

Preventable Prenatal and Neonatal Risk Factors of Type 1 Diabetes in Childhood

Abstract

Background: Childhood type 1 diabetes mellitus (T1DM) is an autoimmune disease which is increasing in incidence, but little is known about the events that trigger the autoimmune process. Most of the time, these processes begin in prenatal and natal periods; therefore, this study aimed to investigate the prenatal and neonatal risk factors of T1DM in childhood. **Methods:** This case-control study has been performed on children with T1DM who referred to the 17th Shahrivar children's hospital. The control group consisted of healthy siblings of the case group. Data were gathered using a form that included maternal and neonatal characteristics. Data were reported by descriptive statistics in SPSS 19. To investigate the effect of quantitative and qualitative variables on the development of T1DM, logistic regression and Chi-square tests were used, respectively. **Results:** Birth weight, birth height, and maternal weight gain during pregnancy had a significant relationship with T1DM (odds ratio [OR] = 1.23, 2.57, and 1.14, respectively). In addition, there was a significant relationship between gestational hypertension (OR = 5.27), neonatal jaundice (OR = 3.42), cesarean section (OR = 2.06), and being non-first-born child (OR = 2.32) and T1DM. Also, premature rupture of membrane, maternal urinary tract infection, and nonexclusive breastfeeding had a significant association with T1DM (OR = 4.37, 3.94, and 2.30, respectively). There were no statistically significant differences between maternal age, sex, neonatal respiratory disease, prematurity, and neonatal infections and T1DM ($P > 0.05$). **Conclusions:** Prenatal and neonatal risk factors can have a significant role in the occurrence of T1DM. Therefore, considering these risk factors can have a preventive effect on T1DM.

Keywords: Child, newborn, pregnancy, type 1 diabetes

Introduction

Type 1 diabetes mellitus (T1DM) is found mostly in children. It is caused by the autoimmune destruction of insulin-producing cells of the pancreas, which leads to hyperglycemia.^[1] In recent decades, the incidence of T1DM has been increasing worldwide. Its cause is multifactorial and consists of genetic susceptibility and environmental triggers, although little is known about the events that trigger the autoimmune process.^[2]

Such rapid changes in the occurrence of T1DM over time cannot be explained by shifts in the genetic material alone, but rather as a result of changes in environmental elements that initiate and aid progression of the disease.^[3]

Additionally, the concordance rate of <50% in identical twins suggests a notable role of

environmental factors in the development of diabetes. The relative increase in its incidence in children <5 years old indicates that environmental exposures in early life could play an important role.^[1]

It seems that in child-onset cases, events that ignite the progressive autoimmune processes, leading to diabetes, occur in the fetal or perinatal period of life. The most compelling example of an environmental risk factor strongly associated with T1DM is the rubella virus infection occurring during fetal life. More recently, fetal exposure to enteroviruses has also been associated with the risk of T1DM.^[3]

T1DM requires intensive continuous management. It can eventually lead to secondary complications and affect multiple organs. Concern has been raised about the increasing incidence of this disease worldwide, given the impact that

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T1DM has on the quality of life and the long-term cost to healthcare systems and individuals with diabetes and their families.^[4]

Various population-based studies originating from prospectively recorded perinatal data either from hospital records or from registry have suggested associations between the risk of T1DM and factors such as maternal preeclampsia, delivery by cesarean section, older maternal age, increased birth weight by gestational age, and neonatal jaundice induced by maternal-fetal blood group incompatibility. Some of these have been confirmed in meta-analyses, whereas others remain controversial.^[5]

Regarding the burden of this chronic disease on society, the healthcare system, patients and their families, this study aimed to demonstrate the relationship between the development of T1DM and fetal/perinatal risk factors.

Methods

Studied population

This case-control study has been performed on children who were referred to the 17th Shahrivar Hospital. The case group encompasses children with T1DM and a control group including healthy siblings of the case group.

Ethical considerations

Ethical approval was obtained from the Vice-Chancellor of Research at Guilan University of Medical Sciences (No. = IR.GUMS.REC.1399.314, Oct 7, 2020), and a consent letter was obtained from parents or guardians.

