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Risk Factors Associated with Early-Onset Type 1 Diabetes Mellitus in Children Under Five Years: A Cross-Sectional Study in Yazd, Iran

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ABSTRACT

Background & Objective: Type 1 diabetes mellitus (T1DM) is a common autoimmune disease in children. Recent trends show a decreasing age at onset, raising concerns about contributing factors. This study aimed to identify factors associated with early-onset T1DM in children under five years of age in Yazd, Iran.

Materials & Methods: This cross-sectional study analyzed 108 newly diagnosed T1DM patients registered with the Iran Rare Diseases Foundation between March 2020 and March 2024. Participants were divided into two groups based on age at diagnosis: ≤5 years and >5 years. Data on family history, pregnancy-related, neonatal, and early childhood factors were collected via standardized checklists and parental interviews. Statistical analyses, including logistic regression, were performed to evaluate factors associated with early-onset T1DM.

Results: Of the participants, 22.2% were diagnosed at ≤5 years of age. Maternal infection during pregnancy was significantly more common among early-onset cases (20.8% vs. 4.8%, p=0.025), increasing the odds of early-onset T1DM by 5.26 times. Introduction of cow's milk at or after one year of age showed a protective effect against early-onset T1DM (OR= 0.07, p=0.027). No other factors were significantly associated with early-onset T1DM.

Conclusion: Maternal infections during pregnancy and early introduction of cow's milk are important factors associated with early-onset T1DM in children under five years of age. These findings highlight the potential role of prenatal and nutritional factors in the development of early-onset T1DM and emphasize the need for targeted prevention strategies.

Keywords: Type 1 diabetes mellitus; Risk factors; Early childhood

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1. Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common autoimmune diseases in childhood, characterized by the autoimmune destruction of pancreatic beta cells, resulting in a lifelong requirement for insulin therapy (1). In recent decades, a notable shift toward an earlier age at T1DM diagnosis has been observed, raising significant concerns within the scientific and clinical communities (2).

Epidemiological studies have reported substantial changes in the incidence and prevalence of T1DM worldwide (3). For instance, Kandemir et al. (2024) reported a 50-year trend in T1DM epidemiology among children and adolescents in Turkey, further confirming the shift toward earlier age at onset (3). Similarly, the EURODIAB study, which analyzed data from 17 European countries, identified the 0- to 4-year age group

as having the greatest increase in annual incidence rates (4). These trends underscore the urgent need to investigate potential risk factors and compare them across various age strata. Furthermore, studies have demonstrated an inverse relationship between age at diagnosis and disease severity and progression (5,6). The early onset of T1DM poses multifaceted challenges; younger children require complex management and are at elevated risk for acute and chronic complications, including diabetic ketoacidosis (DKA) (7).

Additionally, families face significant psychological and economic burdens, while healthcare systems encounter rising treatment costs (8–10). For example, the TEDDY cohort study highlighted that T1DM diagnosed at a younger age is often associated with early appearance of insulin autoantibodies (IAA), indicating a more aggressive disease phenotype (11).

Research suggests that T1DM risk factors vary according to age at onset (12). Discrepancies in the relative importance of these factors across studies can often be attributed to variations in the age groups investigated (12). Both genetic and environmental factors play crucial roles in disease development. Generally, risk factors for T1DM can be categorized as follows:

Genetic factors: Including high-risk HLA gene alleles, family history of diabetes, and other autoimmune conditions (13).

Pregnancy-related factors: Such as birth order (with higher risk in first-born children) (14,15), maternal age (14), maternal infections during gestation, history of preeclampsia, maternal smoking (16), mode of delivery (17), gestational age (18), and history of COVID-19 infection (19).

Neonatal and childhood factors: Including infant feeding practices (e.g., breastfeeding versus formula), the timing of dairy or cereal introduction, and exposure to stressful life events, such as paternal unemployment, maternal hospitalization, severe personal accidents, or bereavement (20,21,22).

Given the rising global incidence of T1DM and the clear trend toward earlier diagnosis, this study aims to evaluate and identify the factors associated with T1DM onset before the age of five years.

2. Materials and Methods

2.1 Study Design

This cross-sectional study included all newly diagnosed T1DM patients registered in the Rare Diseases Foundation of Iran (rda.behdasht.gov.ir) from March 2020 to March 2024. A total of 143 individuals were diagnosed with T1DM, of whom 38 did not respond to follow-up contact attempts.

