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Pregnancy Complications and Adverse Birth Outcomes Among Women With Celiac Disease: A Population-Based Study From England

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OBJECTIVES: Evidence-based information about adverse birth outcomes and pregnancy complications is crucial when counseling women with celiac disease (CD); however, limited population-based data on such risks exist. We estimated these for pregnant women with CD diagnosed before and after delivery.

METHODS: We included all singleton pregnancies between 1997 and 2012 using linked primary care data from the Clinical Practice Research Datalink and secondary care Hospital Episode Statistics data. Risks of pregnancy complications (antepartum and postpartum hemorrhage, pre-eclampsia, and mode of delivery) and adverse birth outcomes (preterm birth, stillbirth, and low birth weight) were compared between pregnancies of women with and without CD using logistic/multinomial regression. Risks were stratified on the basis of whether women were diagnosed or yet undiagnosed before delivery.

RESULTS: Of 363,930 pregnancies resulting in a live birth or stillbirth, 892 (0.25\%) were among women with CD. Diagnosed CD was not associated with an increased risk of pregnancy complications or adverse birth outcomes compared with women without CD. However, the risk of postpartum hemorrhage and assisted delivery was slightly higher among pregnant women with diagnosed CD (adjusted odds ratio (aOR) = 1.34). We found no increased risk of any pregnancy complication among those with undiagnosed CD. We only observed a 1\% absolute excess risk of preterm birth and low birth weight among undiagnosed CD mothers corresponding to aOR = 1.24 (95\% confidence interval (CI) = 0.82–1.87) and aOR = 1.36 (95\% CI = 0.83–2.24), respectively.

CONCLUSIONS: Whether diagnosed or undiagnosed during pregnancy, CD is not associated with a major increased risk of pregnancy complications and adverse birth outcomes. These findings are reassuring to both women and clinicians.

INTRODUCTION

Subclinical pathological evidence of celiac disease (CD) is present in around 1\% of most European populations (1), of which approximately 0.2\% have been clinically diagnosed with CD (2). This suggests that about 10 in 1,000 pregnant women could have some form of latent or undetected CD and that about 2 in 1,000 deliveries per year in the United Kingdom will be in women with known CD. Given this estimated prevalence and the potential adverse physiological effects that CD might engender, it is surprising that very few good studies have been produced that have tried to quantify the risks to the mother and the child around delivery. The studies (3–9) that have tried to quantify the risks of pregnancy and delivery-related adverse events among women with CD can be categorized broadly as either case series of individuals, in single or multiple centers pooled together, or registry based. Most case series (4,10,11) have been based on a small number of pregnant women with known CD (i.e., < 150) or pregnant women who are screened for positive serology leading to the identification of a small number of women with previously undiagnosed CD. Unsurprisingly, the results are conflicting; e.g., Martinelli et al. (11) reported that the 12 pregnant women that they found to have undiagnosed...
CD were more likely to have babies with low birth weight compared with those with negative serology. However, a similar study based on 52 undiagnosed cases from multiple centers found no excess risk of low birth in offsprings (10). Larger studies from Sweden and Denmark (7,8) have used inpatient national registries to identify women with CD, which provide greater number of women but appear to underestimate the prevalence of CD. This may explain their findings of an increased risk of some adverse birth outcomes for both mother (cesarean section) and child (low birth weight, intrauterine growth restriction) (7,8) if the populations they have studied were not generalizable to all women with CD.

It appears therefore that accurate contemporary estimates of the risk of adverse birth outcomes among women with undiagnosed and diagnosed CD that are generalizable to the majority are absent. Therefore, we have carried out a population-based cohort study using primary and secondary health-care data from England with the aim of quantifying the risks of pregnancy complications and adverse birth outcomes among women with CD.

METHODS

Study population

We used the Clinical Practice Research Datalink (CPRD) (12), which is a large longitudinal UK database of computerized primary care (i.e., general practice) records. The vast majority of the UK population is registered with general practitioners (GPs), who are responsible for overseeing a patient’s medical care, which includes coordination of their health care from hospital or other secondary care facilities. The CPRD includes practices that have met training standards in their recording of clinical information using Vision software and who have consented to be included in the database (13). All patients within a consented practice are automatically included.

