Effects of pregnancy on chronic urticaria: Results of the PREG-CU UCARE study

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Key words:
Breastfeeding, disease activity, hormones, pregnancy, urticaria

Short running title: Urticaria during pregnancy

Acknowledgements

We thank Laura Schwenner for providing networking between participant UCARE Centers and the project coordinators.

Abstract

Background: Chronic urticaria (CU) predominantly affects women, and sex hormones can modulate disease activity in female CU patients. As of now, the impact of pregnancy on CU is largely unknown.

Aim: To analyse the course and features of CU during and after pregnancy.

Patients and methods: PREG-CU is an international, multicentre study of the Urticaria Centers of Reference and Excellence (UCARE) network. Data were collected via a 47-item-questionnaire completed by CU patients, who became pregnant within the last 3 years.

Results: A total of 288 pregnancies of 288 CU patients from 13 countries were analysed (mean age at pregnancy: 32.1 ± 6.1 years, duration of CU: 84.9 ±74.5 months; CSU 66.9%, CSU+CIndU 20.3%, CIndU 12.8%). During pregnancy, 51.1% of patients rated their CU as improved, 28.9% as worse, and 20.0% as unchanged. CU exacerbations most commonly occurred exclusively during the third trimester (in 34 of 124 patients; 27.6%) or the first (28 of 124; 22.8%). The risk factors for worsening of CU during pregnancy were having mild disease and no angioedema before pregnancy, not taking treatment before pregnancy, CIndU, CU worsening during a previous pregnancy, treatment during pregnancy and stress as a driver of exacerbations. After giving birth, urticaria disease activity remained unchanged in 43.8% of CU patients, whereas 37.4% and 18.1% experienced worsening and improvement, respectively.

Conclusions: These results demonstrate the complex impact of pregnancy on the course of CU and help to better counsel patients who want to become pregnant and to manage CU during pregnancy.

Introduction

Chronic urticaria (CU) is an inflammatory disease characterized by the appearance of wheals, angioedema, or both for longer than 6 weeks. CU is classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), where signs and symptoms occur in response to definite triggering factors such as cold in cold urticaria and perspiration-inducing activities in cholinergic urticaria (1). CSU is more common in females than males as confirmed by a recent systematic review and metaanalysis of the available epidemiological data, which showed that the point prevalence of CSU is 1.3% in women versus 0.8% in men (2). CIndUs are also more common in females, with a female:male ratio of 2:1 to 3:1 (3). In a study from China, women, across all CindUs, accounted for 58% of patients, with higher rates in some CIndUs, cold urticaria for example, where 66% of patients were female (4). The reasons for this female preponderance in CU are currently unknown and subject of ongoing investigations, but several points are important in this context. First, it is well known that autoimmune diseases are more common in women, with female:male ratios of 3:1 for multiple sclerosis and 15:1 for autoimmune thyroiditis, for example (5). It is now widely accepted that autoantibodies and their activating effects on skin mast cells play a major role in the pathogenesis of CU. In CSU, two types of underlying autoimmunity are postulated; type I autoimmunity (also called autoallergy) with IgE autoantibodies against autoallergens and type IIb autoimmunity with stimulatory IgG and IgM autoantibodies to receptors on mast cells (6). This is supported by the common association of CSU with autoimmune diseases, which has been reported in many studies (7). Second, mast cells, the key drivers of CU pathogenesis, express hormone receptors, and sex hormones can influence mast cell functions including their activation and release of proinflammatory mediators. Estrogens increase histamine release in rat mast cells and sensitized human basophils upon stimulation with anti-IgE (8). Progesterone and testosterone inhibit mast cell secretion, and progesterone was shown to inhibit histamine release from peripheral basophils of urticaria patients (9). The fact that sex-specific differences in the prevalence of CU are only seen after puberty and before menopause supports a role of sex hormones in the pathogenesis of the disease (2).

