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Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes

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Abstract

Background: Diabetes type 1 is associated with an increased risk for infant congenital malformations. It is debated whether this is true also at gestational diabetes. *Aims:* To study occurrence of congenital malformations in infants whose mothers had preexisting or gestational diabetes. *Study design:* A register study covering over 1.2 million Swedish births in 1987–1997 based on the Swedish health registries. *Subjects:* We identified from the Medical Birth Registry 3864 infants born of women with preexisting diabetes and 8688 infants born of women with gestational diabetes. *Outcome measures:* Congenital malformations identified in the Medical Birth Registry, the Registry of Congenital Malformations, and the Hospital Discharge Registry. The rates of congenital malformations among these infants was compared with the population rates. *Results:* At preexisting diabetes, the total malformation rate was 9.5% while the rate at gestational diabetes was similar to the population rate, 5.7%. At preexisting diabetes, certain conditions were more common than expected: orofacial clefts, cardiovascular defects, oesophageal/intestinal atresia, hypospadias, limb reduction defects, spine malformations, and polydactyly. For some of these conditions, an excess was found also for infants whose mothers had gestational diabetes. Infants with multiple malformations were in excess at preexisting diabetes but not at gestational diabetes but the specific type of malformations involved were similar in the two diabetes groups. *Conclusions:* It is suggested that in the group of gestational diabetes exists a subgroup with an increased risk for a diabetes embryopathy, perhaps due to preexisting but undetected diabetes type 2.

Keywords: Diabetes type 1; Gestational diabetes; Congenital malformations

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1. Introduction

It is well known that insulin-dependent type 1 diabetes mellitus is associated with an increased risk for congenital malformations in the offspring (see review by [1]). Some malformations seem to be specifically associated with maternal diabetes type 1: skeletal malformations and notably the so-called syndrome of caudal regression [2] and possibly phocomelia, cardiac malformations, and central nervous system malformations. The risk for congenital malformations among infants of diabetic mothers remains and is related to the standard of the care of such women. Casson et al. [3], during the years 1990–1994 in north west England, described a nearly ten times increased risk for congenital malformations among infants of diabetic women, comparing the rate among the study infants with that derived from a register of congenital malformations where a less complete ascertainment can be expected. Even so a high rate of 9.7 per cent of congenital malformations was found. However, poor glucemic control in very early pregnancy may increase the malformation rate [4] and pre-pregnancy care of women with diabetes can apparently reduce the malformation risk (e.g. [5]).

Towner et al. [6] studied infants of mothers with noninsulin dependent diabetes and found an increased risk for congenital malformations. Maternal HbAlc at initial presentation during pregnancy and maternal age at onset of diabetes were associated with this risk.

There are less convincing information on the teratogenic risk of gestational diabetes (GDM), although the condition has been suggested to be a human teratogenic factor [7]. Ramos-Arroyo et al. [8] reported on the risk for specific birth defects after maternal diabetes, based on data in the Spanish case-control register of congenital malformations. Information on the diabetes status was obtained by interview of case (with a malformed infant) and control (with a normal infant) mothers after the birth of the infants. The crude odds ratio at insulin-dependent maternal diabetes was 5.5 and for major defects even higher, 8.7. Increased risks were seen also for gestational diabetes even though ORs were lower: 1.9 if the mother had used insulin during pregnancy and lower if she had not. Specifically increased risks were seen for central nervous system malformations (including neural tube defects), preaxial polydactyly, and cardiovascular defects, notably transposition of the great vessels. A later study from the same group of authors [9] confirmed the findings and described a specific association between GDM and holoprosencephaly, spine and rib malformations, and urinary tract anomalies.

Schaeffer et al. [10] studied 3743 pregnancies complicated with GDM and found a correlation between maternal blood glucose values and the risk for major–but not minor–congenital malformations in the offspring. Women with GDM were identified in a screening program and congenital malformations were identified by intense paediatric examination of the newborns up to the time of discharge from the delivery unit. Major anomalies were found in 2.9% and minor anomalies in 2.4% of the infants.

The recent contribution by Schaefergraf et al. [11] studied 3764 infants born after pregnancies complicated by GDM and 416 with diabetes type 2 in a referral hospital

in Southern California. Diabetic pregnancies were identified prospectively and newborn children were investigated in detail before discharge. Major congenital anomalies were identified in 2.9% of the infants of the GDM group and in 8.9% ($n = 13$) in the diabetes type II group. The authors concluded that the pattern of congenital malformations seen after maternal GDM resembles that seen after maternal type 1 diabetes. High levels of hyperglycaemia at diagnosis or presentation for care was associated with an increased risk for anomalies in general and specifically for multiple anomalies.

