Inflammatory Intestinal Diseases

Research Article

Inflamm Intest Dis
DOI: 10.1159/000534412

Received: March 9, 2023
Accepted: September 27, 2023
Published online: October 5, 2023

Pregnancy Outcomes in Females with Eosinophilic Esophagitis: A Nationwide Population-Based Study

Lovisa Röjler[a] Amiko M. Uchida[b, c] John J. Garber[c] Olof Stephansson[d] Jonas Söderling[d] Bjorn Roelstraete[e] Jonas F. Ludvigsson[a, e, f]

[a]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; [b]Division of Gastroenterology, Hepatology and Nutrition, University of Utah School of Medicine, Salt Lake City, UT, USA; [c]Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [d]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [e]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [f]Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA

Keywords
Maternal outcome · Fetal outcome · Allergy · Atopy

Abstract
Introduction: Eosinophilic esophagitis (EoE) is a chronic, allergic inflammatory disease of the esophagus. It has a peak incidence in the 2nd and 3rd decades of life. Despite this, little is known about pregnancy outcomes in patients with EoE. ***Methods:*** Using a validated histopathologic and nationwide population-based cohort for the diagnosis of EoE, we examined maternal and fetal outcomes, with preterm birth as the primary outcome, in females with EoE compared to matched controls. Odds ratios (ORs) were calculated using logistic regression. ***Results:*** Between 1992 and 2016, we identified 19 females with EoE who gave birth to 23 children (reference births: $n = 115$). There was 1 (4.3%) preterm birth in the EoE cohort versus 8 (7.0%) in the reference cohort (OR = 0.60; 95% CI = 0.07–5.14). Secondary fetal outcomes included stillbirth, neonatal death, small for gestational age, low birth weight (LBW), and low Apgar score. Of these, LBW (<2,500 g) in patients with EoE compared to controls correlated to an OR of 12.42 (95% CI = 1.26–122.42); however, this finding was based on very low numbers. The remaining fetal outcomes were not significantly different between females with EoE and controls. Secondary pregnancy and maternal outcomes including induction of labor, instrumental delivery, gestational diabetes, or pre-eclampsia were not significantly different between patients with EoE and controls. ***Discussion/Conclusion:*** Overall in this nationwide cohort study, we did not find increased association of preterm birth in patients with EoE.

Introduction

Eosinophilic esophagitis (EoE) is an increasingly common chronic, immune-mediated inflammatory disease of the esophagus [1]. It is a clinicohistological

Lovisa Röjler and Amiko M. Uchida shared co-first authorship.

karger@karger.com
www.karger.com/iid

Correspondence to:
Jonas F. Ludvigsson, jonasludvigsson@yahoo.com

diagnosis where eosinophils infiltrate the esophagus, causing esophageal dysfunction with dysphagia being the most common symptom [2]. EoE is generally treated pharmaceutically with proton pump inhibitors (PPIs) or topical glucocorticoids, or with elimination diets. It affects all ages and sexes, and in females the diagnosis often occurs during child-bearing years, having a peak incidence between 20 and 30 years of age [3]. Despite this temporal association, data on pregnancy outcomes in EoE are sparse leaving patients who desire to become or currently are pregnant with little guidance on outcomes.

To our knowledge, there are only two prior studies on pregnancy outcomes in EoE. In 2016, Burk et al. [4] provided a case series of 4 patients with EoE who either became pregnant or desired to become pregnant. These cases were presented to facilitate discussion of management options and considerations in patients with EoE. The study turned to patients with inflammatory bowel disease as discussion comparators but did not compare pregnant patients with EoE to females from the general population. A more recent retrospective study by Schreiner et al. [5] included 20 females with established EoE (representing 34 pregnancies), who responded to a survey about pregnancy-related complications and fears. They found 56% of patients reported improvement of dysphagia during pregnancy and 20% experienced worsening of this symptom. However, the investigators found that EoE likely did not have negative impacts on pregnancy outcomes.

Using nationwide data on biopsy-verified EoE, we examined pregnancy outcomes in females with EoE and female controls from the general population. We hypothesized that patients with EoE would be at higher risk of adverse pregnancy outcomes than females from the general population.

