Determinants of Type 1 Diabetes Mellitus; A Case-Control Study

Awwad Alenezy [(1)] and Basem M. M. Salama [(2)]

[(1)] Family Medicine Consultant, Family and Community Medicine Department, Faculty of Medicine, Northern Border University (KSA).
[(2)] Community Medicine Department, Damietta Faculty of Medicine, Al-Azhar University (Egypt).
awwad4321@gmail.com

Abstract: Background: Type 1 diabetes mellitus is an autoimmune disease occurring in the pancreatic islets. type 1 diabetes usually have been considered as multifactorial disease in which environmental risk factors trigger an immune-mediated destruction of the pancreatic beta cells in genetically susceptible persons. **The aim** of this study was to investigate the associations of type 1 diabetes mellitus with maternal, neonatal and environmental risk factors. **Subject and methods**: a case-control study was conducted on adolescent school students aged 12-18 years old. Cases were adolescent school students who were diagnosed with type 1 diabetes mellitus and the controls were non-diabetic students (age matched) were randomly selected from the same school. **Results:** The study found that, there was a significant association between type 1 diabetes mellitus and participant's sex, history of childhood viral (mumps, measles and varicella) infections, short exclusive breast feeding, early neonatal illness, family history of type1 diabetes mellitus, pre-eclampsia, gestational diabetes, maternal age ($p < 0.05$). while there was no significant association between type 1 diabetes mellitus and birth order, route of delivery, family history of type 2 diabetes mellitus, family history of thyroid disease and maternal coffee or tea drinking during pregnancy($p > 0.05$). **Conclusion:** From this study it can be concluded that certain maternal, neonatal and environmental risk factors were associated with the development of T1DM.

[Awwad Alenezy and Basem M. M. Salama. **Determinants of Type 1 Diabetes Mellitus; A Case-Control Study.** *Life Sci J* 2013;10(3):1252-1258] (ISSN: 1097-8135). http://www.lifesciencesite.com. 188

Keyword: type 1 diabetes mellitus, risk factor, and environmental factors

1. Introduction

Type 1 diabetes mellitus (T1DM) is perceived as a chronic immune-mediated disease with a subclinical prodromal period characterized by selective loss of insulin-producing β cells in the pancreatic islets of genetically susceptible subjects. The most important genes contributing to disease susceptibility are located in the HLA-DQ locus on the short arm of chromosome 6 [(1)].

The worldwide incidence of T1DM is described to vary by at least 100- to 350-fold among different countries [(2)]. The incidence has been increasing worldwide at an annual rate of approximately 3 %[(3)]. If these trends continue, the number of new cases T1DM in children younger than five years of age may double in some regions between 2005 and 2020 and prevalent cases in children under 15 years will rise by 70 % [(4)].

While genetic factors are thought to explain some of the geographic variability in T1D occurrence, they cannot account for its rapidly increasing frequency. Instead, the declining proportion of newly diagnosed children with high-risk genotypes suggests that environmental pressures are now able to trigger T1D in genotypes that previously would not have developed the disease during childhood[(3)].

The importance of environmental factors towards manifestation T1DM is also supported by many observations: For example population genetics simply do not change enough between generations to account for the dramatic surge in T1D prevalence as observed in, for example, Finland [(5)]. Migration study revealed that being born in Sweden, a country with high T1DM incidence, increases the risk for T1DM in children with a genetic origin in low-incidence countries [(6)]. Also the presence of a 10-fold difference in occurrence among Caucasians living in different areas of Europe, and a tendency to acquire the incidence of the disease of the destination country for people who migrate [(7)]. When people relocate from a region of low to high incidence, their risk of developing T1DM also increases, suggesting a causative role for environmental factor(s). However, wide variations in incidence occur between neighboring areas of similar latitude, suggesting the presence of other contributing risk factors and demonstrating the complexity of the pathogenesis of T1DM [(8)].

