

# You discuss patchy skin with your Pso patients, but do you discuss depression?<sup>1,2</sup>

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Psoriasis (Pso) can have a deep impact on your patients' mental health,<sup>3,4</sup> but talking about it can help them get the support they need. Emotional wellbeing can also improve how effectively they manage their Pso.

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*Little wins in psoriatic disease start here*

#### References:

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PHARMACEUTICAL COMPANIES OF 

## ORIGINAL ARTICLE

# Treatment patterns and outcomes in patients with chronic urticaria during pregnancy: Results of PREG-CU, a UCARE study

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**Abstract**

**Background:** Although chronic urticaria (CU) is a common and primarily affects females, there is little data on how pregnancy interacts with the disease.

**Objective:** To analyse the treatment use by CU patients before, during and after pregnancy as well as outcomes of pregnancy.

**Methods:** PREG-CU is an international, multicentre study of the Urticaria Centers of Reference and Excellence network. Data were collected via a 47-item-questionnaire completed by CU patients who became pregnant during their disease course.

**Results:** Questionnaires from 288 CU patients from 13 countries were analysed. During pregnancy, most patients (60%) used urticaria medication including standard-dose second generation H1-antihistamines (35.1%), first generation H1-antihistamines (7.6%), high-dose second-generation H1-antihistamines (5.6%) and omalizumab (5.6%). The preterm birth rate was 10.2%; rates were similar between patients who did and did not receive treatment during pregnancy (11.6% vs. 8.7%, respectively). Emergency referrals for CU and twin birth were risk factors for preterm birth. The caesarean delivery rate was 51.3%. More than 90% of new-borns were healthy at birth. There was no link between any patient or disease characteristics or treatments and medical problems at birth.

**Conclusion:** Most CU patients used treatment during pregnancy especially second-generation antihistamines which seem to be safe during pregnancy regardless of the trimester. The rates of preterm births and medical problems of new-borns in CU patients were similar to population norms and not linked to treatment used during pregnancy. Emergency referrals for CU increased the risk of preterm birth and emphasize the importance of sufficient treatment to keep urticaria under control during pregnancy.

**INTRODUCTION**

Chronic urticaria (CU) is a mast-cell mediated inflammatory disease characterized by the appearance of wheals, angioedema, or both for longer than 6 weeks. Depending on the presence of triggers, such as cold in cold contact urticaria, CU is classified into chronic inducible urticaria (CIndU) and chronic spontaneous urticaria (CSU).<sup>1</sup>

The prevalence of CU is greater in women than men with a point prevalence in CSU of 1.3% and 0.8%, respectively.<sup>2</sup> Although CU is common and often severe in female patients, little is known about CU during pregnancy. To address this, the global network of Urticaria Centers of Reference and Excellence (UCAREs)<sup>3</sup> performed an international, multicenter study, the PREG-CU.<sup>4</sup> In our first analysis, we found that CU during pregnancy improved in about half of the patients. However, two in five patients reported acute exacerbations of CU especially at the beginning and end of pregnancy. In addition, one in 10 pregnant CU patients required urticaria emergency care and one of six had angioedema during pregnancy. The risk factors for worsening of CU during pregnancy were mild disease and no angioedema before pregnancy, not taking treatment

before pregnancy, CIndU, CU worsening during a previous pregnancy, stress as a driver of exacerbations and treatment during pregnancy.<sup>4</sup>

These findings highlight the need for greater optimization of treatment of CU during pregnancy and understanding of how treatment impacts pregnancy outcomes. To address these unmet needs, we performed a comprehensive PREG-CU analyses that assessed the management in women during pregnancy and lactation and explored outcomes of pregnancy in CU.

**MATERIALS AND METHODS****Study design**

PREG-CU was a cross-sectional, international, multicentre, observational (non-interventional) study performed at Urticaria Centers for Reference and Excellence worldwide (UCARE) April 2018 to September 2019.<sup>3</sup> Complete methods have been published in the first PREG-CU analysis.<sup>4</sup>

Ethics approval was provided by the coordinating centre from Okmeydanı Training and Research Hospital and by

each participating UCARE centre. Written informed consent was taken from all participants prior to inclusion in the study.