Methods

Patient Cohort

The ESPRESSO (Epidemiology Strengthened by histopathology Reports in Sweden) cohort contains all biopsies obtained from the gastrointestinal tract during 1965–2017 at 28 pathology departments in Sweden [6]. The personal identity number is a unique number assigned to each resident in Sweden and allows for large-scale linkages and epidemiological research [7]. We linked data on a large EoE cohort to the nationwide Swedish healthcare registers including the Swedish Medical Birth Register (MBR), Cause of Death Register, and the Patient Register [6, 8–10]. EoE medications administered during pregnancy were assessed using the National Prescribed Drug Register, which began record keeping July 1, 2005. Lastly to assess disease and overall health severity in the 5 years before the first pregnancy, we assessed the diagnostic codes associated with all 19 pregnant patients.

We matched all births from pregnant individuals with EoE with up to five reference individuals from the general population according to age, calendar year of delivery, parity, and county. In additional analyses, we further adjusted for level of education, early pregnancy body mass index (BMI), Nordic country of birth, smoking in early pregnancy, diabetes, and other autoimmune disease (diseases listed in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000534412).

Inclusion Criteria

The diagnosis of EoE was histological, retrieved from the ESPRESSO cohort and generally based on the detection of ≥15 eosinophils/high power field. Our EoE cohort was recently validated and found to have a positive predictive value of 89% [6].

Pregnancy

We included females with EoE aged 16–46 years as a generous window for pregnancy. The study was restricted to singletons between 1992 and 2016. We began follow-up in 1992 since early pregnancy BMI (through maternal weight and height measurements), which may be an important confounder, became available in the MBR that year onward.

Fetal and Maternal Outcomes

Our primary outcome was preterm birth (<37 gestational weeks). Secondary fetal outcomes included stillbirth, neonatal death, small for gestational age (SGA), low birth weight (LBW), and low 5-min Apgar score. Stillbirth was defined as intrauterine death at ≥28 gestational weeks up until 2008 onward and thereafter as intrauterine death at ≥22 gestational weeks (information from the MBR). Neonatal death was defined within 28 days of delivery and determined from the MBR and Cause of Death Register. SGA was defined as <2 standard deviations (reported in the main results below) or <10th percentile below the mean weight for gestational age according to sex. LBW, defined as <2,500 g, and Apgar score <7 at 5 min were also analyzed. Presence of congenital malformations at birth and up to the first year of life was determined from the Cause of Death Register and the Patient Register. Secondary maternal outcomes included induction of labor, caesarean section, instrumental delivery, gestational diabetes, and pre-eclampsia. All outcomes were evaluated in live births except the outcome stillbirth.

Statistical Analyses

Conditional logistic regression was used for both main analyses and subgroup analyses. Odds ratios (ORs) were presented with 95% CIs. Adjustment was performed using two different models: either model 1 where estimates were conditioned on maternal age, year of delivery, parity, and county or model 2 conditioned on the matching set as in model 1 plus adjusting for education, maternal BMI, smoking, pre-existing diabetes, and other autoimmune disorders. Education, maternal BMI, and smoking were included as categorical covariates with a missing indicator in the model. ORs reported in the manuscript were those additionally adjusted in model 2.

Sensitivity Analyses

When conditioning on the matching set, we were unable to cluster on a female who had experienced more than one birth given that we matched on parity. To address this, we performed a sensitivity analysis on parity separating nulliparous females from parous females. As an attempt to reduce intra-familial confounding, we performed sibling sensitivity analyses to examine the role of shared genetic and environmental factors (between siblings) and how that may explain any potential association between EoE and pregnancy outcomes.

Ethics

This study was approved by the Stockholm Ethics Board (2014/1287-31/4) on August 27, 2014. Informed consent was waived since the study was strictly register based [11].