Inclusion and exclusion criteria

Inclusion criteria for the case group were as follows: T1DM, age under 24 years,^[6] and having a healthy sibling. They were regularly visited by the pediatric endocrinologist and based on the clinical and laboratory results, appropriate treatment was indicated. Those who expressed unwillingness to participate were excluded.

Gathering data

Data were gathered by a form including maternal and neonatal characteristics. Maternal characteristics were maternal age during pregnancy, premature rupture of membrane (PROM), urinary tract infection (UTI) in pregnancy, gestational hypertension, weight gain during pregnancy, and mode of delivery. Any other underlying diseases or conditions that occurred during pregnancy were recorded. Neonatal characteristics of both groups at birth such as birth weight, birth length, prematurity, birth order, sex, and type of infant feeding were recorded. Also, the occurrence of diseases such as jaundice, neonatal infections, neonatal respiratory disorders such as respiratory distress syndrome, and any other high-risk conditions was recorded.

Statistical analysis

Data were analyzed by SPSS version 22. Data were reported by descriptive statistics including number, percent, mean, and standard deviation. To investigate the effect of quantitative and qualitative variables on the development of T1DM, logistic regression and Chi-square tests were used, respectively.

Results

In this study, 159 T1DM patients and 159 healthy siblings were enrolled. According to the results presented in Table 1, there was no statistically significant difference between the groups regarding current age, weight, and height ($P > 0.05$). The mean age at diagnosis in the case group was 7.42 ± 3.65 years.

There was no statistically significant difference between maternal age at gestation and the occurrence of T1DM in children (odds ratio [OR] = 1.03, 95% CI: 0.99-1.08, $P = 0.186$). Birth height had a meaningful relationship with T1DM in children. The results showed that being 1 cm taller at birth increased the risk of T1DM by 23% (OR = 1.23, 95% CI: 1.09-1.38, $P = 0.001$). Results showed a significant relationship between birth weight and T1DM in children. Each kilogram increase of birth weight increased the risk of T1DM by 2.57 times (OR = 2.57, 95% CI: 1.52-4.35, $P < 0.0001$). There was a significant relationship between maternal weight gain during pregnancy and T1DM in children. Thus, with every kilogram increase of maternal weight gain during pregnancy, the risk of developing T1DM in the child increased by 1.14 times (OR = 1.14, 95% CI: 1.08-1.21, $P < 0.0001$) [Table 2].

The risk of developing T1DM in girls was 1.14 times higher than in boys. However, the level of significance showed that there was no statistically significant relationship between child sex and T1DM (OR = 1.14, 95% CI: 0.73-1.76, $P = 0.574$). A significant relationship between gestational hypertension and T1DM in children was observed, whereas children whose mothers had high blood pressure during pregnancy were 5.27 times more likely to develop T1DM than children without this condition (OR = 5.27, 95% CI: 1.14-24.44, $P = 0.034$). No association was detected between neonatal respiratory disease and T1DM in children (OR = 1.46, 95% CI: 0.54-3.93, $P = 0.457$).

Table 1: Demographic characteristics of children with T1DM and controls

Demographic characteristics (mean±SD)	Case	Control	t	df	P
Current age	11.75±4.77	12.56±7.40	1.149	316	0.252
Current height	143.70±22.51	140.26±31.38	1.075	316	0.283
Current weight	41.28±17.56	43.80±23.77	-1.122	316	0.263
Age of diagnosis	7.42±3.65	-	-	-	-

T1DM=type 1 diabetes mellitus

Table 2: Perinatal variables of children with T1DM and controls

Variables (mean±SD)	Case	Control	OR (95% CI)	P
Maternal age	25.82±5.12	25.06±5.12	1.03 (0.99-1.08)	0.186
Maternal weight gain	13.72±4.56	11.60±3.41	1.14 (1.08-1.21)	<0.0001
Birth length	50.25±2.16	49.28±2.54	1.23 (1.09-1.38)	0.001
Birth weight	3.31±0.47	3.12±0.45	2.57 (1.52-4.35)	<0.0001