With longer follow-up, the majority of discordant identical twins of patients with T1DM eventually express anti-islet autoantibodies and progress to diabetes, but anti-islet autoantibodies in

the second twin may appear only 30 years after the first twin develops diabetes [9]. In addition, monozygotic twins have historically been considered to have a disease concordance rate of 30%–50%, with dizygotic twins having a concordance of 6%–10%. Despite having exactly the same genome, one twin had the disease, where the other did not; this suggests environmental factors, in addition to genetic factors, can influence disease prevalence[9].

The aim of disease prediction is disease prevention. T1DM could be prevented by avoiding those environmental factors that cause the disease process or modulating the destructive process before the onset of clinical diabetes [10].

The aim of this study was to investigate the associations of T1DM with several maternal, neonatal and environmental risk factors.

Methods:

Aim of the study:

The present study aimed to study the associations of T1DM with several environmental factors in order to better understand the factors that could initiate or accelerate the autoimmune process leading to the disease.

2. Subject and methods:

A case-control study carried out on adolescent school students (aged 15-18 years old) over the period from 1st of December 2012 to the end of April 2013 in Arar city (Saudi Arabia). Cases were adolescent school students with T1DM (were receiving insulin) and the controls were non-diabetic students. All students with T1DM (n= 84 students) were included in the study. For each case, two controls (non diabetic n= 168 students) were randomly selected from the same age group. Informed consent was obtained from all participants. Sample size was determined by the availability of patients.

A questionnaire was designed for collection of the following information; age, sex, age at diagnosis (for diabetic patients only), family history of DM, family history of thyroid disease (as an autoimmune diseases) in the first and second degree relatives. Maternal risk factors during pregnancy; maternal habits (coffee or tea drinking), pre-eclampsia, gestational DM and maternal age. History of early neonatal illness and history of measles, varicella or mumps infectious diseases during early childhood. The questionnaire also included the type of feeding in early life. Informed consent was obtained from the students for recruitment in the study.

Information that should be answered by the students' parents such as family history concerning DM, thyroid disease, maternal risk factors during pregnancy and neonatal and childhood risk factors were provided on a questionnaire taken home by the students themselves.

Statistical analysis

Statistical analysis was undertaken using SPSS computer software (SPSS Version 16 for Microsoft Windows), appropriate statistical tests were used for comparison between the two study groups, Odds ratio (OR) and 95% CI for it were calculated. Results were considered to be statistically significant at $p < 0.05$. Logistic regression analysis was also done for the analysis of different potential risk factors. All significant variables included in the study were subjected to logistic regression analysis to adjust the possible confounders to determine the variables which are associated with T1DM.

3. Results:

Regarding the age at which the student with T1DM diagnosed as a diabetic; 77% of the student (55 of 84) were at or less than 10 years of age at the time of their diagnosis and 23% (19 of 84) were more than 10 years of age at the time of their diagnosis.

Table (1) shows neonatal and childhood risk factors

As regards the sex of the students, females were at a significant higher risk of T1DM than males (OR = 1.8, 95% CI = 1.0 to 3.2). The difference was statistically significant ($p = 0.032$).

History of early neonatal illness were significantly ($p < 0.001$) associated with higher risk (OR = 2.7, 95% CI = 1.5 to 4.8) of T1DM in diabetic group and non-diabetic group.

Regarding childhood viral infection, student exposed to mumps, measles and varicella infection were at higher risk of T1DM (OR = 3.2, 95% CI = 1.0 to 10.7, OR = 2.6, 95% CI = 1.0 to 6.6 and OR = 2.0, 95% CI = 1.0 to 4.6 respectively) compared to non-exposed student.

There was no statistically difference concerning the birth order of participant between diabetic group and non-diabetic group ($p = 0.35$).

As regards route of delivery, there was no statistically difference ($p = 0.5$) in the risk of T1DM in children born by caesarean section compared to children born vaginally (OR = 1.3, 95% CI = 0.8 to 2.2).