An abstract [12] reported on 83 infants of women with pre-existing insulin-dependent diabetes, 53 infants of women who needed insulin during pregnancy, and 165 infants whose mothers had gestational diabetes not needing insulin. They found an increased risk for cardiac defects and (marginally) for vertebral defects in the middle group, and only an increased risk for thymus anomalies in the third group.

The specific question of a relationship between maternal diabetes and congenital heart defects in the offspring was studied by Ferencz et al. [13] using data from the Baltimore–Washington Infant Study, 1981–1989. They verified an increased odds ratio for cardiovascular defects at maternal diabetes type 1 and found evidence for some specificity for certain types of cardiac defects. They also studied the possible impact of gestational diabetes and found some ORs above 1.0, notably for left-sided obstructive lesions (OR = 1.6, 95%CI 1.0–2.6), pulmonary valve atresia with an intact septum (OR = 2.9, 95%CI 1.0–8.3), isolated atrial septal defect (OR = 2.4, 95%CI 1.4–4.3), and patent arterial duct (OR = 2.6, 95%CI 1.0–6.6).

In a previous study by the authors, under publication, an increased use of hospital care because of congenital malformations was demonstrated in infants born of women with GDM compared with other infants. In the present study, we have used the Swedish health registers in order to analyze the risk for a congenital malformation and the specificity in the type of congenital malformation among infants born of women with preexisting diabetes or with GDM.

2. Material and methods

The Swedish Medical Birth Registry, MBR, [14] was introduced in 1973 and contains data from antenatal care, delivery, and the paediatric examination of the newborn. Diagnoses are given as ICD codes. With the introduction of the 9th and 10th revisions of ICD (which occurred in Sweden in 1987 and during 1997, respectively) it became possible to differentiate between preexisting diabetes and GDM in the register. Using data for the years 1987–1997, we identified all infants whose mothers had a code for preexisting diabetes (ICD9, code 6480, ICD10 code 0240) or gestational diabetes (ICD9 code 6488, ICD10 code 0244) in the register.

The presence of a congenital malformation in an infant was ascertained from different sources. Congenital malformations should be registered in the MBR by ICD codes belonging to Chapter 14 of ICD9 and Chapter 17 of ICD10. It was also possible to link information from the Swedish Registry of Congenital Malformations with auxiliary registers [15] and also from a Hospital Discharge Register which

covers all Sweden from 1987 onwards (available up to and including discharges during 1997) with the aid of the unique personal identification number each person living in Sweden has.

For each infant, the best available malformation diagnosis was identified and tabulated. Expected values for some specific malformations or groups of malformations were obtained from all infants born. In order to compare infants with multiple malformations with such infants in the general population, a sample was drawn (1:200) of all Swedish infants with a congenital malformation born during 1987–1997 using the same register sources ($n = 340$).

Differences between observed and expected numbers were evaluated with tests based on Poisson distributions. Odds ratios (OR) were estimated using the Mantel–Haenszel procedure and 95% confidence intervals (95%CI) using a test-based method.

3. Results

Among 1,216,198 infants born during the years 1987–1997, 3,874 infants of mothers with preexisting diabetes (3.2 per 1,000) and 8,684 infants of mothers with GDM (7.2 per 1,000) were identified.

The total rate of infants registered in the Medical Birth Registry with any congenital malformation was 3.7 per cent ($n = 45\,214$) during the period studied. The percentage was 7.0 ($n = 272$) if the mother had a diagnosis of preexisting diabetes, and 3.9 ($n = 343$) if she had a diagnosis of GDM. The OR for having a malformation registered in the Medical Birth Registry, stratified for year of birth, maternal age (5 year class), parity (1,2,3,4 +), and maternal smoking (unknown, 0, < 10 cig/day, $10 +$ cig/day) was 1.95 (95%CI 1.72–2.20) for preexisting diabetes and 1.06 (95%CI 0.95–1.18) for GDM. The total malformation rate is thus not significantly increased among infants with maternal GDM.