Inclusion criteria were diagnosis of T1DM based on classic diabetes symptoms such as polyuria, polydipsia, and weight loss accompanied by hyperglycemia (random plasma glucose ≥200 mg/dL, fasting plasma glucose ≥126 mg/dL, or HbA1c ≥6.5%), and requirement for long-term insulin treatment (3).

Patients with documented secondary forms of diabetes (e.g., cystic fibrosis–related diabetes), documented monogenic diabetes (MODY) or other genetic diabetes when documented in the registry, or cases with missing core diagnostic data were excluded from this study.

Participants were categorized into two age groups: ≤5 years and >5 years (3). Relevant variables were collected using a standardized checklist. Data were obtained through follow-up telephone interviews with the parents of the patients to verify and complete information recorded in the checklist.

This study was approved by the Institutional Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran Approval Code: IR.SSU.REC.1404.009.

Based on the literature review, variables evaluated in this study were divided into three main categories (18,23,24). Genetic factors included family history of diabetes and autoimmune diseases.

Pregnancy-related risk factors included birth order, maternal age, infections during pregnancy, history of preeclampsia, maternal smoking, alcohol and drug use, mode of delivery (vaginal or cesarean section), duration of pregnancy (≥37 weeks or <37 weeks), and history of COVID-19 infection. Maternal infection was defined as any physician-diagnosed infection during pregnancy. Mothers were asked a single question during the interview: “Did you experience any infection during pregnancy for which you consulted a doctor and were given a diagnosis?” Those who answered “yes” were asked to describe the type of infection they had experienced.

Neonatal and childhood risk factors included type of infant feeding (breastfeeding or formula), age at introduction of dairy or cereals, age at introduction of cow’s milk defined as direct consumption of cow’s milk as a beverage, and exposure to stressful events. The occurrence of acute stressful events prior to diabetes onset was assessed through telephone interviews with the participants’ families.

They were asked whether the child had experienced any significant life events, such as serious illness or injury, death of a close family member, or other major changes before the onset of diabetes.

Based on the responses, participants were categorized as having experienced at least one acute stressful event (“yes”) or none (“no”). All collected data were entered into SPSS software for statistical analysis.

2.8 Statistical analysis

Descriptive statistics were computed for all variables. Continuous variables were presented as means and standard deviations (mean ± SD), and categorical variables were summarized as frequencies and percentages. Differences between the two groups of type 1 diabetes onset age (≤5 years vs. >5 years) were assessed using independent samples t-tests for continuous variables and Chi-square or Fisher’s exact tests for categorical variables. Logistic regression analysis was conducted to investigate factors associated with early-onset type 1 diabetes (diagnosis at or before 5 years of age). All analyses were carried out using SPSS software version 22 and GraphPad

Prism software version 8. A two-sided P-value <0.05 was considered statistically significant.

3. Result

3.1 Baseline Demographics and Family History

A total of 108 participants with T1DM were included in the analysis. Of these, 24 children (22.2%) were diagnosed at or before the age of 5 years (**early-onset group**), while 84 (77.8%) were diagnosed after the age of 5 years (**late-onset group**). The median age of participants was 10 years (range: 1–32 years). Males constituted 57.4% of the study population, with no significant difference in sex distribution between the two age groups (p = 0.917).

Baseline demographic, familial, and perinatal characteristics are summarized in Table 1. Mean birth weight did not differ significantly between children diagnosed ≤5 years and those diagnosed later (3.28 ± 0.44 vs. 3.22 ± 0.55 kg; p = 0.636). A positive family history of type 1 diabetes was more frequent in the >5 years group (26.2%) compared with the ≤5 years group (16.7%), although this difference was not statistically significant (p = 0.250). Similarly, no significant differences were observed between the groups regarding family history of type 2 diabetes or autoimmune diseases.

3.2 Maternal Pregnancy-Related Factors

Among pregnancy-related factors, maternal infection during pregnancy was significantly more common among children diagnosed at or before 5 years of age compared with those diagnosed later (20.8% vs. 4.8%, p = 0.025). All reported maternal infections were physician-diagnosed urinary tract infections (UTI) or vaginal infections. Specifically, among the nine mothers who reported an infection during pregnancy, four had vaginal infections, four had UTI, and one reported both conditions.

