Disease Progression and Outcomes of Pregnancies in Women With Eosinophilic Esophagitis

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Title: Disease Progression and Outcomes of Pregnancies in Women With Eosinophilic Esophagitis

Short title: Eosinophilic esophagitis and pregnancy

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Abbreviations:

EoE:	Eosinophilic esophagitis
Eos/hpf:	Eosinophils per high power field
PPI:	Proton pump inhibitors
Th1/2:	T-helper cell ½

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Abstract:

Background & Aims: Eosinophilic esophagitis (EoE) most often affects young patients of reproductive age, yet little is known about its effects during pregnancy. We examined the course of EoE during pregnancy, outcomes of pregnancies, and patient concerns related to pregnancy and EoE.

Methods: We sent a survey that queried demographic and disease-specific characteristics as well as pregnancy-related topics to all 151 female patients treated at 2 EoE centers in Switzerland. We analyzed cross-sectional survey data.

Results: Of 72 patients that returned the survey, we identified 20 patients that had at least 1 pregnancy and analyzed the data on 34 pregnancies. During pregnancy, improvement of dysphagia was reported in 56% (19/34) of all pregnancies, whereas deterioration was reported in 20% (7/34) of all pregnancies. After delivery, dysphagia returned to the pre-pregnancy level in 68% (13/19) of all pregnancies for patients with improvement of dysphagia and 57% (4/7) of all pregnancies for patients with deterioration of dysphagia during pregnancy. Esophagogastroduodenoscopy during pregnancy was required in less than 10% (3/34) of all pregnancies. Pregnancy-related complications occurred in 12% of pregnancies (4/34). The leading patient-reported concerns were fear of heritability (40% of patients, 8/20) and concerns of that use of medication would harm the fetus (30% of patients, 6/20).

Conclusions: Pregnancy affects the course of EoE, with improvement of symptoms reported in most patients. Dysphagia returned to the pre-pregnancy level following delivery. EoE has likely no negative effects on outcomes of pregnancies.

KEY WORDS: esophagus, prenatal, neonate, chronic inflammatory disease

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Introduction

Eosinophilic Esophagitis (EoE) is a chronic immune-mediated disease of the esophagus characterized clinically by symptoms of esophageal dysfunction and histologically by an eosinophil predominant inflammation.[1] Because the peak incidence of this disease is among those between 20 and 30 years of age, female patients are often diagnosed and live with this condition during their reproductive age.[1]

Since EoE has a Th2-type inflammatory pattern [2] and may be considered as "asthma or atopic dermatitis of the esophagus", its disease course during pregnancy might follow the one-third rule: disease ameliorates in a third of patients, disease deteriorates in a third of patients, and disease remain unchanged in a third of patients as in asthma[3]; or that the disease might deteriorate in the majority of patients as in atopic dermatitis.[4] It is generally considered that these allergic and autoimmune diseases course alterations during pregnancy occur as a result of down-regulation of Th1 cells and the up-regulation of Th2 cells,[5, 6] as high concentrations of Th1- and Th17-type cytokines may have deleterious effects on outcome of pregnancy.[7, 8]
In general, patients with chronic diseases may have unique challenges and concerns during pregnancy.[9] From EoE patients' perspective, it is important to know whether this condition has any consequences for a planned pregnancy.

To date, the data on pregnancy in EoE are extremely limited, with a single case series of four pregnant women in EoE published by Burk *et al.*[10] The aim of this study was three-fold: to investigate the clinical course of EoE during pregnancy, to analyze the outcome of the pregnancies in patients with EoE, and to explore the disease-specific concerns female EoE patients might have had before pregnancies.

Methods

We conducted a cross-sectional questionnaire-based study in all female EoE patients treated at EoE Clinics in Olten and Zurich, Switzerland. Diagnosis of EoE was established based on the following criteria: clinically, based on presence of symptoms of esophageal dysfunction and histologically, based on esophageal peak eosinophilia of ≥ 15 eosinophils per high-power field (eos/hpf) in at least one biopsy specimen of the esophagus.[11] Other conditions leading to esophageal eosinophilia were excluded. We developed a German language-based survey that queries the number of pregnancies, pregnancy complications (premature birth, miscarriage, gestational diabetes, high blood pressure, or other complications), mode of delivery, EoE-specific pregnancy-related concerns (fear of heritability, fear of harming the unborn due to medication use, fear of EoE negatively impacting the course of pregnancy, fear of EoE deterioration, or other concerns), the presence of EoE symptoms including dysphagia during pregnancy and following delivery as well as change in EoE symptom severity (improvement or deterioration) in percent (10-30%, 31-50%, 51-70%, 71-100%) following the delivery compared to symptom severity during pregnancy, any EoE-related complication during pregnancy, the need of esophagogastroduodenoscopy during pregnancy, and the medication use and dose during pregnancy. Demographic and disease-specific data, such as age at the time of study enrollment, age at first manifestation and diagnosis of EoE, concurrent allergic diseases, and history of bolus impaction were also collected. The survey was sent and returned by post.