Around 53% of the CPRD practices are linked to Hospital Episode Statistics (HES) (14) data that contain information on all hospitalizations in England including all discharge diagnoses and procedures. The anonymized patient identifiers from CPRD and HES were linked by a trusted third party using the National Health Service number, date of birth, postcode, and gender (15). First, patients were matched exactly according to the National Health Service number (over 90% of patients are automatically included).

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Mothers with CD were defined as those with a medical Read code for a diagnosis of CD in their primary care records (Read codes J690.00 CD, J690.13 Gluten enteropathy, J690.14 Sprue-nontropical, J690100 Acquired CD, and J690z00 CD NOS). We did not include women who had diagnoses of dermatitis herpetiformis (DH); however, women with both diagnoses (CD and DH) were retained in the CD group. Each woman with CD was assigned a date of diagnosis corresponding to the date of her first record of CD or the date of her first prescription of a gluten-free product. These women were then classified as having the CD diagnosis before delivery (diagnosed CD) or afterward (undiagnosed CD) for each pregnancy in the study. Pregnancies among women with a recorded history of CD before the study start date were included in the diagnosed CD group. The method that we used for defining CD has been validated in general practice databases with the positive predictive value ranging between 81 and 89% (2).

Pregnancies in which women’s first diagnosis of CD was recorded in the 12 weeks postpartum were also included in the diagnosed CD group. We used this conservative approach to include women who may have had well-controlled CD not requiring medical/GP contact before or during pregnancy but whose postpartum follow-up may have resulted in a recorded diagnosis. Moreover, the diagnostic work-up/process for CD may be long and therefore these are unlikely to be new diagnoses.

Our comparison group consisted of pregnant women without any recorded diagnoses of CD or DH in their primary or secondary care data. Pregnant women who received a gluten-free prescription in the absence of any CD or DH diagnosis at any point during the study period were also excluded.

Defining outcomes

We extracted information on pregnancy complications, which included postpartum hemorrhage, antepartum hemorrhage, and pre-eclampsia/eclampsia based on International Classification of Disease version 10 codes from secondary care. Mode of delivery was categorized as normal vaginal delivery, assisted vaginal delivery (forceps, breech, or vacuum), and emergency or elective cesarean section. Information on length of gestation was categorized as normal (37–42 weeks), preterm (<37 weeks), or prolonged (>42 weeks), whereas infant’s birth weight was categorized as normal (2,500–4,500 g), low birth weight (<2,500 g), or macrosomia (>4,500 g). We also analyzed birth weight as a continuous variable. Finally, we also extracted information on pregnancies resulting in stillbirths.

Defining maternal covariables

For each pregnancy, information on maternal factors during or before pregnancy was extracted from the women’s medical records. Maternal age at delivery was categorized into six age groups (15–19, 20–24, 25–29, 30–34, 35–39, and 40–44 years), whereas calendar year was considered in three categories (1997–2001, 2002–2007, and 2007–2012). Information on body mass index (BMI; the latest measure recorded by the GP before the estimated date of conception categorized according to World
Health Organization classification), smoking status (the latest measure recorded by the GP before delivery), and ethnicity (as recorded in HES and categorized as white or nonwhite (17)) was also obtained. Socioeconomic status was defined as the area in which the general practice was located, at which the patient was registered (quintiles by rank of Indices of Multiple Deprivation (18)). Finally, pregnant women were defined as having diabetes (pre-existing type 1 or type 2) if it was recorded either in primary or secondary care data, or if they had received a prescription for an antidiabetic medication (insulin or oral hypoglycemic agents) any time before delivery.

