

CLINICAL—ALIMENTARY TRACT

Outcomes of Pregnancies for Women Undergoing Endoscopy While They Were Pregnant: A Nationwide Cohort Study



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BACKGROUND & AIMS: Endoscopy is an integral part of the investigation and management of gastrointestinal disease. We aimed to examine outcomes of pregnancies for women who underwent endoscopy during their pregnancy. **METHODS:** We performed a nationwide population-based cohort study, linking data from the Swedish Medical Birth Registry (for births from 1992 through 2011) with those from the Swedish Patient Registry. We identified 3052 pregnancies exposed to endoscopy (2025 upper endoscopies, 1109 lower endoscopies, and 58 endoscopic retrograde cholangiopancreatographies). Using Poisson regression, we calculated adjusted relative risks (ARRs) for adverse outcomes of pregnancy according to endoscopy status using 1,589,173 unexposed pregnancies as reference. To consider the effects of disease activity, we examined pregnancy outcomes (preterm birth, stillbirth, small for gestational age, or congenital malformations) in women who underwent endoscopy just before or after pregnancy. Secondary outcome measures included induction of labor, low birth weight (<2500 g), cesarean section, Apgar score <7 at 5 minutes, and neonatal death within 28 days. To consider intrafamilial factors, we compared pregnancies within the same mother. **RESULTS:** Exposure to any endoscopy during pregnancy was associated with an increased risk of preterm birth (ARR, 1.54; 95% confidence interval [CI], 1.36–1.75) or small for gestational age (ARR, 1.30; 95% CI, 1.07–1.57) but not of congenital malformation (ARR, 1.00; 95% CI, 0.83–1.20) or stillbirth (ARR, 1.45; 95% CI, 0.87–2.40). None of the 15 stillbirths to women with endoscopy occurred <2 weeks after endoscopy. ARR were independent of trimester. Compared to women with endoscopy <1 year before or after pregnancy, endoscopy during pregnancy was associated with preterm birth (ARR, 1.16) but not with small for gestational age (ARR, 1.19), stillbirth (ARR, 1.11), or congenital malformation (ARR, 0.90). Restricting the study population to women having an endoscopy during pregnancy or before/after, and only analyzing data from women without a diagnosis of inflammatory bowel disease, celiac disease, or liver disease, endoscopy during pregnancy was not linked to preterm birth (ARR, 1.03; 95% CI, 0.84–1.27). Comparing births within the same mother, for which only 1 birth had been exposed to endoscopy, we found

no association between endoscopy and gestational age or birth weight. **CONCLUSIONS:** In a nationwide population-based cohort study, we found endoscopy during pregnancy to be associated with increased risk of preterm birth or small for gestational age, but not of congenital malformation or stillbirth. However, these risks are small and likely due to intrafamilial factors or disease activity.

Keywords: ERCP; IBD; fetal; fetus.

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Each year, more than 12,000 US pregnant women have conditions that are usually evaluated by esophago-gastroduodenoscopy (herein upper endoscopy), another 6000 are in need of lower endoscopy, and another 1000 women have symptomatic choledocholithiasis, which in a nonpregnant woman would have entailed endoscopic retrograde cholangiopancreatography (ERCP).¹ Despite these large numbers, research in pregnancy outcome in women undergoing endoscopy during pregnancy is scarce. In addition to some 30 case reports,¹ we are aware of 9 studies^{2–10} with original data on 379 pregnant women undergoing endoscopy. Of these studies, 2 examined pregnancy outcomes in upper endoscopy (n = 143),^{2,5} 2 examined pregnancy outcomes in sigmoidoscopy or colonoscopy (n = 116),^{3,4,10} and 4 in ERCP (n = 120).^{6–9}

Abbreviations used in this paper: ARR, adjusted relative risk; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; IBD, inflammatory bowel disease; SGA, small for gestational age.

Most current article

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0016-5085/\$36.00

<http://dx.doi.org/10.1053/j.gastro.2016.10.016>

Due to the lack of evidence, endoscopy including ERCP is generally performed only when there are strong indications.¹¹ Guidelines aimed at specific gastrointestinal (GI) disease also tend to discourage endoscopy during pregnancy,^{12,13} even though some organizations note that endoscopy including ERCP may be considered safe.¹³ Despite the lack of knowledge, it is recommended that when endoscopy is necessary, it should be performed during the second trimester.^{12,13} However, so far, the total number of reported pregnant women undergoing endoscopy in the second trimester is <100 and, consequently, the statistical power to detect pregnancy complications that otherwise occur in only a few percent of pregnancies has been extremely low. Few studies have compared pregnancy outcomes in women undergoing endoscopy with those in pregnant controls and no endoscopy,^{2,4,10} and we are aware of no study calculating the relative risk of adverse pregnancy outcomes in pregnant women undergoing endoscopy. Some earlier studies have concluded that endoscopy during pregnancy is safe, but several studies have, in fact, excluded stillbirths and neonatal deaths from the analyses when not occurring immediately after endoscopy.^{2,3,6} Finally other studies have failed to follow-up all pregnant women,^{3,7,8} making it difficult to draw any firm conclusions about the safety of endoscopy during pregnancy.

We carried out a nationwide population-based cohort study examining the risk of adverse pregnancy outcome in pregnant women undergoing endoscopy. We hypothesized that endoscopy during pregnancy would increase the prevalence of adverse pregnancy outcome, especially preterm birth and stillbirth.

Materials and Methods

Registers

The Swedish Medical Birth Registry started in 1973 with data on smoking added in 1983 and body mass index in 1992. Hence, this study was restricted to births taking place from 1992 to 2011. Through this registry, we retrieved data on all pregnancy-related variables, including maternal age, parity, maternal country of birth, early pregnancy smoking status, and delivery year. We divided country of birth into Nordic (Sweden, Denmark, Norway, Finland, and Iceland) vs non-Nordic countries. Smoking status (at the first antenatal visit) is self-reported and was categorized into nonsmoker, 1–9 cigarettes per day, or ≥ 10 cigarettes per day.

The Swedish Patient Registry¹⁴ started in 1964 with complete national coverage from 1987. This registry supplied information on endoscopy and ERCP, but also for GI disease diagnoses, such as inflammatory bowel disease (IBD), celiac disease, and hepatobiliary diseases, we also collected disease data from the patient registry. These diseases were defined according to relevant International Statistical Classification of Diseases and Related Health Problems codes (Supplementary Table 1). The positive predictive values of most diagnoses in this registry are between 85% and 95%.¹⁴

Endoscopy and Endoscopic Retrograde Cholangiopancreatography

We defined exposures according to relevant procedure codes, distinguishing between esophagogastroduodenoscopy (upper),

colonoscopy and sigmoidoscopy (lower), and ERCP. Together these procedures made up our main exposure “any endoscopy.” We did not include endoscopy limited to the oropharynx or the rectum.

Pregnancy Outcomes

Our main outcome measures were preterm birth and stillbirth because we hypothesized that an endoscopy can trigger preterm labor and stillbirth. In Sweden, since mid-2008, stillbirth is recorded from 22 completed gestational weeks, and before that from gestational week 28. Gestational age was determined using ultrasound, and when ultrasound data were missing, we used the first day of the last menstrual period for pregnancy start. Routine ultrasound has been offered to pregnant women in Sweden since the 1990s, and about 95% of the women accept this investigation. Preterm birth was defined as <37 completed gestational weeks, while very preterm birth was defined as <32 completed gestational weeks, and moderate preterm birth as 32–36 gestational weeks. We also examined small for gestational age (SGA; defined as a birth weight >2 SDs below the sex-specific mean for gestational age¹⁵ according to Swedish ultrasound-based reference curves) and congenital malformations (using the same definition as in our earlier paper on congenital malformations in IBD,¹⁶ see also [Supplementary Material](#)). Finally, we examined a number of secondary outcomes: risk of induction of labor, low birth weight (<2500 g), cesarean section, Apgar score <7 at 5 minutes, and neonatal death within 28 days. We also looked at the continuous outcome measures birth weight and gestational age.

This study was approved by the research ethics committee of the Karolinska Institutet, Stockholm, Sweden.

Statistical Analyses

We examined the risk of adverse pregnancy outcomes in women undergoing any type of endoscopy, that is, upper endoscopy, lower endoscopy, or ERCP during pregnancy. For preterm birth, stillbirth, SGA and congenital malformation, we also examined whether risk estimates differed between sigmoidoscopy and full colonoscopy. Analyses were adjusted for maternal age, body mass index, parity, education, smoking, diabetes, civil status, year of birth, and infant sex (see [Table 1](#) for categories).