Being female not only comes with an increased risk of getting CSU, it also affects the course of CSU. Female patients with CU have been reported to experience higher disease activity, higher rates of angioedema, poorer prognosis, longer time to remission, impaired response to treatment with antihistamines and omalizumab, and more frequent association with thyroid autoimmunity, autologous serum skin test positivity and basophil activation test positivity as compared to male patients (10-17).

Against this background, it is important to explore the effects of pregnancy on CU. Women with CU frequently have concerns about becoming pregnant and ask their physicians about the risk of their disease getting worse during pregnancy or requiring additional medication. Answers to these questions are largely lacking in the literature. In a small study from France, pregnancy was linked to increased disease activity in four of 16 patients (18).

To address the gap of knowledge on the course and management of CU during pregnancy, the network of Urticaria Centers of Reference and Excellence (UCARE) (19) performed the PREG-CU study. Here, we report on the results of this study that relate to the impact of pregnancy on CU, the course of CU across pregnancy, CU treatment during pregnancy and changes of CU after pregnancy. The PREG-CU study also explored possible effects of CU on the course and outcome of pregnancy. The analysis of these results is ongoing and will be reported in a subsequent publication.

Materials and Methods

Study design

PREG-CU is a prospective, international, multicenter, observational (non-interventional) UCARE study. It included CU patients treated at member centers of the UCARE network. The study started in April of 2018 and ended in September of 2019. Ethics approval was obtained by the coordinating center, Okmeydanı Training and Research Hospital (date: 09.01.2018 number: 809), and by each participating center as required. Written informed consent was obtained from all participants.

The PREG-CU questionnaire

The aims and scope of the project were defined by the PREG-CU steering committee, which also developed the draft version of the PREG-CU questionnaire. The draft version of the questionnaire was then tested in CU patients at the UCAREs of the steering committee members. Following this, the final version of the questionnaire was developed based on the results of the pilot study and was then translated into the languages of participating countries. The questionnaire included 47 questions about the severity of CU before pregnancy, treatments before pregnancy, treatments received during pregnancy, the trimesters of pregnancy during which the treatments were received, ameliorations or deteriorations in CU, the trimesters in which the ameliorations/deteriorations were observed, emergency referrals, outcomes of pregnancy, presence of angioedema during pregnancy, the course of urticaria and treatments given during breastfeeding (Appendix 1).

Study participants

The PREG-CU questionnaire was distributed to CU patients treated at 21 UCAREs in 13 countries (Appendix 2). Inclusion criteria were as follows: 1) female patients diagnosed by the treating physician as CSU, CIndU or both, 2) pregnancy during the last three years before the study visit, and 3) CU started before pregnancy.

The PREG-CU study analyzed a total of 288 pregnancies, 40.3% of them first pregnancies, of 288 CU patients. Of them, 245 patients had CSU and 93 patients had CIndU (57 had both, 6 had missing data). The mean age of patients was 33.6 ± 5.9 years, their mean age at pregnancy was 32.1 ± 5.6 years, and the mean duration of their CU was 84.9 ±74.5 months. Other demographic data are given in Table 1.

Data analysis

Data were summarized as mean ± standard deviation and median (min.-max.) for continuous variables, frequencies (percentiles) for categorical variables. Student's t test or Mann Whitney U test was used for independent group comparisons, depending on the distributional properties of the data. Chi-square test was used for proportions and Fisher's Exact test was used when the data were sparse. Univariate and multiple logistic regression (LR) analysis were performed to examine risk factors for worsening of the disease during pregnancy. First, univariate LR analysis was performed to examine the factors that are

suspected to increase the risk of worsening in pregnancy. Then, a multiple model was established with variables found to be significant in the univariate analysis results, and risk factors were evaluated using Backward LR elimination method. All analyses were performed IBM SPSS Statistics for Windows, Version 20.0. A p value <0.05 was considered as statistically significant.

Results

Changes and characteristics of chronic urticaria during pregnancy

Chronic urticaria, during pregnancy, more often gets better than it gets worse than it remains unchanged

Most patients rated their CU disease activity, before pregnancy, as mild (35.7%, n=96), moderate (34.2%, n=92) or severe (29.7%, n=80). During pregnancy, 51.1% of patients (n=143) rated their CU as improved, 28.9% (n=81) as worse and 20.0% (n=56) as unchanged (Table 2).