## The PREG-CU questionnaire

Questionnaire development has been discussed in the first PREG-CU analysis.<sup>4</sup> For the current study, the relevant questions were treatment focused: (1) urticaria treatment (including stopping and starting) before, during and after pregnancy; (2) treatment for angioedema including emergency referral for CU; (3) other treatments taken during pregnancy not for urticaria, comorbidities, outcomes of pregnancy (i.e. delivery at full-term, method, medical problems with the newborn) and (4) treatment during lactation.

## Study participants

Patients with CSU, CIndU or both, and who were pregnant during the last 3 years before the study visit with CU starting before pregnancy were included. Patients were excluded if they had acute urticaria during pregnancy, urticaria starting during pregnancy or if >3 years had passed after their last pregnancy.<sup>4</sup>

## Patient population

A total of 288 pregnancies in 288 CU patients ( $n = 188$  CSU;  $n = 36$  CIndU;  $n = 57$  CSU + CIndU; 7 had missing data) from 13 countries and 21 centres worldwide were analysed. Mean age of patients was 33.6 ( $\pm 5.9$ ) years, mean age at pregnancy was 32.1 ( $\pm 5.6$ ) years and duration of CU was 84.9 ( $\pm 74.5$ ) months (Table 1). Patients rated their CU symptom severity as mild (35.7%), moderate (34.2%) and severe (29.7%) before pregnancy. Comorbidities and medications used for these comorbidities are shown in Table 1. Of the 288 newborns, 141 (51.5%) were female and 133 (48.5%) were male, with vaginal and caesarean section delivery in 48.9% and 51.1%, respectively. Caesarean section was correlated with age at pregnancy (i.e. mean age was significantly higher in patients with caesarean section [33 vs. 31;  $p = 0.024$ ]).

## Statistical analysis

Data were summarized as mean  $\pm$  standard deviation or median (min-max) for continuous variables, frequencies (percentiles) for categorical variables. To compare two independent groups with continuous and normally distributed variables Student's *t*-test was used, whereas Mann-Whitney *U* test used for non-normally distributed groups; or Mann-Whitney *U* test was used for independent group

**TABLE 1** Patient demographic characteristics

| Characteristics  |                                     | <i>n</i> (%) |
|------------------|-------------------------------------|--------------|
| Country          | Argentina                           | 5 (1.7)      |
|                  | Brazil                              | 23 (7.9)     |
|                  | Denmark                             | 13 (4.5)     |
|                  | Germany                             | 30 (10.4)    |
|                  | India                               | 10 (3.4)     |
|                  | Iran                                | 10 (3.4)     |
|                  | Ireland                             | 11 (3.8)     |
|                  | Kuwait                              | 70 (24.1)    |
|                  | Poland                              | 7 (2.4)      |
|                  | Russia                              | 20 (6.9)     |
|                  | Spain                               | 13 (4.5)     |
|                  | Turkey                              | 62 (21.4)    |
| United Kingdom   | 14 (4.8)                            |              |
| Residential area | Rural                               | 35 (12.3)    |
|                  | Urban                               | 249 (87.7)   |
| Marital status   | Single                              | 15 (5.2)     |
|                  | Married or domestic partnership     | 267 (92.7)   |
|                  | Divorced or separated               | 6 (2.1)      |
|                  | Widowed                             | 0            |
| Education        | No schooling                        | 1 (0.3)      |
|                  | Primary                             | 39 (13.5)    |
|                  | Secondary                           | 69 (24.0)    |
|                  | Undergraduate                       | 138 (47.9)   |
|                  | Postgraduate                        | 41 (14.2)    |
| Comorbidities    | Thyroid disease                     | 45 (15.6)    |
|                  | Hypertension                        | 7 (2.4)      |
|                  | Asthma                              | 9 (3.1)      |
|                  | Diabetes mellitus                   | 7 (2.4)      |
|                  | Preeclampsia or high-risk pregnancy | 3 (1.0)      |
|                  | High risk diseases                  | 6 (2.0)      |
|                  | Others                              | 18 (6.2)     |
| Other treatments | Thyroid drugs                       | 24 (8.3)     |
|                  | Vitamins                            | 23 (7.9)     |
|                  | Oral antidiabetics or insulin       | 4 (1.4)      |
|                  | Antihypertensives                   | 3 (1.0)      |
|                  | Steroid inhaler, steroid drops      | 4 (1.4)      |
|                  | Proton pump inhibitors              | 1 (0.3)      |
|                  | Hormones                            | 2 (0.6)      |
|                  | Antibiotics                         | 3 (1.0)      |
|                  | Others                              | 11 (3.8)     |

comparisons, depending on the distributional properties of the data. Chi-square test was used for proportions and its counterpart Fisher's Exact test was used when the data were sparse. Univariate logistic regression analysis was also