3.3 Neonatal and Infant Feeding Factors

Regarding neonatal and childhood factors, a significant difference was observed in the age at cow's milk introduction (p = 0.012). Of the four children recorded as having no cow's milk intake, three were in the ≤5 years' group and one was in the >5 years' group. Parents explained that these children had refused cow's milk from infancy, and therefore it was not provided at any point. No significant differences were found between the two groups with respect to delivery type, gestational age at birth, type of infant feeding, age at initiation of complementary feeding, recurrent infections, history of COVID-19 infection, or exposure to acute stressful life events (Table 1).

3.4 Temporal Distribution of T1DM Diagnosis

The annual frequency of newly diagnosed T1DM cases by age group from 2020 to 2024 is illustrated in Figure 1. No statistically significant variation in the distribution of early- and late-onset cases across the study years was observed (p = 0.764).

3.5 Logistic Regression Analysis

Logistic regression analysis was performed to identify factors associated with early-onset T1DM (≤5 years), as shown in Table 2. Maternal infection during pregnancy was significantly associated with early-onset T1DM, with a crude odds ratio (OR) of 5.26 (95% CI: 1.28–21.40; p = 0.021). In contrast, introduction of cow's milk at or after one year of age was associated with a significantly reduced likelihood of early-onset disease (OR = 0.07; 95% CI: 0.01–0.77; p = 0.027), compared with children who had never consumed cow's milk. Other evaluated factors, including family history of diabetes and exposure to acute stressful events, were not significantly associated with age at diagnosis. (Table 2)

Table 1. Baseline Characteristics of participants

	Total	≤ 5 years	> 5 years	p-value
N	108 (100.0)	24 (22.2)	84 (77.8)	
sex				0.917
girl	46 (42.6)	10 (41.7)	36 (42.9)	
boy	62 (57.4)	14 (58.3)	48 (57.1)	
Birth Weight	3.23(0.53)	3.28 (0.44)	3.22 (0.55)	0.636
Family diabetes type 1				0.250
No	82 (75.9)	20 (83.3)	62 (73.8)	
Yes	26 (24.1)	4 (16.7)	22 (26.2)	
Family diabetes type 2				0.652
No	32 (29.6)	8 (33.3)	24 (28.6)	
Yes	76 (70.4)	16 (66.7)	60 (71.4)	
Family autoimmune				0.573

No	76 (70.4)	18 (75.0)	58 (69.0)	
Yes	32 (29.6)	6 (25.0)	26 (31.0)	
Mothers age	25.96 ±5.82	26.08 ±4.85	25.92 ±6.10	0.909
Birth order				0.821
1	56 (51.9)	12 (50.0)	44 (52.4)	
2	33 (30.6)	7 (29.2)	26 (31.0)	
3	14 (13.0)	4 (16.7)	10 (11.9)	
4≤	5 (4.4)	1 (4.2)	4 (4.8)	
Mothers' infection				0.025*
No	99 (97.1)	19 (79.2)	80 (95.2)	
Yes	9 (8.3)	5 (20.8)	4 (4.8)	
Delivery type				0.757
Cesarean section	51 (47.2)	12 (50.0)	39 (46.4)	
Vaginal delivery	57 (52.8)	12 (50.0)	45 (53.6)	
Delivery week				0.600
<37	6 (5.6)	1 (4.2)	5 (6.0)	
37≤	102 (94.4)	23 (95.8)	79 (94.0)	
Type of nutrition				0.350
Breastfeeding	83 (76.9)	20 (83.3)	63 (75.0)	
Formula feeding	6 (5.6)	2 (8.3)	4 (4.8)	
Mix	19 (17.6)	2 (8.3)	17 (20.2)	
Age to start cow's milk				0.012*
under 1 year	7 (6.5)	3 (12.5)	4 (4.8)	
up 1 year	97 (89.8)	18 (75.0)	79 (94.0)	
nothing	4 (3.7)	3 (12.5)	1 (1.2)	
Starting complementary feeding				0.591
< 4 months	2 (1.9)	0 (0.0)	2 (2.4)	
4-6 months	23 (21.3)	4 (16.7)	19 (22.6)	
6≤ months	83 (76.9)	20 (83.3)	63 (75.0)	
Recurrent infection				0.681
No	99 (91.7)	22 (91.7)	77 (91.7)	
Yes	9 (8.3)	2 (8.3)	7 (8.3)	
COVID-19 history (approved by a doctor)				0.581
No	89 (82.4)	20 (83.3)	69 (82.1)	
Yes	19 (17.6)	4 (16.7)	15 (17.9)	
Acute stressful events				0.059
No	64 (59.3)	18 (75.0)	46 (54.8)	
Yes	44 (40.7)	6 (25.0)	38 (45.2)	

