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Short Report: Pathophysiology

A meta-analysis of the association between pre-eclampsia and childhood-onset Type 1 diabetes mellitus

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Abstract

Aims To review and synthesize the evidence for an increased risk of childhood Type 1 diabetes mellitus in children born to mothers diagnosed with pre-eclampsia during pregnancy.

Methods A comprehensive search of the published literature was performed in MEDLINE, Web of Science and EMBASE limited to studies published before August 2010. Crude odds ratios and 95% confidence intervals were calculated from the data reported in each study. Meta-analysis techniques were then used to derive a combined odds ratio and investigate heterogeneity. Sensitivity analyses were conducted by study design, ascertainment of pre-eclampsia and study quality.

Results Data were available from 16 studies including 8315 children with Type 1 diabetes. Overall, there was little evidence of an increase in the risk of Type 1 diabetes in children born to mothers who had pre-eclampsia during pregnancy (OR = 1.10, 95% CI 0.96–1.27; $P = 0.17$). This association did not vary much between studies ($I^2 = 28\%$, P for heterogeneity = 0.14). The association was similar in three cohort studies (OR = 1.05, 95% CI 0.77–1.44; $P = 0.75$) and in seven studies with a low risk of bias (OR = 1.13, 95% CI 0.91–1.40; $P = 0.27$), but was more marked in 13 studies which ascertained pre-eclampsia from obstetrical records or birth registry data (OR = 1.18, 95% CI 1.03–1.36; $P = 0.02$).

Conclusions This analysis demonstrates little evidence of any substantial increase in childhood Type 1 diabetes risk after pregnancy complicated by pre-eclampsia.

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Keywords epidemiology, pre-eclampsia, Type 1 diabetes mellitus

Introduction

Childhood-onset Type 1 diabetes mellitus is caused by the autoimmune destruction of the pancreatic B-cells. The marked increases in incidence in recent decades suggest the role of environmental factors, but factors initiating the destructive process remain largely unidentified. The relatively young age at onset of childhood Type 1 diabetes and long preclinical phase in the disease suggest that factors in early life or *in utero* may play a role. Various complications during pregnancy have been investigated as potential risk factors for Type 1 diabetes, including pre-eclampsia. In 1992 a Swedish study observed an increased risk of Type 1 diabetes in children born to mothers with pre-eclampsia [1]. Subsequently, there have been numerous epidemiological studies that have investigated pre-eclampsia as a

risk factor for Type 1 diabetes [2–13]. However, this research is difficult to interpret because of the number of studies conducted and the different sizes of these studies (and consequent differences in power).

The aim of this review and meta-analysis is to assess the evidence from these studies for an increased risk of childhood-onset Type 1 diabetes after pregnancy complicated by pre-eclampsia and to investigate the consistency of any association between studies.

Patients and methods

The literature search was conducted using MEDLINE, through Ovid Online with the following strategy: [('Pre-Eclampsia' or preclamp or 'Eclampsia' or eclamp or toxemia or toxaemia or gestosis or 'Hypertension, Pregnancy-induced' or ('Hypertension' and 'Pregnancy')) and ['Diabetes Mellitus, Type 1' or IDDM or (diabetes and Type 1)] using the terms in inverted commas as MEDLINE subject heading keywords.

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Similar strategies were employed in searches on Web of Science and EMBASE. In each database, the search was limited to studies published before 1 August 2010. Abstracts were screened independently by two authors (CRC and EBH) to identify studies that were likely to provide relevant data based on the following inclusion criteria: (i) they identified comparable groups with or without Type 1 diabetes; (ii) they included the prevalence of pre-eclampsia in each group or report a corresponding odds ratio or relative risk. The reference lists of all included articles and any citations to the included articles (as identified by Web of Science) were also investigated to identify additional studies.

A structured form was then used to abstract information from the eligible studies. This included details on the study (author, date of publication, country), participants (source, age at diagnosis, source of controls) and pre-eclampsia (definition, method of ascertainment).

Unadjusted odds ratios or relative risks and associated 95% confidence intervals were extracted from each study independently by two authors (CRC and EBH). The standard χ^2 -test for heterogeneity was performed [14] and the I^2 statistic was calculated to measure heterogeneity [15]. Random-effects models were used to calculate pooled odds ratios as some between-study heterogeneity was anticipated in these observational studies [14]. Funnel plots (of the logarithm of the individual study odds ratios against their standard errors) were produced to check for publication bias [14]. Subgroup analyses were performed to assess the sensitivity of the overall result. Subgroup analyses were conducted by subdividing studies by type (case-control or cohort), by ascertainment of pre-eclampsia (obstetrical records or birth registry vs. questionnaire based) and including only studies with a reduced risk of bias (excluding case-control studies with non-population-based or non-randomly selected controls or any study with a response rate of less than 80% in either the cases or controls). Meta-regression techniques were used to formally test whether the odds ratio estimates differed between these subgroups of studies. All statistical analyses were performed using Stata 9.0 (Stata, College Station, TX, USA).