Results

Study Cohort

Between 1992 and 2016, we identified 19 females with EoE who gave birth to 23 children. Births were then matched according to delivery year, maternal age, parity, and county with up to 5 reference births (n = 115). Median maternal age at delivery was 29.7 years (interquartile range = 27.4–33.2) and the median time from EoE diagnosis to delivery was 2.4 years (interquartile range = 1.3–3.5). Nine pregnancies were parous (39.1%) and the mean BMI at first visit to antenatal care was 23.9 (SD = 4.8). Early pregnancy smoking was not seen for any of the EoE births but in 4 (3.5%) reference females (Table 1).

To assess EoE medical therapies used in pregnant patients, we analyzed medications dispensed during the first pregnancy and found of the 19 pregnant patients, 18 had their first pregnancy after July 1, 2005 (when medication registry began). Five pregnant EoE individuals had a prescription for PPI and zero patients had prescriptions for systemic or topical corticosteroids for EoE. A complete list of medication names dispensed/written during pregnancy is provided in online supplementary Table 2.

EoE disease and overall health severity in the 5 years prior to the first pregnancy revealed that six of the 19 pregnant EoE females had a diagnosis related to esophageal obstruction and nine had dysphagia (data not shown). Additionally, pregnant EoE patients and controls had similar Charlson Comorbidities indices compared to reference individuals (Table 1).

Primary Outcome Preterm Birth

There was 1 (4.3%) preterm birth in the EoE cohort versus 8 (7.0%) in the reference cohort. This correlated with an OR of 0.60 for preterm birth among EoE patients (95% CI = 0.07–5.14) in model 1 and was similar for model 2 (OR = 0.21; 95% CI = 0.01–5.43) (Table 2). No comparison could be made between spontaneous and medically indicated preterm birth because of too few cases. This was similar for very preterm birth, defined as <32 weeks.

Secondary Fetal Outcomes

We found no association between EoE and SGA; while the OR conditioned on model 1 matching factors was 1.28 (95% CI = 0.13–12.78), the OR increased, though did not gain statistical significance, to 3.83 (95% CI = 0.17–85.59) after adjusting for additional covariates using model 2.

LBW (<2,500 g) was seen in 3 births to females with EoE (13.0%) and in 2 births in the reference group (1.7%) correlating to an OR of 12.42 (95% CI = 1.26–122.42). There was no difference in Apgar scores at 5 min or congenital malformations in offspring between females with or without EoE (Table 2). No neonatal or intrauterine fetal deaths were observed in either EoE or the reference group.

Secondary Pregnancy and Maternal Outcomes

We found no difference in the risk of caesarean section between EoE and control patients in either model 1 or 2 (OR 1.21; 95% CI = 0.37–3.94 and OR = 1.72; 95% CI = 0.45–6.61); similarly, the indication for caesarean section of elective (OR 0.35; 95% CI = 0.04–2.87) or emergency (OR 3.75; 95% CI = 0.84–16.76) was not significantly different between groups. EoE was not associated with induction of labor, instrumental delivery, gestational diabetes, or pre-eclampsia using model 1 or 2 adjustments (Table 2).

Familial Subgroup Analyses

As an attempt to control for intrafamilial confounding, we performed subgroup analyses comparing 6 females with EoE (n births = 8) with their siblings (n = 7 females, total births n = 13) (Table 3). These analyses found no statistically significant differences concerning fetal growth or pregnancy and maternal outcomes (Table 4).

Discussion

In this nationwide cohort study, we examined pregnancy outcomes in females with EoE. Over a nearly 25-year period, we were able to identify 23 births to patients with EoE. Compared to matched females from the general population, females with EoE were at no increased risk of our main outcome, preterm birth. Additionally, we did

Table 1. Characteristics of females with EoE and matched general population reference females giving birth in 1992–2016