We specifically studied the risk of SGA and congenital malformation according to trimester of endoscopy. In order to rule out that a potentially increased risk of pregnancy outcome was due to underlying GI disease, we examined the risk of adverse pregnancy outcome according to ERCP status in women with a lifetime diagnosis of hepatobiliary disease, upper endoscopy in women with a diagnosis of celiac disease, and lower endoscopy in women with IBD, but also among women who never had any of these diagnoses (“healthy women with endoscopy”). From here onward, hepatobiliary disease, celiac disease, and IBD will be abbreviated as “GI disease.”

To address bias due to underlying disease activity (women with endoscopy during pregnancy are more likely to have more severe disease than those without endoscopy during pregnancy), we examined risk of adverse pregnancy outcome in women undergoing endoscopy during pregnancy vs women having an endoscopy <1 year before or after pregnancy (we studied this in “all women,” but also separately in women with or without a lifetime diagnosis of GI disease).

Table 1. Characteristics of Women Undergoing Endoscopy During Pregnancy 1992–2011 in Sweden

Characteristics	Mother without endoscopy N (%)	Mothers with any endoscopy N (%)	Mother with Upper N (%)	Mother with Lower N (%)	Mother with ERCP N (%)
Total Births	1,589,173	3,052	2,025	1,109	58
Sex					
Female	773,120 (48.6)	1,503 (49.2)	990 (48.9)	565 (51.0)	22 (37.9)
Male	816,053 (51.4)	1,549 (50.8)	1,035 (51.1)	544 (49.0)	36 (62.1)
Calendar period					
1992-1996	387,384 (24.4)	111 (3.6)	84 (4.2)	21 (1.9)	8 (13.8)
1997-2001	334,941 (21.1)	788 (25.8)	581 (28.7)	285 (25.7)	8 (13.8)
2002-2006	397,052 (25.0)	745 (24.4)	500 (24.7)	245 (22.1)	16 (27.6)
2007-2011	469,796 (29.6)	1,408 (46.1)	860 (42.5)	558 (50.3)	26 (44.8)
Maternal age (y)					
-24	252,983 (15.9)	507 (16.6)	367 (18.1)	170 (15.3)	8 (13.8)
25-29	528,191 (33.2)	957 (31.4)	618 (30.5)	362 (32.6)	18 (31.0)
30-34	526,213 (33.1)	984 (32.2)	630 (31.1)	373 (33.6)	21 (36.2)
35-	281,786 (17.7)	604 (19.8)	410 (20.2)	204 (18.4)	11 (19.0)
Country of birth					
Not Nordic	229,860 (14.5)	636 (20.8)	515 (25.4)	118 (10.6)	13 (22.4)
Nordic	1,359,313 (85.5)	2,416 (79.2)	1,510 (74.6)	911 (89.4)	45 (77.6)
Educational level (y)					
≤11 years	957,249 (60.2)	2,025 (66.4)	1,427 (70.5)	666 (60.0)	40 (69.0)
≥12 years	631,924 (39.8)	1,027 (33.6)	598 (29.5)	443 (40.0)	18 (31.0)
Parity					
Nulliparous	683,976 (43.0)	1,294 (42.4)	829 (40.9)	514 (46.4)	10 (17.2)
Multiparous	905,197 (57.0)	1,758 (57.6)	1,196 (59.1)	595 (53.6)	48 (82.8)
Body mass index	167,110 (10.5)			124 (11.2)	5 (8.6)
11 ≤ BMI < 20	877,235 (55.2)	321 (10.5)	206 (10.2)	612 (55.2)	20 (34.5)
20 ≤ BMI < 25	384,613 (24.2)	1,522 (49.9)	961 (47.5)	274 (24.7)	13 (22.4)
25 ≤ BMI < 30	160,215 (10.1)	796 (26.1)	552 (27.3)	99 (8.9)	20 (34.5)
30 ≤ BMI		413 (13.5)	306 (15.1)		
Maternal smoking habits					
Non smoker	1,407,558 (88.6)	2,719 (89.1)	1,770 (87.4)	1,020 (92.0)	47 (81.0)
1-10 cigarettes/day	124,703 (7.8)	229 (7.5)	176 (8.7)	62 (5.6)	7 (12.1)
>=11 cigarettes/day	56,912 (3.6)	104 (3.4)	79 (3.9)	27 (2.4)	4 (6.9)
Mother civil status					
Not living with the father	81,080 (5.1)	226 (7.4)	177 (8.7)	55 (5.0)	5 (8.6)
Living with the father	1,508,093 (94.9)	2,826 (92.6)	1,848 (91.3)	1,054 (95.0)	53 (91.4)
Type 1 or type 2 diabetes					
No	1,579,183 (99.4)	3,003 (98.4)	1,981 (97.8)	1,103 (99.5)	57 (98.3)
Yes	9,990 (0.6)	49 (1.6)	44 (2.2)	6 (0.5)	1 (1.7)

NOTE. The number of unique mothers undergoing endoscopy were: any endoscopy: n=2999; upper: n=2007; lower: n=1078 and ERCP: n=58.

Both genetic and environmental factors influence pregnancy outcome, and we cannot rule out that these co-vary with the risk of GI disease and risk of having an endoscopy. To take intrafamilial confounding into account we compared pregnancy outcome within the same mother (sibling pregnancies).

Ideally, both intrafamilial confounding and underlying disease activity should be adjusted for in the same analysis. This is difficult for dichotomous outcome measures because only births within the same mother where 1 child has a different outcome (eg, preterm birth) than the other (eg, term birth) contributes to the relative risk calculations and few mothers will have contrasting birth outcomes. We addressed this comparing the continuous variables of gestational age and birth weight in 417 mothers undergoing endoscopy in one of several births within <1 year from their index pregnancy exposed to endoscopy.

Finally, to estimate the effect of underlying disease activity, we compared pregnancy outcomes in women having an

endoscopy <1 year before or after pregnancy but never during pregnancy itself vs those who never had a record of endoscopy.

In order to estimate the adjusted relative risks for binary outcomes, we used Poisson regression with cluster robust SEs.¹⁷ For the ordinal outcome variable with categories term birth, moderately preterm birth, and very preterm birth, we used multinomial regression with cluster robust SEs. To avoid mother-specific and time-constant omitted variable bias, we also performed fixed effects Poisson regression with robust SEs for the binary outcomes. In this way, we estimate the within-mother effect of exposure.

For the regression analyses, we adjusted for the potential confounders described in Table 1. The analyses were conducted on observations without missing on the covariates. Only singleton births were used in the analyses. *P* values <.05 were regarded as statistically significant. All tests are 2-sided. All analyses were conducted using Stata, version 13.

Results

Background Data

We identified 1,592,225 pregnancies (Table 1) in 1,002,604 unique women with complete data on all covariates used in this study. Of these some 0.19% (n = 3052) had been exposed to an endoscopy during pregnancy (upper: n = 2025 [0.13%]; lower: n = 1109 [0.07%] and ERCP: n = 58 [$<0.01\%$]). Table 1 presents characteristics of the study participants.

The mean gestational age was not influenced more than marginally in women who underwent endoscopy (no endoscopy: 39.9 weeks; any endoscopy: 39.5 weeks), while mean birth weight was 3562 g and 3479 g, respectively (Table 2). Preterm birth was seen in 4.8% of women

without endoscopy. This compares with 7.6% in women undergoing any endoscopy, a slightly higher percentage in women with lower endoscopy but lower in those with ERCP (Table 2). SGA was noted in 2.5% of reference women compared to 3.6% for those undergoing endoscopy. No difference was seen with regard to the proportion of pregnancies with congenital malformations.