By adding information from further sources (described under Material and Methods), a total of 369 infants with any identified congenital malformation was found when the mother had preexisting diabetes (9.5%) and 499 when the mother had GDM (5.7%). Thus, the other sources added some 40% of cases. Some of these like pylorostenosis could not be identified in the neonatal period which is the basis for the Medical Birth Registry, other are due to under-reporting to the Medical Birth Registry.

Table 1 specifies the main groups of relatively major congenital malformation diagnoses among infants with preexisting maternal diabetes or GDM. This Table is based on all identified cases of congenital malformations and each infant may appear more than once in the Table if it had more than one malformation. Table 2 present less severe malformations in a similar way.

Table 3 groups the malformations into some large groups and give corresponding data for the population. If infants born of mothers with preexisting diabetes are compared with population rates, an excess is seen for orofacial clefts, cardiovascular, oesophageal–gut–anal atresia, hypospadias, limb reduction defects, spine malforma-

Table 1
List of main group of relatively severe congenital malformation diagnoses as identified from all available registers in infants of diabetic mothers[a]

Congenital malformation	Preexisting diabetes	GDM
Neural tube defect	3	3
Microcephaly	1	0
Other brain malformations, possibly, with hydrocephaly	3	13
Hydrocephaly + ASD	1	
Microphthalmia	0	2
Other eye malformation	2	5
Severe ear malformation	2	2
Specified cardiac defects except PDA	100	93
Unspecified cardiac defects	32	19
Choanal atresia	1	1
Pulmonary hypoplasia	1	2
Cystic lung	1	0
Orofacial clefts	19	18
Oesophageal atresia	0	2
Other oesophageal malformation	0	1
Pylorostenosis	6	14
Other stomach malformation	0	1
Small bowel atresia	2	8
Anal atresia	7	8
Megacolon	1	6
Malrotation	2	0
Other gut malformation	2	4
Biliary tract malformation	3	3
Female genital malformation	0	4
Hypospadias	23	25
Other genital malformations	1	4
Kidney agenesis/hypoplasia	3	8
Cystic kidney	3	4
Hydronephrosis	13	21
Bladder exstrophy	2	1
Other urinary tract malformation	5	8
Face/skull malformation	3	9
Varus deformity of foot	14	18
Arthrogryposis	3	0
Knee deformity	2	0
Limb reduction	9	0
Polydactyly	16	16
Syndactyly	5	5
Other limb malformations	4	7
Spine malformation	13	7
Chondro/osteodystrophy	0	3
Diaphragmatic hernia	3	1
Abdominal wall defect	0	1
Situs inversus	1	1
Spleen malformation	3	1
Endocrine organ malformation	1	3
Chromosome anomaly	4	20
Conjoined twins	1	0
Congenital tumour	1	0

[a] Division after type of maternal diabetes. GDM = gestational diabetes. PDA = patent ductus arteriosus.

Table 2
List of main group of less severe congenital malformation diagnoses as identified from all available registers in infants of diabetic mothers[a]

Congenital malformation	Preexisting diabetes	GDM
Preauricular appendices	11	15
Other minor ear malformations	1	3
Branchial malformations	1	2
Pterygium colli	0	1
PDA	25	13
Single umbilical artery	6	1
Laryngeal anomaly	1	0
Tongue tie	3	4
Unstable hip	18	59
Ectopic testis or undescended testis	15	51
Mild foot deformities	1	3
Unspec. malformation of muscles etc.	1	1
Unspec. skin malformation	1	1

[a] Division after type of maternal diabetes. GDM = gestational diabetes. PDA = patent ductus arteriosus.

tions, and polydactyly. For some of these (cardiovascular defects, atresias, and spine malformations) the GDM rates are intermediate between the two other rates. If the expected numbers of specific malformations are calculated in the GDM group from the population rates, statistically significant increases are seen for specified cardiac defects (93 observed and 70 expected), oesophageal/intestinal atresia (16 observed, eight expected), and for spine malformations (seven observed, two expected).