Short exclusive breast feeding period (< 4 months) were significantly associated with higher risk (OR = 1.94, 95% CI = 1.0 to 3.6) of T1DM in diabetic group and non-diabetic group ($p = 0.02$).

Table (2) reveals Family history and maternal risk factors

It was found that there was statistically significant difference (p =0.024) between cases group and controls group as regards family history of T1DM. It also revealed that participant with positive family history of T1DM at a significant higher risk to develop T1DM (OR=3.2, 95% CI = 1.0 to 10. 7). While there was no statistically significant difference (p =0.23) between cases group and controls group as regards family history of T1DM and the participant with positive family history of T1DM at a higher risk to develop T1DM (OR= 1.7, 95% CI = 0.7 to 4.1).

As regards family history of thyroid diseases, higher T1DM risk in cases with a history of thyroid diseases compared to cases without a history of thyroid diseases (OR = 2.0, 95% CI = 0.3 to 12.0). The difference was statistically non significant.

There was no statistically significant difference regarding maternal coffee or tea consumption during pregnancy between diabetic group and non-diabetic group (OR = 1.0, 95% CI = 0.5 to 1.9).

Student whose mothers were suffered from pre-eclampsia or gestational diabetes were at a significant higher risk of T1DM (OR = 3.0, 95% CI = 1.5 to 5.9 and OR = 3.8, 95% CI = 1.8 to 8.0 respectively) compared with children whose mothers were not suffered and the difference between two groups was statistically significant.

There was statistically significant difference between diabetic group and non-diabetic group regarding maternal age. Student whose mothers were 35 years old or over were at a significant higher risk of T1DM (OR = 1.8, 95% CI = 1.0 to 3.3) compared with student whose mothers were below 35 years old.

Table (3) shows that, significant risk factors of T1DM were; early neonatal illness, mumps infection, measles infection, short exclusive breast feeding, family history of T1DM, pre-eclampsia, gestational diabetes and age of the mother.

4. Discussion:

The concordance rate of 50 – 70% among identical twins[9], the seasonality of diabetes incidence and time of birth[11], the association of diabetes with viral infections [12] and the fact that only 10% of HLA - susceptible individuals develop T1DM [11] are among several observations that indicate a possible etiologic role of environmental factors.

Regarding the age at which the student with T1DM diagnosed as a diabetic; 77% of the student (55 of 84) were at or less than 10 years of age at the time of their diagnosis and 23% (19 of 84) were more than 10 years of age at the time of their diagnosis. Many studies found that, the age of presentation of childhood onset T1DM has a bimodal distribution, with one peak at four to six years of age and a second in early puberty (10 to 14 years of age) [13, 14, 15].

Table 1: Distribution of studied groups according neonatal and childhood risk factors:

Variables		Cases (83) No. (%)	Control(168) No. (%)	OR	CI (95%)	p value
Sex	Female	52 (62%)	79 (47%)	1.83	1.0-3.2	0.032
	Male	32 (38%)	89 (53%)			
Early neonatal illness	yes	59 (70%)	79 (47%)	2.7	1.5-4.8	0.001
	No	25 (30%)	89 (53%)			
Mumps infection	yes	9 (11%)	6 (4%)	3.2	1.0-10.7	0.024
	No	75 (89%)	162 (96%)			
Measles infection	yes	13 (15%)	11 (7%)	2.6	1.0-6.6	0.023
	No	71 (85%)	157(93%)			
Varicella infection	yes	18 (21%)	21(13%)	2.1	1.0-4.6	0.03
	No	65 (79%)	145 (87%)			
Birth order	1st	27 (32%)	69 (41%)	Ref.		0.35
	2nd	25 (30%)	40 (24%)	1.6	0.8-3.3	
	3rd +	32 (38%)	59 (35%)	1.4	0.7-2.7	
Route of delivery	Caesarean	39 (46%)	69 (41%)	1.3	0.7-2.2	0.4
	Normal	45 (54%)	97 (59%)			
Exclusive breast feeding (< 4 m*)	yes	61(73%)	97 (59%)	1.94	1.0-3.6	0.02
	No	23 (27%)	69 (41%)			
Total		84	100%	168	100%	