Main Results

Women undergoing endoscopy during pregnancy were at increased risk of all outcomes measures except congenital malformations (Table 3 and Figure 1). In general, risk estimates were higher in women undergoing lower than upper endoscopy. Due to lack of numbers, adjusted relative risks

Table 2. Absolute Number and Percentages of Adverse Pregnancy Outcome According to Endoscopy Status During Pregnancy

Characteristics	Mother without endoscopy N (%)	Mother with any Endoscopy N (%)	Mother with Upper N (%)	Mother with Lower N (%)	Mother with ERCP N (%)
Total	1,589,173	3,052	2,014	1,109	58
Stillbirths	4,852 (0.3)	15 (0.6)	11 (0.5)	4 (0.4)	0 (0)
Live births ^a	1,584,321 (99.7)	3,037 (99.4)	2,025 (99.5)	1,105 (99.6)	58 (100)
Any Preterm birth					
No	1,508,748 (95.2)	2,805 (92.4)	1,875 (93.1)	1,000 (90.5)	55 (94.8)
Yes	75,228 (4.8)	231 (7.6)	139 (6.9)	104 (9.4)	3 (5.2)
Missing data	345 (<0.1)	1 (<0.1)	-	1 (0.1)	-
(Moderate Preterm)	65,645 (4.1)	195 (6.4)	120 (6.0)	85 (7.7)	2 (3.4)
(Very preterm)	9,583 (0.6)	36 (1.2)	19 (0.9)	19 (1.7)	1 (1.7)
Induction of labor					
No	1,397,180 (88.2)	2,513 (82.8)	1,674 (83.2)	911 (82.4)	47 (81.0)
Yes	162,472 (10.3)	492 (16.2)	318 (15.8)	183 (16.6)	9 (15.5)
Missing	24,669 (1.6)	32 (1.1)	22 (1.1)	11 (1.0)	2 (3.4)
Caesarean section					
No	1,355,403 (85.6)	2,429 (80.0)	1,640 (81.4)	857 (77.6)	46 (79.3)
Yes	228,918 (14.4)	308 (20.0)	374 (18.6)	248 (22.4)	12 (20.7)
Stillbirths					
No	1,584,443 (99.7)	2,915 (99.4)	2,014 (99.5)	1,105 (99.6)	58 (100)
Yes	4,850 (0.3)	17 (0.6)	11 (0.5)	4 (0.4)	0 (0)
Apgar score <7 ^b					
No	1,558,265 (98.4)	2,979 (98.1)	1,975 (98.1)	1,082 (97.9)	57 (98.3)
Yes	16,168 (1.0)	40 (1.3)	27 (1.3)	17 (1.5)	0 (0)
Missing	9,888 (0.6)	18 (0.6)	12 (0.6)	6 (0.5)	1 (1.7)
Neonatal death					
No	1,581,779 (99.8)	3,030 (99.8)	2,008 (99.7)	1,103 (99.8)	58 (100)
Yes	2,542 (0.2)	7 (0.2)	6 (0.3)	2 (0.2)	0 (0)
Small for gestational age					
No	1,538,881 (97.1)	2,929 (96.4)	1,937 (96.2)	1,069 (96.7)	57 (98.3)
Yes	39,836 (2.5)	102 (3.6)	73 (3.6)	34 (3.1)	0
Missing	5,604 (0.4)	6 (0.2)	4 (0.2)	2 (0.2)	1 (1.7)
Low birth weight					
No	1,533,574 (96.8)	2,891 (95.2)	1,928 (95.7)	1,038 (93.9)	57 (98.3)
Yes	46,537 (2.4)	142 (4.7)	84 (4.2)	65 (5.9)	0 (0)
Missing	4,210 (0.3)	4 (0.1)	2 (0.1)	2 (0.2)	1 (1.7)
Any major congenital malformation					
No	1,528,166 (96.5)	2,931 (96.5)	1,943 (96.5)	1,067 (96.6)	55 (94.8)
Yes	56,155 (3.5)	106 (3.5)	71 (3.5)	38 (3.4)	3 (5.2)
Gestational age (wk), mean \pm SD	39.9 \pm 1.8	39.5 \pm 2.1	39.6 \pm 2.0	39.4 \pm 2.2	39.3 \pm 1.9
Birth weight (g), mean \pm SD	3562 \pm 556	3479 \pm 596	3479 \pm 586	3478 \pm 627	3524 \pm 514

^aAll percentages except for stillbirths were based on livebirths.

^bApgar score <7 at 5 minutes.

Table 3. Endoscopy During Pregnancy and Relative Risk of Adverse Pregnancy Outcome (All Women)

Characteristics	Mother with any Endoscopy <i>RR (crude), 95%CI</i>	Mother with any Endoscopy <i>ARR, 95%CI</i>	Mother with Upper <i>RR (crude), 95%CI</i>	Mother with Upper <i>ARR, 95%CI</i>	Mother with Lower <i>RR (crude), 95%CI</i>	Mother with Lower <i>ARR, 95%CI</i>	Mother with ERCP ^b <i>RR (crude), 95%CI</i>
Any Preterm birth							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.60; 1.41-1.81	1.54; 1.36-1.75	1.45; 1.24-1.71	1.28; 1.09-1.51	1.98; 1.65-2.38	1.94; 1.61-2.33	1.09; 0.36-3.27
Term birth	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate preterm ^a	1.60; 1.38-1.85	1.55; 1.34-1.80	1.47; 1.22-1.77	1.31; 1.09-1.58	1.95; 1.56-2.44	1.92; 1.53-2.40	0.83; 0.20-3.42
Very preterm ^a	2.02; 1.45-2.81	1.91; 1.37-2.67	1.59; 1.01-2.51	1.30; 0.82-2.05	2.99; 1.90-4.71	2.98; 1.87-4.74	2.86; 0.40-20.64
Induction of labour							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.57; 1.45-1.70	1.41; 1.30-1.52	1.53; 1.38-1.69	1.32; 1.19-1.46	1.60; 1.40-1.83	1.45; 1.27-1.65	1.54; 0.85-2.80
Cesarean section							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.39; 1.29-1.49	1.25; 1.16-1.34	1.28; 1.17-1.41	1.11; 1.01-1.22	1.55; 1.39-1.74	1.45; 1.30-1.62	1.43; 0.86-2.37
Stillbirth							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.61; 0.97-2.67	1.45; 0.87-2.40	1.78; 0.99-3.21	1.50; 0.82-2.74	1.18; 0.44-3.13	1.13; 0.42-3.06	NC
Apgar score<7							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.29; 0.95-1.76	1.20; 0.88-1.64	1.31; 0.90-1.91	1.16; 0.80-1.69	1.51; 0.94-2.41	1.44; 0.90-2.31	NC
Neonatal death							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.44; 0.68-3.01	1.54; 0.73-3.24	1.86; 0.83-4.13	1.87; 0.85-4.13	1.13; 0.28-4.50	1.19; 0.30-4.69	NC
Small for gestational age							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.33; 1.10-1.61	1.30; 1.07-1.57	1.44; 1.15-1.80	1.33; 1.06-1.67	1.22; 0.88-1.70	1.21; 0.87-1.69	NC
Low birth weight							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.59; 1.35-1.87	1.52; 1.30-1.79	1.42; 1.15-1.75	1.25; 1.01-1.54	2.00; 1.58-2.53	1.95; 1.53-2.49	NC
Any major congenital malformation							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.98; 0.82-1.19	1.00; 0.83-1.20	0.99; 0.79-1.25	1.00; 0.80-1.26	0.97; 0.71-1.33	0.98; 0.72-1.34	1.46; 0.48-4.39
Birthweek (<i>wk</i>)	-0.3; -0.4- to -0.2	-0.3; -0.4 to -0.2	-0.2; -0.3 to -0.2	-0.2; -0.3 to -0.1	-0.4; -0.6 to -0.3	-0.4; -0.6 to -0.3	-0.5; -1.0 to 0.0
Birthweight (<i>g</i>)	-82; -104 to -61	-74; -95 to -54	-82; -108 to -56	-66; -91 to -41	-83; -120 to -46	-70; -107 to -34	-37; -169 to -95

RR, Relative risk; ARR, Adjusted Relative Risk; NC, Not calculated.

^aTerm birth (>37 gestational weeks) was used as the reference when examining the risk of moderate preterm and very preterm. Since the outcome in these analyses was not dichotomous we calculated relative rate ratios and adjusted relative rate ratio through multinomial regression.

^bDue to lack of numbers, adjusted relative risks could not be calculated in mothers having an ERCP during pregnancy.

could not be calculated in mothers having an ERCP during pregnancy. None of the crude risk estimates attained statistical significance in ERCP-exposed mothers and most RRs were between 1 and 1.5. Adjusting for covariates, offspring to women undergoing endoscopy during pregnancy had a slightly lower birth weight and shorter gestational age (Table 3).