All statistical analyses were performed using the GraphPad Prism 5.0 (GraphPad Software, Inc., Sand Diego, CA). Quantitative data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented either as median plus interquartile ranges (for data with non-Gaussian distribution) or mean ± SD and range (for normally distributed data). Categorical data were summarized as the percentage of the group total. For quantitative data, differences in distribution between two groups were evaluated using either the Wilcoxon-

116 Mann-Whitney rank test (for data with non-Gaussian distribution) or the Student's t-test (for
117 normally-distributed data). For categorical outcomes, differences in observed frequencies
118 between groups were compared using the chi-squared test, or using the exact Fisher test for
119 groups with a small number of observations ($n<20$).

120 The study was approved by the local ethics committee (No. EKNZ 2015-388).

RESULTS

One hundred and fifty one female patients are treated in EoE clinics in Olten and Zurich, Switzerland. These patients were invited to participate in this study and were send paper-based survey. Seventy-two patients (48%) returned the survey and were included in this study. Of 72 enrolled patients, 20 patients had at least one pregnancy after EoE diagnosis. Six patients (30%) had one pregnancy, whereas 14 patients (70%) had two pregnancies (total of 34 pregnancies) (Figure 1). One patient was pregnant at the time of the survey completion. The demographic and disease-specific characteristics are shown in Table 1.

The course of the dysphagia during pregnancy and after delivery is shown in Figure 2. Most patients experienced improvement in dysphagia during their pregnancies (56%), a quarter of patients observed no change in dysphagia, and a fifth experienced worsening of dysphagia. In patients reporting an improvement of dysphagia, more than half experienced an improvement by 71-100%, whereas in patients with a deterioration, the majority had only a deterioration of less than 30%.

After delivery, the severity of dysphagia returned to the pre-pregnancy state in the majority of patients. The median duration of improvement or deterioration in dysphagia severity during pregnancy was 3.0 months (IQR 0) or 6.0 months (IQR 1 month), respectively. After pregnancy, an improvement in dysphagia severity occurred after a median of 3.1 month (IQR 3.8 month), whilst a deterioration in dysphagia severity occurred after a median of 2.0 month (IQR 5.8 month). During pregnancy, three patients (9%) experienced EoE-related complications requiring esophagogastroduodenoscopy: bolus impactions (n=2), and herpes simplex esophagitis (n=1).

Pregnancy-specific characteristics are shown in Table 2. Complications occurred in four (12%) of the pregnancies including one miscarriage. At the time point of data analysis, one patient was still pregnant.

In 14 pregnancies (41%), patients did not take any EoE-specific medications. Of the remaining pregnancies, swallowed topical corticosteroids (STC), proton-pump inhibitors (PPI), and elimination diet were used in 13 (39%), nine (26%), and two pregnancies (6%), respectively. The rate of EoE-related complications requiring esophagogastroduodenoscopy in patients treated with EoE-specific modalities (2/20, 10%) and that in patients that did not undergo treatment (1/14, 7.1%) did not appear to differ (P = ns). Furthermore, the rate of pregnancy-related complications in patients (who finished their pregnancy) treated with EoE-specific therapies (1/20, 5.0%) and that in patients without treatment (3/13, 23.1%) did not appear to differ (P = ns).

The major concerns reported by patients with prior pregnancy were fear of child inheriting EoE (40%), and fear of harming the child due to EoE medication use (30%). Only a minority of patients were concerned about a negative effect of pregnancy on EoE course or vice versa. Half of the patients (50%) reported no concerns at all (Table 2).

DISCUSSION

Eosinophilic esophagitis (EoE) has an increasing prevalence and frequently affects individuals of child-bearing age. Whilst the study on contribution of genetic and environmental factors to EoE heritability have recently been carried out,[12] the studies on impact of a pregnancy on esophageal inflammation and clinical disease course as well as outcome of pregnancies in EoE patients are scarce. In this survey-based study, we describe the case series of 20 EoE patients that experienced 34 pregnancies. Our main findings are as follows: 1) more than half of the EoE patients experienced symptom improvement during pregnancy; 2) the rate of pregnancy-related complications was low; and 3) major concerns reported by patients were fear of child inheriting EoE and harming the unborn child due to EoE medication use.

Given that during pregnancy clinical worsening of several autoimmune diseases, such as asthma and atopic dermatitis, was demonstrated in several studies[3, 4], we learned with interest that more than half of the patients (56%) reported a marked improvement in their dysphagia, whereas only a minority (20%) of patients experienced deterioration of dysphagia severity. Our data pave way for prospective studies closely examining the alterations in EoE course during pregnancy as well as mechanistic work aimed to explore whether the pregnancy results in changes in levels of expression of various cytokines compared to pre/post-pregnancy state.