Table 2. **Factors associated with developing type 1 diabetes in children under 5 years of age**

Variables	OR (95%CI)	P-value
Family diabetes type 2	0.80(0.30-2.11)	0.653
Family diabetes type 1	0.56(0.17-1.83)	0.340
Mothers' infection	5.26(1.28-21.40)	0.021*
Age to start cow's milk		
nothing	Ref	-
under 1 year	0.25(0.2-3.77)	0.317
up 1 year	0.07(0.01-0.77)	0.027*
Acute stressful events	0.40(0.14-1.12)	0.104

Note: ***Significant at P-vale<0.05; CI: confidence interval**

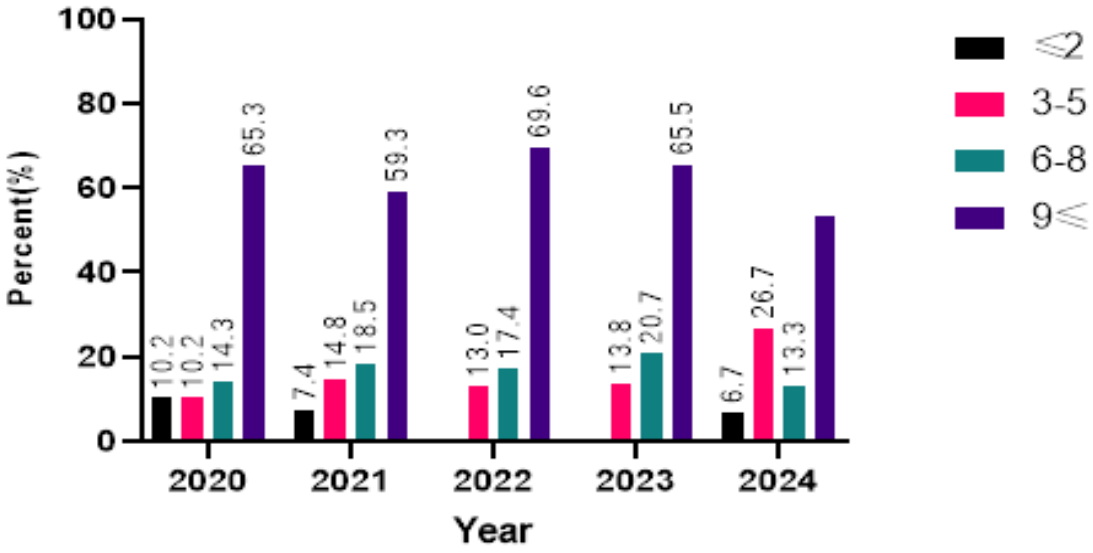

Figure 1. Frequency of T1DM by age of onset from 2020 to 2024 **(Prepared by Authors, 2026)**.

Note: **The figure represents the annual frequency of newly diagnosed T1DM cases (N = 143) from March 2020 to March 2024, stratified by age at onset (≤5 years vs. >5 years). No statistically significant difference was observed in the temporal distribution of new cases between the two age groups over the study period (p = 0.764).**

4. Discussion

This study evaluated factors associated with the onset of T1DM in children diagnosed at or before the age of five years compared to those diagnosed later in Yazd, Iran. A key finding of the present study was the effect of the timing of cow's milk introduction.

Introducing cow's milk at or after 12 months of age significantly reduced the likelihood of early-onset T1DM (before age 5), highlighting the potential role of infant feeding practices in modulating disease risk.