Using full colonoscopy during pregnancy as reference, we found that women undergoing sigmoidoscopy were at increased risk of preterm birth (RR, 1.66; 95% confidence interval [CI], 1.06–2.60), but at no increased risk of SGA (ARR, 1.23; 95% CI, 0.57–2.64) or congenital malformation (ARR, 0.71; 95% CI, 0.37–1.38). No relative risk was calculated for stillbirth due to lack of positive events.

Of the 15 stillbirths to women with endoscopy, none occurred <17 days after endoscopy (median interval, 168 days). Examining the time interval between endoscopy in the third trimester and birth, we found no evidence that late endoscopy might trigger childbirth (Figure 2). We found no increased risks of SGA according to trimester of endoscopy (trimesters 1, 2, and 3, respectively: reference; ARR, 0.89; ARR, 1.04). Neither was there any difference in the risk of congenital malformations (trimesters 1, 2, and 3, respectively: reference; ARR, 1.03; ARR, 1.05).

Pregnancy Outcomes According to Gastrointestinal Disease Status

Restricting our data to women who never had a diagnosis of IBD, celiac disease, or hepatobiliary disease, risk estimates decreased, but most often remained statistically significantly increased (Supplementary Material and Figure 1). When we instead studied women with any of these GI diseases (combined or separately), the risk of adverse pregnancy outcome such as preterm birth was higher in women undergoing endoscopy (Supplementary Material and Figure 1).

Comparison With Controls Having Endoscopy <1 Year Before or After Pregnancy

Restricting our control population to women with endoscopy <1 year before or after pregnancy, only preterm birth (ARR, 1.16) and induction of labor (ARR, 1.11) remained significantly increased in pregnancies exposed to endoscopy (Supplementary Material and Figure 1). Limiting our analyses to women without GI disease (where the potential disease activity should play less of a role), endoscopy was not linked to any of our outcomes (Supplementary Material and Figure 1).

Within-Mother Analyses (Sibling Pregnancies)

To address intrafamilial factors, we then examined pregnancy outcome in siblings with the same mother. In this analysis, endoscopy exposure was associated with preterm birth (ARR, 1.32), cesarean section (ARR, 1.10) and low birth weight (ARR, 1.45) (Supplementary Material and Figure 1).

Within-Mother Analyses <1 Year Before or After Endoscopy-Exposed Pregnancy

Restricting controls to sibling pregnancies <1 year within the index pregnancy, pregnancies exposed to endoscopy did not differ with regard to gestational age (adjusted mean difference, –0.8 days; $P = .395$) or birth weight (adjusted mean difference, +32 g; $P = .924$). These differences are equivalent to a reduction of –0.3% in pregnancy duration and an increase of +0.7% in birth weight.

Women With an Endoscopy Before or After Pregnancy

Compared with women never having an endoscopy, those women having an endoscopy before or after pregnancy (but never during pregnancy) were also at increased risk of adverse pregnancy outcome, such as preterm birth (ARR, 1.38) and stillbirth (ARR, 1.47) (Supplementary Material and Figure 1).

Discussion

In this population-based study, we compared pregnancy outcomes in 3000 pregnancies exposed to endoscopy with about 1.6 million pregnancies without endoscopy exposure. While endoscopy was linked to adverse pregnancy outcome, we suggest that most if not all of the excess risks are due to disease activity. Also women having an endoscopy outside pregnancy were at increased risk of adverse pregnancy outcomes.

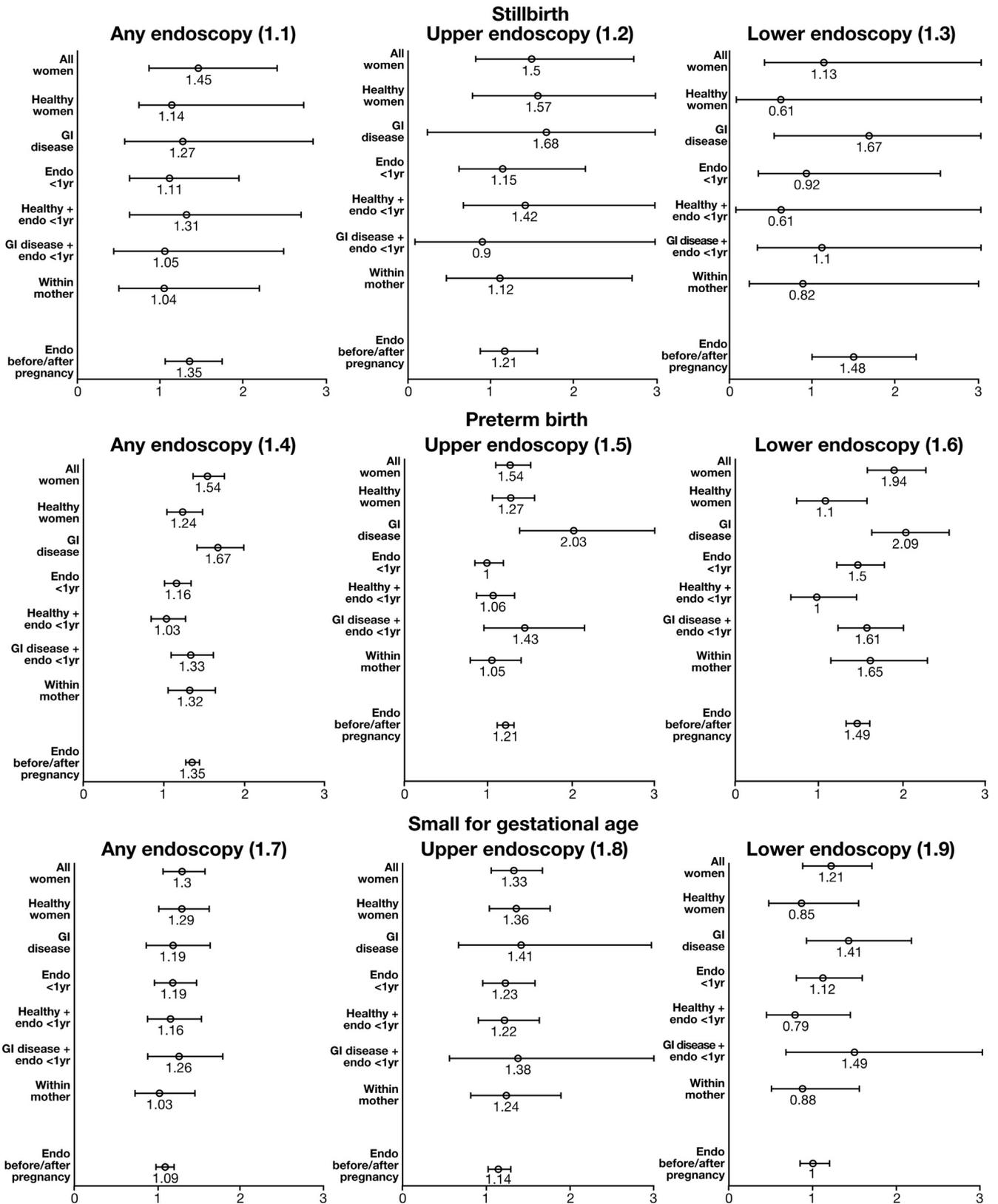
Earlier Literature

In 1996, Cappell et al published 2 papers on pregnancy outcomes in women undergoing endoscopy.^{2,3} They concluded that endoscopy was not linked to adverse fetal outcomes, but stillbirths and 1 involuntary abortion among women with endoscopy were not considered because they took place in high-risk pregnancies. More importantly, the studies only had the statistical power to detect a many-fold increased risk of preterm birth, for example, while the current study had the power to detect a 20% increase in preterm birth. More recent studies^{5,10} have shown conflicting results, but study power has been low.

Strengths and Limitations

The main strength of this study is the high statistical power and our use of both general population controls and sibling controls. Overall, there were 4852 stillbirths during follow-up, 15 of which occurred in women undergoing endoscopy during pregnancy. Importantly, none of these took place just after endoscopy. Other strengths include our adjustment for potential confounders and the control for intrafamilial factors.