**TABLE 2** Treatment changes during pregnancy

| Treatments used before pregnancy, <i>n</i> (%) | Continued use during pregnancy, <i>n</i> (%) | Stopped and did not switch to other regular medication, <i>n</i> (%) | Stopped and switched to other regular medication |                   |                   |                |                   |               |               |                 |
|--|--|--|--|-------------------|-------------------|----------------|-------------------|---------------|---------------|-----------------|
|  |  |  | Total, <i>n</i> (%)                              | SD-sgAH, <i>n</i> | HD-sgAH, <i>n</i> | fgAH, <i>n</i> | AH-comb, <i>n</i> | Oma, <i>n</i> | GCS, <i>n</i> | Other, <i>n</i> |
| Total, <i>n</i> = 166, 100%                    | 60 (36.1)                                    | 47 (28.3)  | 59 (35.5)  | 35                | 5                 | 11             | 4                 | 1             | 3             | 0               |
| SD-sgAH, <i>n</i> = 65, 39.1%                  | 35 (53.8)                                    | 22 (33.8)  | 8 (12.3)   | -                 | 2                 | 4              | 0                 | 1             | 1             | 0               |
| HD-sgAH, <i>n</i> = 38, 22.9%                  | 5 (13.1)                                     | 8 (21)   | 25 (65.8)  | 17                | -                 | 5              | 2                 | 0             | 1             | 0               |
| fgAH, <i>n</i> = 10, 6%                        | 6 (60.0)                                     | 1 (10.0)   | 3 (30.0)   | 2                 | 1                 | -              | 0                 | 0             | 0             | 0               |
| AH-comb, <i>n</i> = 7, 4.2%                    | 0  | 4 (57.1)   | 3 (42.8)   | 3                 | 0                 | 0              | -                 | 0             | 0             | 0               |
| LTRA-comb, <i>n</i> = 11, 6.6%                 | 0  | 3 (27.3)   | 8 (72.7)   | 3                 | 1                 | 2              | 1                 | 0             | 1             | 0               |
| Oma, <i>n</i> = 22, 13.2%                      | 10 (45.4)                                    | 3 (13.6)   | 9 (40.9)   | 9                 | 0                 | 0              | 0                 | -             | 0             | 0               |
| GCS, <i>n</i> = 8, 4.8%                        | 3 (37.5)                                     | 3 (37.5)   | 2 (25.0)   | 1                 | 0                 | 0              | 1                 | 0             | -             | 0               |
| Other <sup>a</sup> , <i>n</i> = 5, 3%          | 1 (20.0)                                     | 3 (60.0)   | 1 (20.0)   | 0                 | 1                 | 0              | 0                 | 0             | 0             | -               |

Abbreviations: AH-comb, antihistamine combinations; Cs-A, cyclosporine; CU, chronic urticaria; fgAH, first generation H1 antihistamine; GCS, glucocorticosteroids; HD-sgAH, higher-dose second-generation antihistamine; LTRA-comb, leukotriene antagonist and antihistamine combinations; oma, omalizumab; SD-sgAH, standard-dose second-generation antihistamine.

<sup>a</sup>Autologous whole blood injection, calcium.

performed to examine risk factors for different dependent variables. A significance level of 0.05 was considered in all analyses. All analyses were performed with IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.

## RESULTS

### Most patients who plan to become pregnant continue to use their current urticaria medication

Before planning to become pregnant, 204/288 (70.8%) patients used regular treatment (i.e. continuous medication that aims to prevent the signs and symptoms of CU). Of these 204 patients, 81.4% (*n* = 166) continued to use their medication once they decided to become pregnant, while 18.6% (*n* = 38) stopped their treatment. Patients who stopped their treatment included: 18/83 (22%) of patients receiving a standard-dosed second-generation H1-antihistamine (SD-sgAH), 2/40 patients (5%) on a higher than standard-dosed sgAH (HD-sgAH) and 8/30 (26.7%) on omalizumab treatment others were on first generation-AH (fg-AH) 2/12 (16.7%), antihistamine-combinations and leukotriene antagonist-combinations (AH-comb/LTRA-comb) 4/22 (18.2%), ciclosporin-A (Cs-A) 1/1 (100%), systemic glucocorticosteroids (SCS) 2/10 (20%), other 1/5 (20%).

