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Case Report

Pregnancy Outcomes of Patients with Asthma under Omalizumab Treatment: Case Report of a Country based Experience on 22 Pregnancies and 23 Infants

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Abstract

A prospective multicenter study reported safety of omalizumab in pregnant asthmatics. However, real life data about

the topic is scarce. Therefore, we aimed to report outcomes of pregnant patients with asthma under omalizumab treatment and their infants in our county. Patients with asthma who received omalizumab for at least 6 months and at least one dose during their pregnancy were retrospectively evaluated using a questionnaire regarding their demographic features, disease- and therapy-related parameters, and the health of their infants. 20 pregnant patients and their 23 infant's data were analyzed. The mean delivery age was 31.8 ± 7.4 years. They received omalizumab for 28.9 ± 21.8 months. Eight (36.4%) patients showed exacerbation of the disease during pregnancy. Forced expiratory volume in 1 second (FEV1) and asthma control test (ACT) scores at the starting time of omalizumab administration, first month of the pregnancy, and after delivery were 71 ± 18%, 83.4 ± 10.5%, and 80.5 ± 13% (FEV1), and 11.9 ± 4.9, 20.2 ± 2.6, and 20.4 ± 2.2 (ACT), respectively.

One patient gave birth to twin infants, two patients to two infants each, and 17 to one infant each. Infant exposure to omalizumab was only one dose (300 mg omalizumab) for the twins, the first trimester for one infant, second and third trimester for four infants, and during all pregnancy and breastfeeding periods for 16 infants. Three (13%) infants had low birth weight and five (21.7%) were born prematurely. No congenital anomalies were detected. Seven (30.4%) infants presented atopic diseases during their life. Omalizumab treatment during pregnancy seems to be safe for both patients and their infants.

Keywords: ACT; Exacerbation; Gestation; Case study; Prematurity; Spirometry

1. Introduction

Asthma affects 330 million individuals worldwide and around 4 million in Turkey [1, 2]. This disease has been reported in 8% of pregnant individuals [3, 4]. The health condition of one-third of pregnant patients with asthma is not affected by the physiological, hormonal, and immune changes that occur during the gestation period, one-third shows improvement, and one-third shows progression and ingravescence [3, 4]. There are sufficient data concerning the continuation of satisfactory asthma control during pregnancy, and, therefore, appropriate asthma treatment for pregnant women with asthma to deliver a healthy infant [5]. In this context, many reports on omalizumab, which is used by severe allergic asthma patients during pregnancy, have been published [6, 7]. The Observational Study of the Use and Safety of Xolair® (omalizumab) during pregnancy (EXPECT), the largest prospective study on this subject, which has examined 228 pregnant women and 233 infants, identified a birth anomaly rate of 8.1% and preterm delivery rate of 15%. These rates are not different from the outcomes of the Quebec External Comparator Cohort (QECC) study, which involves the most extensive overall cohort of pregnant women with asthma [6].

In addition, in EXPECT vs. QECC, there was a lower rate of small for gestational age (SGA) infants of mothers receiving omalizumab (9.7% vs. 15.8%) [6]. In contrast, in the position paper of the European Academy of Allergy and Clinical Immunology (EAACI) Society regarding the administration of biological drugs for allergy during gestation, the rates of congenital anomalies and low birth weight have been reported as 4% each and that of preterm

birth in singletons as 14% for omalizumab, based on the outcomes of 11 different publications [7]. Real-life data on the efficacy of omalizumab in patients with asthma have been collected and released in Turkey; however, no data related to gestation have been reported [8]. Although the case notices of all studies conducted previously across the world reported that the administration of omalizumab is safe in gestation, the number of pregnant patients in these case series was between one and four [7]. In our case report, we worked with the largest real-life data sample reported from one county: 22 pregnancies and 23 infants. Therefore, we aim to share our experience regarding the safety of omalizumab in both mothers and infants by a retrospective review of the relevant data from Turkey.