Statistical analysis
We calculated the proportions of pregnancies with complications or adverse birth outcomes that occurred in women with and without a diagnosis of CD. These proportions were then stratified by the status of the pregnancy with respect to having diagnosed or undiagnosed CD. We used logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess the associations of CD overall, diagnosed CD, and undiagnosed CD with each pregnancy complication and adverse birth outcome. For categorical outcomes (e.g., mode of delivery), multinomial logistic regression was used and relative risk ratios and corresponding 95% CIs were calculated. These estimates were adjusted for all potential confounders: maternal age, BMI, smoking status, diabetes, ethnicity, calendar year, and socioeconomic status. Missing information on BMI, smoking status, and birth weight was categorized as a separate category and included in the analysis. We used linear regression to calculate the mean grams of difference in the birth weight of infants born to women with CD compared with those born to women without CD while adjusting for all covariables. As some women experienced more than one pregnancy during the study period, a clustering term (in our regression models) was fitted. For the purpose of this study, we only considered pregnancy complication or adverse birth outcome to be truly associated with CD if we observed an absolute risk difference (between women with and without CD) of 3% or more. All outcomes with the absolute risk difference of less than 3% were considered to be within the random variation of the data.

Sensitivity analyses
We undertook four additional analyses to ensure the robustness of our results. First, we repeated our analysis by restricting the group of women with CD to only those who had received a gluten-free prescription to increase the specificity of our disease definition. Second, we assessed whether there is an independent increase in the risk of adverse birth outcomes regardless of the mode of delivery. This was done by restricting our analysis to only those women who underwent a normal vaginal delivery. All analyses were carried out using Stata SE version 11.2 (Stata Statistical Software, College Station, TX).

Ethical statement
This study was approved by the Independent Scientific Advisory Committee reference number = 10_193R.

RESULTS
Study population
Among 276,586 women in our study population, there were 364,186 singleton pregnancies resulting in a live birth or a stillbirth. We excluded 0.07% (n = 256) of pregnancies in women with DH without CD (0.01%) or who had gluten-free prescriptions without any evidence of concurrent CD (0.05%). This resulted in a total of 363,930 pregnancies, which were included in the analysis. The overall proportion of pregnancies among women with CD was 0.25% (892 out of 363,930) with the median age at diagnosis of 29 years (inter quartile range = 20.2–34.7). Of these pregnancies, 62% (n = 551) were among women with diagnosed CD and 38% (n = 341) among women with undiagnosed CD.

Table 1 shows the maternal characteristics for all pregnancies in women with and without CD. Compared with women without CD, women with CD had lower BMI, were less likely to be smokers and had a higher prevalence of diabetes. Pregnant women with diagnosed CD were slightly older than those with undiagnosed CD but otherwise had similar maternal characteristics.

Pregnancy complications and adverse birth outcomes among women with CD
Table 2 shows the absolute risks of pregnancy complications and adverse birth outcomes among pregnancies in women with diagnosed and undiagnosed CD and those in women without CD. Overall, pregnancies in women with CD had a slightly higher incidence of postpartum and antepartum hemorrhage, preeclampsia/eclampsia, cesarean section delivery, assisted delivery, stillbirth, preterm birth, and low-birth-weight babies compared with pregnant women without CD (absolute risk difference of < 2.5%), all of which were not statistically significant.

Diagnosed CD
Among pregnancies in women diagnosed with CD, we found a slightly higher risk of postpartum hemorrhage with an absolute risk (AR) of 13.2% (Table 2) than women without CD. This corresponded to a 3.5% excess absolute risk and a 34% increased adjusted relative risk (OR = 1.34 (95% CI = 1.04–1.72)) compared with pregnancies in women without CD (Table 3). There was no statistically significant increased risk of preeclampsia/eclampsia, antepartum hemorrhage, or cesarean section delivery. We observed a greater risk of assisted deliveries among those with diagnosed CD (AR = 15% vs. 12% in women without CD), which corresponded to a 34% increased relative risk (adjusted OR (aOR) = 1.34, 95% CI = 1.05–1.71) and a 3% excess absolute
risk. The risk of stillbirth, preterm birth, and babies born with low birth weight was similar among pregnancies in women with diagnosed CD and without CD. Finally, there was no mean difference in the birth weight of babies born to women with diagnosed CD compared with women without CD (adjusted mean difference $= -15$ g; 95% CI = $-72$ g to 41 g).