Patients who stopped medication because they desired to become pregnant did so, on average, 4.6 months (range: 1–12 months) before becoming pregnant. Specifically, patients who discontinued SD-sgAHs, HD-sgAHs and omalizumab did so in 3.5, 10.5 and 4 months, respectively, before becoming pregnant.

### Most patients stop or change their regular treatment when they become pregnant

Most patients (63.9%, *n* = 106/166) who used regular treatment before pregnancy changed (i.e. switched to another treatment) or stopped regular treatment altogether once the pregnancy began (Table 2).

Almost one third (28.3%; *n* = 47/166) of those who used medication before pregnancy, stopped and did not change to another treatment once pregnant. The rates of stopping treatment altogether were highest for SD-sgAH therapy (33.8%; *n* = 22/65), followed by HD-sgAH therapy (21.0%; *n* = 8/38) and omalizumab (13.6%; *n* = 3/22; Table 2).

### Most patients use treatment for CU during pregnancy

During pregnancy, most patients (60%; *n* = 173/288) used urticaria medication (Table 3); the most commonly used regular treatments were SD-sgAHs (35.1%; *n* = 101), first

generation H1 antihistamine (fgAHs; 7.6%;  $n = 22$ ), HD-sgAHs (5.6%;  $n = 16$ ), omalizumab (5.6%;  $n = 16$ ), AH and leukotriene antagonists (LTRA) combinations (2.1%;  $n = 6$ ) and glucocorticoids (GCS; 3.1%;  $n = 9$ ). Cetirizine was the most commonly used AH during pregnancy (37.4%;  $n = 46$ ), followed by loratadine (18, 14.6%) and levocetirizine and fexofenadine (7.3%; each;  $n = 9$ ).

During pregnancy, 11 (3.8%) patients received intravenous glucocorticoid treatment for exacerbations of urticaria. Of the 28 patients who had emergency referral due to urticaria exacerbations, 39.3% were on SD-sgAHs (others were on 2 HD-sgAH, 1 fg-AH, 2 omalizumab and 4 GCS plus AHs, respectively).

### Nine of 10 pregnancies in patients with CU result in full term birth

Of the 288 newborns, 141 (51.5%) were female and 133 (48.5%) were male. There were no differences between urticaria patients who gave female or male birth (i.e. overall course of pregnancy, exacerbations, preterm birth or newborn's medical problems). There were four twin births.

Of 274 patients with CU, for whom information on pregnancy outcomes were available, 240 (87.6%) gave full-term births. Of the remaining 34 pregnancies, 28 (10.2%), 3 (1.0%), 2 (0.7%) and 1 (0.3%) resulted in preterm birth, spontaneous abortion, postterm birth and foetal death, respectively. Preterm birth rates of patients who did and did not receive treatment during pregnancy were similar (11.6%,  $n = 19/164$  vs. 8.7%,  $n = 9/103$ ;  $p = 0.59$ ).

Paired comparisons showed that preterm births were significantly more common in patients who gave birth to twins

(9.3%;  $n = 25$  out of 269 vs. 66.6%;  $n = 2$  out of 3;  $p = 0.01$ ), emergency referral for CU during pregnancy (23.1%,  $n = 6$  vs. 9.1%,  $n = 22$ ;  $p = 0.04$ ), treatment during the first trimester (16.2%,  $n = 18$  vs. 6.3%,  $n = 10$ ;  $p = 0.02$ ) and treatment with omalizumab during pregnancy (28.6%,  $n = 4$  vs. 9.4%,  $n = 24$ ;  $p = 0.05$ ). Multivariate logistic regression analyses, which included 29 demographic or disease characteristics such as medication use at each trimester (Table 4), identified two predictors for preterm birth; giving birth to twins was linked to a 13.3-fold increase in preterm birth ( $p = 0.016$ ), and emergency referral for urticaria exacerbation was linked to a 4.2-fold increase in preterm birth ( $p = 0.016$ ), whereas treatment during first trimester and treatment with omalizumab during pregnancy were no longer significant risk factors for preterm birth.