Group	Births in females with EoE (*N* births = 23)	Births in reference females (*N* births = 115)
N females	19	115
Maternal age at delivery, years		
Mean (SD)	29.8 (4.6)	29.7 (4.5)
Median (IQR)	29.7 (27.4–33.2)	29.8 (27.0–32.8)
Range, min–max	18.1–37.8	17.2–38.4
Categories, *n* (%)		
17 years–<25 years	3 (13.0)	15 (13.0)
25 years–<35 years	17 (73.9)	85 (73.9)
≥35 years	3 (13.0)	15 (13.0)
Year of delivery, *n* (%)		
2003–2010	2 (8.7)	10 (8.7)
2011–2014	6 (26.1)	30 (26.1)
2015–2016	15 (65.2)	75 (65.2)
Year of EoE onset/index date, *n* (%)		
2001–2010	5 (21.7)	25 (21.7)
2011–2013	12 (52.2)	60 (52.2)
2014–2015	6 (26.1)	30 (26.1)
Disease duration/time from index date, years		
Mean (SD)	2.5 (1.4)	2.4 (1.5)
Median (IQR)	2.4 (1.3–3.5)	2.4 (1.1–3.5)
Range, min–max	0.6; 5.9	0.1; 6.7
Categories, *n* (%)		
<1 year	4 (17.4)	25 (21.7)
1–<3 years	9 (39.1)	46 (40.0)
≥3 years	10 (43.5)	44 (38.3)
Maternal country of birth, *n* (%)		
Nordic	20 (87.0)	102 (88.7)
Other	3 (13.0)	13 (11.3)
Civil status of the mother, *n* (%)		
Living with a partner	19 (82.6)	104 (90.4)
Other/missing	4 (17.4)	11 (9.6)
Level of education, *n* (%)		
≤9 years	2 (8.7)	9 (7.8)
10–12 years	7 (30.4)	41 (35.7)
>12 years	14 (60.9)	65 (56.5)
Parity, *n* (%)		
Nulliparous	14 (60.9)	70 (60.9)
Parous	9 (39.1)	45 (39.1)
BMI in early pregnancy		
Mean (SD)	23.9 (4.8)	24.6 (4.7)
Median (IQR)	22.7 (20.1–26.4)	23.7 (21.3–26.3)
Range, min–max	18.8–33.5	16.6–41.3
Categories, *n* (%)		
<18.5	0	4 (3.5)
18.5–<25	14 (60.9)	66 (57.4)
25–<30	3 (13.0)	25 (21.7)
≥30	3 (13.0)	14 (12.2)
Missing	3 (13.0)	6 (5.2)
Smoking in early pregnancy, *n* (%)		
Yes	0	4 (3.5)
No	20 (87.0)	105 (91.3)
Missing	3 (13.0)	6 (5.2)
Comorbidities[a], *n* (%)		
Diabetes	0	0
Other autoimmune diseases	1 (4.3)	3 (2.6)

Table 1 (continued)

Group	Births in females with EoE (*N* births = 23)	Births in reference females (*N* births = 115)
Charlson Comorbidity Index[a]		
Mean (SD)	0.1 (0.3)	0.1 (0.4)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Range, min–max	0.0–1.0	0.0–3.0
Categories, *n* (%)		
0	21 (91.3)	106 (92.2)
1	2 (8.7)	8 (7.0)
2	0	0
≥3	0	1 (0.9)

[a]Within 5 years before start of pregnancy.

not find evidence of additional adverse pregnancy outcomes (stillbirth, neonatal death, SGA, low Apgar score, induction of labor, caesarean section, instrumental delivery, gestational diabetes, or pre-eclampsia) except for an increased risk of LBW <2,500 g.

While we found an increased risk of LBW in children born to females with EoE, we believe this may be a chance finding given the small number of subjects and absence of association of EoE status with SGA delivery. LBW was based on only 3 LBW children to patients with EoE; however, we cannot rule out a true risk increase nor that some individuals with poor growth (not fulfilling the criteria for SGA) were induced and therefore born before they had attained 2,500 g.

Our results are largely consistent with the prior findings from a survey-based query of pregnant patients with EoE where the investigators reported a low percentage of adverse pregnancy outcomes. The study by Schreiner et al. [5] was of similar sample size, though did not have a comparator arm, and assessed for varied pregnancy outcomes compared to our study. They found the percent of patients with overall pregnancy complication was 12%, and preterm birth occurred in 3% of patients, which is low. Overall, these studies combined suggest relative safety of pregnancy outcomes for patients with EoE.