Chronic inflammation might have a negative impact on the outcome of pregnancies, either as a consequence of the disease activity itself or due to side effects of the treatment. In EoE, the risks of an uncontrolled disease activity as well as side effects of corticosteroids and potential nutritional deficits in those adhering to dietary regimens are all grounds for concern for healthcare professionals taking care of EoE patients. This was not the major concern for our EoE patients, as only one of the twenty patients feared that EoE might negatively impact the course of pregnancy. Our data show that the course of the pregnancies and deliveries were uneventful in almost 90% of all cases. A miscarriage occurred in one patient (3%). Since the miscarriage rate in high-income countries is approximately 10% in young women, it appears

that the prevalence of miscarriage in EoE patients is similar to that observed in the general population. [13] In addition, the incidence of premature birth (3%) and the rate of placental abruption (3%) in our study population is similar to that in other northern European countries (premature birth is observed in approximately 5% of patients, whilst placental abruption is observed in approximately 1% of patients).[14,15]. In summary, we did not document a negative impact of the underlying EoE on the course and the outcome of the pregnancies.

Almost one third of patients had concerns that their medication could have a negative impact on the outcome of the pregnancy. The only approved medication for treatment of EoE are swallowed topical corticosteroids (STC), which have a favorable safety profile and represent the first-line treatment in non-pregnant patients.[16,17,18] Topically-acting corticosteroids can be safely administered during pregnancy in patients with skin diseases and asthma.[19,20] However, one must keep in mind that STC are metabolized differently depending on the mode of application. In our study, three pregnancy-related complications occurred in patients that did not undergo any treatment (3/13; 21.3%), and one complication (1/20; 5.0%) occurred in the group undergoing treatment. The one complication in a patient treated with STC was a herpes esophagitis. However, that was supposed to be unrelated to the medication and more a surrogate marker for an uncontrolled EoE. In summary, the rate of pregnancy-related complications was not higher in patients adhering an anti-inflammatory treatment with STC during pregnancy when compared to that in patients taking no medications for EoE management.

Mode of delivery is an important topic for expectant mothers regardless of whether they have a chronic disease or not. In Switzerland, caesarean section rate of 33% is one of the highest worldwide.[14] Our analysis demonstrated that more than 40% of our EoE patients had a caesarean section. As such, the rate of caesarean section in our population is consistent with nation-wide rates.

Parents affected by chronic diseases often fear of transmitting the disease to their children. Our data show that almost half of the EoE patients were concerned that the offspring might

212 inherit the disease. This fear is justified, as the risk for first-degree relatives to be affected with
213 EoE is about 2.3%.[12] However, the environmental exposures increase the rate of EoE
214 development to a much greater extent than genetic background.[12] Furthermore, the risk for
215 transmitting EoE from father to the offspring is at least twice as likely as that from mother to
216 the offspring. Therefore, we have no reasons to discourage female EoE patients from having
217 children based on the increased risk of disease inheritance alone.

218 Our study has several limitations. Relatively small number of patients was examined.
219 However, since the prevalence of EoE is three-fold lower in female than in male patients[1], it is
220 difficult to study female patients that are of childbearing age and experienced pregnancy.
221 Despite the low number, our study represents the largest number of pregnant EoE patients ever
222 examined. Given the retrospective nature of the study, symptoms were assessed using a non-
223 validated instrument. We did not collect the age when the women experienced pregnancy.
224 However, the mean age in our population was not much higher than the mean age of having
225 children in average population in Switzerland (32 years). In addition, given that only three
226 patients underwent esophagogastroduodenoscopy for emergency reasons, we could not
227 examine the relationship between symptom severity and biologic findings. Nevertheless, given
228 the clinical need and almost complete absence of literature on course of pregnancy in patients
229 with EoE, these data might be useful for management of these patients.

230 Based on our analysis and on practical experience, we provide the following four
231 clinical suggestions: 1.) Female EoE patients considering pregnancy should be informed that to
232 date no increased maternal and fetal risk was observed in pregnant EoE patients on and off
233 EoE-specific medication; 2.) In patients having inactive disease at the beginning of a pregnancy,
234 a cessation of the treatment may be considered, provided that the patients undergo regular
235 monitoring of EoE during pregnancy; 3.) In patients with active disease at the beginning of the
236 pregnancy the treatment should be continued and 4). After delivery, patients having had an

improvement in symptoms during pregnancy must be advised to pay attention to a worsening of symptoms.

In conclusion, our analysis indicates that clinical course of EoE appears to be favorable in pregnancy. Use of EoE-specific medications during pregnancy appears to be safe, as we could not detect a higher rate of pregnancy-related complications in patients having an EoE-specific therapy.

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There is no conflict of interest for the work under consideration for publication.

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Legends:

Figure 1: Flow diagram.

Figure 2: Course of dysphagia during and after pregnancy.

Table 1: Demographic and disease-specific characteristics of the study population.

Table 2: Pregnancy-specific characteristics in patients with EoE.