*m =months

Table 2: Distribution of studied groups according Family history and maternal risk factors:

Variables		Cases (84) No. (%)	Control (168) No. (%)	OR	CI (95%)	*P* value
Family history of T1DM	Yes	9 (11%)	6 (4%)	3.2	1.0-10.7	0.024
	No	75 (89%)	162 (96%)			
Family history of T1DM	Yes	11 (13%)	14 (8%)	1.7	0.7-4.1	0.23
	No	73 (87%)	154 (92%)			
Family history of thyroid disease	Yes	3 (4%)	3 (2%)	2.0	0.3-13.0	0.38
	No	81 (96%)	165 (98%)			
Maternal coffee or tea drinking	Yes	21 (25%)	43 (26%)	1.0	0.5-1.9	0.92
	No	63 (75%)	125 (74%)			
Pre-eclampsia	Yes	27 (32%)	23 (14%)	3.0	1.5-5.9	< 0.001
	No	57 (68%)	145 (86%)			
Gestational diabetes	Yes	25 (30%)	17 (10%)	3.8	1.8-8.0	< 0.001
	No	59 (70%)	151(90%)			
Age of mother at pregnancy (years)	< 35	48 (57%)	117 (70%)	1.8	1.0-3.3	0.03
	≥ 30	36 (43%)	49 (30%)			
Total		84	100%	168	100%	

Table (3): Factors related to T1DM according to multivariable logistic regression analysis:

Variables	OR	CI (95%)	*P* value
Early neonatal illness	3.2	2.4 -5.8	< 0.001
Mumps infection	2.6	1.4 -7.4	0.037
Measles infection	1.7	2.9-5.3	0.028
Exclusive breast feeding	2.5	2.7-4.4	0.04
Family history of 1DM	4.7	2.5-8.6	0.045
Pre-eclampsia	4.2	3.2-5.8	< 0.001
Gestational diabetes	5.1	3.4- 6.3	< 0.001
Age of the mother	2.87	3.7-4.4	0.025

This study revealed that, T1DM was significantly associated with sex of the participants, and there was slightly higher risk of association in females than males students. This is in agreement with several studies [14, 16] and in disagreement with other studies [5, 17, 19]. Although most autoimmune diseases are more common in females, other studies reported no significant difference in the overall incidence of childhood T1DM between boys and girls [15, 19, 20].

Our study showed that a significant association between history of early neonatal illness and risk of T1DM. Similar results were obtained by **Svensson *et al.*** [21] who reported that neonatal respiratory diseases, infections and jaundice are risk factors for T1DM. **Snell-Bergeon *et al.*** (22) revealed the association of reported illnesses during infancy and later development of islet autoimmunity (IA).

Regarding early childhood viral infections, History of mumps and measles and varicell**a** infection was significantly associated with diabetes in our study. Regarding mumps this is coincides with **Ramondetti *et al.*** [23] study who found that, a significant association was observed between T1DM and history of mumps (P = 0.034), while in the same study, there was no statistical significance between the incidence of measles cases and T1DM (P = 0.269).

Both specific childhood viral infections and a low overall infection load in childhood (hygiene hypothesis) have been proposed as possible environmental determinants of T1DM. Viruses implicated include mumps, rubella, enteroviruses, cytomegalovirus, rotavirus and parvovirus. Direct β cell destruction, inflammation, molecular mimicry and transient lymphopenia have been suggested as immune-mediated mechanisms [24].

In our study birth order of participants was not significantly associated with T1DM. This is in disagreement with other study which revealed that children second born (OR 1.12, p=0.03) or third or later born (OR 1.08, p=0.17) had a slightly higher risk of T1DM than first born children [25].