Of the patients who experienced improvement after becoming pregnant, disease activity was decreased during the entire pregnancy in 51 patients (34.5%). In 25.7%, 16.2% and 13.5% of patients, disease activity improved exclusively during the first, the second, and the last two trimesters, respectively.

CU exacerbations most often occur during the first and third trimester

Of 288 patients, 124 (43.5%) experienced exacerbations of their CU during pregnancy. CU exacerbations occurred most commonly exclusively in the third trimester (34 of 124; 27.6%) or in the first trimester (28 of 124; 22.8%). Less commonly, exacerbations occurred during the second trimester only (13 of 124; 10.6%), during the second and third (12 of 124; 9.8%), during the first and second (8 of 124; 6.5%) and during the first and third (4 of 124; 3.3%) trimesters. In 24 of 124 patients (19.5%), episodes of exacerbations occurred across the entire duration of their pregnancies.

One in ten pregnant CU patients requires urticaria emergency care

A total of 28 of 288 (9.8%) women attended an emergency department during their pregnancy because of their CU, 13 of them once, 7 twice, and 8 patients three times or more. Emergency department visits were most common in the third trimester (14 patients) followed by the first and second trimester (11 and 7 patients, respectively).

One of six women with CU has angioedema during pregnancy

Four of ten patients with CU (110 of 288; 38.2%) had experienced angioedema before they became pregnant, and 50 of them (45.5%, corresponding to 17.4% overall) experienced angioedema during their pregnancy. Of those 50 patients, 11, 7, and 8 had angioedema exclusively during the first, second, and third trimester, respectively, and 8 patients developed angioedema in all trimesters. Seven (4.1%) of the 178 patients without angioedema before pregnancy developed angioedema during their pregnancy.

Risk factors and drivers of CU worsening during pregnancy

The factors that were evaluated as possible contributors to the worsening of CU during pregnancy are presented at Table 3.

CU patients with low disease activity and angioedema before pregnancy are at increased risk of CU worsening during pregnancy

CU worsening occurred in 42.7% patients who had mild disease before pregnancy, more often than in those with moderate (25.3%) or severe (36.3%) disease ($p<0.001$). Mild/moderate CU disease activity before pregnancy was linked to a 2.8-folds increased risk of worsening during pregnancy as compared to having severe disease ($p<0.001$). Mild disease activity increased the risk of worsening by 3.0-folds compared to moderate/severe disease activity ($p<0.001$), as assessed by univariate LR analyses. Having no angioedema before pregnancy was linked to higher rates of CU worsening during pregnancy, twice as high as compared to those in patients with angioedema before pregnancy (35.2% versus 17.6%; $p=0.002$). Having no angioedema before pregnancy increased the risk of CU worsening during pregnancy 2.5 folds ($p=0.002$; univariate LR analyses).

CU treatment is linked to changes of CU during pregnancy

Only 28 of 288 patients were not on CU treatment before they became pregnant, and they showed a higher rate of CU worsening (69.2%) than patients who were (33%; $p=0.014$). Having no treatment before pregnancy was associated with a 2.8 folds risk of getting worse during pregnancy ($p=0.037$; univariate LR analyses).

During pregnancy, 173 (60.7%) of patients received treatment, whereas 112 (39.3%) did not. Half of the patients (49.6%) who received treatment got worse during pregnancy as compared to 13.8% who did not ($p<0.001$). Receiving treatment during pregnancy was

associated with a 5-folds increased risk of getting worse during pregnancy ($p<0.001$; univariate LR analyses)

CIndU is a risk factor for CU worsening during pregnancy

Patients with CIndU or CSU plus CIndU had a 2.0 folds increased risk of getting worse during pregnancy ($p=0.027$, univariate LR analysis).

