%)			
Recurrence of atopic dermatitis	0 (0%)	13 (46.4%)	4 (3.3%)
Impetigo	0 (0%)	1 (3.5%)	1 (0.8%)
Systemic medication taken during pregnancy , n (%)			
No	57 (61.3%)	21 (75.0%)	78 (64.5%)
Yes	39 (41.9%)	7 (25.0%)	46 (38%)
Systemic medication, n (%)			
Antibiotics	9 (9.7%)	0 (0%)	9 (7.4%)
Antiemetics	7 (7.5%)	0 (0%)	7 (5.8%)
Acetylsalicylic acid	4 (4.3%)	1 (3.5%)	5 (4.1%)
Levothyroxine	4 (4.3%)	1 (3.5%)	5 (4.1%)
Nifedipine	4 (4.3%)	0 (0%)	4 (3.3%)
Methyldopa	2 (2.2%)	0 (0%)	2 (1.7%)
Insulin	2 (2.2%)	0 (0%)	2 (1.7%)

Tapazole	2 (2.2%)	0 (0%)	2 (1.7%)
Antiepileptics	1 (1.1%)	0 (0%)	1 (0.8%)
Antihistamine	0 (0%)	2 (7.1%)	2 (0.8%)
Prednisone	0 (0%)	2 (7.1%)	2 (0.8%)
Ursodeoxycholic acid	1 (1.1%)	0 (0%)	1 (0.8%)
Heparin	1 (1.1%)	0 (0%)	1 (0.8%)
Paracetamol	0 (0%)	1 (3.5%)	1 (0.8%)
Reason of systemic medication use n (%)			
Urinary tract infection	8 (8.6%)	0 (0%)	8 (6.6%)
Nausea	7 (7.5%)	0 (0%)	7 (5.8%)
Hypothyroidism	4 (4.3%)	1 (14.3%)	5 (4.1%)
Hypertension	4 (4.3%)	0 (0%)	4 (3.3%)
Gestational diabetes	2 (2.2%)	0 (0%)	2 (1.7%)
Intrahepatic cholestasis of pregnancy	1 (1.1%)	0 (0%)	1 (0.8%)
Migraine	0 (0%)	1 (14.3%)	1 (0.8%)
Raynaud's phenomenon	1 (1.1%)	0 (0%)	1 (0.8%)
Sympathetic ophthalmia	0 (0%)	1 (14.3%)	1 (0.8%)
Preterm Premature rupture of membrane	1 (1.1%)	0 (0%)	1 (0.8%)
Thromboembolic risk prevention	0 (0%)	1 (14.3%)	1 (0.8%)
Itching	0 (0%)	2 (7.14%)	2 (1.6%)
Poor AD disease control	0 (0%)	1 (14.3%)	1 (0.8%)
Pre-pregnancy thrombosis	1 (1.1%)	0 (0%)	1 (0.8%)
Pregnancy trimester in which systemic medication were taken, n (%)			
I	1 (1.1%)	1 (3.5%)	2 (1.6%)
II	1 (1.1%)	0 (0%)	1 (0.8%)
III	1 (1.1%)	2 (7.1%)	3 (2.5%)
Throughout the entire period of pregnancy	1 (1.1%)	2 (20.0%)	3 (2.5%)

** In a logistic models, with the following covariates: exposure, age, smoke, partner age, concomitant gynaecological disease, concomitant thyroid disease, history of pregnancy/neonatal/congenital/post-partum complications
***These events are defined as following: spontaneous abortion = pregnancy loss within 20 weeks' gestation; stillbirth= pregnancy loss later than 20 weeks' gestation; preterm birth = gestational age of less than 37 weeks; small for gestational age= below the 10th percentile of the gestational-age-specific birth weight; low birth weight = <2500g)