2. Case Report Method

This retrospective case report was approved by the Institutional Ethic Committee (06.08.2019 date 83045809-604.01.02-123451 number); Helsinki Declaration was signed by all co-authors. This study was conducted in Turkey from August 15, 2019 to October 31, 2019. The centers participating in the Turkish omalizumab data survey [8] were called for participation in this study. A structured questionnaire was prepared by the authors to collect information regarding demographic parameters of the mothers, as follows; prick test results and total IgE levels at the beginning of omalizumab administration; spirometry, asthma control test (ACT), and whole blood count results at the beginning of omalizumab administration, beginning of the pregnancy, and after the delivery of the infant; exacerbation rate during pregnancy; treatment-related parameters; and infant demographic parameters and health. Patients with asthma who received omalizumab for at least 6 months and at least one dose during pregnancy and had a live-birth were retrospectively evaluated using a questionnaire. The data of the patients are presented as exact numbers and percentages. Numerical variables are presented as mean ± standard deviation. The evaluation of spirometry data, ACT scores, and whole blood count data at different time points were compared using Student's t-test and ANOVA tests. All data were evaluated within a 95% confidence interval with a significance level of $p<0.05$.

3. Results

The data correspond to 20 pregnant patients with asthma (22 pregnancies) and their 23 infants. One patient gave birth to twin infants, two patients to two infants each, and 17 to one infant each when they were on omalizumab.

3.1 Maternal demographics and clinical characteristics

Four patients (18%) were over 34 years old. The majority of the patients lived in urban areas (95.5%) and 59% were housewives. Mean asthma duration before treatment with omalizumab was 12.2 ± 8.1 years (range, 2–40 years). Only eight (36.4%) of the patients showed exacerbation (requiring oral corticosteroid treatment for three or more days) during pregnancy. All of them used inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA). Demographic and clinical data of the patients are presented in Table 1.

Age (years)	
Mean ± standard deviation (SD)	31.8 ± 7.4
Median (Range: Min-Max))	31 (25-47)
N, % <34 y	4 (18%)
Living Area (N and %)	
Urban	21 (95.5%)
Rural	1 (4.5%)
Education (N and %)	
Illiterate	2 (9%)
Primary school	6 (27.3%)
High school	7 (31.8%)
University	7 (31.8 %)
Occupation (N and %)	
Housewife	13 (59%)
Officer	7 (31.8%)
Self-employed	2 (9.1%)
Asthma history before omalizumab (years)	
Mean ± SD	12.2 ± 8.1
Median (Range: Min-Max)	10 (2-40)
Smoking history (N and %)	1 patient ex-smoker (5pack-year), 4.3%
BMI	
Mean ± standard deviation (SD)	26.3 ± 4.9
Median (Range: Min-Max)	24 (20-37)
N, % <30 (obesity)	5 (22.7%)
Comorbidities (N and %)	
Allergic rhinitis	16 (72%)
Exacerbation rate during pregnancy (with oral corticosteroids) (N and %)	8 (36.4%)
1 exacerbation case (N and %)	3 (13.6%)
2 exacerbation cases (N and %)	5 (22.7%)
Medications other than omalizumab (N and %)	
Inhaled corticosteroid (ICS)	2 (9.1%)
ICS + long acting beta agonist (LABA)	22 (100%)
Leukotrien receptor antagonists (LTRA)	15 (68.2%)
Tiotropium	2 (9.1%)
H1 receptor antagonists	6 (27.3%)
Nasal corticosteroids	9 (40.9%)

Table 1: Maternal demographics and clinical and therapeutic characteristics of 22 pregnancies.

3.2 Maternal spirometry, ACT, and whole blood count results

Spirometry parameters, ACT, and whole blood count results at the starting time of omalizumab administration, during pregnancy, and after delivery are presented in Table 2. There were no considerable differences between results at the beginning of pregnancy and after delivery. No correlation was found between forced expiratory volume in 1 second (FEV1) and prematurity ($p>0.05$).