Results

The searches of MEDLINE, Web of Science and EMBASE identified seven eligible articles [2,4,6,7,9,10,13]. Three more articles were identified from examination of reference lists [1,3,5]. A further three articles [8,11,12] were identified from Web of Science because they had cited one of the nine identified studies. Two of these articles were not included in the meta-analysis as data could not be extracted from the published reports [3,11]. Other reports on cases (and controls) contained in included studies were omitted, such as McKinney *et al.* [16] and Jones *et al.* [17]. The 11 remaining articles included 16 studies as one publication reported results from five independent studies and another reported results from two studies.

These 16 studies included 8315 cases of childhood-onset Type 1 diabetes. Characteristics of the included studies are

shown in Table 1. Most were case-control studies, but three were cohort studies. All but two of the studies identified children with Type 1 diabetes using national or regional childhood Type 1 diabetes registers. Most studies ascertained pre-eclampsia from pre-existing records such as obstetrical records, birth registry data or other clinical databases. Three studies ascertained pre-eclampsia from maternal questionnaires.

Overall (Fig. 1), children born to mothers with pre-eclampsia had on average a 10% increase in their risk of developing Type 1 diabetes (OR = 1.10, 95% CI 0.96–1.27) but this association was not significant ($P = 0.17$). This association did not vary much between studies ($I^2 = 28\%$, P for heterogeneity = 0.14). The funnel plot (Fig S1) was approximately symmetrical, providing little evidence of publication bias.

The overall pooled estimates in three cohort studies (OR = 1.05, 95% CI 0.77–1.44; $P = 0.75$) and 13 case-control studies (OR = 1.13, 95% CI 0.96–1.32; $P = 0.14$) were similar (meta-regression P for difference in pooled estimates = 0.65). There was some indication of a difference in the pooled estimates from the 13 studies which ascertained pre-eclampsia from obstetrical records or birth registry data (OR = 1.18, 95% CI 1.03–1.36; $P = 0.02$) compared with the three studies which ascertained pre-eclampsia from questionnaires (OR = 0.87, 95% CI 0.68–1.12; $P = 0.28$), but this was of borderline statistical significance (meta-regression P for difference in pooled estimates = 0.05). In seven studies with a low risk of bias (excluding case-control studies with non-population-based or non-randomly selected controls or any study with a response rate of less than 80% in either the cases or controls) the pooled odds ratio was 1.13 (95% CI 0.91–1.40; $P = 0.27$).

Discussion

Overall, this meta-analysis demonstrates little evidence of any association between maternal pre-eclampsia and childhood-onset Type 1 diabetes risk. This finding was fairly consistently observed in all studies and was similar in cohort studies and studies with a low risk of bias.

To our knowledge, this is the first meta-analysis to investigate the relationship between pre-eclampsia and Type 1 diabetes in the offspring. The strength of this analysis is that it included 8315 children with Type 1 diabetes, thus providing the power to identify associations with maternal pre-eclampsia of relatively small magnitude.

One weakness of this study is the possible effect of inaccurate reporting of pre-eclampsia. There was wide variation in the rates of pre-eclampsia in the control subjects (ranging from 2 to 16%, as shown in Fig. 1), some of which may reflect differences in the definition of pre-eclampsia, and differences in the ascertainment methods, between studies and countries. A sensitivity analysis revealed a more marked (and statistically significant) 18% increase in diabetes risk in children born to mothers with pre-eclampsia in 12 studies which ascertained pre-eclampsia by obstetrical records or birth registry data. However, this finding

Table 1 Characteristics of included studies investigating the association between maternal pre-eclampsia and Type 1 diabetes mellitus, ordered by publication date

