Coeliac disease and risk of birth defects in pregnancy

Coeliac disease (CD) is prevalent in patients of reproductive age, but the impact on pregnancy and fetal development is unclear. The British Society of Gastroenterology recommends serological testing for CD in patients with chronic diarrhoea,[1] but CD may be underrecognised in women without the classic symptoms.[2] We studied the association between CD and the risk of birth defects in pregnant women.

We analysed a cohort of live births between 1989 and 2016 in Quebec, Canada using discharge summaries from the Maintenance and Use of Data for the Study of Hospital Clientele database. We used diagnostic codes to identify women with CD and infants with different types of birth defects. We determined whether CD was present during prenatal follow-up, or if women required hospitalisation for CD before or after pregnancy. We used log-binomial regression models with robust SE to estimate associations between CD and birth defects adjusted for maternal characteristics.

This study comprised 2 184 888 infants, including 125 081 with birth defects and 2238 whose mothers had CD. CD was associated with 1.58 times the risk of heart defects (95% CI 1.12 to 2.22) and 1.56 times the risk of urinary defects (95% CI 1.06 to 2.32) compared with no CD (table 1). The risk of heart defects was greater for women with two or more coeliac-related hospitalisations (risk ratio (RR) 3.06, 95% CI 1.81 to 5.15) and for CD diagnosed after delivery (RR 1.94, 95% CI 1.31 to 2.88) (figure 1). The association with heart defects was also stronger before 2000 (RR 2.29, 95% CI 1.41 to 3.72). There was no association with other types of defects.

Few studies have investigated the relationship between CD and birth defects despite the increasing incidence of CD in women.[3] In our study, CD was associated with heart and urinary defects. The association with heart defects was stronger for CD diagnosed after delivery, which includes potentially undetected cases that were already present during pregnancy. These findings are reminiscent of a study of 52 304 infants in Sweden, where CD was also associated with heart defects, especially CD diagnosed after pregnancy.[4] A study of 562 332 infants in the UK found a greater chance of neural tube defects for CD diagnosed after pregnancy.[5] Undetected CD may lead to malabsorption, mucosal inflammation and circulating proinflammatory cytokines,[3 6] factors that may contribute to birth defects. The weaker association with CD diagnosed before delivery suggests that gluten-free diets may help reduce the risk.

Women hospitalised two or more times for CD had a greater risk of birth defects, implying that clinically severe or refractory CD may be particularly problematic.

Table 1 Association between coeliac disease and birth defects

	Prevalence of birth defects per 1000 (95% CI)		Risk ratio (95% CI)	
	Coeliac disease	No coeliac disease	Unadjusted	Adjusted*
Any defect	61.2 (51.3 to 71.1)	57.2 (56.9 to 57.6)	1.07 (0.91 to 1.27)	1.06 (0.90 to 1.25)
Central nervous system	2.7 (0.5 to 4.8)	2.1 (2.0 to 2.1)	1.32 (0.59 to 2.94)	1.27 (0.57 to 2.83)
Heart	14.3 (9.4 to 19.2)	8.8 (8.7 to 8.9)	1.64 (1.16 to 2.31)	1.58 (1.12 to 2.22)
Urinary	11.6 (7.2 to 16.1)	7.2 (7.1 to 7.3)	1.62 (1.09 to 2.40)	1.56 (1.06 to 2.32)
Genital	1.8 (0.0 to 3.5)	3.5 (3.4 to 3.6)	0.51 (0.19 to 1.37)	0.51 (0.19 to 1.35)
Musculoskeletal	26.4 (19.7 to 33.0)	26.5 (26.3 to 26.8)	1.00 (0.77 to 1.29)	1.00 (0.77 to 1.30)
Ear/eye/nose	4.5 (1.7 to 7.2)	5.4 (5.3 to 5.5)	0.83 (0.45 to 1.54)	0.82 (0.44 to 1.51)
Orofacial cleft	0.9 (0.0 to 2.1)	1.2 (1.1 to 1.2)	0.78 (0.20 to 3.13)	0.77 (0.19 to 3.09)
Respiratory	1.3 (0.0 to 2.9)	1.2 (1.2 to 1.2)	1.10 (0.26 to 4.72)	1.08 (0.25 to 4.63)
Digestive	0.4 (0.0 to 1.3)	3.1 (3.0 to 3.2)	0.14 (0.02 to 1.02)	0.14 (0.02 to 1.01)
Abdominal wall	0.4 (0.0 to 1.3)	0.6 (0.5 to 0.6)	0.80 (0.11 to 5.67)	0.79 (0.11 to 5.58)
Chromosomal	0.9 (0.0 to 2.1)	1.9 (1.8 to 1.9)	0.46 (0.12 to 1.84)	0.44 (0.11 to 1.78)