Changes in CU disease activity during pregnancy are linked across pregnancies

Eighty-nine (31.4%) patients had CU during a previous pregnancy, with 28 (31.4%), 19 (21.3%) and 24 (26.9%) patients, respectively, reporting improvement, worsening and no change in their disease activity during that previous pregnancy. Changes in CU activity were linked across pregnancies: 27 of 28 patients (96.4%) with CU improvement during their previous pregnancy also improved during the next, and 12 of 19 patients (63.2%) who had worsening of their CU during the previous pregnancy also got worse during the next (Table 4). Worsening of CU during a previous pregnancy was associated with a 4.9 folds increased risk of getting worse during the current pregnancy ($p=0.001$; univariate LR analyses).

Changes in CU activity during the menstrual cycle are not linked to changes during pregnancy

Most patients (74%, 205 of 288), before their pregnancy, had not experienced changes in CU disease activity linked to their menstrual cycle. In the 61 of 72 (84.7%) women who did, CU exacerbations occurred during the premenstrual period (n = 34, 12.3%), during menstruation (n = 11, 4%), or both (n = 16, 5.8%). Overall, patients with and without changes of CU activity linked to their menstrual cycle showed similar rates of exacerbations during pregnancy (42.5% versus 43.7%; $p = 0.86$; Table 5).

Stress is a common driver of exacerbations during pregnancy

Of 124 patients with exacerbations during pregnancy, 114 provided information on what triggered these exacerbations. Stress was the most common reason for exacerbations, in 30.7% of patients, followed by discontinuation of treatment, in 14% of patients. All other reasons, including infections and the use of medications, were reported to drive exacerbations by less than 5% of patients each (Table 3).

Having mild disease before pregnancy and receiving treatment during pregnancy are independent and relevant risk factors for CU worsening during pregnancy

Next, we assessed the risk factors for CU worsening during pregnancy that were identified by univariate LR analyses, i.e. mild disease, angioedema, CIndU, worsening during the previous pregnancy, and treatment, by multiple regression analysis. This identified mild disease before pregnancy (OR 3.5; p=0.001) and treatment during pregnancy (OR 5.5; p=0.001) as independent, relevant and significant risk factors for worsening of CU during pregnancy (Fig 1).

Urticaria disease activity stays the same or worsens in the majority of CU patients after giving birth

After having given birth, 116 (43.8%) patients rated their CU as unchanged, 81 (37.4%) as worse and 48 (18.1%) as improved. Of the patients whose urticaria improved during pregnancy, 50% experienced worsening after giving birth, whereas 33.6% and 16.4% reported no change and further improvement, respectively (p <0.001). Patients with CU worsening during pregnancy showed no change of their disease activity after giving birth in 52% of cases, improvement in 26%, and further worsening in 22.1% (p=0.002).

Discussion

PREG-CU is the first multicenter study of chronic urticaria (CU) during pregnancy. Our findings demonstrate that patients more often experience CU improvement than worsening, but that exacerbations are common, especially during the first and last trimester and can lead to ER visits. Importantly, we identified, for the first time, features and risk factors linked to CU exacerbation during pregnancy, such as mild disease and no angioedema before pregnancy, not taking treatment before pregnancy, CIndU, CU worsening during a previous pregnancy , treatment during pregnancy and stress as a driver of exacerbation. These findings can help to improve the care of CU patients who want to become pregnant and those who are. They also raise interesting questions that need to be addressed by future research.

Why does CU, during pregnancy, more often get better than not? More than half of our patients' CU improved during pregnancy. It is tempting to speculate that the unique immunological changes linked to pregnancy affect the pathogenesis of CU. Pregnancy is characterized by immune tolerance mechanisms that aim to protect the fetus and placenta from being attacked by the maternal immune system as "foreign." Regulatory T cells play a central role in mediating this tolerance, by inhibiting type 1 and type 17 immunity (20). Successful pregnancy outcome has been related to these effects of regulatory T cells and decreased Th1 and Th17 responses. Together with the hormonal changes during pregnancy that favor a switch to Th2-type cytokine profiles, this is held to explain, at least in part, the ameliorating effects of pregnancy observed in several autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, and psoriasis (21). CSU, in a sizeable subpopulation of patients, is an autoimmune disease, with mast cell-activating IgG autoantibodies that drive the development of its signs and symptoms. Patients with this CSU subtype can be expected to benefit from the immunological changes linked to pregnancy. Our findings provide circumstantial evidence that this may, indeed, be the case. Autoimmune CSU is more prevalent in women than in men, so our patient population is, *a priori*, enriched for patients with autoimmune CSU. Up to 38 percent of women as compared to 13 % of men with CSU, for example, are reported to have a positive basophil test, a hall mark feature of autoimmune CSU (17).