### Caesarean delivery is common in CU patients

The caesarean delivery rate was 51.3%, with 133 vaginal versus 140 caesarean deliveries. The rates of caesarean delivery differed substantially between countries and were highest in Poland (71%), Turkey (66%) and Brazil (65%) and lowest in Spain (13%), the UK (27%) and Ireland (27%). Caesarean delivery rates were higher in patients with comorbidities than without (56/93 [60.2%] vs. 81/174 [46.5%];  $p = 0.03$ ). Patients who delivered by caesarean section were older (i.e.,  $32.8 \pm 5.5$  years old vs. those who delivered vaginally ( $31.2 \pm 5.8$  years,  $p = 0.024$ )). The age at pregnancy was the only factor linked to caesarean delivery in multivariate logistic regression analyses; every 1 year of increase in age increased the likelihood of caesarean delivery by 1.05-fold ( $p = 0.046$ ).

**TABLE 3** Urticaria treatments received during pregnancy trimesters

| Treatments         | First trimester (n) | Second trimester (n) | Third trimester (n) | Total, n (%) |
|--------------------|---------------------|----------------------|---------------------|--------------|
| No treatment       | 170                 | 169                  | 155                 | 115 (39.9)   |
| Received treatment | 118                 | 119                  | 133                 | 173 (60)     |
| SD-sgAH            | 78                  | 74                   | 72                  | 101 (35.1)   |
| HD-sgAH            | 2                   | 4                    | 7                   | 16 (5.6)     |
| fgAH               | 5                   | 9                    | 20                  | 22 (7.6)     |
| AH-comb            | 5                   | 6                    | 7                   | 5 (1.7)      |
| LTRA-comb          | 1                   | 0                    | 0                   | 1 (0.4)      |
| Oma                | 8                   | 6                    | 9                   | 16 (5.6)     |
| GCS                | 6                   | 6                    | 3                   | 9 (3.1)      |
| Other <sup>a</sup> | 1                   | 2                    | 2                   | 3 (1)        |
| Not specified      | 12                  | 12                   | 13                  |              |

Abbreviations: AH-comb, antihistamine combinations; fgAH, first generation H1 antihistamine; GCS, glucocorticosteroids; HD-sgAH, higher-dose second-generation H1 antihistamine; LTRA-comb, leukotriene antagonist and antihistamine combinations; oma, omalizumab; SD-sgAH, standard-dose second-generation H1 antihistamine.

<sup>a</sup>Autologous whole blood injection, calcium.

### Nine of 10 newborns of mothers with CU are healthy

Less than 10% of newborns from CU patients (7.9%;  $n = 23/288$ ) had medical problems at birth; there was one still birth. Neonatal intensive care unit (NICU) requirement due to immaturity of the lungs (4.5%;  $n = 13/288$ ), jaundice (1.0%;  $n = 3/288$ ) and anomalies <1%; ( $n = 2/288$  [cleft lip, heart defect]) were the most common problems. Newborns of patients who received urticaria treatment during pregnancy showed a similar rate of medical problems at birth compared with those who did not (6.9%,  $n = 12$  vs. 9.9%,  $n = 11$ ;  $p = 0.39$ ). There was no link between any patient or disease characteristics and medical problem at birth.

### Most CU patients breastfeed their babies and take their CU medication

Eight of 10 (78.8%) women with CU breastfed their babies. Of the 58 patients who did not breastfeed, 12 (20.7%)