As regards the rout of delivery our study revealed that, **rout of delivery** was not significantly associated with T1DM. This is in consistent with another researcher [26] while this is in contrary with **Cardwell *et al.*** [25] Who found that, increase in the risk of T1DM in children born by caesarean section compared to children born vaginally.

Our study found that short exclusive breast feeding (less than 4-6 months period) was significantly associated with T1DM. This is in consistent with **Alves *et al.*** [27] results that found that a short breast feeding period (less than 4 months) may contribute to T1DM.

Similar results were reported by many researchers (28, 29) who concluded that breast feeding modifies the risk of beta cells autoimmunity even years after finishing breast feeding. Early exposure to cow's milk, associated with T1DM [30, 31].

However, other studies [32, 33] did not confirm the role of the duration of the breast feeding or the introduction of cow's milk feeding as a risk factor for T1DM.

Prospective birth cohort studies show that the first signs of beta cell autoimmunity may be initiated during the first year of life. This implies that risk factors for beta cell autoimmunity and T1DM must be operative in infancy. Early nutrition provides essential exogenous exposures in that period. Most studies suggest that the early introduction of complex foreign proteins may be a risk factor for beta cell autoimmunity [34].

In this study, the risk of T1DM was significantly associated with family history of T1DM in first and second degree relatives. This finding is similar to that reported by other studies [35, 36, 37].

In contrast, the risk of T2DM was not significantly associated with family history T1DM in first and second degree relatives. This result is consistent to that reported by **Zalloua *et al.*** [38] He also stated the delayed onset of T1DM in a child of a parent with T2DM may suggest the presence of a common genetic predisposition for diabetes.

T1DM and T2DM frequently co-occur in the same family, suggesting common genetic susceptibility [39]. Inheritance of HLA-DR3 and HLA-DR4 appears to confer a 2 to 3 fold increased risk for the development of T1DM. When both HLA-DR3 and HLA-DR4 are inherited the relative risk for the development of T1DM is increased by 7-10 folds. It is estimated that 48 percent of the familial aggregation can now be ascribed to known loci, and the Major Histocompatibility Complex (MHC) contributes 41 percent [40].

Regarding family history of thyroid disease, the study showed that no statistically significant association of family history of thyroid disease and T1DM, similar results was reported by [41] who reported no significant association regarding thyroid dysfunction (P = 0.410). In contrast other study showed that there was a statistically significant association of family history of thyroid disease and T1DM [36, 42].

T1DM and autoimmune thyroid disease are the most common autoimmune endocrine disorders. A common genetic factor was suggested because of similar pathogenesis and tendency to occur together. HLA-DR3 was the major HLA allele contributing to the genetic susceptibility to T1DM and autoimmune thyroid disease [43]. In addition, CTLA- + 49 A/G and CT60 gene polymorphism was found to confer genetic susceptibility to T1DM, particularly in patients with thyroid autoimmunity [44].

This study revealed that maternal coffee or tea consumption during pregnancy was not associated with the risk of T1DM a similar result was reported by **Virtanen *et al.*** [45] In contrast to our results, other study found that, drinking coffee or tea by mothers during pregnancy was significantly associated with T1DM, **Visalli *et al.*** [29]

Pre-eclampsia was significantly associated with adolescent T1DM in our study. Preeclampsia as a risk factor has been reported by some [46, 47] but not all studies [26, 48].

Our study showed that maternal gestational diabetes was significantly associated with risk of T1DM. This is coincides with **Cardwell *et al.*** [49] who found potential association between maternal gestational diabetes and risk of T1DM. In contrast, another studies [41, 46, 48] revealed that, gestational diabetes were not significantly associated with T1DM in the child.

Maternal age at delivery was significantly associated with T1DM in our study. This result is consistent to that reported by **Cardwell *et al.*** [50] who found that, increases in maternal age at delivery associated with increase in the risk of T1DM.

