Research Square

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Preterm Birth and the Risk for Childhood Celiac Disease of the Offspring

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Research Article

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Abstract

Purpose: Preterm infants may be predisposed to immune-mediated disorders due to an immature immune system and an altered gut microbiome. We investigated whether offspring born preterm (<37 weeks) are at an increased independent risk of developing childhood celiac disease compared to term offspring.

Methods: A population-based cohort study (1991-2021) included all singleton deliveries at a single tertiary medical center. Celiac disease diagnoses up to 18 years of age were retrieved from hospital and community records. A multivariable Cox proportional-hazards model was utilized to compare the study groups, adjusting for maternal age, maternal celiac disease, and small for gestational age (SGA)**.**

Results: Of 356,109 included singleton deliveries, 24,511 (6.9%) were preterm. Crude celiac disease prevalence was higher in preterm versus term offspring (0.7% vs. 0.5%, p=0.012), with a non-significant trend toward higher cumulative incidence (Log-rank, p=0.087). In the multivariable Cox model, after adjusting for maternal age, maternal celiac disease, and SGA, prematurity was not independently associated with celiac disease in the offspring (adjusted hazard ratio 1.14, 95%CI 0.97-1.34, *p*=0.103).

Conclusion: While PTB is associated with a higher crude rate of disease, it is not an independent risk factor once adjusted for maternal characteristics and SGA.

1 | INTRODUCTION

During a normal pregnancy, the maternal immune system plays a pivotal role in fetal development [1]. A well-regulated synergy between activation and suppression of the maternal immune system is essential to protect the fetus during pregnancy and to enable the normal development of the fetal immune system during childhood [2]. Disruption of this immunological synchrony can lead to various pregnancy pathologies and complications, such as miscarriage and preterm birth [3, 4].

Preterm birth (PTB), defined as birth before the 37th week of gestation [5], is a global challenge affecting approximately 11% of live births worldwide and accounting for 35% of neonatal mortality [6]. In recent decades, there has been a marked increase in PTB survival rates [7]. However, surviving preterm infants are at risk for various health complications, due to incomplete organ system development, potentially leading to lifelong morbidity [8]. The immature immune system of preterm infants exhibits deficits in both innate and adaptive immunity [9], which increases susceptibility to early-life infections and later neurodevelopmental, cardiometabolic, autoimmune, and inflammatory disorders [10].

Celiac disease is an autoimmune disorder precipitated by the ingestion of gluten-containing foods and affects the small intestine [11, 12]. The disease affects not only the small intestinal mucosa but also multiple extraintestinal organs, resulting in bone, liver, neurological, skin, and reproductive system disorders [13]. This lifelong inflammatory disease has genetic and environmental components and is prevalent in approximately 1% of the western population, primarily affecting children [14].

Certain adverse pregnancy complications have been associated with higher risk for celiac disease in the offspring, mainly intrauterine growth restriction (IUGR), neonatal infections and cesarean delivery [15, 16, 17]. In addition, an association was recently noted between fertility treatments and celiac disease of the offspring [18]. Although PTB has not been consistently identified as a risk factor for celiac disease [19, 20], it has been postulated that genetic modulation driven by the inflammatory process of preterm initiation of labor in the fetus [21, 22] or the altered intestinal bacterial colonization of the preterm infant may be linked to the development of autoimmune intestinal diseases [23].

Epidemiological evidence links PTB to an increased risk of additional autoimmune and inflammatory disorders, such as asthma and type 1 diabetes [1]. This association implies a generalized vulnerability of the preterm immune system, likely stemming from the interruption of normal immune tolerance induction in utero. Thus, the susceptibility to celiac disease may be a manifestation of this broader autoimmune propensity, rather than a mechanism exclusive to gluten intolerance.

Hence, considering the roles of the immune system in both preterm birth and celiac disease, we aim to investigate a potential association between being born prematurely and the offspring's risk of developing celiac disease up to adulthood.

2 | MATERIALS AND METHODS

Study Design and Population. This was a retrospective population-based cohort study conducted between the years 1991–2021 at the Soroka University Medical Center (SUMC), the sole tertiary hospital in the southern region of Israel (Negev). The study population is characterized by significant stability with minimal outward migration, effectively functioning as a stable cohort. As SUMC serves as the sole tertiary medical center in the region, virtually all deliveries, pediatric hospitalizations, and specialist consultations occur within this single healthcare system. This setting substantially minimizes loss to follow-up and preserves data integrity. Consequently, medical records from birth through adolescence remain continuously available for the vast majority of offspring, enabling a highly reliable assessment of morbidity over an extended period. Accordingly, the study is based on non-selective population data.