T1DM=type 1 diabetes mellitus

Furthermore, results showed that there was a statistically significant relationship between neonatal jaundice and T1DM. Neonatal jaundice was associated with a 3.42 times higher risk of developing T1DM in childhood (OR = 3.42, 95% CI: 2.07-5.64, $P < 0.0001$). Comparison of the potential perinatal risk factors between groups is shown in Table 3. There was a statistically significant relationship between birth order and T1DM. Thus, the risk of developing T1DM in non-first born children was 2.32 times higher than in first-born children (OR = 2.32, 95% CI: 1.48-3.64, $P < 0.0001$). A significant relationship between the mode of delivery and T1DM in children was seen. Thus, children born by cesarean section were 2.06 times more likely to have T1DM than the children born by natural vaginal delivery (OR = 2.06, 95% CI: 1.30-3.25, $P = 0.002$). There was no significant association between prematurity and the risk of T1DM in children (OR = 1.79, 95% CI: 0.51-6.22, $P = 0.363$). Premature rupture of the membrane had a statistically significant relationship with the risk of T1DM in children. The OR showed that mothers who had premature rupture of the membrane were 4.37 times more likely to have a child with T1DM than the mothers without this condition (OR = 4.37, 95% CI: 2.01-9.47, $P < 0.0001$).

There was a significant relationship between maternal UTI in pregnancy and T1DM in children. Thus, in children whose mothers had experienced UTI during pregnancy, the risk of developing T1DM was 3.94 times higher than in children without this condition (OR = 3.94, 95% CI: 1.92-8.06, $P < 0.0001$). There was no statistically significant relationship between neonatal infections and T1DM (OR = 1.42, 95% CI: 0.44-4.57, $P = 0.558$). There was a meaningful relationship between the type of milk consumed during infancy and T1DM. The risk of developing T1DM in children who were nonexclusively breastfed (in combination with formula) was 2.35 times higher than in children who were exclusively breastfed. Also, the probability of developing T1DM in children who were just formula fed during infancy was 2.30 times higher than in children who were exclusively breastfed (OR = 2.35, 95% CI: 1.16-4.77, $P = 0.018$ and OR = 2.30, 95% CI: 1.30-4.07, $P = 0.004$, respectively) [Table 3].

Discussion

A total of 318 participants were included in this study, of

Table 3: Potential perinatal risk factors of T1DM in cases and controls

Variables	Case	Control	OR (95% CI)	P
Child sex				
Female	76	71	1.14 (0.73-1.76)	0.574
Male	83	88		
Gestational hypertension				
Yes	10	2	5.27 (1.14-24.44)	0.034
No	149	157		
Respiratory disorder				
Yes	10	7	1.46 (0.54-3.93)	0.457
No	149	152		
Neonatal jaundice				
Yes	72	31	3.42 (2.07-5.64)	<0.0001
No	87	128		
Birth order				
First	63	96	2.32 (1.48-3.64)	<0.0001
Not first	96	63		
Delivery mode				
C/S	110	83	2.06 (1.30-3.25)	0.002
NVD	49	76		
Delivery time				
Preterm	7	4	1.79 (0.51-6.22)	0.363
Term	152	155		
PROM				
Yes	33	9	4.37 (2.01-9.47)	<0.0001
No	126	150		
Maternal UTI				
Yes	36	11	3.94 (1.92-8.06)	<0.0001
No	123	148		
Neonatal infection				
Yes	7	5	1.42 (0.44-4.57)	0.558
No	152	154		
Type of feeding				
Breast feeding	92	121	-	-
Formula feeding	42	24	2.30 (1.30-4.07)	0.004
Mixed	25	14	2.35 (1.16-4.77)	0.018

PROM=premature rupture of membrane, T1DM=type 1 diabetes mellitus, UTI=urinary tract infection

whom 159 were children with T1DM and 159 were their healthy siblings. In this study, the case and control groups had the same height, and this indicated their good control with intensive insulin therapy. This result was consistent with previous studies.^[7-9] These findings present the important role of insulin therapy and intensified treatment in the growth velocity of diabetic children.