Conclusion:

Exposure to environmental risk factors during pregnancy, neonatal period and early childhood are thought to play an important role in triggering the immune process leading to the development of T1DM.

Recommendations:

Our study recommended that, exclusive breast feeding (for 4-6 months), prevention of viral infections and early neonatal illness good antenatal care to prevent pre-eclampsia, gestational diabetes and other factors might play a role in lowering the risk of developing the disease.

References

1. **Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C. (2010):** Genetics of type 1 diabetes: What's next? Diabetes 59: 1561–1571.
2. **Karvonen M, Viik-Kajander M, Moltchanova** E, **Libman** I, **LaPorte** Rv, **Tuomilehto** J.**(2000):** Incidence of childhood type 1 diabetes worldwide.

Diabetes Mondiale (DiaMond) Project Group. Diabetes Care, 23(10), 1516-1526.

3. **Borchers AT, Uibo R, Gershwin ME(**2010**):** The geoepidemiology of type 1 diabetes. Autoimmun Rev; 9(5):A355-A365.
4. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltés G. (2009): Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet, 373(9680): 2027- 2033.
5. **Harjutsalo V, Sjoberg L, Tuomilehto J(2008):** Time trends in the incidence of type 1 diabetes in Finnish children: A cohort study. Lancet 371: 1777–1782.
6. **Soderstrom U, Aman J, Hjern A. (2012):** Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment. Acta Paediatr, 101(1), 73-77.
7. **Knip M, Veijola, R, Virtanen, SM, Hyoty, H, Vaarala O, Akerblom HK (2005).** "Environmental Triggers and Determinants of Type 1 Diabetes". Diabetes 54: S125–S136.
8. **Levitsky, LL and Misra M.** (2013): Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents. Up To Date: Apr 2013.
9. **Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. (2008):** Concordance for islet autoimmunity among monozygotic twins. N Engl J Med 359: 2849–2850.
10. **Leslie R. D., Ho-Le, L., Beyan H. (2013):** Viruses and Autoimmune Diabetes: A History. Taylor, K.W. H. Hyoty, A. Toniolo, A.J. Zuckerman (eds.), Diabetes and Viruses, Springer Science ch 2(7-12).
11. **Fyfe MC, White JR, Taylor A, Chatfi eld R, Wargent E, Printz RL, *et al.* (**2007**):.** Glucokinase activator PSN - GK1 displays enhanced antihyperglycaemic and insulinotropic actions. *Diabetologia*; **50** : 1277 – 1287.
12. **Johnson D, Shepherd R, Gill D, Gorman T, Smith DM, Dunne MJ (**2007**):** Glucose- dependent modulation of insulin secretion and intracellular calcium ions by GKA50, a glucokinase activator. *Diabetes*; **56** : 1694 – 1702
13. **Felner EI, Klitz W, Ham M, Lazaro, A M. Stastny5, P., Dupont B. *et al.* (2005): G**enetic interaction among three genomic regions creates distinct contributions to early- and late-onset type 1 diabetes mellitus. Pediatr Diabetes; 6:213.
14. **Taplin CE, Craig, ME, Lloyd M, Silink M, Howard N J, Taylor C. *et al.* (2005):** The rising incidence of childhood type 1 diabetes in New South Wales, 1990-2002. Med J Aust, 183(5), 243-246.