#### Undiagnosed CD

Among pregnancies in women with undiagnosed CD, we found no overall increased risk of postpartum hemorrhage, pre-eclampsia/eclampsia, antepartum hemorrhage, or having an assisted delivery or emergency cesarean section (Tables 2 and 3). Compared with pregnancies among women without CD, the risk of preterm birth

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**Table 1. Basic characteristic of pregnancies among women with and without CD**

| Variables                | Without CD (total=363,038) | With CD (total=892) | Diagnosed CD (total=551) | Undiagnosed CD (total=341) |
|--------------------------|-----------------------------|--------------------|--------------------------|-----------------------------|
|                          | $n$ $\%$                    | $n$ $\%$          | $n$ $\%$                | $n$ $\%$                    |
| **Age at delivery (years)** |                             |                    |                          |                             |
| 15–19                    | 21,182 5.8                 | 38 4.3            | 23 4.2                   | 15 4.4                      |
| 20–24                    | 62,217 17.1                | 93 10.4           | 57 10.3                  | 36 10.6                     |
| 25–29                    | 95,665 26.4                | 223 25.0          | 132 24.0                 | 91 26.7                     |
| 30–34                    | 110,712 30.5               | 308 34.5          | 171 31.0                 | 137 40.2                    |
| 35–39                    | 60,911 16.8                | 176 19.7          | 129 23.4                 | 47 13.8                     |
| 40–44                    | 12,351 3.4                 | 54 6.1            | 39 7.1                   | 15 4.4                      |
| **Body mass index (kg/m$^2$)** |                             |                    |                          |                             |
| Normal (18.5–24.9)       | 158,324 43.6               | 438 49.1          | 269 48.8                 | 169 49.6                    |
| Underweight (<18.5)      | 11,802 3.3                 | 63 7.1            | 39 7.1                   | 24 7.0                      |
| Overweight (25–29.9)     | 65,726 18.1                | 137 15.4          | 94 17.1                  | 43 12.6                     |
| Obese (30)               | 41,109 11.3                | 74 8.3            | 40 7.3                   | 34 10.0                     |
| Missing                  | 86,077 23.7                | 180 20.2          | 109 19.8                 | 71 20.8                     |
| **Smoking status**       |                             |                    |                          |                             |
| Smoker                   | 79,782 22.0                | 146 16.4          | 100 18.1                 | 46 13.5                     |
| Non-smoker               | 283,256 78.0               | 746 83.6          | 451 81.9                 | 295 86.5                    |
| **Ethnicity**            |                             |                    |                          |                             |
| White                    | 264,312 72.8               | 684 76.7          | 427 77.5                 | 257 75.4                    |
| Non-white                | 37,148 10.2                | 55 6.2            | 30 5.4                   | 25 7.3                      |
| Missing                  | 61,578 17.0                | 153 17.2          | 94 17.1                  | 59 17.3                     |
| **Pre-existing diabetes**|                             |                    |                          |                             |
| No                       | 359,094 98.9               | 852 95.5          | 525 95.3                 | 327 95.9                    |
| Yes                      | 3,944 1.1                  | 40 4.6            | 26 4.8                   | 14 4.2                      |
| **Calendar year**        |                             |                    |                          |                             |
| 1997–2001                | 72,837 20.1                | 204 22.9          | 81 14.7                  | 123 36.1                    |
| 2002–2007                | 127,055 35.0               | 321 36.0          | 171 31.0                 | 150 44.0                    |
| 2007–2012                | 163,146 44.9               | 367 41.1          | 299 54.3                 | 68 19.9                     |
| **SES quintile**         |                             |                    |                          |                             |
| 1 (Least deprived)       | 54,305 15                  | 168 18.8          | 102 18.5                 | 66 19.4                     |
| 2                        | 75,309 20.7                | 210 23.5          | 123 22.3                 | 87 25.5                     |
| 3                        | 70,955 19.5                | 178 20.0          | 111 20.1                 | 67 19.6                     |
| 4                        | 83,323 23                  | 179 20.1          | 106 19.2                 | 73 21.4                     |
| 5 (Most deprived)        | 79,146 21.8                | 157 17.6          | 109 19.8                 | 48 14.1                     |