Autoimmune CSU is characterized, among other features, by high disease activity (22), which we found to be linked to higher rates of decreased disease activity during pregnancy, whereas patients with mild disease before becoming pregnant, a feature of non-autoimmune CSU (23), showed higher rates of worsening during pregnancy. That, exacerbations of CU during pregnancy as well as emergency referrals and angioedema attacks were least common during the second trimester, when Th2 skewing is strongest, also supports this notion (24). Along these lines, patients with autoallergic CSU, where IgE autoantibodies drive skin mast cell activation and disease activity, may be expected to be more likely to experience increased disease activity during pregnancy, when immunity is skewed towards Th2. Our study did not assess patients for biological or clinical markers of autoimmune CSU such as a positive basophil test, low IgE levels, or autoimmune comorbidities (6). This should also be explored in future studies, by comparing patients with features of autoallergic CSU such as IgE autoantibodies to thyroid peroxidase or interleukin-24 to those without, with respect to the course of their pregnancies to test the hypothesis that patients with autoimmune CSU show higher rates of improvement during pregnancy as compared to patients with other subtypes of CSU ie the autoallergic subtype.

That one in ten pregnant CU patients requires urticaria emergency care and that one of six women with CU has angioedema during pregnancy are among the most important findings of our study, for two reasons. First, these rates are lower than those previously reported for non-pregnant CU patients. In two recent multicenter studies with sizeable numbers of patients, ASSURE and AWARE, 14.8% and 33.5% of patients required emergency care, as compared to 9.8% in our study. Rates for angioedema of up to 70% have been reported in CU and were 40.3% in ASSURE (25) and 45% in AWARE (26), as compared to 17.4% in our study. These findings support the notion that pregnancy, overall, ameliorates CU disease activity. Knowledge of risk factors for emergency care and the rate of patients affected by severe exacerbations and angioedema can help to guide better management and strategies to prevent these events.

What are the risk factors of CU worsening during pregnancy? Our study identified six such factors. Unexpectedly, we identified mild disease and having no angioedema before pregnancy as risk factors for CU worsening during pregnancy, possibly because patients with already severe disease activity are less likely to experience an increase in signs and symptoms as worsening of their disease, a ceiling effect. The more likely explanation is that

patients with already high disease activity are more likely to experience improvement as demonstrated by our results. The third risk factor, no CU treatment before pregnancy, is probably linked to the first two. Patients with mild disease and no angioedema can be expected to be more likely to receive no treatment. The fourth factor; having CIndU is also linked to worsening during pregnancy, and doubles the risk. The fifth risk factor for worsening of CU is increased disease activity during a previous pregnancy. Almost two thirds of patients who had worsening of their CU during a previous pregnancy also got worse during the one investigated in our study. This is in line with a previous report by Gluck and coworkers on patients with asthma (28) where the effects of pregnancy also tended to be consistent across successive gestations, and 9 of 10 patients in our study had improved disease during a previous pregnancy and the current one. Receiving treatment during pregnancy was the sixth and strongest "risk factor" for worsening of disease during pregnancy, but should rather be seen as a consequence of worsening rather than a driver; the worse the disease, the more treatment is needed. As for drivers of CU exacerbation, stress is an important one, and this comes as no surprise as stress is also a risk factor for CU exacerbation outside of pregnancy and pregnancy is linked to higher levels of stress (27). Importantly, our multivariate regression analyses identified both mild disease before pregnancy and treatment during pregnancy as independent and relevant risk factors linked to worsening of CU during pregnancy.