Among the limitations is our lack of knowledge about the duration of the endoscopy, the type of sedation and bowel preparation used, the position of the patient at endoscopy, and the indication for the procedure. There are no Swedish



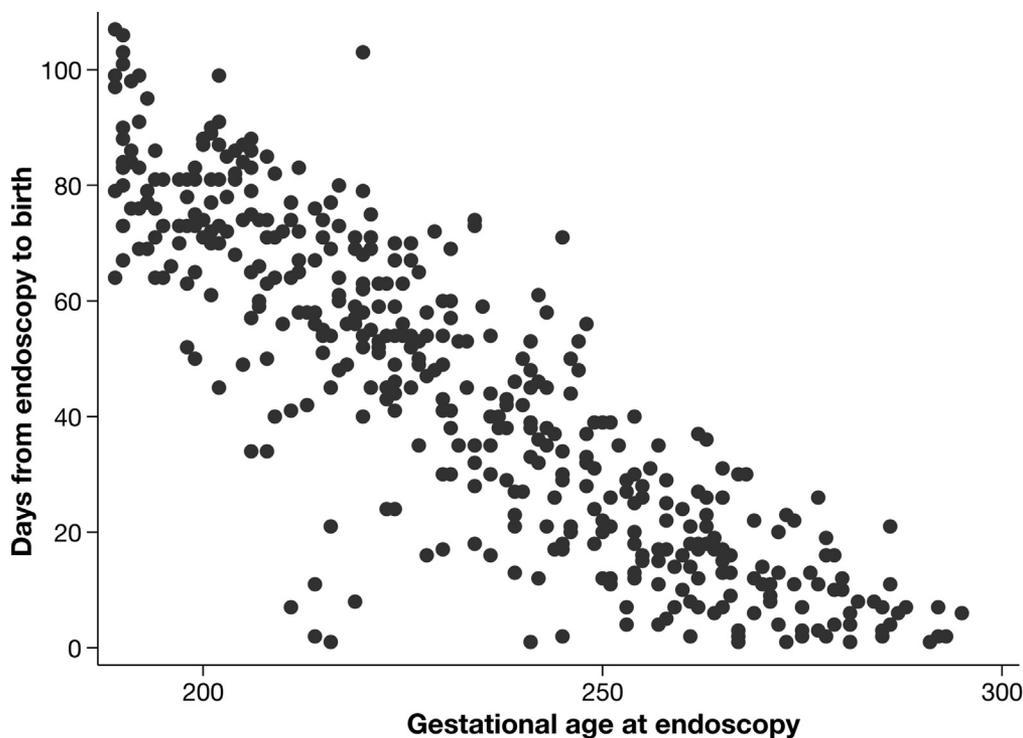


Figure 2. Relationship between days from endoscopy to birth (y-axis) according to gestational age at endoscopy (x-axis).

national data on sedation in endoscopy, but drugs frequently used are midazolam, fentanyl, and propofol. Given the minimal excess risks seen in endoscopy during pregnancy when we considered proxies for disease activity (eg, through using women undergoing endoscopy before and after pregnancy as reference) and familial factors, it is unlikely that any of the drugs, including anesthesia, had any major effect on pregnancy outcomes, including on congenital malformation, but smaller risk increases due to individual drugs cannot be ruled out. Also, we could not examine early spontaneous abortions because stillbirths in Sweden are only registered from gestational week 22 (and until 2008 from week 28) and, therefore, our data on stillbirths are restricted to the second half of pregnancy. We did not correct for multiple comparisons. We aimed to examine the safety of endoscopy during pregnancy and, had we corrected for the large number of comparisons (in order to

reduce the risk of type 1 error), we would have been highly likely to miss minor excess risks in pregnancies exposed to endoscopies.

Finally, our data on smoking were self-reported and may have underestimated the true prevalence of smoking (although adjustment for smoking had no major effect on our RRs).

We used several approaches to tackle the lack of detailed information on disease activity, for instance, we used pregnancies taking place <1 year before or after the index pregnancy as reference, and also stratified for presence of GI disease. However, we acknowledge the lack of direct information on disease treatment and on actual disease activity indices, such as Mayo Score and Crohn's Disease Activity Index in patients with IBD. Undiagnosed celiac disease and newly diagnosed celiac disease (when the diet may not yet have influenced mucosal healing) have both been linked to

Figure 1. Risk of stillbirth, preterm birth, small for gestational age, and congenital malformations. *Upper 95% CI >3.00. See Table 3 and Supplementary Material for exact data. Endo, endoscopy. GI includes celiac disease, IBD, or liver disease in Figure 1. *All women:* Endoscopy during pregnancy and relative risk of adverse pregnancy outcome (corresponds to Table 3). *Healthy women:* Endoscopy during pregnancy and risk for adverse pregnancy outcome in healthy women (corresponds to Supplementary Table 2). *GI disease:* Endoscopy during pregnancy and risk for adverse pregnancy outcome in women with IBD, celiac disease, or hepatobiliary disease (Supplementary Tables 3 and 4). *Endo <1yr:* Pregnancies exposed to endoscopy compared to [reference] pregnancies where the woman had an endoscopy <1 year before or after pregnancy (Supplementary Table 5). *Healthy + endo <1yr:* Mothers without celiac disease, IBD, or liver disease. Pregnancies exposed to endoscopy compared to [reference] pregnancies where the woman had an endoscopy <1 year before or after pregnancy (Supplementary Table 6). *GI disease + endo <1yr:* Mothers with celiac disease, IBD, or liver disease. Pregnancies exposed to endoscopy compared to [reference] pregnancies where the woman had an endoscopy <1 year before or after pregnancy (Supplementary Table 7). *Within mother:* Sibling comparisons. Risk of adverse pregnancy outcome in the same mother when exposed to endoscopy vs not exposed) (Supplementary Table 8). *Endo before/after pregnancy:* Risk of adverse pregnancy outcome in women with endoscopy <1 year before or after pregnancy but not during pregnancy vs women who have no record of endoscopy (Supplementary Table 9).

adverse pregnancy outcome,¹⁸ and so has treatment of IBD.¹⁹ It should also be noted that adverse pregnancy outcome was, in fact, more common in women having an endoscopy just before or after pregnancy (these women never had an endoscopy during pregnancy).

Although we had great power to examine upper and lower endoscopy, the number of women undergoing ERCP during pregnancy was limited, and smaller excess risks cannot be ruled out. Finally, bias is an issue in all observational studies. While selection bias is unlikely (>99% of all somatic inpatient care in Sweden is registered in the patient registry, and this registry also includes hospital-based outpatient care since 2001¹⁴), we cannot rule out other forms of bias. We tried to minimize bias through comparing pregnancies to the same mother within <1 year from the index pregnancy. Short of trials where pregnant women are randomly assigned to undergo endoscopy, we believe that our study design offers the best chance to examine the effects of endoscopy during pregnancy. That said, we acknowledge that residual confounding is still possible.²⁰

Clinical Implications

Earlier recommendations suggest that endoscopy should only be performed during pregnancy if there are strong indications and, if so, not during the second trimester.¹³ Our study shows that endoscopy is unlikely to have a more than marginal influence on pregnancy outcome independently of trimester. Neither does it seem that sigmoidoscopy is preferable to a full colonoscopy in the pregnant woman. We cannot explain this latter finding, but it is possible that in women with particularly severe GI disease where endoscopy is inevitable, the physician will prefer a sigmoidoscopy rather than a full colonoscopy and, under such circumstances, the sigmoidoscopy will signal a more severe disease.

Conclusions

Adverse pregnancy outcomes are rare in women undergoing endoscopy during pregnancy. Potential excess risks, if any, seem minimal and should be weighed against the need for timely investigation and treatment of women where an underlying GI disease may be a more severe threat to pregnancy outcome than the endoscopy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2016.10.016>.

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Received August 24, 2016. Accepted October 14, 2016.

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Acknowledgments

This project (2008/1182-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on September 3, 2008.

Data sharing: Other researchers can apply for our data through the Swedish National Board of Health and Welfare.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of interest

The authors disclose no conflicts.

Funding

This project was supported by grants from the Swedish Society of Medicine and the Stockholm County Council, and the Swedish Research Council (grant 2013-2429).

Supplementary Material

Definition of Gastrointestinal Diseases

IBD: (Crohn: ICD-9: 555 (ICD-10: K50 (Ulcerative colitis: ICD-9: 556 (ICD-10: K51)

Celiac disease (ICD-9: 579 (ICD-10: K90).

