



# RISK OF BIRTH DEFECTS ASSOCIATED WITH MATERNAL PREGESTATIONAL DIABETES: A POPULATION-BASED COHORT STUDY IN NORTHERN ITALY

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## Introduction

Most epidemiologic studies indicated an excess risk of birth defect in the offspring of mothers affected by pregestational diabetes of type 1 and/or type 2, but relative risk estimates have been statistically unstable, with limited control for potential confounders such as age, ethnicity and smoking, and little attention to specific birth-defects. We designed a large population-based cohort study in Northern Italy, using administrative databases and a population-based Birth-Defect Registry, to investigate the possible teratogenic effect of pregestational diabetes.

## Materials and methods

We conducted a population-based cohort study in the Northern Italy Emilia-Romagna region using administrative databases and a population-based Birth Defects Registry. From hospital discharge records we identified all diabetic pregnancies during 1997-2010, and a sample of non-diabetic pregnancies matched for maternal characteristics (age, province of residence, year and hospital of delivery).

We also collected where available information on maternal smoking during pregnancy and periconceptional antidiabetic drug prescriptions, from which we inferred the type of diabetes. We used conditional logistic regression models to compute relative risks (RR), and we evaluated interactions by computing the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP).

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## Results

A final number of 2,269 diabetic women delivering a single child and 10,648 non-diabetic women were included in the analysis. Overall, sixty-two newborns to diabetic women had at least one congenital anomaly while the corresponding number for non-diabetic parturients was 162. The RRs of having a congenital anomaly diagnosed in the offspring in both the overall diabetic cohort and its drug-prescription-confirmed cohort subgroup was 1.73 (1.28-2.33) and 2.02 (1.33-3.09), respectively (table 1). When we limited the analysis to diabetic women aged less than 35 years receiving only insulin therapy – considered to be affected by type 1 diabetes – or to all women receiving a prescription of oral glucose-lowering drug during the study period – considered to be affected by type 2 diabetes – only the latter group experienced an excess risk. RRs were elevated for both the Caucasian group and the single Italian nationality, while RRs decreased and became statistically very unstable for the Asiatic nationality subgroup, albeit remaining above the unity, and no excess risk in the subgroup of women from Central-South Africa. RRs were generally increased above the unity for most categories of birth defects and some specific anomalies (tables 2-3). Inclusion of smoking habits in a multivariate regression model showed that smoking interacted with maternal diabetes in increasing teratogenic risk, particularly in type 1 diabetic women (table 4). In period-specific analyses, RRs considerably decreased for over time, showing no further excess for type 1 diabetes in the most recent periods (table 5).

Table 1. Relative risk of congenital anomalies associated with pregestational diabetes, Emilia-Romagna region, 1997-2010<sup>a</sup>

	Diabetic mothers (anomalies/births)	Non-diabetic mothers (anomalies/births)	RR	95% CI	P
Overall diabetes	62/2,269	162/10,648	1.73	1.28-2.33	<0.001
Type 1 diabetes	5/408	25/1,923	0.87	0.33-2.32	0.787
Type 2 diabetes	22/469	21/2,188	4.51	2.46-8.29	<0.001

<sup>a</sup>Pregestational maternal diabetes estimated to be type "1" if the women was aged < 35 years at delivery and had prescriptions of insulin but no oral glucose-lowering drugs in the 2004-2010 period, and type "2" if she was recorded as ever receiving a prescription of oral glucose-lowering drugs in the 2004-2010 period

Table 4. Relative risk of congenital anomalies associated with maternal type 1 and type 2 diabetes, smoking and their interaction, Emilia-Romagna region, 1997-2010

Maternal diabetes	Smoking	Type 1 diabetes			Type 2 diabetes		
		RR	95% CI	P	RR	95% CI	P
No	No <sup>a</sup>	Reference			Reference		
No	Yes <sup>b</sup>	0.62	(0.08-4.91)	0.655	1.15	(0.14-9.69)	0.898
Yes	No <sup>a</sup>	0.36	(0.05-2.79)	0.326	4.81	(1.49-15.52)	0.009
Yes	Yes <sup>b</sup>	4.05	(0.48-34.07)	0.197	5.70	(0.64-50.78)	0.119
		RERI=4.07 (-4.55, 12.69)			RERI=0.74 (-11.58, 13.07)		
		AP=1.00 (0.626, 1.38)			AP=0.13 (-1.79, 2.05)		