**TABLE 4** Multivariate analysis results for risk factors for giving preterm birth

| Risk factors                        |         | Regression coefficient (B) | SE        | OR     | 95% CI lower | 95% CI upper | p Value |
|-------------------------------------|---------|----------------------------|-----------|--------|--------------|--------------|---------|
| Treatment before pregnancy          | None    |                            |           |        |              |              | 0.307   |
|                                     | SD-sgAH | -0.984                     | 0.903     | 0.374  | 0.064        | 2.193        | 0.276   |
|                                     | HD-sgAH | 0.074                      | 0.864     | 0.929  | 0.171        | 5.054        | 0.932   |
|                                     | Oma     | 1.004                      | 0.988     | 2.729  | 0.394        | 18.903       | 0.309   |
|                                     | Cs-A    | -19.350                    | 28420.719 | 0.000  | 0.000        |              | 0.999   |
|                                     | GCS     | -0.200                     | 1.173     | 0.818  | 0.082        | 8.159        | 0.864   |
|                                     | Others  | -18.840                    | 22942.333 | 0.000  | 0.000        |              | 0.999   |
| Oma use during pregnancy            | Yes/No  | 0.190                      | 0.858     | 1.209  | 0.225        | 6.499        | 0.825   |
| Emergency referral during pregnancy | Yes/No  | 1.436                      | 0.602     | 4.205  | 1.292        | 13.689       | 0.017   |
| Treatment during first trimester    | Yes/No  | 0.865                      | 0.484     | 2.375  | 0.920        | 6.133        | 0.074   |
| Twins                               | Yes/No  | 2.591                      | 5217.881  | 13.348 | 1.635        | 108.978      | 0.016   |

Note: Birth before 37 weeks and after 42 weeks was considered as preterm and post term, respectively. Some comorbidities were considered as predisposing factors to high-risk pregnancies: hypertension plus diabetes mellitus, hypertension plus antiphospholipid antibody syndrome, hereditary angioedema, angina, Graves plus mitral valve prolapses. Bold values indicate statistically significant.

Abbreviations: Cs-A, cyclosporine; GCS, glucocorticosteroids; HD-sgAH, higher-dose second-generation H1 antihistamine; oma, Omalizumab; OR, odds ratio; SD-sgAH, standard-dose second-generation H1 antihistamine; SE, standard error; tx, treatment.

**TABLE 5** Treatments received during breastfeeding

| Treatments         | n   | %    |
|--------------------|-----|------|
| SD-sgAH            | 85  | 61.5 |
| HD-shAH            | 19  | 13.7 |
| fg- AH             | 7   | 5.1  |
| AH-comb/LTRA-comb  | 4   | 2.8  |
| Oma                | 11  | 8.0  |
| GCS                | 6   | 4.3  |
| Other <sup>a</sup> | 6   | 4.3  |
| Total              | 138 | 100  |

Abbreviations: AH-comb, antihistamine combinations; fgAH, first generation H1 antihistamine; GCS, glucocorticosteroids; HD sgAH, higher-dose second-generation H1 antihistamine; LTRA-comb, leukotriene antagonist and antihistamine combinations; oma, omalizumab; SD-sgAH, standard-dose second-generation H1 antihistamine.

<sup>a</sup>Autologous whole blood injection, calcium.

indicated severe urticaria/angioedema and/or taking medications as main reasons for not breastfeeding. More than half of the patients who breastfed (i.e. 54.3%;  $n = 138/254$ ), used urticaria medication. Of these, 62% and 14% used SD-sgAHs and HD-sgAHs, respectively, whereas 8% received omalizumab (Table 5). Most patients who received treatment while breastfeeding ( $n = 138$ ; 54.4%), also did so while pregnant ( $n = 115/138$ ; 83.3%). Inversely, two thirds (66.5%) of the patients who received treatment during pregnancy also received treatment during breastfeeding.

## DISCUSSION

These new data from the PREG-CU study demonstrated that most pregnant CU patients need to treat their urticaria,

that antihistamines are the most commonly used medication, and that rates of preterm births and medical problems of newborns are similar to those of the normal population and not linked to treatment used during pregnancy.<sup>5-8</sup>

In addition, discontinuation of urticaria treatment is uncommon in patients planning to become pregnant. Interestingly, only one in five patients (20%) stopped their current urticaria treatment, including omalizumab, once the decision to become pregnant was made. Patients may be comfortable with becoming pregnant on their established treatment or they may fear an exacerbation of disease if they stop. Those who discontinued seem to have a suitable medication wash out period before becoming pregnant, that is longer than five medication half-lives (e.g. omalizumab =  $5 \times 26$  days).