15. **Samardzic, M., Marinkovic, J., Kocev N, Curovic N, TerzicN *et al.* (2010):** Increasing incidence of childhood type 1 diabetes in Montenegro from 1997 to 2006.Pediatr Diabetes, 11(6), 412-416.
16. **Kadiki, O. A. & Roaeid, R. B. (2002):** Incidence of type 1 diabetes in children (0-14 years) in Benghazi Libya (1991-2000).Diabetes Metab, 28(6 Pt 1), 463-467.
17. **Quinn M, Fleischman A, Rosner B, Nigrin DJ, Wolfsdorf JI (2006):** Characteristics at diagnosis of type 1 diabetes in children younger than 6 years. J Pediatr; 148:36
18. **Bizzarri, C., Patera, P. I., Arnaldi C, Petrucci S, Bitti ML, Scrocca R, *et al.* (2010):** Incidence of type 1 diabetes has doubled in Rome and the Lazio region in the 0- to 14-year age-group: a 6-year prospective study (2004-2009). Diabetes Care, 33(11), e140.
19. **Svensson, J., Lyngaae-Jorgensen, A., Carstensen B, Simonsen LB, Mortensen HB**, **(2009):** Long-term trends in the incidence of type 1 diabetes in Denmark: the seasonal variation changes over time. Pediatr Diabetes 10(4), 248-254.
20. **Teeaar, T., Liivak, N., Heilman K, Kool P., Šor R., Paal M, *et al.* (2010):** Increasing incidence of childhood-onset type 1 diabetes mellitus among Estonian children in 1999-2006. Time trend analysis 1983-2006. Pediatr Diabetes 11(2), 107-110.
21. **Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K (2005):** Danish Study Group of Childhood Diabetes. Early childhood risk factors associated with type 1 diabetes–is gender important? Eur J Epidemiol; 20(5):429-434.
22. **Snell-Bergeon JK, Smith J, Dong F, Barón AE, Barriga K, Norris JM, Rewers M(2012):** Early childhood infections and the risk of islet autoimmunity: the Diabetes Autoimmunity Study in the Young (DAISY). Diabetes Care.; 35(12):2553-8.
23. **Ramondetti F, Sacco S, Comelli M, Bruno G, Falorni A, Iannilli A, *et al.* (2012):** Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. Diabet Med.; 29(6):761-6.
24. **Bortell R, Pino SC, Greiner DL, Zipris D, Rossini AA. (200*8*):**. Closing the circle between the bedside and the bench: Toll-like receptors in models of virally induced diabete*s. Ann N Y Acad Sci*; 1150:112-22*.*
25. **Cardwell C. R., Stene L. C, Joner G., Cinek O., Svensson J., Goldacre M. J. *et al.* (2008):**Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia 51:726–735.
26. **Stene LC, Magnus P, Lie TL, Sovik O, Joner G. (**2003**):** No association between preeclampsia or caesarian section and incidence of type 1 diabetes among children: a large, population-based cohort study. Pediatric Research.; 54(4):487–490.
27. **Alves JG, Figueiroa JN, Meneses J, Alves GV. (2012):** Breastfeeding protects against type 1 diabetes mellitus: a case-sibling study. Breastfeed Med.;7(1):25-8.
28. **Holmberg H, Wahlberg J, Vaarala O, Ludvigsson J(2007):** Short duration of breast-feeding as a risk-factor for beta-cell autoantibodies in 5-year-old