Definition of Congenital Malformations

For live-born children, information on congenital abnormalities diagnosed during the first year of life was collected from the Birth and Patient Registry in Sweden and the Danish National Patient Registry. The codes used to identify congenital abnormalities were 740–759 in International Statistical Classification of Diseases and Related Health Problems (ICD)-9 and Q00 to Q89 in ICD-10. Diagnoses of congenital dislocation of the hip (754D in ICD-9 and Q65.0–6 in ICD-10) and undescended testis (752F in ICD-9 and Q53 in ICD-10) were not included because of their poor expected validity. Also excluded were preauricular appendage or tag (744B in ICD-9 and Q17.0 in ICD-10), tongue tie (750A in ICD-9 and Q38.1 in ICD-10), congenital non-neoplastic nevus (Q82.5 in ICD-10), chromosomal abnormalities (758 in ICD-9 and Q90–99 in ICD-10), and congenital malformation syndromes due to known exogenous causes (Q86 in ICD-10).

Definition of Procedures

Esophagogastroduodenoscopy: 2861, 2880, 2881, 4480, 4483, 4486, 4487, 4488, 4489, 4490, 9021, 4686, 4687, 9003, 9004, 9021, UJC, UJD, UJF02, UJF05.

Colonoscopy and sigmoidoscopy (*): 9011, 9012*, 9023, 4685*, 4688, 4689, 4674, 4684, UJF32, UJF35, UJF42*, UJF45*.

ERCP: 9014, 5388, 5394, UJK02, UJK05.

Supplementary Table 1. Definitions of Hepatobiliary Diseases

Disease group	ICD-9	ICD-10
Infectious hepatitis	70	B15–19
Hepatitis A		B15
Hepatitis B		B16 + B18.0 + B18.1
Hepatitis C		B17.1 + B18.2
Bilirubin disorders	277E	E80
Hemochromatosis	275A	E83.1
Wilson	275B	E83.0
Portal vein thrombosis	452	I81
Budd–Chiari	453A	I82
Liver alcoholic	571A–D	K70
Liver toxic disease	573D	K71
		K70.4 K71.1
Liver failure	570 572C	K72
Liver chronic hepatitis	571E	K73
Liver fibrosis cirrhosis	571 571F	K74
Primary biliary cirrhosis	571G	K74.3
		K75.4 K75.5
Liver other inflammatory	572	K75.9
Liver other	573	K76
Liver not classified	571W 571X	K77
Gallstone disease	574	K80
Cholecystitis	575	K81
Gallbladder other	576	K82
Cholangitis	576B	K83
Primary sclerosing cholangitis		K83.0A
Gallbladder biliary pancreas, other		K87
Post-cholecystectomy syndrome		K91.5
Icterus	782E	R17
Hepatosplenomegaly	789B	R16.0
Imaging		R93.2
Varices	456A–C	I85
Portal hypertension	572D	K76.6
Ascites	789F	R18
The following operation codes indicated liver disease		
	5350–5359	JKA20 JKA21
		JKB11 JKB30
	5388 5394	JKE00 JKE02 JKE06
	9014	JKE12
	5341	JKE15 JKE18 JFK10

ICD, International Statistical Classification of Diseases and Related Health Problems.

Supplementary Table 2. Endoscopy During Pregnancy and Risk for Adverse Pregnancy Outcome in Healthy Women (Without Any Diagnosis of Inflammatory Bowel Disease, Celiac Disease, or Hepatobiliary Disease)

Characteristics	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.24 (1.04 to 1.48)	1.27 (1.05 to 1.55)	1.10 (0.75 to 1.61)
Moderate preterm	1.23 (1.00 to 1.51)	1.28 (1.02 to 1.60)	1.03 (0.66 to 1.61)
Very preterm	1.44 (0.88 to 2.33)	1.41 (0.83 to 2.39)	1.64 (0.68 to 3.98)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.35 (1.21 to 1.50)	1.33 (1.18 to 1.50)	1.23 (0.98 to 1.55)
Cesarean section			
No	Ref	Ref	Ref
Yes	1.11 (1.01 to 1.22)	1.06 (0.95 to 1.18)	1.23 (1.02 to 1.49)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.14 (0.74 to 2.72)	1.57 (0.78 to 3.18)	0.61 (0.08 to 4.49)
Apgar score <7			
No	Ref	Ref	Ref
Yes	1.17 (0.79 to 1.74)	1.25 (0.82 to 1.90)	1.34 (0.65 to 2.76)
Neonatal death			
No	Ref	Ref	Ref
Yes	1.77 (0.74 to 4.26)	2.14 (0.92 to 4.99)	1.19 (0.18 to 7.84)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.29 (1.01 to 1.63)	1.36 (1.04 to 1.76)	0.85 (0.47 to 1.53)
Low birth weight			
No	Ref	Ref	Ref
Yes	1.20 (0.95 to 1.52)	1.21 (0.93 to 1.56)	1.01 (0.67 to 1.79)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	1.01 (0.80 to 1.28)	1.06 (0.82 to 1.37)	0.96 (0.59 to 1.55)
Birth week	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)	0.0 (-0.2 to 0.1)
Birth weight, g	-50 (-76 to -27)	-70 (-98 to -42)	28 (-21 to 078)

NOTE. Values are ARR (95% CI).

Supplementary Table 3. Endoscopy During Pregnancy and Risk for Adverse Pregnancy Outcome in Women With Celiac Disease, Inflammatory Bowel Disease or Hepatobiliary Disease (Combined)^a

Characteristics	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.67 (1.41 to 1.99)	2.03 (1.37 to 2.99)	2.09 (1.67 to 2.61)
Moderate preterm	1.69 (1.37 to 2.09)	2.16 (1.32 to 3.54)	2.13 (1.61 to 2.81)
Very preterm	2.19 (1.38 to 3.47)	2.88 (0.90 to 9.27)	3.51 (1.88 to 6.53)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.29 (1.14 to 1.46)	1.09 (0.75 to 1.58)	1.34 (1.11 to 1.61)
Cesarean section			
No	Ref	Ref	Ref
Yes	1.27 (1.15 to 1.41)	1.20 (0.94 to 1.54)	1.16 (1.00 to 1.35)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.27 (0.57 to 2.83)	1.68 (0.23 to 12.44)	1.67 (0.53 to 5.28)
Apgar score <7			
No	Ref	Ref	Ref
Yes	1.12 (0.69 to 1.83)	0.99 (0.25 to 3.99)	1.30 (0.66 to 2.55)
Neonatal death			
No	Ref	Ref	Ref
Yes	0.94 (0.23 to 3.80)	4.88 (0.64 to 36.94)	1.90 (0.23 to 15.91)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.19 (0.86 to 1.64)	1.41 (0.67 to 2.96)	1.41 (0.92 to 2.16)
Low birth weight			
No	Ref	Ref	Ref
Yes	1.73 (1.38 to 2.16)	1.81 (1.05 to 3.10)	2.20 (1.65 to 2.95)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	0.95 (0.70 to 1.30)	0.83 (0.35 to 1.96)	0.92 (0.60 to 1.42)
Birth week	-0.3 (-0.5 to -0.2)	-0.3 (-0.7 to 0.0)	-0.5 (-0.7 to -0.3)
Birth weight, g	-93 (-129 to -57)	-132 (232 to -31)	-119 (-174 to -65)

NOTE. Values are ARR (95% CI).

^aUpper endoscopy comparisons restricted to women with a lifetime diagnosis of celiac disease. Lower endoscopy comparisons restricted to women with a lifetime diagnosis of IBD. Any endoscopy comparisons restricted to women with celiac disease, IBD, or hepatobiliary disease (see text for definitions).