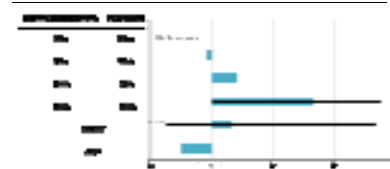


Table 2. Relative risk of congenital anomalies associated with maternal pregestational diabetes, Emilia-Romagna region, 1997-2010

Major groups of congenital anomalies	ICD-9	Malformed births to diabetic/non-diabetic women	RR	95% CI	P
All anomalies	740-759	76/202	1.73	1.28-2.33	<0.001
Nervous system	740-742	0/4	-	-	-
Eye, ear, face and neck	743-744	2/9	1.00	0.21-4.68	1.000
Cardiovascular	745-747	23/56	1.79	1.09-2.93	0.021
Respiratory	748	0/0	-	-	-
Cleft palate and/or cleft lip	749	4/13	1.44	0.47-4.45	0.525
Digestive system	750-751	4/18	1.02	0.34-3.03	0.970
Genito-urinary	752-753	13/31	1.84	0.95-3.54	0.070
Musculo-skeletal	754-756	18/36	2.26	1.27-4.04	0.006
Integument	757	0/7	-	-	-
Chromosomal anomalies	758	5/10	2.19	0.73-6.55	0.161
Other and unspecified	759	7/18	1.64	0.67-4.00	0.276
Multiple congenital anomalies		8/20	1.72	0.75-3.96	0.203

Table 3. Relative risk of selected congenital anomalies associated with maternal pregestational diabetes, Emilia-Romagna region, 1997-2010

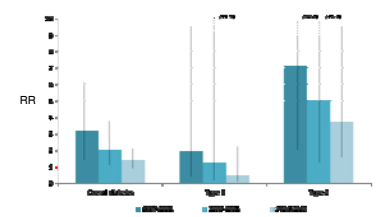
Specific defects	ICD-9	Malformed births to diabetic/non-diabetic women	RR	95% CI	P
Transposition of great vessels	745.1	1/3	1.57	0.16-15.15	0.695
Tetralogy of Fallot	745.2	6/6	4.16	0.82-21.03	0.085
Ventricular septal defect	745.4	10/29	1.48	0.70-3.09	0.300
Atrial septal defect	745.5	5/8	2.71	0.86-8.49	0.087
Hypoplasia and other penile anom.	752.6	5/14	1.25	0.29-5.45	0.767
Renal agenesis	753.0	1/3	1.57	0.16-15.15	0.695
Limb defects	755	6/14	2.01	0.77-5.26	0.154
Extra-ribs	756.33	2/0	-	-	-
Oral cleft	749	4/13	1.44	0.47-4.45	0.525
Oral cleft - adjusted		3/6	2.22	0.54-9.19	0.271

## Conclusions

In our population, maternal pregestational diabetes was associated with increased risk of birth defects in the offspring. However, we found little evidence of excess risk associated with type 1 pregestational diabetes. RR in this group was higher than in non-diabetic women in the first study period but it disappeared in the subsequent periods, possibly indicating improved disease control over time. Conversely, women affected by type 2 diabetes had an excess risk of birth defects; also in this population RRs decreased over time, though women affected by type 2 disease still showed in the latest period RRs well above the unity. Most birth defects categories exhibited increased risks, including cardiovascular, chromosomal, musculoskeletal, and genitourinary anomalies as well as oral clefts. Smoking interacted with diabetes in increasing the risk of these birth defects. Overall, this study indicates that maternal type-2 diabetes increases the risk of specific birth defects in the offspring, whereas for type-1 diabetic mothers and particularly in the most recent years this was not the case.

Table 5. Period-specific relative risk of congenital anomalies associated with type 1 and type 2 pregestational maternal diabetes, Emilia-Romagna region

Year periods	All diabetic pregnancies			Type 1 diabetes			Type 2 diabetes		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
1997-2001	3.14	1.56-6.34	0.001	1.93	0.37-9.98	0.431	7.13	2.03-24.95	0.002
2002-2005	1.98	1.02-3.86	0.044	1.25	0.14-11.18	0.842	5.00	1.45-17.27	0.011
2006-2010	1.42	0.96-2.10	0.081	0.49	0.11-2.20	0.353	3.74	1.56-8.98	0.003



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