	Starting time of omalizumab	**Beginning of pregnancy**	**After pregnancy (1-3 months)**
Spirometry			
FVC (L)	3.05 ± 0.55	3.61 ± 0.55	3.21 ± 0.49
FVC (%)	83.6 ± 18.8	92.3 ± 12.2	89.9 ± 10.0
FEV1 (L)	2,39 ± 0.80	3.00 ± 0.95	2.62 ± 0.78
FEV1 (%)	71.0 ± 18.2	83.4 ± 10.5	80.5 ± 13.0
FEV1/FVC (%)	76.8 ± 20.4	87.2 ± 21.5	89.9 ± 10.0
ACT score	11.95 ± 4.95	20.16 ± 2.64	20.40 ± 2.18
Whole blood count			
Hemoglobin (g/dL)	12.9 ± 1.0	12.3 ± 1.2	12.1 ± 1.5
Hematocrite (%)	37.6 ± 3.7	35.9 ± 3.9	34.4 ± 3.9
MPV	9.5 ± 1.8	9.4 ± 1.8	9.6 ± 1.7
Trombocytes/mm^3	271 545 ± 63 120	273 263 ± 63 625	262 571 ± 59 815
Eosinophils/mm^3	447.8 ± 297.1	356.1 ± 246.9	226.7 ± 198.7
Eosinophils (%)	4.58 ± 2.74	2.92 ± 1.98	1.81 ± 1.79

Table 2: Spirometry parameters, asthma control test (ACT) scores, and whole blood count results. (Mean ± standard deviation (SD)).

3.3 Omalizumab exposure results

Omalizumab exposure level, interval, and duration are presented in Table 3. Patients had asthma for 12.2 ± 8.1 years and they received omalizumab for 28.9 ± 22.3 months. The twins received only one dose of omalizumab, one infant received the drug in the first trimester, four infants in the second and third trimester, and 16 infants during all pregnancy and breastfeeding periods.

Omalizumab exposure	
Time before pregnancy (months) (mean ± SD)	28.9 ± 22.3
Dose (mg)	
150 (N and %)	4 (18.2%)
225 (N and %)	2 (9.1%)
300 (N and %)	11 (50%)
375 (N and %)	2 (9.1%)
Other (N and %)	3 (13.6%)
Dose Interval	
Every 2 weeks (N and %)	5 (22.7%)
Every 4 weeks (N and %)	17 (77.3%)
Exposure time	
1st trimester (N and %)	3 (13.6%)
2nd trimester + 3rd trimester (N and %)	4 (18.2%)
All trimesters and breastfeeding period (N and %)	16 (69.6%)

Table 3: Omalizumab exposure of 23 infants.

3.4 Pregnancy and infant outcomes

Ten patients were delivering their first infant. Seventeen (73.9%) patients underwent a cesarean section. No labor complications were noted. Pregnancy and infant outcomes are given in Table 4. The mean delivery age was 31.8 ± 7.2 years. No congenital anomalies were detected. Seven infants had allergic diseases during their lives. The mean APGAR index for newborn infants was 8.7 ± 1.2. Only one newborn infant had an APGAR index below 8 (5). The mean delivery weight was 3055.8 ± 563.3 g. Premature births were seen in five patients (21.7%).

Birth weight (mg) (mean ± SD)	
All infants	3055.8 ± 563.3
Singletons	3109.1 ± 540.3
Twins	2062.5 ± 12.5
Low birth weight* (N and %)	
All infants	3 (13.04%)
Singletons	1 (4.76%)
Twins	2 (100%)
Birth height (cm) (mean ± SD)	48.2 ± 3.7
Gestational age (mean ± SD)	37.3 ± 2.2

Premature birth** (N and %)	5 (21.7%)
Gender: Male/Female (N and %)	9/14 (39.1/60.9%)
APGAR Score (mean ± SD)	8.7 ± 1.2
Low APGAR score*** (N and %)	1 (4.76%)
Infants with any allergic diseases (N and %)	6 (26.09%)
Actual age of infants (weeks) (mean ± SD) (range)	31.2 ± 28.9 (range: 7-120)

* Low birth weight was defined as < 2.5 kg.
** Premature birth was defined as less than 37 weeks of gestation.
*** Low APGAR score is defined as an APGAR score lower than 8

Table 4: Pregnancy and infant outcomes.