CD, celiac disease; SES, socioeconomic status.
Type 1 or type 2 diabetes before conception.
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was roughly similar among those with undiagnosed CD (6.5% vs. 7.6%; aOR = 1.24; 95% CI = 0.82–1.88). We found that pregnancies in women with undiagnosed CD resulted in babies with a mean birth weight 65 g lower than babies born to women without CD; however, this difference was not statistically significant at the 5% level (95% CI = –151 g to 20 g) after adjusting for all potential confounding factors.

Sensitivity and other analyses
Sixty-seven percent of pregnant women with CD received a gluten-free prescription during the study period. Our findings for both diagnosed and undiagnosed CD remained broadly consistent when we added celiac cases recorded solely in the secondary care data (n = 176) and restricted our analysis to only those cases who received a gluten-free prescription (n = 595; Table 4). However, we did find a statistically significant increased risk of infants with low birth weight born to mothers with CD compared with those without CD (aOR = 1.83; 95% CI = 1.05–3.17). When we included pregnancies in women with CD who had been classified as diagnosed because of their diagnosis being in the postpartum period as undiagnosed, our risk estimates remained unchanged (Table 5). Similarly, our estimates for pregnancy complications and adverse birth outcomes remained unchanged when we restricted our analysis to pregnant women who underwent normal vaginal delivery (Table 5). This was with the exception of postpartum hemorrhage, which was not associated with increased risk among women with diagnosed CD.

DISCUSSION
Main findings
In this large nationally representative cohort of more than 360,000 singleton pregnancies resulting in a live birth or a stillbirth, we have provided contemporary, generalizable, population-based...
estimates of the proportion of pregnancies in England that occur in women either with a diagnosis of CD before delivery or following it and their risk of pregnancy complications and adverse birth outcomes. We found that 0.25% of pregnancies were among women who had or went on to develop CD, of which over one-third are not diagnosed until after delivery. With the exception of postpartum hemorrhage and assisted delivery, we observed no increased risk of pregnancy-associated complications or adverse birth outcomes among the pregnancies in women with diagnosed CD compared with those without the diagnosis. Similarly, we also found that undiagnosed CD is not associated with pregnancy complications and adverse birth outcomes.

Strength and limitations
We have conducted one of the largest studies to determine the risk of pregnancy complications and adverse birth outcomes in CD using data from both primary and secondary care while adjusting for important confounding factors such as BMI, smoking status, and maternal diabetes. Our study used an open cohort approach, with prospectively collected data from across England covering 3% of the total UK population with a similar age and sex distribution to the population as a whole. Furthermore, HES is the primary source of maternity statistics in England where birth outcomes have been externally validated with high accuracy (19). Although our study lacked information on the severity of CD, the use of general practice data to ascertain CD diagnosis makes our study findings not only generalizable to the singleton pregnancies resulting in a live birth or a stillbirth in England but also to other developed nations with similar health-care systems. A weakness of this study is the lack of histological and serological information common to cohorts that have been studied in specific secondary or tertiary centers or with complete linkages to pathology systems. However, because the definition of CD that we have used is based on recording of a clinical diagnosis by the GPs, it reflects the real world of clinical practice, as it occurs in the general population of the United Kingdom. This, in turn, has allowed us to study a large number of pregnancies, which would not otherwise be easily possible in a bespoke cohort study. Fortunately, this method of defining CD has been validated in general practice databases with a positive predictive value ranging between 81 and 89%, which increases when prescription data are also used (2). When we increased the specificity of our diagnosis by restricting
### Table 4. Sensitivity analysis: risk of pregnancy complications and adverse birth outcomes among women with CD compared with those without CD