In this study, results demonstrated that T1DM was more common in children born by cesarean section. This finding was consistent with Cardwell *et al.*^[10] and Waernbaum *et al.*'s^[5] findings and inconsistent with Dahlquist *et al.*'s^[3] results. These different results compared to previous studies may be due to pregestational obesity and greater weight gain during pregnancy,^[11] which suggests that these factors

led to cesarean section and the delivery mode was not an independent risk factor for T1DM. Various mechanisms suggested the cesarean section as a risk factor. It has been associated with altered immune functions like reduced Th1 responses and increased risk for autoimmune diseases, including T1DM, probably through altered gut microbiome composition.^[5,10] Additionally, it has been reported that administering anesthetic drugs can induce cell damage during cesarean section.^[12]

In this study, researchers did not find a significant relationship between gestational age and the risk of T1DM, which was consistent with Stene *et al.*^[3] and Dahlquist *et al.*^[3] and inconsistent with Cardwell *et al.*,^[10] although in a recent large study by Waernbaum *et al.*,^[5] in 2019, results showed a reduced risk of diabetes at gestational age less than 32 weeks and an increased risk of diabetes at a gestational age of 32-36 weeks. These differences may be due to the lack of quantitative reports of gestational age in this study. As it was mentioned, gestational age was classified as preterm and term. However, Waernbaum *et al.* compared participants with less than 32 and 32-36 weeks of gestation.

In this study, there was no significant association between neonatal infections and T1DM. This result was consistent with Dahlquist *et al.*^[3] and Waernbaum *et al.*^[5] and inconsistent with Liao *et al.*^[2] The lack of significant association between neonatal infections and the risk of T1DM in the current study did not exclude the possibility of infectious disease *in utero* or in the early neonatal period as a risk factor for diabetes because many viral diseases during pregnancy commonly remain undiagnosed. Therefore, considering total infections including asymptomatic viral infections with larger sample size is recommended.

This study showed that T1DM was 3.42 times more common in children who experienced neonatal jaundice than in the children without this condition. This finding was consistent with the result of Dahlquist *et al.*^[3] and Liao *et al.*^[2] and inconsistent with the result of Waernbaum *et al.*^[5] These differences reflect different study designs, methods of jaundice ascertainment, number of participants, and different degrees of genetic and environmental predisposition to T1DM in different ethnic populations. Although the underlying mechanisms are undefined, it suggests that bilirubin overload may affect the neonatal immune system, triggering an aberrant immune response and initiating pancreatic islet autoimmunity, thus leading to selective pancreatic β -cell destruction and eventually T1DM in some genetically susceptible cases. Hyperbilirubinemia itself is not associated with DNA damage, but both conventional and intensive phototherapy can lead to increased oxidative stress, DNA damage, and altered cytokine levels, all of which are associated with the pathogenesis of T1DM.^[2]

This study found that diabetes was more common in children with longer length at birth. The risk of developing

T1DM had increased 1.23 times for every centimeter increase in birth length. This result conformed to Dahlquist *et al.*'s^[3] findings that demonstrated the protective influence of having a short birth length on developing T1DM. This relationship may be due to the influence of difference in HLA, which Larsson *et al.*^[14] investigated in 2008 and reported similar birth length in cases and their HLA-matched controls. In this study, there was no matching regarding the HLA type. Therefore, the mean birth length of diabetic patients was reported to be higher than that of healthy controls, which does not contradict the above-mentioned study. The fact that birth length difference was not observed when compared with HLA-matched children in Larsson *et al.*'s^[14] study suggested that diabetes high-risk HLA was conspicuously associated with growth development *in utero* and can affect birth length. In addition, in 2020, Liu *et al.*^[15] reported that growth patterns in early life were associated with the development of T1DM regardless of HLA. Therefore, it seems that performing further studies assessing the relationship between growth patterns in the first year of life and the development of T1DM is recommended.

There was no significant association between maternal age during pregnancy and the subsequent development of T1DM. This result was inconsistent with Dahlquist *et al.*^[3] and Cardwell *et al.*^[10] But in 2008, Rosenbauer *et al.*^[16] found that children whose mothers were older than 40 years or younger than 20 years were more susceptible to developing T1DM. Although Stene *et al.*^[17] did not detect significant association among first-born children, they reported a significant relationship in fourth-born children. It cannot be ignored that with increasing maternal age, the risk of complicated pregnancy and cesarean delivery increases,^[18] and these risk factors can affect the incidence of T1DM. But the mothers who attended this study were relatively young and did not show a wide age range. Therefore, a selection bias may have occurred.