Importantly, our findings are contrasting to data in asthma, a similar pathophysiological disease to EoE, where an association of maternal asthma and increased risk of preterm birth has been described in a national cohort study among others [12–14]. While there are biologically similar mechanisms of allergy between asthma and EoE given similar therapies appear effective for both, other atopic diseases such as maternal eczema and allergic rhinoconjunctivitis were protective against adverse pregnancy outcomes, suggesting not all allergy, including EoE, affects pregnancy equally [12]. Similarly, in a regional retrospective cohort of the southeastern USA, investigators examined maternal atopic dermatitis and allergic rhinitis and birth outcomes [15]. They did not find statistical differences on maternal atopy to the infant in regard to birth outcomes, largely in line with our findings here.

The strengths of this study include utilization of a nationwide histologic-based cohort that was recently validated and found to have a positive predictive value of 89% [6]. While histologic validation of EoE diagnosis is an important strength, we recognize the limitation that not all esophageal eosinophilia and associated histologic features represent EoE. Nonetheless, having a nationwide population cohort is important since to counteract selection bias. Studies on EoE from tertiary centers may select EoE patients with more severe disease than in an average EoE patient, with potential impact on the outcome of interest.

Additional strengths include utilization of the unique personal identity number assigned to all residents in Sweden, which allowed us to link clinical data to the MBR and ascertain pregnancy outcomes (to ascertain congenital malformations, we included data from the Patient Register and the Cause of Death Register to increase sensitivity). The MBR has otherwise high-quality data and allowed us to examine a wide range of outcomes [9]. To allow adjustment for BMI, which can independently affect pregnancy outcomes, we limited our data to births from 1992 and onward when these data began to be collected.

To our knowledge, our study is the first of its kind to include controls to assess pregnancy outcomes in females with EoE. Control subjects were retrieved from the

Table 2. Pregnancy and birth outcomes for females with EoE and reference females

Group	Births in females with EoE	Births in reference females	OR* (95% CI)	OR** (95% CI)
N live births	23	115		
Preterm birth				
Any preterm birth	1 (4.3%)	8 (7.0%)	0.60 (0.07–5.14)	0.21 (0.01–5.43)
Medically indicated	0	2 (1.7%)	–	–
Spontaneous	1 (4.3%)	6 (5.2%)	0.82 (0.09–7.24)	1.02 (0.06–16.71)
Very preterm birth	0	0	–	–
Fetal growth				
SGA <−2 SD	1 (4.3%)	4 (3.5%)	1.28 (0.13–12.78)	3.83 (0.17–85.59)
SGA <10th percentile	4 (17.4%)	11 (9.6%)	1.95 (0.57–6.61)	1.65 (0.35–7.80)
LBW (<2,500 g)			–	–
All live births	3 (13.0%)	2 (1.7%)	12.42 (1.26–122.42)	–
Term births (GA ≥ w37 + 0)	2 (9.1%)	1 (0.9%)	–	–
Other neonatal outcomes				
Apgar <7 at 5 min	1 (4.3%)	2 (1.7%)	2.50 (0.23–27.57)	4.22 (0.26–68.33)
Congenital malformations	1 (4.3%)	6 (5.2%)	0.82 (0.09–7.24)	1.60 (0.11–23.92)
Neonatal death	0	0	–	–
N all births	23	115		
Intrauterine fetal death				
Stillbirth	0	0	–	–
Pregnancy and maternal outcomes				
Induction of labor	3 (13.0%)	21 (18.3%)	0.68 (0.18–2.48)	0.75 (0.19–2.94)
Caesarean section	4 (17.4%)	17 (14.8%)	1.21 (0.37–3.94)	1.72 (0.45–6.61)
Elective	1 (4.3%)	13 (11.3%)	0.35 (0.04–2.87)	0.51 (0.06–4.39)
Emergency	3 (13.0%)	4 (3.5%)	3.75 (0.84–16.76)	–
Instrumental delivery	2 (8.7%)	11 (9.6%)	0.90 (0.18–4.45)	0.70 (0.11–4.39)
Gestational diabetes	1 (4.3%)	1 (0.9%)	5.00 (0.31–79.94)	0.70 (0.11–4.39)
Pre-eclampsia	0	6 (5.2%)	–	–