| Variables                          | Restrictive celiac definition\(^a\) (total CD=595) adjusted odds ratio (95% CI) | Addition of Celiac cases from secondary care (total CD=1,068) adjusted odds ratio (95% CI) |
|------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|                                    | Diagnosed CD (n=371) | Undiagnosed CD (n=224) | Diagnosed CD (n=604) | Undiagnosed CD (n=464) |
| Postpartum hemorrhage\(^b\)        | 1.53 (1.14–2.05)       | 0.89 (0.54–1.46)       | 1.31 (1.03–1.68)       | 0.98 (0.64–1.28)       |
| Preeclampsia/eclampsia\(^b\)       | 0.85 (0.48–1.78)       | 1.27 (0.45–3.51)       | 1.16 (0.67–2.00)       | 1.23 (0.63–2.40)       |
| Antepartum hemorrhage\(^b\)        | 1.24 (0.80–1.93)       | 1.11 (0.61–2.02)       | 1.30 (0.92–1.84)       | 1.29 (0.87–1.91)       |
| Assisted delivery\(^c,d\)          | 1.24 (0.92–1.69)       | 0.98 (0.65–1.48)       | 1.32 (1.04–1.68)       | 0.96 (0.72–1.28)       |
| Elective cesarean\(^c,d\)          | 1.11 (0.78–1.57)       | 1.13 (0.68–1.86)       | 1.13 (0.86–1.50)       | 1.30 (0.93–1.83)       |
| Emergency cesarean\(^c,d\)         | 1.11 (0.78–1.57)       | 0.94 (0.61–1.43)       | 1.24 (0.96–1.59)       | 0.86 (0.63–1.18)       |
| Stillbirth\(^e\)                   | 1.24 (0.31–4.97)       | 2.11 (0.53–8.35)       | 1.96 (0.81–4.72)       | 2.08 (0.78–5.54)       |
| Pre-term birth\(^f\)               | 1.12 (0.74–1.69)       | 1.22 (0.73–2.04)       | 1.12 (0.81–1.56)       | 1.31 (0.93–1.84)       |
| Low birth weight(<2,500g)\(^g\)    | 1.03 (0.60–1.74)       | 1.83 (1.05–3.17)       | 1.08 (0.81–1.46)       | 1.50 (1.00–2.24)       |

CD, celiac disease; CI, confidence interval.
Adjusted for smoking status, age, ethnicity, diabetes, BMI, social class and calendar year.
\(^a\)Celiac diagnosis with gluten-free prescriptions.
\(^b\)Analysis based on pregnancy without complication under study.
\(^c\)Analysis based on normal vaginal delivery.
\(^d\)Results from multi-nominal regression analysis (relative risk ratios, 95% CI).
\(^e\)Analysis based on live birth.
\(^f\)Analysis based on normal gestational length.
\(^g\)Analysis based on live birth with normal birth weight.

### Table 5. Sensitivity analysis: risk of pregnancy complications and adverse birth outcomes among women with CD compared with those without CD

| Variables                          | Treating postpartum celiac as incident case (total CD=892) adjusted odds ratio (95% CI) | Restricting analysis to only those who underwent normal vaginal delivery (total CD=523) adjusted odds ratio (95% CI) |
|------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|                                    | Diagnosed CD (n=549) | Undiagnosed CD (n=343) | Diagnosed CD (n=371) | Undiagnosed CD (n=224) |
| Postpartum hemorrhage\(^a\)        | 1.34 (1.04–1.73)       | 0.94 (0.62–1.39)       | 1.22 (0.81–1.84)       | 0.58 (0.27–1.25)       |
| Preeclampsia/eclampsia\(^a\)       | 1.16 (0.66–2.05)       | 1.24 (0.56–2.75)       | 0.49 (0.12–2.00)       | 2.12 (0.83–5.39)       |
| Antepartum hemorrhage\(^a\)        | 1.20 (0.83–1.73)       | 1.27 (0.80–2.01)       | 1.36 (0.84–2.20)       | 1.16 (0.62–2.18)       |
| Assisted delivery\(^b,c\)          | 1.34 (1.05–1.72)       | 1.01 (0.73–1.40)       | —                     | —                     |
| Elective cesarean\(^b,c\)          | 1.10 (0.82–1.48)       | 1.38 (0.93–2.04)       | —                     | —                     |
| Emergency cesarean\(^b,c\)         | 1.26 (0.97–1.63)       | 1.02 (0.72–1.43)       | —                     | —                     |
| Stillbirth\(^d\)                   | 1.27 (0.41–3.92)       | 2.13 (0.69–6.58)       | 0.65 (0.09–4.63)       | 1.04 (0.15–7.19)       |
| Pre-term birth\(^d,e\)             | 1.12 (0.78–1.56)       | 1.29 (0.86–1.93)       | 0.51 (0.26–0.99)       | 1.37 (0.80–2.35)       |
| Low birth weight(<2500g)\(^d,e\)   | 1.11 (0.73–1.69)       | 1.43 (0.88–2.32)       | 0.59 (0.28–1.27)       | 1.47 (0.76–2.83)       |