4. Discussion

In our case report of 22 pregnancies and 23 infants, asthma exacerbation was seen only in 36.4% of the pregnancies. FEV1 levels, ACT scores, and eosinophilia at the start of pregnancy were not statistically significant than after pregnancy ($p>0.05$). Patients received omalizumab for 28.9 ± 22.3 months before pregnancy. The twins received only one dose of omalizumab, one infant received it in the first trimester (two doses), four infants in the second and third trimester, and 16 infants during the entire pregnancy and breastfeeding period. No malformations were detected in the newborns and only one newborn had an APGAR index below 8. Nevertheless, premature birth was seen in five infants (21.7%) and seven infants had allergic diseases during their life. Maternal age is an important risk factor for congenital anomalies. The median age of our patients was 31 years (range, 25–47 years). It was equal to that in the EXPECT cohort and higher than that in the QECC cohort (31 and 27.7, respectively) [6]. Furthermore, the percentage of subjects younger than 35 years was 82% in our study but 74.8% in the EXPECT cohort and 85.7% in the QECC cohort [6]. However, the infants in our study did not present any anomalies. The majority of our patients were from urban areas (95%), 59% were housewives, and 63.6% were high school or university graduates. Compared with other pregnant groups studied in our country, our pregnant patients with asthma were more educated, had different occupations, and were less commonly from rural areas [9]. Coming from urban areas means more exposure to traffic pollution, which may lead to preterm birth [10]. Only one patient was an ex-smoker. The major comorbidity was allergic rhinitis, with a 72% rate, and only five patients (22.5%) were obese. In contrast, in the EXPECT study, the rate of obese patients was 46.7% [6]. Furthermore, our patients did not have comorbidities such as diabetes, which might have increased the risk of certain lung diseases in infants [11].

Asthma duration before omalizumab administration had a range of 2 to 40 years and all the patients had been using ICS and LABA combinations before and during their pregnancy. Other add-on drugs used during pregnancy were also non-teratogenic; patients had used similar drugs in EXPECT and QECC studies [6]. Moreover, whereas Yilmaz et al. [9] pointed out non-adherence to treatment in pregnant asthma patients, we did not encounter it in our patients.

Exacerbation was observed in eight (36.4%) of our patients. In a study conducted by Schatz et al. [12], with 1739 pregnant patients with asthma, 30% of the patients who had previously been identified as having mild asthma had progressed towards moderate to severe asthma, but in subjects with severe asthma, only 23% had progressed towards moderate and mild asthma. Furthermore, Schatz et al. [12] showed that 13% of mild, 16% of moderate, and 52% of severe asthma cases presented at least one exacerbation case. This suggests that there is a correlation between asthma severity and increased risk of exacerbation. The exacerbation was reported to occur mostly between weeks 17 and 24; in other words, mostly in the second trimester of gestation [3]. In conclusion, even though pregnant women with severe asthma are considered to be at higher risk of an attack, the ones with mild asthma are also at risk.

Furthermore, it has been demonstrated that inflammation is associated with a risk of lack of asthma control, which is due to failure to administer ICS, decrease in treatment adherence, or obesity [13]. Uncontrolled maternal asthma results in poor outcomes in infants [14]. Spirometry parameters, ACT scores, and whole blood count results at the beginning of pregnancy and after delivery showed non-considerable differences in our patients. However, one-third of the exacerbation cases resulted from oral steroid use. In contrast, an exacerbation rate of up to 45% in pregnant patients with asthma has been reported [4]. However, their exacerbation rate, ACT score, and FEV1, as well as blood test results at the beginning of pregnancy were not different from the ones after pregnancy ($p>0.05$); the decrease in eosinophil count after pregnancy was also not significant ($p>0.05$). Similarly, Fazel et al. [15] found non-considerable differences in eosinophil levels between controlled and uncontrolled pregnant patients with asthma and healthy pregnant women. Meanwhile, Palmsten et al. [16] used a modified ACT (p-ACT) [15]. They reported that lower p-ACT scores were associated with previous exacerbation, and were not associated with future exacerbation during pregnancy. Furthermore, De Araujo GV et al. [17] evaluated the importance of ACT in pregnancy and pointed out that physicians did not require spirometry to assess the level of asthma control and that ACT can be used in the primary care of expectant mothers with asthma. Patients had different exposure durations to omalizumab before pregnancy and the doses and dose intervals of omalizumab were different. Two-thirds of our patients received omalizumab during their entire pregnancy and breastfeeding periods, whereas exposure during the entire pregnancy was 83% in the EXPECT study [6]. Our case study is a retrospective real-life projection of Turkey, whereas EXPECT is a prospective observational registry study from the US, and this may mean some attitudinal differences between patients and physicians.