The study protocol was approved by the institutional review board (SUMC IRB).

Definitions and Study Groups. The primary exposure was PTB, defined as birth before the 37th week of gestation [5]. The main outcome measure was a documented diagnosis of celiac disease in the offspring (followed up to the age of 18 years). Celiac diagnosis in the offspring was determined based on the ICD-9 code 579.0. The study population included all singleton live births at SUMC during the study period. Exclusion criteria comprised multiple gestations, fetuses with chromosomal abnormalities or congenital malformations, and perinatal mortality cases. Offspring born preterm (< 37 weeks) were compared to offspring born at term (≥ 37 weeks). Follow-up was terminated if any of the following occurred: diagnosis of celiac disease, death, end of the study period, or when the child reached 18 years of age.

Data Collection. Data were collected from two distinct databases that were cross-linked and merged. Maternal data were extracted from the SUMC Obstetrics and Gynecology computerized database covering the study period. This database contains demographic information and detailed pregnancy courses, including obstetrical complications and perinatal outcomes. Data regarding celiac diagnosis of the offspring were extracted from 'Clalit' Health Services community-based clinics and SUMC pediatric hospitalization records. These records include ICD-9 based diagnoses from both community encounters and hospitalizations. Maternal and offspring data were merged based on the mother's ID number and the offspring's ID number assigned at birth.

Statistical Analysis. All statistical analyses were performed using SPSS software (version 29). Continuous variables are presented as means ± standard deviation (SD). Categorical variables were compared using the chi-square test, while the Student's t-test was utilized for continuous variables with normal distribution. A Kaplan-Meier survival curve was generated to compare the cumulative incidence of celiac disease between the study groups over time. A multivariable Cox proportional hazards model was used to control for potential confounders based on their clinical relevance and included maternal age, maternal celiac disease and small for gestational age (SGA) offspring. SGA was defined as offspring birthweight lower than the 5th percentile for gestational age and gender. For all analyses, a p-value < 0.05 was considered statistically significant.

3 | RESULTS

The study cohort comprised 356,109 singleton deliveries that met the eligibility criteria. Of these, 24,511 (6.9%) were preterm births. Table 1 details the demographic and clinical characteristics of the study population. Maternal age did not differ significantly between the groups. Conversely, women who delivered prematurely exhibited higher burdens of maternal morbidity. Specifically, rates of recurrent pregnancy loss, use of fertility treatments, diabetes mellitus, and hypertensive disorders were all significantly elevated in the preterm group compared to the term delivery group. Finally, maternal celiac disease rates were higher in mothers with preterm birth.

Obstetrical and perinatal outcomes are summarized in Table 2. Newborns in the preterm group had a markedly lower mean birthweight and a higher prevalence of being small for gestational age (SGA). Additionally, the preterm group was characterized by significantly higher rates of cesarean sections and perinatal mortality compared to the control group.

The long-term cumulative incidence of celiac disease is presented in the Kaplan-Meier survival curve (Fig. 1). Although the curve demonstrates a certain trend toward higher cumulative incidence of celiac disease among offspring born preterm, this trend did not reach statistical significance (Log-rank p = 0.087).

Table 3 displays the results of the univariable and multivariable analyses. Initially, the univariable analysis demonstrated an association between PTB and an increased risk of celiac disease (crude OR 1.22, 95% CI 1.04–1.44). However, after controlling for potential confounders (specifically maternal age,

maternal celiac disease, and SGA) using a Cox proportional hazards model, this association was attenuated and was no longer statistically significant (adjusted HR 1.14, 95% CI 0.97–1.34, $p = 0.103$). Thus, PTB was not identified as an independent risk factor for celiac disease in this cohort.

4 | DISCUSSION

While we initially hypothesized a positive correlation between PTB and celiac disease based on biological plausibility [1, 2], and also observed higher rates of celiac disease in this group, the multivariable analysis revealed a more nuanced picture. We found that PTB *per se* was not an independent risk factor. In fact, the association lost statistical significance after adjusting for confounders, including SGA and maternal celiac disease [24]. These findings might suggest that the increased crude risk is likely driven by intrauterine growth restriction rather than shortened gestation alone, a specific association supported by previous observations [15, 16, 17].