CD, celiac disease; CI, confidence interval.
Adjusted for smoking status, age, ethnicity, diabetes, body mass index, social class, and calendar year.
\(^a\)Analysis based on pregnancy without complication under study.
\(^b\)Analysis based on normal vaginal delivery.
\(^c\)Analysis based on normal gestational length.
\(^d\)Analysis based on live birth.
\(^e\)Analysis based on normal birth weight.
our analysis only to cases with a supporting gluten-free prescription, our estimates remained broadly similar for both diagnosed and undiagnosed CD, indicating that any misclassification inherent to our overall definition is likely to have had a small effect on our estimates. We do acknowledge that CD diagnoses recorded in inpatient data in England have not been validated. For this reason, we only included them in our sensitivity for which our estimates remained unaltered.

It is important to highlight that 33% of pregnant women with CD diagnosis did not receive gluten-free prescriptions, which may be due to a number of factors. For instance, these prescriptions are expensive and aside from during pregnancy/early postpartum (or if other comorbidities are present) women of this age do not routinely get free prescriptions in England, and hence they may purchase specific gluten-free products directly. Moreover, a relatively short duration of follow-up (i.e., our inability to capture those prescriptions) and a high proportion of "prevalent" cases (i.e., women giving up those prescriptions later on after diagnosis) may also be contributory factors. Another limitation of this study is the lack of compliance data on a gluten-free diet among those with diagnosed CD. Similar to most studies conducted on the topic, we assumed that all women with diagnosed CD are broadly compliant with a gluten-free diet, which seems reasonable given previous evidence suggesting that complete nonadherence to a gluten-free diet is uncommon among patients with CD (20). There could of course be some misclassification in terms of children of mothers with and without CD in our study. It is likely that some mothers without CD in our study may have undiagnosed disease throughout the whole study period. This, however, should only bias our results toward the null, i.e., of no increase in the risk of pregnancy complications and adverse birth outcomes.

We also recognize that our lack of complete data on BMI and birth weight could bias our estimates. However, we treated missing data as a separate category and included them in our analysis. The fact that we were able to use data on BMI does, however, give us an advantage over other studies (3,7,8) in this field, which have been previously unable to. We observed lower proportions of pregnant women with undiagnosed CD in more recent years compared with those with diagnosed CD. This was probably owing to the fact that in order to be undiagnosed a pregnancy needs to occur earlier in the data and vice versa for those with diagnosed CD. It is important to note that our study may have limited power to show small excess risks for certain outcomes (e.g., stillbirths). Therefore, one cannot rule out minor risk increases associated with these outcomes owing to a potential for type 2 error.

Comparison with previous literature
The overall prevalence of CD in our study among pregnant women was calculated to be 0.25%. Although this proportion is much lower than most small-scale hospital-based studies (1%) (4,11), it is not surprising as our cases included those with a clinical diagnosis of CD as opposed to positive serology identified via screening. Our proportions are still higher than those reported by most large registry-based studies (around 0.07%) (7,8). This may be due to their reliance on inpatient hospital data and lack of outpatient or primary care data leading to the underestimation of the prevalence. We did not observe increased risks of preterm birth and low birth weight among those with diagnosed CD, a finding consistent with the available population-based studies (3,7,8,11). Our finding of a 34% increased risk of postpartum hemorrhage and assisted deliveries among those with diagnosed CD is new, as previous studies have not reported this.