What are the implications of this for clinical practice? Patients who want to become pregnant and have mild disease and no angioedema, are not on CU treatment, have CIndU, or had worsening of their CU during a previous pregnancy may be advised to seek expert help and treatment right at the start of their pregnancy, to avoid loss of disease control, worsening and exacerbations including emergency room visits. The fact that patients who received treatment during pregnancy more often had worsening of CU as compared to patients who did not receive treatment for CU during pregnancy should not be an argument to not treat. Patients who received treatment during pregnancy are likely to be the ones with higher disease activity to begin with and were probably receiving treatment because of worsening of their disease rather than vice versa.

What could explain the observed changes in urticaria disease activity after giving birth? Half of the patients who improved during pregnancy experienced worsening after giving birth, and half of the patients who experienced worsening of their disease during

pregnancy got better after giving birth. In the post-partum period, Th2 skewing subsides, and Th1 and Th17 autoimmune disorders tend to get worse, whereas Th2-driven disorders tend to improve (29). It is possible that patients with Th1/Th17-driven CU are more likely to experience increased disease activity after birth, whereas CU patients with Th2-linked autoallergic CU show improvement. This hypothesis should be tested in future studies.

In conclusion, CU, during pregnancy, more often gets better than it gets worse than it remains unchanged. The fact that most patients with CU, and especially those with severe CU, experience improvement of their disease, is good news and should be communicated to patients who want to become pregnant. On the other hand, three of ten CU patients must expect that their disease will get worse, especially during the beginning and end of their pregnancy. Prospective studies are needed to test the relevance and reliability of the predictors for CU worsening during pregnancy identified by our study.

Table legends

Table 1. Demographic characteristics of the patients

Table 2: Disease activity changes during pregnancy

Table 3: Factors that affect worsening of cu during pregnancy

Table 4. Effect of previous pregnancy on worsening of urticaria during pregnancy

Table 5: Effect of premenstrual flare ups on cu activity during pregnancy

Figure legends

Figure 1: Forest plot showing univariate and multiple logistic regression analysis results for the factors that contribute to worsening of CU during pregnancy

Appendix 1: The PREG-CU Questionnaire

Appendix 2: List of participating centers and number of patients recruited to the PREG-CU

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS			
		n	**%**
Diagnosis (n=281)	CSU	188	66.9
	CIndU	36	12.8
	CSU+CIndU	57	20.3
Stop medications before conception (n=280)	No	185	66.1
	Yes	38	13.6
	Taking on demand	57	20.4
Severity before pregnancy (n=269)	No symptoms	1	0.4
	Mild	96	35.7
	Moderate	92	34.2
	Severe	80	29.7
Comorbidities (n=279)	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
	Asthma + thyroid disease	1	0.3
Other treatments (n=271)	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

CSU: Chronic spontaneous urticaria CIndU: Chronic inducible urticaria

High risk diseases: hypertension plus diabetes mellitus, hypertension plus antiphospholipid antibody syndrome, hereditary angioedema, angina, Graves plus mitral valve prolapses