When conceptualizing this study, we designed the multivariable model to isolate the independent effect of PTB while minimizing confounding bias. First, we controlled for maternal age to mitigate some of the impact of obstetrical complications associated with age, ensuring that the observed risk was not driven by maternal demographics [5]. Additionally, maternal celiac disease was included to account for genetic predisposition [11, 14]. This adjustment was essential to distinguish the environmental impact of the birth event from hereditary susceptibility [1, 6, 10]. Finally, we differentiated between SGA infants and prematurity. While the latter refers to delivery timing, SGA reflects the pathological effects of intrauterine growth restriction [25]. By adjusting for SGA, we aimed to determine whether shortened gestation per se, independent of fetal growth pathology, acts as a driver for celiac disease [15, 16].

The results of the adjusted model highlight a crucial distinction between the timing of delivery and the quality of intrauterine growth. While preterm neonates are exposed to the extra-uterine environment prematurely, fetuses diagnosed as SGA often suffer from prolonged in-utero stress and placental insufficiency. This chronic deprivation may have a more profound impact on the 'fetal programming' of the immune system and gut barrier function than the gestational age at birth alone. Therefore, the increased risk observed in the univariate analysis likely reflects the significant overlap between PTB and growth restriction, rather than an independent effect of prematurity.

Our investigation is premised on the understanding of celiac disease as a multifactorial autoimmune disorder, emerging from the interplay between genetic predisposition and environmental exposures [11, 14]. In this context, preterm infants represent a unique population. Their physiologically immature immune system displays deficiencies in both innate and adaptive responses [6, 9]. This vulnerability not only predisposes them to infections but creates a pro-inflammatory environment that could theoretically precipitate an autoimmune reaction [3, 10]. Furthermore, in contrast to the gut of term infants, typically colonized by beneficial anaerobic bacteria such as Bifidobacteria within the first week of life, the gut of preterm infants exhibits a marked delay in this process. This disruption is frequently exacerbated by environmental exposures in the neonatal intensive care unit (NICU) and antibiotic administration.

Consequently, the altered microbial environment may compromise intestinal barrier integrity and disrupt the maturation of gut-associated lymphoid tissue (GALT). This mechanism is suggested to increase susceptibility to immune-mediated intestinal diseases in later life [23].

Our results demonstrate that the association between prematurity and celiac disease attenuates significantly when fetal growth restriction is taken into account. This observation is clinically significant. It redirects focus from the timing of delivery (which showed no independent statistical significance) to the quality of intrauterine growth and placental health. These findings align with the broader scientific literature regarding long-term sequelae of adverse in-utero conditions [7, 8], reinforcing the concept that such exposures carry critical, long-term health implications for the offspring. It also challenge the prevailing view that prematurity *per se* acts as a universal trigger for autoimmunity due to immune system immaturity, a theory often cited regarding other immune mediated conditions [1]. Instead, our results align with robust data from large scale Scandinavian cohorts, specifically the nationwide Swedish studies by Mårild et al. [15] and Sandberg-Bennich et al. [16]. These studies similarly identified fetal growth restriction as a significant risk factor, while finding no independent association with PTB after adjusting for confounders.

Notably, our study validates these findings in a distinct population with different genetic backgrounds and environmental exposures compared to the more homogeneous Scandinavian cohorts. While the Swedish population is characterized by specific HLA genotypes and high gluten consumption, our cohort represents a diverse Middle Eastern population. The similar findings across such varied populations suggests a fundamental biological mechanism related to placental insufficiency and intrauterine programming, rather than a phenomenon specific to a certain population.

A primary strength of this study lies in the extensive cohort encompassing over 350,000 deliveries. As the sole tertiary center for the Negev region, the medical center serves a non-selective population sample. Furthermore, data integration with Clalit Health Services provides a comprehensive platform ensuring long-term continuity of care. This unique setting permits reliable tracking of celiac diagnoses from birth through adolescence with negligible loss to follow-up.

We also considered the possibility of detection bias given that preterm infants typically undergo more frequent medical surveillance. Theoretically, the intensity of this monitoring could lead to higher diagnosis rates and skew the results. However, screening for celiac disease is not part of standard care protocols and is generally pursued only upon specific clinical indication. Moreover, if surveillance bias were the primary driver, we would expect a uniformly increased risk across the preterm population.