*Conditioned on matching set (maternal age, calendar year of delivery, parity, and county). **Conditioned on matching set and further adjusted for level of education, early pregnancy BMI, Nordic country of birth, smoking in early pregnancy, diabetes, and other autoimmune disease.

general population to reflect average females in Sweden. Controls were matched on maternal age, year of delivery, parity, as well as county. Additionally, we adjusted for level of education as a proxy for socioeconomic status. Low socioeconomic status has previously been linked to adverse pregnancy outcomes [16]. Swedish healthcare is tax funded and free of charge during pregnancy and that may have further reduced impacts of socioeconomic status in this study. Finally, to take residual confounding into consideration we performed sibling analyses. While these had limited statistical power, they yielded similar results to the population-based comparisons.

Among the limitations of our study is the limited statistical power given the low number of births in females with EoE in Sweden during the examined time period. This low rate could be attributed to the well-established male predominance of EoE in a 3:1 ratio compared to females. Additionally, it is possible that the paucity of data surrounding pregnancy and EoE might influence patients away from pregnancy. We had initially intended to examine spontaneous versus medically indicated preterm birth but were unable to do so for lack of statistical power. We did not have the statistical power to examine very preterm birth (<32 gestational weeks), but given the neutral association with any preterm birth, it is unlikely that EoE is associated with subtypes of preterm birth. Another limitation is that we were unable to review the individual medical chart data for each of the 19 pregnant patients. This limited our ability to track patient symptoms, duration of treatments, and dietary therapies. The fact that most associations were null, and that we had limited power, meant that we abstained from any

Table 3. Characteristics of females with EoE and their siblings giving birth in 1992–2016

Group	Births in females with EoE (*N* births = 8)	Births in siblings (*N* births = 13)
N females	6	7
Maternal age at delivery, years		
Mean (SD)	31.4 (3.0)	30.3 (4.7)
Median (IQR)	30.7 (29.4–33.5)	30.8 (26.3–32.6)
Range, min–max	27.5–36.8	23.9–39.2
Categories, *n* (%)		
17 years–<25 years	0	1 (7.7)
25 years–<35 years	7 (87.5)	9 (69.2)
≥35 years	1 (12.5)	3 (23.1)
Year of delivery		
2003–2010	0	3 (23.1)
2011–2014	4 (50.0)	6 (46.2)
2015–2016	4 (50.0)	4 (30.8)
Year of EoE onset/index date		
2001–2010	2 (25.0)	5 (38.5)
2011–2013	4 (50.0)	4 (30.8)
2014–2015	2 (25.0)	4 (30.8)
Disease duration/time from index date, years		
Mean (SD)	2.1 (1.4)	0.5 (3.7)
Median (IQR)	1.9 (0.9–3.6)	−0.1 (−2.2–2.7)
Range, min–max	0.6; 3.8	−5.5; 7.4
Categories, *n* (%)		
<1 year	2 (25.0)	7 (53.8)
1–<3 years	3 (37.5)	3 (23.1)
≥3 years	3 (37.5)	3 (23.1)
Maternal country of birth, *n* (%)		
Nordic	8 (100)	13 (100)
Other	0	0
Civil status of the mother, *n* (%)		
Living with a partner	6 (75.0)	12 (92.3)
Other/missing	2 (25.0)	1 (7.7)
Level of education, *n* (%)		
≤9 years	0	0
10–12 years	1 (12.5)	5 (38.5)
>12 years	7 (87.5)	8 (61.5)
Parity, *n* (%)		
Nulliparous	4 (50.0)	7 (53.8)
Parous	4 (50.0)	6 (46.2)
BMI in early pregnancy		
Mean (SD)	25.7 (4.7)	26.5 (4.7)
Median (IQR)	24.2 (22.7–29.1)	25.7 (22.5–27.6)
Range, min–max	20.7–33.1	21.2–35.0
Categories, *n* (%)		
<18.5	0	0
18.5–<25	3 (37.5)	6 (46.2)
25–<30	2 (25.0)	4 (30.8)
≥30	1 (12.5)	3 (23.1)
Missing	2 (25.0)	0
Smoking in early pregnancy, *n* (%)		
Yes	0	0
No	6 (75.0)	13 (100.0)
Missing	2 (25.0)	0
Comorbidities[a]		
Diabetes	0	0
Other autoimmune diseases	0	0

[a]Within 5 years before start of pregnancy.