Some infants have more than one malformation diagnosis. These are summarized

Table 3
Some large groups of major congenital malformations according to maternal diabetes status[a]

Congenital malformations	Preexisting diabetes	GDM	Per 10 000 population
Neural tube defects	3 (7.8)	3 (3.5)	8.2
Brain malformations including hydrocephaly	4 (10.4)	15 (17.3)	12.1
Orofacial clefts	19 (49.2)	18 (20.7)	20.9
Specified cardiac defects	101 (261.4)	93 (107.0)	80.5
Unspecified cardiac defects	32 (82.8)	19 (21.9)	24.8
Oesophageal/gut atresia	12 (31.1)	16 (18.4)	8.7
Pylorostenosis	6 (15.5)	14 (16.1)	17.5
Hypospadias	23 (59.5)	25 (28.8)	25.5
Polydactyly	16 (41.4)	16 (18.4)	11.6
Limb reductions	9 (23.3)	0 (0)	6.3
Spine malformations	13 (33.6)	7 (8.1)	2.7
Total number of malformed infants	369	499	
Total number of infants	3864	8688	

[a] Numbers refer to number of infants with at least one of the malformations listed. Rates per 10 000 births within brackets. GDM = gestational diabetes.

Table 4
Summary of multi-malformed infants at preexisting maternal diabetes or gestational diabetes and in the population sample[a]

	Preexisting diabetes	GDM	Population sample
Two malformations	15	10	9
Three + malformations	7	7	6
Unspecified number	0	2	1
Involving:			
Cleft lip and/or palate	8	4	1
Cardiovascular defect	11	10	6
Oesophageal/gut/anal atresia	8	5	3
Limb reduction	6	0	3
Hypospadias	2	3	1
Spine malformation	2	1	0
Polydactyly	0	0	1
At least two of these malformations	12 (60%)	7 (41%)	5 (33%)

[a] For details, see Appendix A. GDM = gestational diabetes.

in Table 4 and are specified in Appendix A. Thus, 22 among 369 infants (6.0% of malformed infants and 5.7 per 1000 of all infants) had more than one malformation if the mother had preexisting diabetes, and for 343 infants born of women with GDM the corresponding number was 19 (5.5% of malformed infants and 2.2 per 1000 of all infants). The corresponding number among the sample of 340 malformed infants drawn from the total population was 16 (5% of malformed infants, 2.6% per 1000 of all infants). There is thus a clear-cut increase in the risk for a multi-malformed infant at preexisting diabetes but not at GDM.

In this Table, the malformations which occurred in excess in infants born of women with preexisting diabetes are specifically shown. Most of these are more frequent also among multi-malformed infants when the mother had a preexisting diabetes compared with the population sample but numbers are small. The GDM group is intermediary for some of them, also for orofacial clefts.

4. Discussion

Among infants whose mothers had a preexisting diabetes, the total rate of congenital malformations identified when all available health registers were used was 9.5% which is close to what has been described in the literature after detailed paediatric examination of the newborns [3]. The ascertainment of congenital malformations using the various Swedish health registers apparently is comparable with ascertainment based on detailed case studies.

The risk estimate of congenital malformations among infants of women with preexisting diabetes was close to a doubling when only diagnoses in the Medical Birth Registry was used for the estimate and is slightly lower (1.7) when a ‘complete’

ascertainment of malformations is used (based on all registries). This may indicate a more complete registration of infant malformations in case the mother has a preexisting diabetes.

Among infants born of women with preexisting diabetes, an increased risk was seen specifically for some types of congenital malformations: orofacial clefts, cardiac defects, oesophageal or intestinal atresia, hypospadias, polydactyly, limb reductions, and spine malformations. By and large these 12 findings agree with previous findings in the literature. We found no excess of neural tube defects but numbers are low.

The total risk of a congenital malformation among infants born of women with GDM is close to the population rate both when one studies only infants with malformations registered in the Medical Birth Registry and when infants with malformations identified also with other registers. The OR for infants to have a malformation recorded in the Medical Birth Registry is 1.06, not significantly increased, and the total rate of identified malformations is 5.7% both when the mother had GDM and in the background population. This contrasts to reports in the literature as summarized in the Introduction.

When we analyzed specific types of congenital malformations, there was an increase in some of the conditions which were associated with preexisting diabetes also in infants born of women with GDM: specific cardiac defects, oesophageal/intestinal atresia, and spine malformations. Also for brain malformations and polydactyly, an increase was seen but those could be random. Also among infants with multiple malformations, those born by women with GDM seemed to be intermediate between infants born of mothers with preexisting diabetes and all infants in the population but numbers are small. These observations support the results previously reported [11,12].