Furthermore, this study showed a positive association between nonexclusive breastfeeding and T1DM, which indicated an OR = 2.30 for formula-fed infants and an OR = 2.35 for the children who were fed with a combination of breast milk and formula. Therefore, performing more studies assessing the probable higher risk of T1DM in combination-fed children is recommended. These findings were consistent with Rosenbauer *et al.*,^[19] who conducted a systematic review to investigate the association between the type of feeding, time of introduction of formula or cow's milk, duration of breastfeeding, and the development of T1DM. Their results indicated that a short duration and/or a lack of breastfeeding may constitute a risk factor for the development of T1DM later in life,^[20] which supported the current results. Another review performed by Pereira *et al.*^[21] investigated the influence of breastfeeding as a protective agent against the onset of T1DM in children and concluded that the lack of breastfeeding was

a modifiable risk factor for T1DM. Bottle-fed children had more rapid growth, so the overload hypothesis can support this result. The other probable underlying mechanisms included the protective agents in breast milk and the lack of exposure to foreign complex proteins that effect autoimmunity processes. All these together suggest that early exposure to complex foreign proteins available in the formula can be a risk factor for autoimmune destruction of β cells and the development of T1DM.

This study also found that the mean weight gain of mothers during pregnancy was higher in the case group than in the control group. For every kilogram increase in weight gain in mothers, the incidence of diabetes had increased 1.14 times in their children. In line with this result, Rasmussen *et al.*^[22] reported in 2009 that both maternal body mass index (BMI) ≥ 30 kg/m² and weight gain of ≥ 15 kg during pregnancy can increase the risk of islet autoimmunity in offspring, with a high genetic susceptibility for T1DM. In a cohort study, Hussien *et al.*^[23] reported that higher maternal BMI in the first trimester was associated with increased risk of T1DM only in offspring of parents without diabetes. In 2018, Lindell *et al.*,^[24] in a prospective, population-based case-control study, reported that maternal obesity was a significant risk factor for T1DM in the offspring ($P = 0.04$). Maternal obesity in pregnancy was associated with the risk of fetal hyperinsulinemia due to the transfer of glucose and other nutrients across the placenta, stimulating fetal insulin secretion and future diabetes.^[23] Hyperinsulinemia and active pancreatic β cells are more susceptible to destruction and further T1DM.^[24] Although its mechanism is not defined yet, it seems that it occurs due to immune system stimulation.

This study showed a strong association between gestational hypertension and T1DM. T1DM was 5.27 times more common among children whose mothers experienced gestational hypertension. There are few articles assessing the relationship between preeclampsia and childhood T1DM, including Dahlquist *et al.*,^[3] who confirmed the association between preeclampsia and an increased risk of T1DM. On the contrary, Waernbaum *et al.*,^[5] in 2019, could not confirm earlier findings of an association between preeclampsia, eclampsia, or maternal hypertension in the mother and T1DM in the child. The bioactive factors induced by placental ischemia due to the effect of pregnancy-induced hypertension (PIH) might cross the placental barrier into the fetal circulation. It seems that maternal PIH could cause significant fetal immune system derangements. Lower CD4/CD8 T-cell ratios, a higher percentage of natural killer (NK) cells and alternative complement pathway activity, and monocyte activation in the umbilical cord blood were found in fetuses born to PIH mothers compared to those born to normotensive mothers. Fetal hypoxia due to placental ischemia could induce these immunological reactions.^[23] So, early immunological disturbance of the child may be a trigger for the later development of T1DM.

In this study, T1DM was significantly more common among the children whose mothers had experienced UTI during pregnancy in comparison with the children whose mothers were without this condition. In 2018, Yue *et al.*^[26] reported that maternal gestational infections (not only UTI) were associated with 32% increased odds of T1DM or islet autoimmunity in the offspring. Also, in another study, Waernbaum *et al.*^[5] reported the association between later risk for T1DM and UTIs during pregnancy. A maternal infection could induce antibodies that could be transmitted to the fetus through the placenta. On the other hand, the fetal immune system could also drive the T cells to respond to infection. Pathogen-specific T cells can be found in cord blood samples from children whose mothers had infections during pregnancy;^[26] hence, it could be explained how maternal UTI could trigger initial destruction to fetal beta cells.

