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Celiac Disease and Congenital Malformations: Muddying the Waters

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In the last two decades, many studies have linked the diagnosis of celiac disease to unfavorable outcomes in pregnancy including preterm birth, intrauterine growth retardation and low birth weight.^{1–2} As a result, strict adherence to a gluten-free diet is recommended in all patients with diagnosed celiac disease, including those who are asymptomatic, who are attempting to conceive and/or are pregnant. What is less clear, however, is whether parental celiac disease influences the rate of congenital malformation in the offspring of celiac mothers and fathers. In this issue of *Clinical Gastroenterology and Hepatology*, Zugna and colleagues report a large cohort study which attempts to answer that question.³

There have been several attempts in the past to establish the risk of congenital malformation in offspring born to patients with celiac disease.^{4–5} *A priori*, the risk of congenital malformation in patients with celiac disease, especially neural tube defects which are in large part due to folic acid deficiency, would seem to be higher given the malabsorptive state associated with active intestinal inflammation. The small case series and cohort studies published to date however, featuring both studies of patients with celiac disease being tested for neural tube defects and patients with neural tube defects being tested for celiac disease, are underpowered and inconclusive.

The current study therefore is well positioned to answer this question as it reports on a robust nationwide Swedish cohort (approximately 8,700 patients with celiac disease and 29,000 matched controls) with a relatively large number of well-defined outcomes of interest. The authors main conclusion was that in mothers with diagnosed celiac disease, the overall Odds Ratio (OR) for any congenital malformation was 1.15 (95% Confidence Interval (CI) 1.05–1.26) when controlling for birth year, maternal age, educational level, parity, maternal thyroid disease, maternal diabetes and rheumatoid arthritis. In fathers with celiac disease, controlling for the same factors, the risk was 1.14 (95% CI 1.00–1.29). The

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authors reported similar findings in undiagnosed mothers with celiac disease (OR 1.16; 95% CI 1.04–1.29).

Reviewing the results from by far the largest cohort study ever to specifically address this question, do we now have enough evidence to tell parents with celiac disease that they have to worry about a small, but increased risk of congenital malformations in their offspring? Unfortunately, the answer is probably no, as this study has limitations which do not allow for a definitive conclusion to be drawn.

The most important reason why we can't answer this question is because the study design does not allow us to adequately control for by far the most important variable – exposure to gluten and the expected correlative intestinal inflammatory response. The authors have carefully vetted patients to include only cases with known celiac disease based on small bowel biopsy. In addition, the primary outcome – congenital malformations – is very well characterized.

However, as the authors themselves acknowledge, gluten exposure – i.e. are patients following a gluten free diet – cannot be evaluated. They have tried to control for exposure by evaluating both diagnosed and undiagnosed patients separately. Although mothers with undiagnosed celiac disease (and by proxy exposure to gluten) had a higher rate of any malformation compared to mothers with diagnosed celiac disease (and by proxy no or limited exposure to gluten), the rate was really negligible. Therefore without being able to accurately quantify the primary exposure variable, the conclusions from the study need to be tempered.

In addition, when evaluating the specific types of congenital malformations which occurred, only cardiac defects were found at an increased rate in mothers with undiagnosed celiac disease, and orofacial clefts at a decreased rate in mothers with diagnosed celiac disease. Notably, the presence of neural tube defects, which would be expected to be less common in patients with diagnosed celiac disease (and by extension on a gluten free diet), was not significantly decreased. The reported discrepant effect of celiac disease on causing or protecting against different types of congenital malformation suggests that the presence of additional unmeasured confounders such as folic acid exposure, unknown disease-causing genetic traits inherent to celiac disease, and/or the rate of elective pregnancy termination for the different types of malformations may have influenced the results.

How can this study be used clinically? As the authors comment in the last sentence of the discussion, readers are encouraged to exercise caution in interpreting these findings given the presence of uncontrolled confounding. There is clearly evidence that pregnant mothers with celiac disease should follow a gluten free diet to prevent adverse pregnancy outcomes. The combination of a diminutive absolute risk, inability to accurately measure one of the primary exposures of interest, and the presence of unmeasured confounders, however, prevents this study from providing enough evidence to support the recommendation of a gluten-free diet for the prevention of congenital malformations.

The results of the study and the inherent biases of retrospective cohort studies in general further underscore the importance of developing a prospective national or international

database to follow patients longitudinally with well-characterized celiac disease. This would allow for better characterization of exposure to gluten via small bowel biopsy and serological markers, prospective exploration of the clinical impact of genetic variants implicated in the diagnosis and severity of celiac disease, and more robust, well-defined outcome data. Our patients and their families deserve this effort. Until that time, best evidence will rest in the hands of retrospective cohort studies which always must be interpreted with caution.

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Abbreviations

CI	Confidence Interval
OR	Odds Ratio

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