TABLE 2: DISEASE ACTIVITY CHANGES DURING PREGNANCY

		n	%
Exacerbation during pregnancy (n=285)	No Yes	161 124	56.5% 43.5%
Reason for exacerbation (n=114)	Medication Infection Stres Stopping medication Others	3 4 35 16 56	2.6% 3.5% 30.7% 14.0% 49.1%
Improvement during pregnancy (n=278)	No Yes	130 148	46.8% 53.2%
Improvement trimester	First trimester Second trimester Third trimester 1st+3rd trimester 1st+2nd trimester 2nd+3rd trimester 1st+2nd+3rd trimester	38 24 11 0 4 20 51	25.7% 16.2% 7.4% 0.0% 2.7% 13.5% 34.5%
Emergency (n=286)	No Yes	258 28	90.2% 9.8%
Number of emergency referrals (n=28)	Once Twice More than Thrice	13 7 8	46.4% 25.0% 28.6%
Emergency referrals trimester (n=26)	First trimester Second trimester Third trimester 1st+3rd trimester 1st+2nd trimester 2nd+3rd trimester 1st+2nd+3rd trimester	9 2 9 1 1 4 0	34.6% 7.7% 34.6% 3.8% 3.8% 15.4% 0.0%
AE before pregnancy (n=280)	No Yes	170 110	60.7% 39.3%
AE during pregnancy (n=283)	No Yes	233 50	82.3% 17.7%
Angioedema trimester	First trimester Second trimester Third trimester 1st+3rd trimester 1st+2nd trimester 2nd+3rd trimester 1st+2nd+3rd trimester	11 7 8 2 8 4 7	23.4% 14.9% 17.0% 4.3% 17.0% 8.5% 14.9%
Overall rating of pregnancy (n=280)	Got better Got worse No change	143 81 56	51.1% 28.9% 20.0%
After birth (n=265)	Ameliorated Worsened Stayed the same It started after a while Disappeared completely	48 99 116 1 1	18.1% 37.4% 43.8% 0.4% 0.4%

AE: Angioedema

TABLE 3: FACTORS THAT EFFECT WORSENING OF CU DURING PREGNANCY			
		Worsening of CU	**p**
Severity	Mild	41 (42.7)	**<0.001**
	Moderate	23 (25.3)	
	Severe	29 (36.3)	
Treatment before pregnancy	Standard-dose H1-AH	35 (28.9)	0.427
	High-dose or combination H1-AH incl. LTRA	25 (30.1)	
	Omalizumab	5 (14.7)	
	Cyclosporine	0 (0)	
	Systemic steroid	2 (15.4)	
Angiodema before pregnancy	Yes	19 (17.6)	**0.002**
	No	58 (35.2)	
Diagnosis	CSU	58 (32)	
	CIndU	7 (20)	0.115
	CSU+CIndU	11 (20)	
Treatment during pregnancy	Yes	67 (39.2)	**<0.001**
	No	12 (11.3)	
Comorbidities	Thyroid disease	15 (34.1)	0.375
	Hypertension	1 (14.3)	
	Asthma	4 (44.4)	
	Diabetes mellitus	4 (57.1)	
	Preeclampsia or high risk pregnancy	1 (33.3)	
	High risk diseases	2 (33.3)	
	Others	2 (11.8)	
Other Treatments	Thyroid drugs	9 (39.1)	0.075
	Vitamins	6 (27.3)	
	Oral antidiabetics or insulin	4 (100)	
	Antihipertensives	1 (33.3)	
	Steroid inhaler, steroid drops	2 (50)	
	Proton pump inhibitors	0 (0)	
	Hormones	2 (100)	
	Antibiotics	0 (0)	
	Others	3 (27.3)	
Sexuality	Female	39 (28.5)	1.000
	Male	37 (28.7)	
Twins	Yes	1 (25.0)	1.000
	No	75 (28.6)	

CSU: Chronic spontaneous urticaria, CIndU: Chronic inducible urticaria, H1-AH: H1-antihistamines, LTRA: Leukotriene antagonists, High risk diseases: hypertension plus diabetes

mellitus, hypertension plus antiphospholipid antibody syndrome, hereditary angioedema, angina, Graves plus mitral valve prolapses

TABLE 4. EFFECT OF PREVIOUS PREGNANCY ON WORSENING OF URTICARIA DURING PREGNANCY

		Worsening of CU	p
This is my first pregnancy	n	28	**0.001***
	%	25.2	
I did not have chronic urticaria during my previous pregnancies	n	25	
	%	32.5	
Chronic urticaria got better during my previous pregnancies	n	1	
	%	3.6	
Chronic urticaria got worse during my previous pregnancies	n	12	
	%	63.2	
Chronic urticaria did not change during my previous pregnanciesI don't remember	n	7	
	%	29.2	
I don't remember	n	6	
	%	42.9	
Other	n	1	
	%	25.0	