In animal models, prenatal exposure to antibiotics influenced gut bacterial composition in children and could increase the risk of T1DM in the offspring, depending on the type of antibiotic used.^[5] Therefore, besides the infections, antibiotic therapy can be a trigger to initiate the diabetes process.

Results have demonstrated that the overall sex ratio for the incidence of T1DM is roughly equal in children and there is no meaningful association between sex and the risk of T1DM. In some previous studies, the incidence of T1DM was higher among girls,^[2,27] and some studies showed a greater incidence among boys^[28] or an average equal distribution between girls and boys. In 2018, Weng *et al.*^[29] reported a difference in the incidence of T1DM in girls and boys, depending on their age categories. In 2020, Liao *et al.*^[2] reported that girls had a greater risk of T1DM than boys. There is no substantial explanation for this inconsistency, but it seems that genetic variation could cause these different results. Sayad *et al.*,^[30] in 2013, studied HLA-DRB1 and -DQB1 genes, which have the strongest association with T1DM, and reported different distribution by sex in Iran.

Findings showed that the incidence rate of T1DM increased with birth weight; each kilogram increase in birth weight increased the incidence of diabetes 2.57 times. This finding was in line with most of the studies that assessed the relationship between birth weight and the risk of childhood T1DM.^[3,5,10,13,31,32] Inconsistent with this result, Rosenbauer *et al.*^[16] reported that low birth weight was more frequent among diabetic than control children. In 2018, Goldacre *et al.*^[32] reported that children born with a higher weight than the average birth weight experienced a higher incidence of T1DM than the children born with medium birth weight, while the children with a low birth weight (<2500 g) experienced lower incidence. Also, in 2019, Waernbaum *et al.*^[5] reported that birth weight z score was positively associated with an increased risk for

T1DM. The association between high birth weight and high maternal BMI and T1DM supported the so-called overload or acceleration hypothesis, suggesting that a high pre- or postnatal growth rate may accelerate ongoing β -cell destruction by nutrient overload.^[5] Thus, increased growth *in utero* may lead to an increased risk of later immune-mediated destruction of the pancreatic β cells.^[13] Also, there is evidence of an association between established T1DM high-risk HLA genotypes and higher birth weight in the general population.^[31] In this study, PROM had occurred significantly higher in mothers whose children had T1DM. Results of this study are consistent with those of Waernbaum *et al.*^[5] and Stene *et al.*,^[33] which suggested that PROM led to complicated delivery, which predicted a higher risk of β -cell autoimmunity. It seems that complicated labor can affect the fetal immune system, which results in medium to long-term consequences like autoimmune diseases. Results showed that T1DM was more common in non-first-born children in comparison with the first-born ones. This finding was consistent with the results of Dahlquist's^[3] study which suggested being a first-born child as a protective factor for T1DM. Inconsistent with this result, in 2015, Razavi *et al.*,^[34] in a cross-sectional, descriptive study, reported that most patients (42%) were first children of the family. In 2011, Cardwell *et al.*^[10] found that in children with early diagnosed diabetes (<5 years of age), there was some evidence of a reduction in the risk of T1DM in non-first-born children, but there was no association between birth order and childhood diabetes diagnosed between 5 and 15 years.^[35]

There was no meaningful association between neonatal respiratory infections and T1DM. This result was in line with some studies including Ayati *et al.* in 2020.^[12] Similar results were reported by Visalli *et al.*^[36]

There was no significant association between neonatal infections and the risk of T1DM. Although Dahlquist *et al.*^[3] reported neonatal respiratory distress as a risk factor and several studies found the role of neonatal diseases including respiratory distress and infections as a risk factor for T1DM, it seems that newer and more active treatments could have diminished the possible effect of respiratory infections on the neonatal immune system.