*Risk ratio for coeliac versus no coeliac disease, adjusted for maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, ≥40), parity (0, 1, ≥2), multiple birth (yes, no), comorbidity (pre-existing diabetes, pre-existing hypertension, pre-eclampsia, epilepsy or mood disorders, anaemia or other blood disorders, obesity, maternal birth defects, and tobacco or substance use), socioeconomic deprivation (yes, no) and period of conception (1989–1999, 2000–2016).

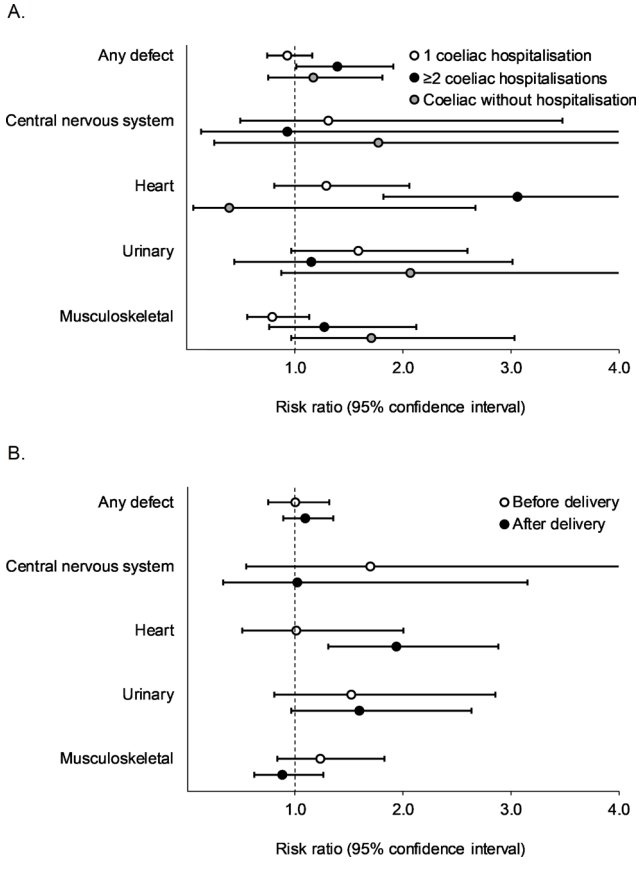

Figure 1 Coeliac disease severity and risk of selected birth defects. (A) Number of coeliac hospitalisations and (B) time of coeliac diagnosis. Risk ratio for coeliac disease versus no disease, adjusted for maternal age at delivery, parity, multiple birth, comorbidity, socioeconomic deprivation and period of conception. Bars represent 95% CI.

Associations were stronger before 2000, when severe CD with the classic presentation was more frequent.[2] Severe villous atrophy may lead to delayed mucosal recovery and prolonged vitamin deficiencies.[7] Vitamins are fundamental for fetal development, and multivitamin supplements during pregnancy may reduce the risk of heart and urinary defects.[8–10]

We used hospital data in which associations may be attenuated due to misclassification of CD or birth defects. We did not have information on ethnicity, paternal CD, dietary habits or supplements, and cannot rule out residual confounding. We cannot account for pregnancy terminations, more frequent diagnosis of mild CD over time due to anti-tissue transglutaminase antibody testing,[3] and folic food fortification, which may have reduced the risk of neural tube defects later in the study.

The findings of this study suggest that CD, particularly undetected or untreated CD, may increase the risk of heart and urinary birth defects. Women with CD may benefit from prenatal counselling and dietary modification to prevent birth defects.

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