*Fisher's exact P value

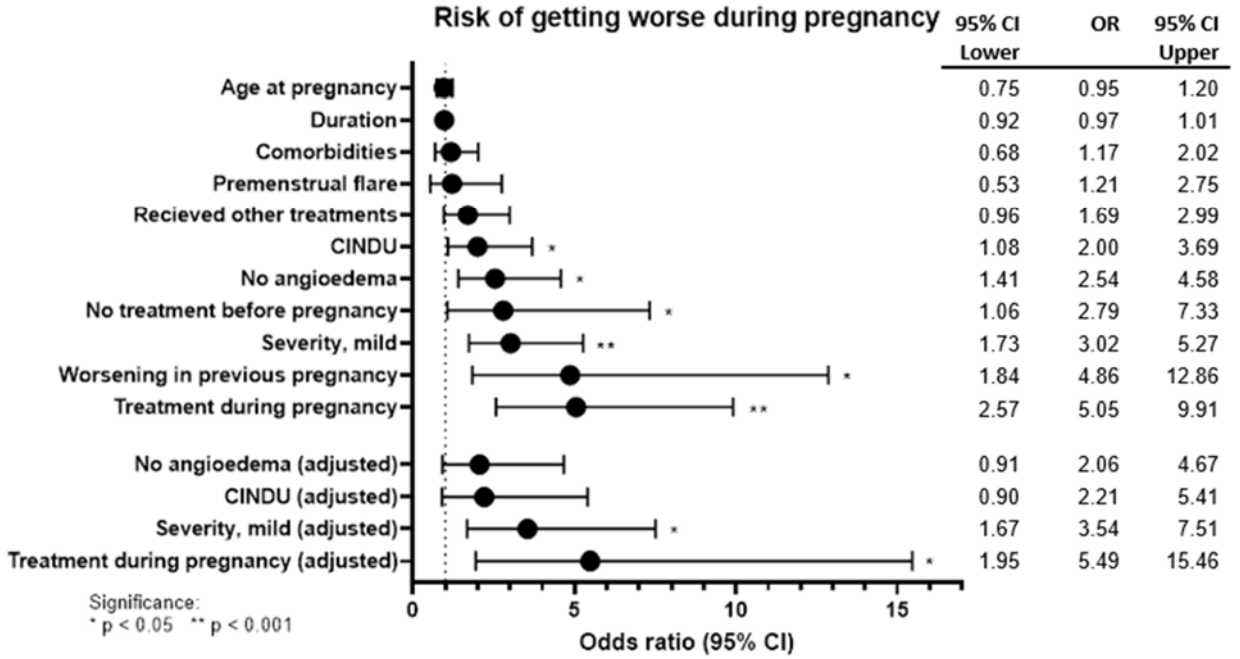
TABLE 5: EFFECT OF PREMENSTRUAL FLARE UPS ON CU ACTIVITY DURING PREGNANCY

		PMS (n,%)	No Change (n,%)	p
Exacerbations	Yes	14 (14.1)	85 (85.9)	1.000
	No	20 (14.5)	118 (85.5)	
Exacerbation Trimester	First trimester	6 (28.6)	15 (71.4)	0.132*
	Second trimester	0 (0.0)	11 (100.0)	
	Third trimester	3(10.3)	26 (89.7)	
	1st+3rd trimester	0 (0.0)	3 (100.0)	
	1st+2nd trimester	2 (40.0)	3 (60.0)	
	2nd+3rd trimester	0 (0.0)	9 (100.0)	
	1st+2nd+3rd trimester	3 (15.0)	17 (85.0)	
Overall	Got Better	22 (18.5)	97 (81.5)	0.140
	Got Worse	9 (12.9)	61 (87.1)	
	No Change	3 (6.5)	43 (93.5)	
Got Worse	Yes	9 (12.9)	61 (87.1)	0.692
	No	25 (15.2)	140 (84.8)	

PMS: Increased disease activity during premenstrual periods

*Fisher's exact P value

Figure 1: Forest plot showing univariate and multiple logistic regression analysis results for the factors that contribute to worsening of CU during pregnancy



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