Conclusions

Environmental agents, genetic factors, and autoimmunity have been shown to be effective in the pathogenesis of T1DM. The authors believe that prenatal and neonatal environmental factors could affect two other areas. Therefore, this study recommends further studies on larger populations and considering other factors to assess the interaction between perinatal and neonatal situations affecting T1DM. Prenatal and neonatal risk factors can have a significant role in the occurrence of T1DM. Therefore, considering these risk factors can have a preventive effect on T1DM. Based on the results, it can be concluded that

identifying and avoiding exposure to risk factors, providing prenatal care, improving parents' knowledge and awareness of predisposing factors, and performing specific training programs, and conducting optimal follow-up to evaluate the effectiveness of interventions are simple and effective preventive strategies.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Key message

- Prenatal risk factors can have a significant role in the occurrence of T1DM.
- Considering neonatal risk factors can have a preventive effect on T1DM.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Cardwell CR, Stene LC, Ludvigsson J, Rosenbauer J, Cinek O, Svensson J, *et al.* Breast-feeding and childhood-onset T1DM: A pooled analysis of individual participant data from 43 observational studies. *Diabetes Care* 2012;35:2215-25.
2. Liao P-F, Tsai J-D, Chen H-J, Pan H-H, Hung T-W, Chang H-Y, *et al.* Neonatal hyperbilirubinemia is associated with a subsequent increased risk of childhood-onset T1DM. *Paediatr Int Child Health* 2020;40:35-43.
3. Dahlquist GG, Patterson C, Soltesz G. Perinatal risk factors for childhood T1DM in Europe. The EURODIAB Substudy 2 Study Group. *Diabetes Care* 1999;22:1698-702.
4. Lawrence JM, Mayer-Davis EJ. What do we know about the trends in incidence of childhood-onset T1DM?. *Diabetologia* 2019;62:370-2.
5. Waernbaum I, Dahlquist G, Lind T. Perinatal risk factors for T1DM revisited: A population-based register study. *Diabetologia* 2019;62:1173-84.
6. Sawyer SM, Azzopardi PS, Wickremaratne D, Patton GC. The age of adolescence. *Lancet Child Adolesc Health* 2018;2:223-8.
7. Chiarelli F, Giannini C, Mohn A. Growth, growth factors and diabetes. *Eur J Endocrinol* 2004;151:U109-17.