Several limitations should be acknowledged. Primarily, the retrospective design allows for the identification of statistical associations but limits our ability to infer causality. Moreover, we lacked detailed clinical data regarding the preterm offspring treatment in the Neonatal Intensive Care Unit (NICU), and specifically the duration of antibiotic therapy and breastfeeding patterns, which are critical factors known to shape the neonatal microbiome [23]. It should also be noted that our analysis was confined to diagnoses made up to age 18, meaning that cases of adult-onset celiac disease were not

captured. Finally, while the centralization of healthcare in the region minimizes bias, we cannot rule out incomplete data for a small minority of children who may have received care in other institutions.

In conclusion, our findings indicate that PTB is not an independent risk factor for celiac disease when adjusting for maternal characteristics and fetal growth restriction. Future research should focus on other risk factors for celiac disease such as placental pathologies and environmental factors to better elucidate these suggested associations.

Declarations

The authors received no financial support for the research, authorship, or publication.

The authors declare no conflict of interest.

ChatGPT was utilized solely for phrasing and grammatical improvements.

The authors reviewed and validated the final text and assume full responsibility for the content of the publication.

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This study is submitted as part of the requirements for M.D. degree at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board (Helsinki Committee) of Soroka University Medical Center. In accordance with guidelines for retrospective studies using de-identified data, the requirement for individual informed consent was waived.

Consent for publication

All authors have reviewed and consented to the publication of this manuscript.

Competing interests

Not applicable.

Authors' information

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Author Contribution

O.D. wrote the original draft preparation. E.S. and G.G. contributed to study conceptualization, methodology, validation, and writing—review and editing. G.G. also provided supervision and project administration. T.W. contributed to methodology, validation, formal analysis, and data curation. E.S. also contributed to data curation. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and confidentiality regulations of Soroka University Medical Center and Clalit Health Services, but are available from the corresponding author upon reasonable request and subject to ethical approval.

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Tables

Table 1. Maternal characteristics of women with and without preterm birth (PTB)

Maternal characteristics	Women with PTB (n=24,511)	Women with term delivery (n=331,598)	OR (95% CI)	P value
Maternal age at birth, years (mean ± SD)	28.2 (± 6.3)	28.2 (± 5.7)		0.388
Parity				<0.001
1	7,126 (29.1%)	78,901 (23.8%)		
2-4	11,669 (47.6%)	173,055 (52.2%)		
5+	5,713 (23.3%)	79,603 (24.0%)		
Recurrent pregnancy loss [a], n (%)	1,417 (5.8%)	12,808 (3.9%)	1.53 (1.44 – 1.61)	<0.001
Fertility treatments [b], n (%)	902 (3.7%)	6,805 (2.1%)	1.82 (1.70 – 1.95)	<0.001
Diabetes mellitus [c], n (%)	1,641 (6.7%)	15,363 (4.6%)	1.47 (1.40 – 1.55)	<0.001
Hypertensive disorders [d], n (%)	2,967 (12.1%)	13,706 (4.1%)	3.19 (3.06 – 3.33)	<0.001
Maternal celiac disease, n (%)	51 (0.2%)	438 (0.1%)	1.57 (1.18 - 2.10)	0.002

[a] Defined as 2 or more pregnancy losses before 20 weeks' gestation

[b] Including ovulation induction (OI) and the use of in-vitro fertilization (IVF)

[c] Including pre-gestational and gestational diabetes

[d] Including chronic (pre-gestational) and gestational hypertension, preeclampsia and eclampsia

Table 2. Perinatal outcome of women with and without preterm birth (PTB)

Characteristic	Women with PTB (n=24,511)	Women with term delivery (n=331,598)	OR (95% CI)	P value
Gestational age at birth, weeks (mean ± SD)	34.1 (± 2.8)	39.3 (± 1.2)	-	<0.001
Cesarean delivery, n (%)	7,521 (30.7%)	42,363 (12.8%)	3.02 (2.93 – 3.11)	<0.001
Birthweight, grams (mean ± SD)	2,353 (± 692)	3,262 (± 443)	-	<0.001
Low birthweight (<2500 grams), n (%)	13,126 (53.6%)	11,532 (3.5%)	32.01 (31.02 - 33.02)	<0.001
Small for gestational age (SGA) [a], n (%)	1,272 (5.2%)	14,938 (4.5%)	1.16 (1.09 – 1.23)	<0.001
Low Apgar (<7) at 5 minutes, n (%)	759 (3.3%)	1,269 (0.4%)	8.85 (8.08 - 9.70)	<0.001
Perinatal mortality [b], n (%)	1,911 (7.8%)	913 (0.3%)	30.63 (28.27 – 33.17)	<0.001