Table 4. Pregnancy and birth outcomes for females with EoE and their siblings

Group	Births in females with EoE	Births in siblings	OR* (95% CI)	OR** (95% CI)
N live births	8	13		
Preterm birth				
Any preterm birth	0	1 (7.7%)		
Medically indicated	0	0		
Spontaneous	0	1 (7.7%)		
Very preterm birth	0	0		
Fetal growth				
SGA <−2 SD	1 (12.5%)	1 (7.7%)	2.00 (0.13–31.98)	
SGA <10th percentile	2 (25.0%)	5 (38.5%)	0.61 (0.09–4.14)	
LBW (<2,500 g)				
All live births	1 (12.5%)	0		
Term births (GA ≥ w37 + 0)	1 (12.5%)	0		
Other neonatal outcomes				
Apgar <7 at 5 min	0	0		
Congenital malformations	1 (12.5%)	1 (7.7%)		
Neonatal death	0	0		
N all births	8	13		
Intrauterine fetal death				
Stillbirth	0	0		
Pregnancy and maternal outcomes				
Induction of labor	2 (25.0%)	1 (7.7%)	2.00 (0.13–31.98)	
Caesarean section	1 (12.5%)	2 (15.4%)	0.47 (0.04–5.68)	
Elective	0	1 (7.7%)	–	
Emergency	1 (12.5%)	1 (7.7%)	1.00 (0.05–18.91)	
Instrumental delivery	2 (25.0%)	1 (7.7%)	4.91 (0.33–73.98)	
Gestational diabetes	0	0	–	
Pre-eclampsia	0	0	–	

*Conditioned on matching set (family). **Conditioned on matching set and further adjusted for level of maternal age, calendar year of delivery, parity, education, early pregnancy BMI, Nordic country of birth, smoking in early pregnancy, diabetes, and other autoimmune disease.

medication-specific statistical analyses other than reporting written prescriptions (of which there were five PPIs and zero systemic or EoE topical steroids) during pregnancy. PPI use during pregnancy was recently linked to congenital malformations, but this was primarily seen in case-control studies, and not all included studies had limited exposure to the first trimester when fetal development occurs [17]. In contrast, a large-scale Danish study of >5,000 exposed pregnancies found no association between PPI use in the first trimester and malformations, and even with a 2-fold increased risk of malformations in EoE we would not have been able to link any excess risk to PPI use in EoE [18]. As above, we were unable to examine any potential role of dietary treatment in EoE. This would otherwise be important since maternal diet, particularly limiting proteins found in common EoE diet therapy, during pregnancy may underlie the increased association with LBW in exposed pregnancies we describe here. We were unable to investigate the effect of endoscopic procedures done for EoE and pregnancy outcomes. However, in a recent study, upper endoscopy was not linked to adverse pregnancy outcome when exposed (to endoscopy) and unexposed pregnancies in the same mother were compared with each other [19].

While our sample size was limited, our findings represent a critical step forward in providing evidence that can help inform guidance for providers and patients with EoE who are currently or attempting to become pregnant. Likely due to limited data, the current American Gastroenterological Association joint taskforce with Allergy and Immunology guidelines do not contain guidance on the management of EoE in pregnant patients and future studies are needed to further substantiate and explore

pregnancy management in patients with EoE [20]. In conclusion, this population-based cohort study of 23 births to females with EoE and 115 control females found no increased risk of preterm birth, or any other adverse pregnancy outcome, except for an increased risk of LBW. The finding of potentially increased risk of LBW however was based on only 3 children with LBW and should be interpreted with caution.