8. Santi E, Tascini G, Toni G, Berioli MG, Esposito S. Linear growth in children and adolescents with T1DM mellitus. *Int J Environ Res Public Health* 2019;16:3677.
9. Gillani S, Iqbal A, Kazmi N. Severe growth failure and poorly controlled T1DM mellitus in a 7-year-old girl: Mauriac syndrome. *J Coll Physicians Surg Pak* 2019;29:590-1.
10. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, *et al.* Caesarean section is associated with an increased risk of childhood-onset T1DM mellitus: A meta-analysis of observational studies. *Diabetologia* 2008;51:726-35.
11. Seligman LC, Duncan BB, Branchtein L, Gaio DSM, Mengue SS, Schmidt MI. Obesity and gestational weight gain: Cesarean delivery and labor complications. *Rev Saude Pública* 2006;40:457-65.
12. Ayati M, Mosayebi Z, Movahedian AH. Association between perinatal risk factors and development of T1DM in children. *J Compr Pediatr* 2020;11:e82902.
13. Stene LC. Birth weight and childhood onset T1DM: Population based cohort study. *BMJ* 2001;322:889-92.
14. Larsson HE, Hansson G, Carlsson A, Cederwall E, Jonsson B, Jönsson B, *et al.* Children developing T1DM before 6 years of age have increased linear growth independent of HLA genotypes. *Diabetologia* 2008;51:1623-30.
15. Liu X, Vehik K, Huang Y, Elding Larsson H, Toppari J, Ziegler AG, *et al.* Distinct growth phases in early life associated with the risk of T1DM: The TEDDY Study. *Diabetes Care* 2020;43:556-62.
16. Rosenbauer J, Herzig P, Giani G. Early infant feeding and risk of T1DM mellitus—A nationwide population-based case-control study in pre-school children. *Diabetes Metab Res Rev* 2008;24:211-22.
17. Stene LC, Magnus P, Lie RT, Søvik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset T1DM: Population based cohort study. *BMJ* 2001;323:369.
18. Darsareh F, Aghamolaei T, Rajaei M, Madani A. Determinants of caesarian birth on maternal demand in the Islamic Republic of Iran: A review. *East Mediterr Health J* 2017;23:441-8.
19. Rosenbauer J, Herzig P, Kaiser P, Giani G. Early nutrition and risk of T1DM mellitus--A nationwide case-control study in preschool children. *Exp Clin Endocrinol Diabetes* 2007;115:502-8.
20. Patelarou E, Girvalaki C, Brokalaki H, Patelarou A, Androulaki Z, Vardavas C. Current evidence on the associations of breastfeeding, infant formula, and cow's milk introduction with T1DM mellitus: A systematic review. *Nutr Rev* 2012;70:509-19.
21. Pereira PF, Alfenas R de CG, Araújo RMA. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. *J Pediatr* 2014;90:7-15.
22. Rasmussen T, Stene LC, Samuelsen SO, Cinek O, Wetlesen T, Torjesen PA, *et al.* Maternal BMI before pregnancy, maternal weight gain during pregnancy, and risk of persistent positivity for multiple diabetes-associated autoantibodies in children with the high-risk HLA genotype: The MIDIA study. *Diabetes Care* 2009;32:1904-6.
23. Hussen HI, Persson M, Moradi T. Maternal overweight and obesity are associated with increased risk of T1DM in offspring of parents without diabetes regardless of ethnicity. *Diabetologia* 2015;58:1464-73.
24. Lindell N, Carlsson A, Josefsson A, Samuelsson U. Maternal obesity as a risk factor for early childhood T1DM: A nationwide, prospective, population-based case-control study. *Diabetologia* 2018;61:130-7.
25. Chen S-N, Wang P-H, Hsieh M-F, Tsai H-W, Lin L-T, Tsui K-H. Maternal pregnancy-induced hypertension increases the subsequent risk of neonatal candidiasis: A nationwide population-based cohort study. *Taiwan J Obstet Gynecol* 2019;58:261-5.
26. Yue Y, Tang Y, Tang J, Shi J, Zhu T, Huang J, *et al.* Maternal infection during pregnancy and T1DM mellitus in offspring: A systematic review and meta-analysis. *Epidemiol Infect* 2018;146:2131-8.
27. Albishi LA, Altoonisi MM, Ablewi SM, Osman RH, Ahmed NA, Fararjeh M. Clinical demographic patterns of T1DM in Saudi Children in Tabuk City, 2000-2010. *J Diabetes Mellitus* 2017;741-54.
28. Kyvik KO, Nystrom L, Gorus F, Songini M, Oestman J, Castell C, *et al.* The epidemiology of T1DM mellitus is not the same in young adults as in children. *Diabetologia* 2004;47:377-84.
29. Weng J, Zhou Z, Guo L, Zhu D, Ji L, Luo X, *et al.* Incidence of T1DM in China, 2010-13: Population based study. *BMJ* 2018;360:j5295.
30. Sayad A, Akbari MT, Pajouhi M, Mostafavi F, Kazemnejad A, Zamani M. Investigation the role of gender on the HLA-DRB1 and -DQB1 association with T1DM mellitus in Iranian patients. *Cell J* 2013;15:108-15.
31. Cardwell CR, Stene LC, Joner G, Davis EA, Cinek O, Rosenbauer J, *et al.* Birthweight and the risk of childhood-onset T1DM: A meta-analysis of observational studies using individual patient data. *Diabetologia* 2010;53:641-51.
32. Goldacre RR. Associations between birthweight, gestational age at birth and subsequent T1DM in children under 12: A retrospective cohort study in England, 1998-2012. *Diabetologia* 2018;61:616-25.
33. Stene LC, Barriga K, Norris JM, Hoffman M, Erlich HA, Eisenbarth GS, *et al.* Perinatal factors and development of islet autoimmunity in early childhood: The diabetes autoimmunity study in the young. *Am J Epidemiol* 2004;160:3-10.
34. Razavi Z, Karimpourian A, Aramian LM, Bazmamoun H. Demographic characteristics of type 1 diabetic children and adolescents in Hamadan, Iran. *J Res Health Sci* 2015;15:196-9.
35. Cardwell CR, Stene LC, Joner G, Bulsara MK, Cinek O, Rosenbauer J, *et al.* Birth order and childhood T1DM risk: A pooled analysis of 31 observational studies. *Int J Epidemiol* 2011;40:363-74.
36. Visalli N, Sebastiani L, Adorisio E, Conte A, De Cicco AL, D'Elia R, *et al.* Environmental risk factors for T1DM in Rome and province. *Arch Dis Child* 2003;88:695-8.