In general, treatment approach in this study population was consistent with guideline-based management.<sup>1</sup> The stepwise algorithm of the guidelines recommends starting with a SD-sgAH, increasing the dose up to four-fold in non-responders, then switching to omalizumab in antihistamine-refractory patients. Guidelines suggest the same for pregnant patients: use of modern second-generation H1-antihistamines preferably loratadine with a possible extrapolation to desloratadine, cetirizine or levocetirizine. Similarly, in this population, we found that cetirizine and loratadine were the most commonly used antihistamines followed by levocetirizine and fexofenadine. Guidelines also suggest that the use of fgAH should be avoided given their sedative effects; but if these are to be given, it would be wise to know that the use of first-generation H1-antihistamines immediately before parturition could cause respiratory depression and other adverse effects in the neonate (the first-generation H1-antihistamines with the greatest safety in pregnancy are chlorpheniramine and diphenhydramine).<sup>1</sup> In our study, we observed that fgAHs were less commonly

discontinued by the patients and many of them preferred to continue using these treatments during pregnancy (7.6%). Regardless, sgAHs were the most preferred medication by the majority of the patients/physicians (35%).

We observed that once pregnant, patients' treatment approach became more conservative: only 13% continued to use HD-sgAH, 21% stopped and did not receive any treatment, and others changed mostly to SD-sgAH. Importantly, there are no reliable data demonstrating the safety of higher than standard doses of antihistamines during pregnancy and as discussed by the guidelines, the lack of safety studies on the use of HD-sgAH during pregnancy should be a matter of a careful risk: benefit discussion between patient and physician.<sup>1</sup>

We found that use of antihistamines during pregnancy whether standard or higher dose, even at the first trimester or last trimester, were not associated with preterm risk nor medical problems in the newborn; however, the rate of patients who used HD-sgAH was low ( $n = 16$ ).

Although we found preterm birth rate higher in patients who used omalizumab during pregnancy vs. those who did not, after adjusting for other variables (twins, emergency referral for CU, treatment of urticaria during the first trimester), there was no significant difference between the groups. One of the other confounders was emergency referral for CU during pregnancy which might reflect the severity of CU that led to preterm birth. Moreover, to date, in pregnant CU patients receiving omalizumab, there has been no evidence of increased adverse events nor teratogenicity associated with omalizumab exposure.<sup>9,10</sup> Notably, in the EXPECT trial of asthma patients, although the anomaly risk and preterm birth risks were found statistically similar between asthmatic patients who used omalizumab during pregnancy vs. the cohort who did not, the preterm risk was slightly higher in the omalizumab group (15% vs. 11.3%; NS). From 16 patients (~6%) who used omalizumab during pregnancy in the current study, four patients had preterm birth and among these, two used GCS along with omalizumab. This effect might be linked to GCS use which has been associated with increased risk of preterm birth.<sup>11</sup> Our data indicate that omalizumab can be considered as safe to use for severe CU cases during pregnancy in antihistamine-resistant patients, but further research is needed in order to establish this information.

In this study, outcomes of pregnancy in CU patients were similar to the general population. Overall, the preterm birth rate of the general population is ~10% (12%, 9.4% and 9.3% for low-, middle- and high-income countries)<sup>5</sup> which is similar to our findings in pregnant women with CU. The preterm birth rate (10.2%) we found in CU patients was not as high as reported for autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.<sup>12</sup> However, it was also not low as reported for patients with atopic diseases such as atopic dermatitis or allergic rhinitis.<sup>13</sup>

In this study, emergency referrals for CU and twin birth were risk factors for preterm birth. Importantly, 40% of

patients who had emergency referrals for CU were on treatment with standard dose of antihistamines which may reflect that undertreated CU patients might have increased emergency referrals and as a result might experience preterm births. Physicians and/or patients might have been hesitant to up-dose antihistamines during pregnancy which results in urticaria exacerbations.

Fewer than 10% of newborns from mothers with CU had medical problems at birth; the most common was respiratory distress syndrome (RDS) with a 4.5% frequency which is similar to that found in the general population (3%–7%).<sup>6,7</sup> Newborns of mothers receiving urticaria treatment demonstrated a similar rate of medical problems compared with those who did not. The NICU admission rate for infants of CU patients was lower than the general population (4.5% vs. 10.9%–14.5%).<sup>8</sup> The caesarean section (C/S) rate in this study population was high compared with the global C/S rate which has been reported as 18.6% worldwide.<sup>14</sup> In paired analysis, the variables that were linked to C/S were the mother's age at pregnancy and comorbidities accompanying CU such as thyroid disease, asthma and hypertension. In the multivariate analysis, the only risk factor was mother's age at pregnancy. The high C/S delivery rate in CU pregnancies might be linked to the high rate of comorbidities in CU patients more broadly.