First author, year* [reference]	Type 1 diabetes mellitus				Control subjects				Reported method of pre-eclampsia ascertainment	Low risk of bias§
	Design	Country	Ascertainment method (years diagnosed)	Age at diagnosis (years)	n†	Resp. rate (%)‡	Source (matching criteria)	n†	Resp. rate (%)‡	
Dahlquist, 1992 [1]	C-C	Sweden	Swedish Childhood Diabetes Registry (1978–1988)	0–14	2757	98	Swedish Medical Birth Registry (year of birth, delivery unit)	8271	100	Yes
McKinney, 1997 [2]	C-C	UK (England)	Yorkshire Childhood Diabetes Register (1993–1994)	0–15	196	92	General practitioner records (age, sex)	325	82	Yes
Eurodiab, 1999 [4]	C-C	Bulgaria	W. Bulgaria Type 1 diabetes register (1991–1994)	0–14	125	72	Schools and polyclinics (age)	438	78	No
	C-C	Lithuania	Lithuanian Type 1 diabetes register (1989–1994)	0–14	114	85	Polyclinics (age)	262	72	No
	C-C	UK (Northern Ireland)	Northern Ireland Type 1 diabetes register (1989–1994)	0–14	155	78	General practitioner records (age)	374	62	No
	C-C	Latvia	Latvian Type 1 diabetes register (1989–1994)	0–14	128	93	Population register (age)	292	73	No
	C-C	Luxembourg	Luxembourg Type 1 diabetes register (1989–1995)	0–14	55	98	Pre-schools and schools (age)	172	94	Yes
Rami, 1999 [5]	C-C	Austria	Vienna Type 1 diabetes register (1989–1994)	0–14	79	73	Schools (age, sex)	292	67	No
Stene, 2003 [6]	Cohort	Norway	Norwegian Childhood Diabetes Registry (1989–1998)	0–14	1824	100	Norwegian medical birth registry	1 380 778	NA	Yes
Stene, 2004 [7]	C-C	Norway	Norwegian Childhood Diabetes Registry (1998–2000)	0–14	545	73	Norwegian population registry	1668	56	No
Sadauskaite-Kuhne, 2004 [8]	C-C	Sweden	SE Sweden Type 1 diabetes register (1995–2000)	0–15	517	100	Population register	1131	73	No
	C-C	Lithuania	Lithuanian Type 1 diabetes register (1996–2000)	0–15	286	100	Outpatient clinic	813	95	No¶
Svensson, 2005 [9]	C-C	Denmark	Danish register of childhood diabetes (1996–1999)	0–14	490	81	Danish population register (age, sex)	696	48	No

Table 1 (Continued)

First author, year* [reference]	Type 1 diabetes mellitus			Control subjects			Reported method of pre-eclampsia ascertainment	Low risk of bias§			
	Design	Country	Ascertainment method (years diagnosed)	Age at diagnosis (years)	Resp. rate (%) ‡	Source (matching criteria)					
				n†	?	n†			Resp. rate (%) ‡		
Ivins, 2007 [10]	Cohort	England	Hospital admission (ICD diabetes code) (1963–1999)	0–14	?	411	Oxfordshire/West Berkshire maternity records	292 733	NA	Clinical maternity record	Yes
Algert, 2009 [12]	Cohort	Australia	Hospital admission (ICD diabetes code) (2000–2005)	0–6	?	272	Midwives' database	501 768	NA	Midwives Data Collection	Yes
Robertson, 2010 [13]	C-C	UK (Scotland)	Scottish Study Group for the Care of Diabetes in the Young Register (1984–2005)	0–15	100	361	Aberdeen Maternity Neonatal Databank (year of birth)	1083	100	Database Aberdeen Maternity Neonatal Databank	Yes

*Year of publication.

†Number included in analysis of pre-eclampsia.

‡Reported response rate.

§Low risk of bias studies excludes studies with non-population based or non-randomly selected controls and any study with a response rate of under 80% in either cases or controls.

¶Failed low risk of bias criteria due to non-population based controls, all other studies failed low risk of bias criteria due to a response rate of under 80% in either cases or controls.

C-C, case-control; ICD, International Classification of Diseases; NA, not applicable; ?, unknown.

FIGURE 1 Meta-analysis of the association between maternal pre-eclampsia and Type 1 diabetes mellitus (including 8315 cases) using a random-effects model.

should perhaps be treated cautiously because, even within these studies, the ascertainment of pre-eclampsia was not standardized (for instance, the range of pre-eclampsia rates in the control subjects was from 2 to 16%). This was one of a number of subgroup analyses investigated and the difference in the pooled estimates between studies ascertaining pre-eclampsia obstetrical records or birth registry data (compared with studies using maternal questionnaires) was of only borderline significance.

Another weakness of this meta-analysis is that adjustments could not be made for potentially confounding factors such as maternal age, vitamin D deficiency, maternal Type 1 diabetes or Caesarean section delivery, which are associated with both pre-eclampsia risk [18–20] and Type 1 diabetes risk [1,2,4,12,21]. As with all meta-analysis, there is the possibility that studies containing relevant data were missed by the searches and, perhaps of more concern, that studies showing no association were not published, although the funnel plot (Fig. S1) revealed little evidence of such publication bias. Two studies were identified which contained relevant data but which could not be included in the meta-analysis. A Danish study [11] reported no association with all diabetes mellitus up to age 27 years (but could not be included because data were not reported for childhood-onset Type 1 diabetes). Another Danish study [3] reported that pre-eclampsia was ‘not found to differ significantly’ between cases of childhood-onset Type 1 diabetes and control subjects (but could not be included because data were not reported). These studies are unlikely to influence the main finding as neither study demonstrated evidence of associations between pre-eclampsia and Type 1 diabetes.

In conclusion, this meta-analysis demonstrates little evidence of any substantial difference in Type 1 diabetes risk in children born after pregnancy complicated by pre-eclampsia.

Competing interests

Nothing to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Funnel plot of the association between pre-eclampsia and Type 1 DM.

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