Supplementary Table 4. Endoscopy During Pregnancy and Risk for Adverse Pregnancy Outcome in Women With Celiac Disease, Inflammatory Bowel Disease, or Hepatobiliary Disease (Separate Categories)^a

Characteristics	Celiac disease			IBD			Hepatobiliary disease		
	Mother with any endoscopy	Mother with upper	Mother with lower	Mother with any endoscopy	Mother with upper	Mother with lower	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.36 (0.76 to 2.43)	1.02 (0.48 to 2.17)	2.37 (1.00 to 5.63)	2.19 (1.77 to 2.70)	3.35 (2.19 to 5.12)	2.09 (1.67 to 2.61)	1.10 (0.79 to 1.51)	1.16 (0.81 to 1.67)	1.21 (0.62 to 2.32)
Moderate preterm	1.56 (0.81 to 3.00)	1.13 (0.49 to 2.60)	2.87 (1.05 to 7.85)	2.23 (1.71 to 2.91)	3.79 (2.05 to 6.99)	2.13 (1.61 to 2.81)	1.06 (0.73 to 1.55)	1.22 (0.80 to 1.85)	1.05 (0.47 to 2.36)
Very preterm	NC	NC	NC	3.84 (2.15 to 6.87)	7.47 (2.23 to 25.07)	3.51 (1.88 to 6.53)	1.37 (0.61 to 3.07)	0.93 (0.30 to 2.90)	2.37 (0.58 to 9.66)
Induction of labor									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.13 (0.75 to 1.70)	1.00 (0.61 to 1.64)	1.67 (0.86 to 3.22)	1.34 (1.12 to 1.60)	1.38 (0.83 to 2.32)	1.34 (1.11 to 1.61)	1.34 (1.13 to 1.60)	1.30 (1.06 to 1.60)	1.63 (1.16 to 2.28)
Cesarean section									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.79 (0.54 to 1.17)	0.91 (0.62 to 1.34)	0.51 (0.17 to 1.53)	1.20 (1.04 to 1.38)	1.62 (1.19 to 2.22)	1.16 (1.00 to 1.35)	1.23 (1.06 to 1.44)	1.19 (1.00 to 1.42)	1.39 (0.98 to 1.97)
Stillbirth									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.29 (0.30 to 17.66)	2.88 (0.36 to 22.88)	NC	2.09 (0.75 to 5.82)	4.43 (0.59 to 33.04)	1.67 (0.53 to 5.28)	1.23 (0.40 to 3.80)	1.65 (0.54 to 5.09)	NC
Apgar score <7									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.29 (0.32 to 5.15)	0.82 (0.11 to 5.93)	2.70 (0.44 to 16.64)	1.34 (0.71 to 2.55)	1.26 (0.18 to 9.01)	1.30 (0.66 to 2.55)	0.90 (0.41 to 2.01)	1.02 (0.43 to 2.47)	0.76 (0.11 to 5.35)
Neonatal death									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	7.43 (0.75 to 73.65)	9.46 (0.89 to 101.12)	NC	1.71 (0.20 to 14.21)	NC	1.90 (0.23 to 15.91)	NC	NC	NC
Small for gestational age									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.26 (0.04 to 1.84)	0.34 (0.05 to 2.41)	NC	1.39 (0.92 to 2.10)	2.69 (1.19 to 6.08)	1.41 (0.92 to 2.16)	1.05 (0.63 to 1.75)	1.33 (0.78 to 2.26)	0.74 (0.19 to 2.88)
Low birth weight									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.65 (0.22 to 1.95)	0.84 (0.28 to 2.52)	NC	2.23 (1.69 to 2.94)	2.97 (1.61 to 5.47)	2.20 (1.65 to 2.95)	1.15 (0.76 to 1.75)	1.36 (0.87 to 2.14)	1.06 (0.40 to 2.79)
Any major congenital malformation									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.48 (0.12 to 1.90)	0.64 (0.16 to 2.54)	NC	0.93 (0.62 to 1.41)	1.11 (0.37 to 3.36)	0.92 (0.60 to 1.42)	0.83 (0.51 to 1.38)	0.85 (0.48 to 1.53)	0.26 (0.04 to 1.81)
Birth week	0.0 (-0.3 to 0.3)	0.1 (-0.2 to 0.5)	-0.4 (-1.0 to 0.2)	-0.6 (-0.7 to -0.4)	-1.0 (-1.6 to -0.4)	-0.5 (-0.7 to -0.3)	-0.2 (-0.3 to 0.0)	-0.1 (-0.3 to 0.1)	-0.4 (-0.8 to 0.0)
Birth weight, g	-42 (-129 to 46)	-42 (-148 to 63)	-46 (-185 to 93)	-128 (-181 to 75)	-267 (-445 to -90)	-119 (-174 to -65)	-44 (-95 to 8)	-41 (-103 to 21)	-58 (-169 to 53)

NOTE. Values are ARR (95% CI).

NC, not calculated due to lack of data.

^aUpper endoscopy comparisons restricted to women with a lifetime diagnosis of celiac disease. Lower endoscopy comparisons restricted to women with a lifetime diagnosis of IBD. Any endoscopy comparisons restricted to women with celiac disease, IBD, or hepatobiliary disease (see text for definitions).

Supplementary Table 5. All Women: Pregnancies Exposed to Endoscopy Compared to [Reference] Pregnancies Where the Woman Had an Endoscopy <1 Year Before or After Pregnancy

Characteristics	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.16 (1.01–1.34)	1.00 (0.84–1.19)	1.50 (1.24–1.83)
Moderate preterm	1.13 (0.96–1.33)	0.99 (0.81–1.21)	1.44 (1.14–1.83)
Very preterm	1.52 (1.03–2.23)	1.06 (0.65–1.73)	2.43 (1.50–3.96)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.11 (1.02–1.22)	1.05 (0.95–1.17)	1.17 (1.02–1.34)
Cesarean section			
No	Ref	Ref	Ref
Yes	1.02 (0.94–1.10)	0.93 (0.85–1.02)	1.18 (1.06–1.33)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.11 (0.63–1.94)	1.15 (0.61–2.15)	0.92 (0.34–2.52)
Apgar score <7			
No	Ref	Ref	Ref
Yes	1.06 (0.75–1.49)	1.05 (0.70–1.58)	1.31 (0.80–2.15)
Neonatal death			
No	Ref	Ref	Ref
Yes	1.08 (0.49–2.56)	1.46 (0.60–3.58)	0.79 (0.18–3.43)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.19 (0.96–1.47)	1.23 (0.96–1.58)	1.12 (0.80–1.58)
Low birth weight			
No	Ref	Ref	Ref
Yes	1.18 (0.98–1.41)	0.99 (0.79–1.24)	1.56 (1.21–2.00)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	0.90 (0.73–1.10)	0.92 (0.72–1.17)	0.88 (0.64–1.21)
Birth week	–0.1 (–0.2 to 0.0)	0.0 (–0.1 to 0.1)	–0.2 (–0.4 to –0.1)
Birth weight, g	–34 (–57 to –11)	–28 (–54 to –1)	–37 (–74 to 0)

NOTE. Values are ARR (95% CI).

Supplementary Table 6. Mothers Without Celiac Disease, Inflammatory Bowel Disease, or Liver Disease

Characteristics	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.03 (0.84–1.27)	1.06 (0.86–1.32)	1.00 (0.68–1.48)
Moderate preterm	1.01 (0.80–1.28)	1.05 (0.82–1.35)	0.93 (0.58–1.48)
Very preterm	1.19 (0.68–2.09)	1.20 (0.66–2.18)	1.46 (0.58–3.70)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.07 (0.95–1.20)	1.06 (0.93–1.21)	1.01 (0.81–1.28)
Cesarean section			
No	Ref	Ref	Ref
Yes	0.97 (0.87–1.08)	0.93 (0.83–1.05)	1.11 (0.91–1.34)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.31 (0.63–2.69)	1.42 (0.67–3.02)	0.61 (0.08–4.65)
Apgar score <7			
No	Ref	Ref	Ref
Yes	1.10 (0.71–1.71)	1.21 (0.76–1.93)	1.30 (0.62–2.76)
Neonatal death			
No	Ref	Ref	Ref
Yes	1.17 (0.44–3.14)	1.57 (0.59–4.14)	0.81 (0.11–5.82)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.16 (0.88–1.53)	1.22 (0.91–1.63)	0.79 (0.44–1.44)
Low birth weight			
No	Ref	Ref	Ref
Yes	0.97 (0.75–1.26)	0.98 (0.74–1.29)	0.95 (0.58–1.56)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	0.92 (0.71–1.19)	0.98 (0.74–1.29)	0.87 (0.53–1.42)
Birth week	0.0 (–0.1 to 0.1)	–0.1 (–0.2 to 0.1)	0.1 (–0.1 to 0.2)
Birth weight, g	–31 (–59 to –3)	–49 (–79 to –18)	39 (–12 to 90)

NOTE. Values are ARR (95% CI). Pregnancies exposed to endoscopy compared to [reference] pregnancies where the woman had an endoscopy <1 year before or after pregnancy.