Overall, we found no increased risk of low birth weight and preterm birth among undiagnosed celiac mothers. This finding is consistent with a multicenter study conducted by Greco et al. (10) where 5,055 mothers were screened for CD, of which 51 (1%) had a positive result. The study concluded that undiagnosed CD, although common in pregnancy, is not associated with an excess risk of preterm delivery, low birth weight, abortion, or intrauterine growth restriction. Our findings do, however, contradict some of the largest registry-based studies to date (3,7,8). For instance, Ludvigsson et al. (7) in their population-based study demonstrated that women with undiagnosed CD were 71% more likely to have preterm birth and over two times more likely to have infants with low birth weight. These different findings to ours could be because the cases identified through hospital-based registers may suffer from a more severe form of disease than those diagnosed within the general population. Our study showed no increased risk of cesarean section in the undiagnosed CD group in contrast to an increased risk among this group in Swedish data (7). One explanation could be the difference in the medical indication and the incidence of cesarean sections in the United Kingdom and Sweden (26% (21) vs. 17% (22)). Although we did not find an increased risk of stillbirth, we did not assess the risk of earlier fetal losses in our study, and previous studies have indicated that women with CD may have increased risk of miscarriage (9,11), which needs further assessment. With regard to overall fertility, although there is mixed evidence as to whether women with unexplained infertility may be more likely to have undiagnosed CD than the general population (23,24), there is evidence (9) suggesting that women with CD have fertility rates similar to those of the general population. The study by Tata et al. (9) showed no difference in the fertility rate for women with incident vs. prevalent CD, and the prevalence of CD in women who had children was 0.2%, which was similar to the overall prevalence of the disease in the female population.

The only persistently increased risk that we observed was a 34% increased risk of postpartum hemorrhage and assisted deliveries among those with diagnosed CD, which has not been reported before. This may be due to the higher proportion of women undergoing assisted delivery, which may increase the likelihood of postpartum hemorrhage compared with normal vaginal delivery (25). This increased risk in women with diagnosed CD may therefore be due to more assisted deliveries rather than disease-related per se.

Conclusion and implications
Most women with CD diagnosed either before or after pregnancy will have a pregnancy and delivery that is not complicated by
an adverse event. Our findings do suggest that among women already diagnosed with CD there may be a small increase in the risk of a pregnancy being complicated by a postpartum hemorrhage, but the reasons for this are not entirely clear. Overall, our results should be reassuring to both women and practitioners. However, this study does not preclude that the lack of increased risk observed among pregnant women with CD was due to an adequate treatment of CD before childbirth, thereby optimizing maternal health.

CONFLICT OF INTEREST
Guarantor of the article: Alyshah Abdul Sultan, PhD.
Specific author contributions: A.A.S. and J.W. conceived the idea for the study, with K.M.F., C.C., J.F.L., N.N.D., L.B., and L.J.T. also making important contributions to the design of the study. A.A.S. managed the data management and analysis and wrote the first draft of the manuscript. All authors were involved in the interpretation of the data, contributed toward critical revision of the manuscript, and approved the final draft. A.A.S. had full access to all of the data and final responsibility for the decision to submit for publication.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE
✓ About 10 in 1,000 pregnant women could have some form of latent or undetected CD and that about 2 in 1,000 deliveries per year in the United Kingdom will be in women with known celiac disease.
✓ There is lack of evidence on the risk of pregnancy complications among women with CD.
✓ Most studies conducted on the subject often suffer from either selection bias or inadequate power, which limits the generalizability of the study findings.

WHAT IS NEW HERE
✓ Most women with CD diagnosed either before or after pregnancy will have a pregnancy and delivery that is not complicated by an adverse event.
✓ Women diagnosed with CD may have a slightly increased risk of postpartum hemorrhage, but the reasons for this are not clear.

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