[a] SGA = Birthweight<5th percentile for gestational age and gender

[b] Defined as antepartum fetal death (>28 weeks' gestation), stillbirth and early neonatal death up to 30 days post-partum

Table 3. The association between prematurity and celiac disease: Univariate analysis and results from a Cox proportional hazards model

	Preterm birth (n=24,511)	Term birth (n=331,598)	Crude OR (95% CI)	P value	Adjusted* HR (95% CI)	P value
Celiac in the offspring	163 (0.7%)	1,797 (0.5%)	1.23 (1.04 - 1.44)	0.012	1.14 (0.97 - 1.34)	0.103

* Adjusted for maternal celiac disease, maternal age at birth and small for gestational age (SGA) infants (<5th percentile for gestational age and gender)

Figures

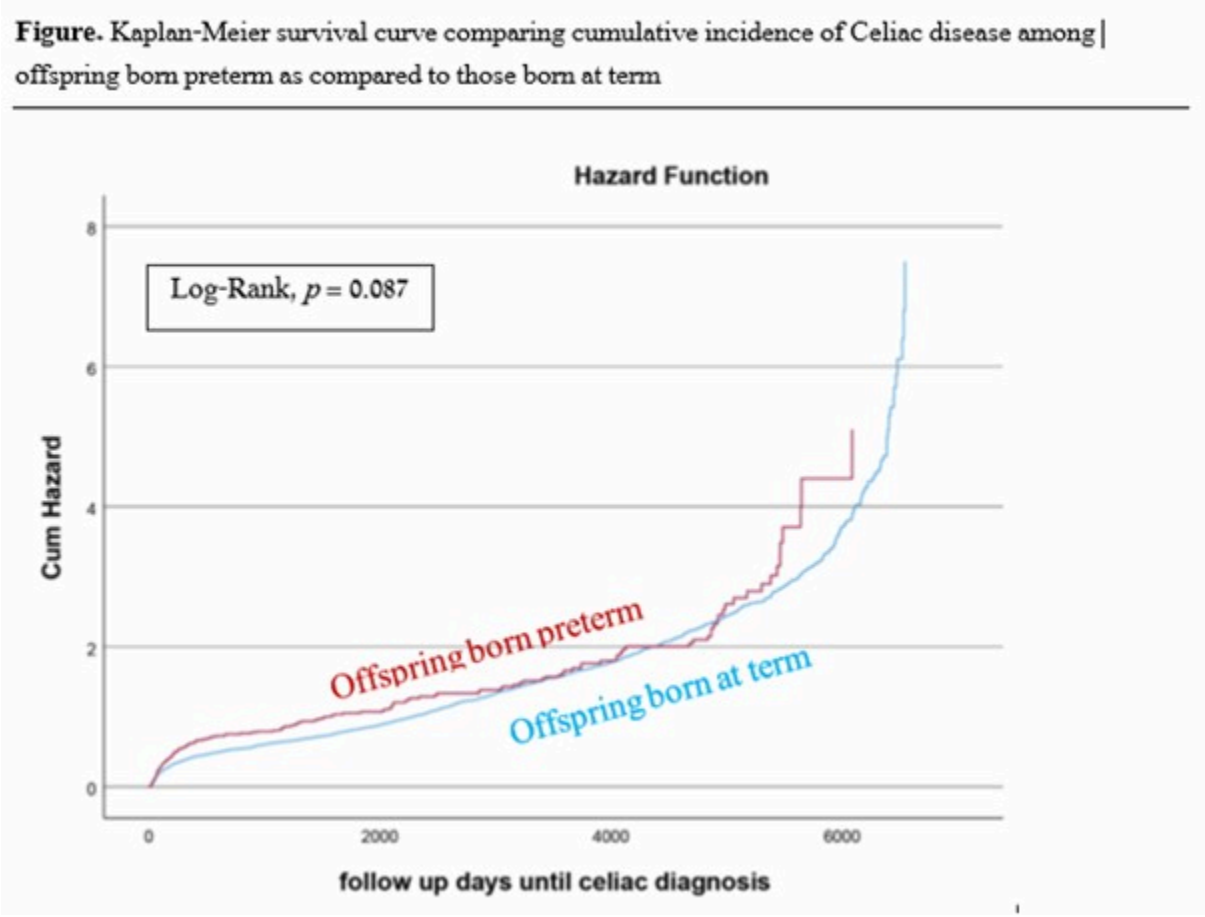


Figure 1

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