However, the literature on the timing of cow's milk introduction remains inconsistent. For example, Virtanen et al. found no association between age at cow's milk introduction and T1DM, although their data showed that children consuming ≥3 glasses of cow's milk per day had a higher rate of diabetes-related autoantibody seroconversion compared with those with lower intake (25). Similarly, Niinistö et al. reported that frequent cow's milk consumption after infancy increased the risk of islet autoimmunity and progression to T1DM in genetically susceptible children (26). Collectively, these studies emphasize milk quantity rather than timing as the primary exposure of interest. In contrast, our findings suggest that the timing of introduction may independently influence the risk of very early-onset T1DM, offering a complementary perspective to existing evidence. It is also important to note that previous studies have been conducted in heterogeneous populations, ranging from high-risk cohorts to general-population samples. Underlying genetic predisposition can modify the effect

of dietary exposures; for instance, the DAISY study demonstrated that cow's milk increased autoimmunity risk only among children with low- or intermediate-risk HLA genotypes (27). These differences may partly explain the inconsistent findings reported across studies.

A number of epidemiological studies and meta-analyses have investigated whether maternal infection during pregnancy influences the risk of T1DM in offspring (28, 29). A systematic review and meta-analysis pooling data from 18 studies reported a significant association for maternal infection during pregnancy (29). These findings suggest that in utero exposure to infections may predispose to autoimmune processes, possibly by affecting fetal immune development or inducing immune activation in the fetus. The All Babies in Southeast Sweden (ABIS) cohort showed that maternal respiratory tract infection during the first trimester of pregnancy was independently associated with increased risk of T1DM in the child; in contrast, other types of infections (including urinary or non-respiratory infections) or use of antibiotics did not show a robust association (30).

In our study, maternal infection physician-diagnosed UTI or vaginal infections during pregnancy increased the risk of T1DM in children ≤5 years (OR = 5.26; 95% CI: 1.28–21.40; p = 0.021). Given the existing literature, several points merit emphasis. First, most associations in meta-analyses pertain to viral infections during pregnancy, particularly enteroviruses or other systemic/placenta-invasive pathogens (28, 29). Second, evidence for bacterial genitourinary infections during pregnancy (UTI or vaginal infections) as risk factors for T1DM in offspring remains sparse; few studies have explicitly evaluated these infection types. For example, the ABIS cohort did not find an association between non-respiratory (e.g., genitourinary) maternal infections and T1DM (30). Therefore, although our findings of a five-fold increased odds of early-onset T1DM in children whose mothers had UTI or vaginal infection during pregnancy are intriguing, they must be interpreted cautiously. Several large prospective studies, such as DiPiS, have shown that early-life severe life events (SLE), especially in the first two years, are significantly associated with an increased risk of developing T1D in children (HR 1.67 to 2.2) (31).

However, other studies, particularly the ABIS study, did not confirm this association (32). Additionally, older case-control studies have suggested that certain types of stressful events, such as the loss of a loved one or the threat of loss, may increase the risk of T1D in children, especially between the ages of 5 and 9 years (RR ≈ 1.8) (33).

In the current study, we did not find a significant difference between the groups with or without severe life events concerning the age of onset of diabetes (below vs. above 5 years).

This discrepancy in the literature highlights the complexity of the role of stressful life events as an environmental factor in the development of T1D, and suggests that its effects may depend on the timing of exposure, the type of event, and genetic background (34–36).

Despite this, the findings of the present study, which indicate no significant association between acute stressful events and the onset of T1D in different age groups, may be due to methodological limitations.

To provide a more accurate understanding of these relationships, it is suggested that future studies use validated and standardized acute stressful events assessment tools.

5. Conclusion

In summary, our findings suggest that maternal infections during pregnancy including UTI or vaginal infection and early introduction of cow's milk are important determinants of early-onset T1D.

These results highlight the complex interplay of prenatal, nutritional, and metabolic factors in the development of T1D in young children. Future multicenter studies with larger cohorts and genetic profiling are warranted to validate and expand upon these findings.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study was approved by the Institutional Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran Approval Code: IR.SSU.REC.1404.009.

6.3 Authors' Contributions

All authors made substantial contributions to this work. N.M conceived and designed the study and supervised the entire project.

Z.F and N.N contributed to the study design, data analysis and interpretation, and critically revised the manuscript. A.Kh and H.MK participated in data collection. N.I was involved in study design, data collection, and drafting the initial manuscript. All authors reviewed and endorsed the final manuscript.

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest.

6.5 Fund or Financial Support

None

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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