children from the general population;ABIS Study Group. Br J Nutr; 97(1):111-116.

29. **Visalli N, Sebastiani L, Adorisio E, Conte A, De Cicco AL, D'Elia R, *et al.* (2003):** Environmental risk factors for type 1 diabetes in Rome and province; IMDIAB Group. Arch Dis Child; 88(8):695-698.
30. **Akerblom HK., Virtanen S M, Ilonen J, Savilahti E, Vaarala O, Reunanen A, *et al.* (2005):** Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. Diabetologia, 48(5): 829 837
31. **Virtanen SM, Knip M. (**2003**):** Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr; 78:1053-67.
32. **Hummel M, Fuchtenbusch M, Schenker M, Ziegler AG. (2000):** No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study. Diabetes Care; 23(7):969-974.
33. **Couper JJ, Steele C, Beresford S, Powell T, McCaul K, Pollard A, *et al.* (1999):** Lack of association between duration of breast-feeding or introduction of cow's milk and development of islet autoimmunity. Diabetes; 48(11):2145- 2149.
34. **Knip M, Virtanen SM, Akerblom HK. (2010):** Infant feeding and the risk of type 1 diabetes. Am J Clin Nutr; 91(5):1506S-1513S.
35. **Wahlberg J, Fredriksson J, Nikolic E, Vaarala O, Ludvigsson J (**2005**):** ABISStudy Group. Environmental factors related to the induction of betacell autoantibodies in 1-yr-old healthy children. Pediatr Diabetes;6(4):199-205.
36. **Moussa MA, Alsaeid M, Refai TM, Abdella N, Al-Sheikh N, Gomez JE. (2005):** Factors associated with type 1 diabetes in Kuwaiti children. Acta Diabetol;42(3):129-137.
37. **Weires MB, Tausch B, Haug PJ, Edwards CQ, Wetter T, (2007):** Familiality of diabetes mellitus. Exp Clin Endocrinol Diabetes.; 115(10):634-640.
38. **Zalloua P A, ShbaklO H, Halaby G., Terwedow H., (2002):**Type-2 Diabetes Family History Delays the Onset of Type-1 Diabetes. J Clin Endocrinol Metab, July, 87(7):3192–3196
39. **Tuomi T. (2005):** Type 1 and type 2 diabetes: what do they have in common? Diabetes; 54(Suppl 2):S40-S45.
40. **Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K. *et al.* (2007):** Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet, 39(7): 857-864.
41. **Alhonen S., korhonen S.,apanainen P., knip M., Veijola R., (2011):** Extended Family History of Diabetes and Autoimmune Diseases in Children With and Without Type 1 Diabetes. DIABETES CARE; 34(1).
42. **Tsirogianni A., Pipi E., Soufleros K. (2009):** Specificity of islet cell autoantibodies and coexistence with other organ specific autoantibodies in type 1 diabetes mellitus. Autoimmun Rev, 8(8): 687-691.
43. **Levin L, Ban Y, Concepcion E, Davies TF, Greenberg DA, Tomer Y. (2004):** Analysis of HLA genes in families with autoimmune diabetes and thyroiditis. Hum Immunol; 65(6):640-647.
44. **Jin P, Xiang B, Lin J, Huang G, Zhou WD, Zheng C, *et al.* (2009):** Association of CTLA-4 + 49A/G and CT60 gene polymorphism with type 1 diabetes and thyroid autoimmunity. Zhonghua Yi Xue Za Zhi; 89(18):1246-1249.
45. **Virtanen SM, Räsänen L, Aro A, Ylönen K, Lounamaa R, Akerblom HM. *et al.* (1994):** Is children's or parent's coffee or tea consumption associated with the risk for type 1 diabetes mellitus in children? *Eur J Clin Nutr*; 48:279–85.
46. **Algert CS, McElduff A, Morris JM, Roberts CL. (2009):** Perinatal risk factors for early onset of Type 1 diabetes in a 2000-2005 birth cohort. Diabet Med; 26(12):1193-1197.
47. **Stene LC, Barriga K, Norris JM, Hoffman M, Klingensmith G, Erlich HA, *et al.* (2004):** Perinatal factors and development of islet autoimmunity in early childhood: the diabetes autoimmunity study in the young. Am J Epidemiol; 160(1):3-10.
48. ***Levins R, Roberts SE, Goldacre MJ.* (*2007*):** *Perinatal factors associated with subsequent diabetes mellitus in the child: record linkage study. Diabet Med; 24: 664–670.*
49. **cardwell CR, Carson DJ, Patterson CC. (2005):** Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. Diabetic Medicine; 22(2):200–206.
50. **Cardwell CR, Stene LC,Joner G, Bulsara MK, Cinek O, Rosenbauer J. *et al.* (2010):** Maternal age at birth and childhood type 1 diabetes: a pooled analysis of 30 observational studies. Diabetes; 59:486–494.

7/25/2013