Supplementary Table 7. Mothers with Celiac Disease, Inflammatory Bowel Disease, or Liver Disease^a

Characteristics ^b	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.33 (1.09 to 1.61)	1.43 (0.95 to 2.15)	1.61 (1.25 to 2.06)
Moderate preterm	1.30 (1.03 to 1.64)	1.47 (0.87 to 2.45)	1.61 (1.18 to 2.19)
Very preterm	1.99 (1.17 to 3.38)	2.03 (0.57 to 7.15)	2.58 (1.24 to 5.37)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.18 (1.03 to 1.35)	0.99 (0.68 to 1.46)	1.30 (1.05 to 1.59)
Cesarean section			
No	Ref	Ref	Ref
Yes	1.08 (0.96 to 1.21)	1.08 (0.83 to 1.41)	1.04 (0.89 to 1.22)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.05 (0.44 to 2.48)	0.90 (0.08 to 11.37)	1.10 (0.32 to 3.84)
Apgar score <7			
No	Ref	Ref	Ref
Yes	0.98 (0.58 to 1.67)	1.07 (0.26 to 4.48)	1.37 (0.64 to 2.92)
Neonatal death			
No	Ref	Ref	Ref
Yes	1.09 (0.21 to 5.65)	NC	0.93 (0.09 to 10.13)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.26 (0.88 to 1.79)	1.38 (0.61 to 3.11)	1.49 (0.93 to 2.40)
Low birth weight			
No	Ref	Ref	Ref
Yes	1.50 (1.16 to 1.93)	1.37 (0.78 to 2.41)	1.87 (1.35 to 2.60)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	0.88 (0.63 to 1.23)	0.97 (0.41 to 2.32)	0.96 (0.61 to 1.52)
Birth week	-0.2 (-0.3 to 0.0)	-0.1 (-0.4 to 0.3)	-0.3 (-0.6 to -0.1)
Birth weight, g	-43 (-82 to -5)	-70 (-174 to 33)	-76 (-134 to -18)

NOTE. Values are ARR (95% CI).

NC, not calculated due to lack of data.

^aPregnancies exposed to endoscopy compared to [reference] pregnancies where the woman had an endoscopy <1 year before or after pregnancy.

^bUpper endoscopy comparisons restricted to women with a lifetime diagnosis of celiac disease. Lower endoscopy comparisons restricted to women with a lifetime diagnosis of IBD. Any endoscopy comparisons restricted to women with celiac disease, IBD, or hepatobiliary disease (see text for definitions).

Supplementary Table 8. Sibling Comparisons: Risk of Adverse Pregnancy Outcome in the Same Mother (When Exposed to Endoscopy vs Not Exposed)

Characteristics	Mother with any endoscopy	Mother with upper	Mother with lower
Any preterm birth			
No	Ref	Ref	Ref
Yes	1.32 (1.05 to 1.64)	1.05 (0.78 to 1.40)	1.65 (1.16 to 2.35)
Induction of labor			
No	Ref	Ref	Ref
Yes	1.13 (0.99 to 1.29)	1.13 (0.96 to 1.33)	1.04 (0.83 to 1.31)
Cesarean section			
No	Ref	Ref	Ref
Yes	1.10 (1.00 to 1.21)	1.04 (0.93 to 1.17)	1.18 (1.01 to 1.39)
Stillbirth			
No	Ref	Ref	Ref
Yes	1.04 (0.50 to 2.18)	1.12 (0.46 to 2.72)	0.82 (0.23 to 2.97)
Apgar score <7			
No	Ref	Ref	Ref
Yes	0.98 (0.56 to 1.72)	1.15 (0.60 to 2.21)	0.96 (0.42 to 2.21)
Neonatal death			
No	Ref	Ref	Ref
Yes	0.90 (0.35 to 2.33)	1.53 (0.49 to 4.78)	0.70 (0.15 to 3.31)
Small for gestational age			
No	Ref	Ref	Ref
Yes	1.03 (0.73 to 1.45)	1.24 (0.82 to 1.89)	0.88 (0.50 to 1.54)
Low birth weight			
No	Ref	Ref	Ref
Yes	1.45 (1.05 to 2.00)	1.21 (0.79 to 1.84)	1.96 (1.22 to 3.15)
Any major congenital malformation			
No	Ref	Ref	Ref
Yes	0.81 (0.58 to 1.13)	0.75 (0.50 to 1.13)	0.87 (0.50 to 1.54)
Birth week	-0.2 (-0.3 to -0.1)	0.0 (-0.1 to 0.1)	-0.4 (-0.5 to -0.2)
Birth weight, g	-41 (-65 to -16)	-20 (-49 to 10)	-64 (-107 to -20)

NOTE. Values are ARR (95% CI). We did not examine the risk of moderate and very preterm effect because multinomial regressions cannot be calculated using fixed effects. Therefore, we only present data on "preterm birth" (yes/no).

Supplementary Table 9. Risk of Adverse Pregnancy Outcome in Women With Endoscopy <1 Year Before or After Pregnancy but Not During Pregnancy vs Women Who Have No Record of Endoscopy

Characteristics	Mother with any endoscopy		Mother with upper		Mother with lower	
	RR (crude) (95% CI)	ARR (95% CI)	RR (crude) (95% CI)	ARR (95% CI)	RR (crude) (95% CI)	ARR (95% CI)
Any preterm birth						
No						
Yes	1.38 (1.30 to 1.47)	1.35 (1.27 to 1.44)	1.32 (1.22 to 1.43)	1.21 (1.11 to 1.31)	1.55 (1.41 to 1.70)	1.49 (1.36 to 1.65)
Moderate preterm	1.42 (1.32 to 1.52)	1.39 (1.30 to 1.50)	1.34 (1.22 to 1.48)	1.23 (1.12 to 1.35)	1.64 (1.48 to 1.83)	1.59 (1.42 to 1.77)
Very preterm	1.34 (1.12 to 1.62)	1.28 (1.06 to 1.55)	1.32 (1.04 to 1.68)	1.21 (0.95 to 1.55)	1.24 (0.91 to 1.69)	1.20 (0.87 to 1.65)
Induction of labor						
No						
Yes	1.44 (1.38 to 1.50)	1.27 (1.22 to 1.32)	1.48 (1.41 to 1.56)	1.28 (1.22 to 1.35)	1.41 (1.32 to 1.51)	1.20 (1.12 to 1.28)
Cesarean section						
No						
Yes	1.39 (1.34 to 1.44)	1.25 (1.21 to 1.29)	1.30 (1.25 to 1.36)	1.12 (1.08 to 1.18)	1.59 (1.51 to 1.67)	1.40 (1.33 to 1.47)
Stillbirth						
No						
Yes	1.47 (1.14 to 1.90)	1.35 (1.05 to 1.74)	1.44 (1.04 to 1.99)	1.21 (0.87 to 1.69)	1.55 (1.04 to 2.30)	1.48 (0.98 to 2.22)
Apgar score <7						
No						
Yes	1.24 (1.07 to 1.44)	1.16 (1.00 to 1.34)	1.33 (1.11 to 1.59)	1.24 (1.03 to 1.49)	1.05 (0.81 to 1.35)	0.97 (0.75 to 1.26)
Neonatal death						
No						
Yes	1.19 (0.81 to 1.73)	1.30 (0.89 to 1.91)	1.30 (0.82 to 2.06)	1.37 (0.85 to 2.27)	1.02 (0.53 to 1.96)	1.16 (0.59 to 2.27)
Small for gestational age						
No						
Yes	1.09 (0.99 to 1.21)	1.09 (0.98 to 1.20)	1.19 (1.05 to 1.34)	1.14 (1.01 to 1.29)	0.98 (0.82 to 1.16)	1.00 (0.84 to 1.19)
Low birth weight						
No						
Yes	1.34 (1.23 to 1.46)	1.30 (1.20 to 1.42)	1.38 (1.24 to 1.53)	1.26 (1.13 to 1.40)	1.40 (1.23 to 1.59)	1.34 (1.17 to 1.53)
Any major congenital malformation						
No						
Yes	1.08 (0.99 to 1.17)	1.09 (1.00 to 1.18)	1.06 (0.96 to 1.18)	1.07 (0.96 to 1.20)	1.06 (0.93 to 1.21)	1.05 (0.92 to 1.21)
Birth week	-0.2 (-0.3 to -0.2)	-0.2 (-0.2 to -0.2)	-0.2 (-0.3 to -0.2)	-0.1 (-0.2 to -0.1)	-0.3 (-0.4 to -0.3)	-0.3 (-0.3 to -0.2)
Birth weight, g	-46 (-56 to -37)	-42 (-52 to -33)	-57 (-69 to -44)	-40 (-52 to -27)	-47 (-63 to -31)	-39 (-55 to -24)