Table 2 supplementary: Multiple logistic regression model: stepwise selection

Variable	Reference level	Odds Ratio (95% CI)	P-value
Dupilumab exposure	Yes	3.842 (0.962-15.343)	0.0568
Age	-	0.901 (0.802-1.012)	0.0778
Smoke*	Yes	0.378 (0.080-1.783)	0.2188
Patient's partner aged ≥ 40 years	Yes	2.800 (0.753-10.415)	0.1245
Concomitant gynecological diseases	Yes	2.178 (0.643-7.376)	0.2112
Concomitant thyroid diseases	Yes	2.632 (0.721-9.612)	0.1430
Adverse events in previous pregnancies**	Yes	9.272 (3.060-28.093)	<.0001

* In the month prior to conception or in pregnancy **Defined as the presence of any adverse pregnancy, neonatal, congenital/, post-partum events

Figure 1. (A) Boxplots representing the values of Eczema Area Severity Index (EASI),SCORing Atopic Dermatitis (SCORAD) , and Dermatology Life Quality Index (DLQI) at the initiation of

dupilumab therapy (baseline) and at three different time points following discontinuation of the drug, namely 3 months (T1), 6 months (T2), and 9 months (T3). (B-E) Barplots showing the difference between any adverse pregnancy, congenital, post-partum, and neonatal events in the exposed group to dupilumab compared to the non-exposed group

Supplementary Table 1. Drug exposure other than dupilumab during pregnancy

Supplementary Table 2. Multiple logistic regression model: stepwise selection

References

1. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.

2. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303.

3. Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. *J Eur Acad Dermatol Venereol*. 2020;34(6):e256-e257. doi:10.1111/jdv.16235

4. Vestergaard C, Wollenberg A, Barbarot S, et al. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period [published correction appears in J Eur Acad Dermatol Venereol. 2020 Feb;34(2):426-427].

5. Adam DN, Gooderham MJ, Beecker JR, et al. Expert consensus on the systemic treatment of atopic dermatitis in special populations [published online ahead of print, 2023 Jan 25]. *J Eur Acad Dermatol Venereol*.

6. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf [Accessed June 29, 2023]

7. https://www.strobe-statement.org/checklists/cohort studies [accessed 30 June 30,2023]

8. Costley M, Murphy B. Severe atopic dermatitis treated successfully with dupilumab throughout pregnancy. *Clin Exp Dermatol*. 2022;47(5):960-961.

9. Mian M, Dunlap R, Simpson E. Dupilumab for the treatment of severe atopic dermatitis in a pregnant patient: A case report. *JAAD Case Rep*. 2020;6(10):1051-1052. Published 2020 Aug 9.

10. Khamisy-Farah R, Damiani G, Kong JD, Wu JH, Bragazzi NL. Safety profile of Dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from

the WHO individual case safety reporting database (VigiBase™). *Eur Rev Med Pharmacol Sci*. 2021;25(17):5448-5451.

11. Akhtar NH, Khosravi-Hafshejani T, Akhtar D, Dhadwal G, Kanani A. The use of dupilumab in severe atopic dermatitis during pregnancy: a case report. *Allergy Asthma Clin Immunol*. 2022;18(1):9. Published 2022 Feb 3.

12. Akuffo-Addo E, Nicholas MN, Lansang P. Reported Pregnancy Outcomes in Women With Severe Atopic Dermatitis Treated With Dupilumab: A Systematic Review [published online ahead of print, 2023 Jan 31]. *J Cutan Med Surg*. 2023;12034754231152223.

13. Escolà H, Figueras-Nart I, Bonfill-Orti M, et al. Dupilumab for atopic dermatitis during pregnancy and breastfeeding: Clinical experience in 13 patients [published online ahead of print, 2023 May 5]. *J Eur Acad Dermatol Venereol*. 2023;10.1111/jdv.19165.

14. Schoder K, Zhu Y, Schneeweiss S, et al. Use of systemic immunomodulating medications in pregnant women with atopic dermatitis: A nationwide US study. *J Am Acad Dermatol*. 2023;89(1):178-181.

15. Sitek AN, Li JT, Pongdee T. Risks and safety of biologics: A practical guide for allergists. *World Allergy Organ J*. 2023;16(1):100737. Published 2023 Jan 16.