Acknowledgments

All authors approved the final version of the article, including the authorship list.

Statement of Ethics

The study was approved by the Regional Ethics Committee, Stockholm, Sweden (Protocol no 2014/1287-31/4 and 2018/972-32). All methods were carried out in accordance with relevant guidelines and regulations. Consent was not required as all data were anonymized before analyses.

Conflict of Interest Statement

Dr. Uchida is on a Medical Advisory Board for Sanofi-Genzyme (unrelated to this study) and AstraZeneca. Dr. Garber has received research support from the American Partnership for Eosinophilic Disorders (APfED) and Takeda Pharmaceuticals. None of those studies have any relation to the present study. Dr. Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). That study has received funding from Janssen corporation.

Funding Sources

L.R. was supported by a grant from the Region Örebro Län, Sweden. J.J.G. received research support from the American Partnership for Eosinophilic Disorders (APfED) and Takeda Pharmaceuticals. J.F.L. was supported by Karolinska Institutet. This project also received funding from the Frimurare Barnhuset foundation.

Author Contributions

L.R. and A.M.U. constructed the first draft of the manuscript. J.F.L. completed the final version of the manuscript and is the guarantor of the article. L.R., J.G., and J.F.L. designed the study. O.S., J.S., and B.R. assisted and provided statistical analyses. All authors read, edited, and agreed with the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the Swedish National Board of Health, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Swedish National Board of Health.

References

1 O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of eosinophilic esophagitis. Gastroenterology. 2018;154(2):333–45.
2 Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018;155(4):1022–33 e10.
3 Arias A, Perez-Martinez I, Tenias JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016;43(1):3–15.
4 Burk CM, Long MD, Dellon ES. Management of eosinophilic esophagitis during pregnancy. Dig Dis Sci. 2016;61(7):1819–25.
5 Schreiner P, Meissgeier S, Safroneeva E, Greuter T, Rogler G, Schoepfer A, et al. Disease progression and outcomes of pregnancies in women with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2020;18(11):2456–62.
6 Rojler L, Glimberg I, Walker MM, Garber JJ, Ludvigsson JF. Validation of the diagnosis of eosinophilic esophagitis based on histopathology reports in Sweden. Ups J Med Sci. 2021;126.
7 Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659–67.
8 Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–73.
9 Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med. 1990;18(2):143–8.
10 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
11 Ludvigsson JF, Haberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491–508.
12 Tronnes H, Wilcox AJ, Markestad T, Tollanes MC, Lie RT, Moster D. Associations of maternal atopic diseases with adverse pregnancy outcomes: a national cohort study. Paediatr Perinat Epidemiol. 2014;28(6):489–97.
13 Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. BJOG. 2011;118(11):1314–23.
14 Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. BJOG. 2013;120(7):812–22.

15 Johnson A, Mason T, Kirby RS, Ledford D, Salihu HM. Examining the association between maternal atopy and birth outcomes using a retrospective cohort in the southeastern region of the USA. BMJ Open. 2017;7(11):e017161.
16 Kim MK, Lee SM, Bae SH, Kim HJ, Lim NG, Yoon SJ, et al. Socioeconomic status can affect pregnancy outcomes and complications, even with a universal healthcare system. Int J Equity Health. 2018;17(1):2.
17 Li CM, Zhernakova A, Engstrand L, Wijmenga C, Brusselaers N. Systematic review with meta-analysis: the risks of proton pump inhibitors during pregnancy. Aliment Pharmacol Ther. 2020;51(4):410–20.
18 Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010;363(22):2114–23.
19 Ludvigsson JF, Lebwohl B, Ekbom A, Kiran RP, Green PH, Hoijer J, et al. Outcomes of pregnancies for women undergoing endoscopy while they were pregnant: a nationwide cohort study. Gastroenterology. 2017;152(3):554–63 e9.
20 Hirano I, Chan ES, Rank MA, Sharaf RN; AGA Institute Clinical Guidelines Committee, Joint Task Force on Allergy-Immunology Practice Parameters, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. Gastroenterology. 2020;158(6):1776–86.