The cause of the increased risk for congenital malformations in infants of women with diabetes type 1 is not quite clear. Mills et al. [16] found no correlation between the glycemic control of the woman during the organogenetic period and the risk for congenital malformations but Greene et al. [4] found that the risk for a major congenital malformation was higher when the woman had an HbA1 above 14.4 than below 9.3 and suggested that a very poor metabolic control in early pregnancy markedly increased the risk while a moderately increased HbA1 did not affect malformation rates. Maternal vasculopathy has been implicated [17] in the origin of diabetes teratogenesis. Most likely, a multifactorial model exists as also suggested by animal experiments (e.g. [18]).

The normal total malformation rate but the indicated increase in some specific malformations, typical of the embryopathy of diabetes type 1, suggests that within the study group of GDM pregnancies, a subgroup with an increased risk of the same magnitude as that at diabetes type 1 may exist. A possible candidate could be undetected diabetes type 2, a condition which according to Towner et al. [6] is associated with an increased risk for congenital malformations. Another possibility is that this subgroup consists of diabetes type 1 women with a miscoding of the diabetes condition from preexisting to GDM had occurred. In a previous paper, under publication, we investigated this possibility and estimated that about one per cent of women with a diagnosis of GDM actually had preexisting diabetes. Given a 9.5%

malformation rate among the infants of such women, this would represent eight malformed infants among the 343 found which can hardly explain the excess of the malformations specific for diabetic embryopathy.

Appendix A. Specified list of infants with more than one major malformation

Preexisting maternal diabetes
Anencephaly; cleft palate
Hydrocephaly; ASD
Cleft palate; VSD
Cleft palate; pulmonary malformation
Cleft palate; unilateral cystic kidney; limb reduction; coloboma; spine malformation
Cleft lip/palate; unspecified cardiovascular defect
Cleft lip/palate; ASD; hypospadias
Cleft lip/palate; anal atresia; VSD; limb reduction; other gut malformation
Cleft lip/palate; bladder exstrophy; limb reduction; anal atresia; double vagina/uterus; VSD; thumb duplication
Small bowel atresia; biliary tract malformation; megacolon
Anal atresia; VSD
Anal atresia; biliary tract malformation
Anal atresia; spine malformation; other gut malformation; varus deformity
Anal atresia; unilateral kidney agenesis; sacral agenesis; biliary tract malformation; choanal atresia; system venous malformation
Anal stenosis; bilateral kidney hypoplasia; gut malrotation; limb malformation; pulmonary hypoplasia
Hypospadias; unspecified cardiac defect
Urethral stenosis; unspecified cardiac defect
Skull malformation; hydronephrosis
Skull malformation; varus deformity
Arthrogryposis; limb reduction
Deformity upper limb; VSD
Spleen malformation; situs inversus

Maternal gestational diabetes
Spina bifida; anal atresia
Microphthalmia; ECD and CoA
Cleft palate; facial malformation
Cleft lip/palate; ASD; pulmonary hypoplasia
Cleft lip/palate; hydronephrosis; ear malformation
Truncus communis; cleft lip/palate
Truncus communis; pulmonary malformation; chest malformation
ECD; malformation in upper gastrointestinal tract

Esophageal atresia; small bowel atresia; spine malformation
Pylorostenosis; unspecified cardiac defect
Pylorostenosis; urethral stenosis
Small bowel atresia; hydronephrosis; pulmonary artery anomaly
Anal atresia; other gastrointestinal malformation; ureter/kidney malformation; spine malformation
Anal atresia; kidney agenesis; spine malformation; skin malformation
Hypospadias; VSD
Penis malformation; VSD
Hydronephrosis; ASD
Unspecified multi-malformed infant ($n = 2$).

Population data
Spina bifida; malrotation of the gut
Hydrocephaly; oesophageal atresia; anal atresia; spine malformation; syndactyly
Hydrocephaly; urethral atresia; syndactyly
CNS malformation; anal atresia; hydronephrosis
Brain malformation; microphthalmia; VSD; genital malformation
Ear dysplasia; limb reduction; common truncus
Cleft lip/palate; VSD
Small gut atresia; megacolon
Limb reduction defect; TGV
Limb reduction defect; pulmonary hypoplasia
Kidney agenesis; polydactyly
Kidney agenesis; urethra atresia; arthrogryposis; unspecified genital malformation
Hypospadias; unspecified cardiac defect
Skull/face malformation; pes equinovarus
Skull/face malformation; unspecified vascular defect
Unspecified multi-malformed infant with hydronephrosis

Abbreviations
ASD = atrial septum defect, CoA = coarctation of aorta, ECD = endocardial cushion defects, TGV = transposition of large vessels, VSD = ventricular septum defect.

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