This study has limitations. This was a retrospective analysis which might include recall bias. We did not have the data on low birth weight or small for gestational age, nor did we include data on miscarriage. Disease activity or severity during pregnancy and after birth were not monitored. Data on other risk factors for pregnancy outcomes such as mothers' BMI, alcohol and tobacco use during pregnancy were not assessed. We believe prospective studies of pregnant CU patients which evaluate patients during pregnancy with the defined patient reported outcome tools is needed.

## CONCLUSIONS

Most CU patients use treatment during pregnancy and such treatments especially SG-AHs seems to be safe during pregnancy regardless of the trimester. The outcomes of pregnancy in patients with CU were similar compared with the general population and not linked to treatment used during pregnancy. Notably, emergency referral for CU was an independent risk factor for preterm birth. Caesarean delivery rate was high in CU patients probably linked to comorbidities associated with the disease. Overall, these findings suggest that patients should continue their treatments using an individualized dose to provide optimal symptom control.

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### CONFLICT OF INTEREST

Dr. Kocatürk reports personal fees from Novartis, İbrahim Etem-Menarini and Sanofi, outside the submitted work. Dr. Al-Ahmad has received speaker fees from Novartis, AstraZeneca and Sanofi. Dr. Şavk, Dr. Daniylcheva, Dr. Godse, Dr. Khoshkhui, Dr. Gelincik, Dr. Değirmen-tepe, Dr. Demir, Dr. Kasperska-Zajac, Dr. Rudenko, Dr. Valle, Dr. Medina, Dr. Zhao and Dr. Baygul have nothing to disclose. Dr. Krause is or recently was a speaker and/or advisor for, and/or has received research funding from Berlin Chemie, Novartis and Takeda, outside the submitted work. Dr. Giménez-Arnau has held roles as a Medical Advisor for Sanofi, Uriach, Genentech, Novartis, Amgen, ThermoFisher, Roche, Almirall and has research grants supported by Instituto Carlos III/FEDER, Novartis and Uriach; she also participates in educational activities for Almirall, Genentech, Glaxo SmithKline, LEO Pharma, Menarini, MSD, Novartis, Sanofi, Avene and Uriach. Dr. Fomina is or recently was a speaker and/or advisor for, and/or has received research funding from: AstraZeneca, CSL Behring, Glaxo SmithKline, MSD, Novartis, Sanofi and Shire/Takeda. Dr. Thomsen reports grants and other from Novartis outside the submitted work, Dr. Conlon reports grants from Novartis, grants from Takeda, outside the submitted work, Dr. Marsland reports grants and personal fees from Novartis, personal fees from Roche, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Galderma, personal fees from Almirall, outside the submitted work; Dr. Criado reports personal fees from Takeda Novartis, Abbvie, and Sanofi outside the submitted work, Dr. Ensina reports personal fees from NOVARTIS, personal fees and non-financial support from SANOFI, outside the submitted work, Dr. Bauer is or recently was a speaker and/or advisor for, and/or has received research funding from Novartis, Genentech, Leo Pharma, Sanofi, Regeneron, Shire, Takeda, Amgen, AstraZeneca, Abbvie, Celldex, Lilly, Pharvaris, Almirall and Biofrontera, Dr. Staubach reports grants, personal fees, and non-financial support from Novartis, personal fees from Dr Pflieger, personal fees from Sanofi, outside the submitted work, Dr. Bouillet reports grants and non-financial support from Novartis, grants, personal fees and non-financial support from Takeda, grants and non-financial support from CSL Behring, non-financial support from PHARMING, non-financial support from GSK, outside the submitted work. Dr. Su Küçük reports personal fees from Novartis, İbrahim Etem-Menarini and Sanofi, Dr. Mauer reports grants and personal fees from Allakos, grants from Amgen, personal fees from Aralez, grants and personal fees from ArgenX, grants from AstraZeneca, personal fees from Celldex, grants and personal fees from CSL Behring, grants and personal fees from FAES, grants and personal fees from Genentech,

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### DATA AVAILABILITY STATEMENT

Data are openly available in a public repository that issues datasets with DOIs.

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