The gestational median age was 37.3 years in our patients and there was a higher rate of cesarean section (73.9%) in our study patients. Furthermore, five infants (21.7%) had premature birth and three (13% of all infants) had low birth weight. Compared to the EXPECT study, the low birth weight rate was similar, but the premature birth rate was higher in our study [6]. Additionally, only one infant had a low APGAR score, and we found that the seven infants with allergic diseases demonstrated genetic predisposition and omalizumab did not have an effect in this situation. Meanwhile, no considerable differences between mothers with and without asthma regarding the duration

of gestation, birth weight, low APGAR scores, or neonatal respiratory difficulties were found in the study by Fazel et al. [15]. Furthermore, none of our patients had infants with congenital anomalies; however, this may be due to our small sample size. In fact, in 2008, Blais and Forget [18] reported that the malformation probability in 4300 pregnant women with asthma was increased. It has been reported that this is particularly correlated with exacerbation in the first trimester (odds ratio 1.48, 95% CI 1.04–2.09) [18]. The most notable outcomes in this regard have been suggested by a meta-analysis consisting of 40 studies and 1 637 180 individuals conducted by Murphy et al. [19] in 2011. In this study, it was observed that the risk of low birth weight infants was increased in pregnant women with asthma [relative risk (RR) 1.46, 95% confidence interval (CI) 1.22–1.75], there was a slight decrease in intrauterine growth (IUGR) (RR 1.22, 95% CI 1.14–1.31), preterm delivery was increased (RR 1.41, 95% CI 1.22–1.61), and pre-eclampsia risk was also slightly higher (RR 1.54, 95% CI 1.32–1.81) [19]. It has been reported that IUGR and preterm delivery are due to maternal hypoxemia and altered placental function in asthma [20]. Additionally, in a study conducted on 2123 pregnant women with asthma, it was observed that low FEV1 values are correlated with premature infants and pre-eclampsia [21]. Conversely, we did not find any correlation between FEV1 and prematurity. In the study conducted by Murphy et al. [19], it was suggested that preterm delivery and pre-eclampsia decreased upon ensuring control through proper asthma treatment. Thus, it can be concluded that such complications occur due to the lack of proper treatment.

Limitations

As the case report was retrospective, we could not obtain all the data for the whole duration of the pregnancies. Moreover, other patients on omalizumab during pregnancy may exist in our country; we presented only those cases for which the physicians agreed to participate in the study.

5. Conclusion

About one-third of our patients with severe asthma on omalizumab had exacerbation during pregnancy. However, the spirometry, ACT scores, and blood count results after the delivery of the infants were not considerably different from those before pregnancy. Two-thirds of our patients received omalizumab during the entire gestation and breastfeeding periods and premature birth was seen in one-fifth of the patients. Overall, omalizumab treatment during pregnancy seems to be safe for both patients and their infants.

Declaration of Interest Statement

Conflict of Interest: Authors reports that they have no conflict of interest related the submitting work. But they report other than the submitting work; Gemicioglu B received grants from Novartis, Deva, Abdi Ibrahim, Sanofi, Astra Zeneca, GSK, Chiesi, Sandoz. Karakaya G received grants from Novartis, Astra Zeneca, GSK, Meda. Bavbek S received grant from Astra Zeneca, Novartis, GSK. Ediger D received grant from Novartis, Sanofi, AstraZeneca, GSK, MSD. Oğuzulgen IK received grants from AstraZeneca, GSK, Deva. Özşeker ZF received grants from

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