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ARTICLE

Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study

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Abstract
Aims The aim of this study was to quantify the risk of major congenital anomaly, and to assess the influence of peri-conception HbA_{1c} and other clinical and socio-demographic factors on the risk of congenital anomaly occurrence in offspring of women with type 1 and type 2 diabetes diagnosed before pregnancy.
Methods This was a population-based cohort study using linked data from registers of congenital anomaly and diabetes in pregnancy. A total of 401,149 singleton pregnancies (1,677 in women with diabetes) between 1996 and 2008 resulting in live birth, fetal death at ≥20 weeks' gestation or termination of pregnancy for fetal anomaly were included.
Results The rate of non-chromosomal major congenital anomaly in women with diabetes was 71.6 per 1,000 pregnancies (95% CI 59.6, 84.9), a relative risk of 3.8 (95% CI 3.2, 4.5) compared with women without diabetes. There was a three- to sixfold increased risk across all common anomaly groups. In a multivariate analysis, peri-conception glycaemic control (adjusted OR [aOR] 1.3 [95% CI 1.2, 1.4] per 1% [11 mmol/mol] linear increase in HbA_{1c} above 6.3% [45 mmol/mol]) and pre-existing nephropathy (aOR 2.5 [95% CI 1.1, 5.3]) were significant independent predictors of congenital anomaly. Associations with gestation at booking (aOR 1.1 [95% CI 1.0, 1.1]) and parity (aOR 1.6 [95% CI 1.0, 2. 5]) were not significant. Unadjusted risk was higher for women from deprived areas or who did not take folate. Type and duration of diabetes, ethnicity, age, BMI, preconception care, smoking and fetal sex were not associated with congenital anomaly risk.
Conclusions Peri-conception glycaemia is the most important modifiable risk factor for congenital anomaly in women with diabetes. The association with nephropathy merits further study.

Keywords Congenital abnormalities · Diabetes · Hyperglycaemia · Nephropathy · Preconception

Abbreviations

aOR	Adjusted odds ratio
EUROCAT	European surveillance of congenital anomalies
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile range
LOWESS	Locally weighted scatter plot smoothing
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey

Introduction

Pregnancies complicated by pre-existing diabetes are at high risk of adverse outcome, including stillbirth, perinatal

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mortality, congenital anomaly, Caesarean section and macrosomia [1, 2]. The global prevalence of type 2 diabetes is increasing particularly at younger ages, resulting in an increasing proportion of pregnancies complicated by diabetes. Congenital anomalies are a major cause of stillbirth and neonatal death for babies born to women with diabetes [2, 3] and a substantial proportion end in termination of pregnancy. They are also important contributors to mortality and morbidity throughout infancy and childhood, and survivors may have considerable ongoing health and social care needs.

The risk of congenital anomaly in women with diabetes is strongly associated with glycaemic control, indicated by higher levels of HbA_{1c} in pregnancies affected by congenital anomaly [4–6]. However, similar rates of congenital anomaly have been reported in women with type 1 and 2 diabetes, despite generally lower HbA_{1c} levels in type 2 diabetes [1]. This may reflect differences in other variables that are associated with congenital anomaly risk, such as maternal age, BMI, smoking, ethnicity and socioeconomic status. Previous studies have not assessed the extent to which these factors may modify the effect of glycaemia in the development of congenital anomaly in women with diabetes.

This study combined data from established population-based registers with comprehensive ascertainment to quantify the risk of major congenital anomaly in pregnancy in women with type 1 and type 2 diabetes, and to assess the influence of clinical and sociodemographic risk factors in addition to peri-conception HbA_{1c}.

Methods

Study population The study area in the north of England (UK) has a population of about 3 million and 31,000 deliveries per year. This analysis included all singleton pregnancies to women resident in the region, resulting in live birth, stillbirth (≥24 weeks gestation), late fetal loss (20–23 weeks gestation), or termination of pregnancy following prenatal diagnosis of a fetal anomaly (any gestation), during the period 1996–2008.

Pregnancies in women with and without pre-existing diabetes The Northern Diabetes in Pregnancy Survey (NorDIP) records details of all known pregnancies, irrespective of outcome, in women resident in the study area and diagnosed with diabetes at least 6 months prior to conception [7]. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. Demographic and clinical variables are collected, including pre-pregnancy and antenatal HbA_{1c} (DCCT-aligned since 2000). The total number of registered singleton live and stillbirths was obtained from the UK Office for National Statistics.

Congenital anomaly cases The Northern Congenital Abnormality Survey (NorCAS) collects information on all cases of congenital anomaly (up to six anomalies for each case) diagnosed to age 12 years, including those arising in fetal loss or termination of pregnancy for fetal anomaly. The register uses multiple sources of ascertainment [8]. The NorDIP and NorCAS are held on a single linked database at the Regional Maternity Survey Office in Newcastle.

Classification of congenital anomalies All major congenital anomalies were coded according to the International Classification of Diseases 10th revision (ICD-10; www.who.int/classifications/icd/en/) and categorised using European surveillance of congenital anomalies (EUROCAT) criteria (www.eurocat@ulster.ac.uk), by group (the system affected), subtype (the individual disorder), and syndrome (where applicable). Chromosomal anomalies were defined as any anomaly in the number of chromosomes or in the structure of at least one chromosome resulting in a genetically unbalanced genotype (ICD-10 codes: Q90–92, Q93, Q96–99). Non-chromosomal anomalies are all remaining major congenital anomalies included in the EUROCAT classification scheme [9, 10].

Isolated cases (with one anomaly diagnosis only) were assigned to their primary anomaly group and subtype. Cases with two or more non-chromosomal anomalies were reviewed to identify a primary group or subtype, or to confirm a diagnosis of multiple anomalies. Cases were classified as multiple anomalies if they had two or more unrelated anomalies across separate organ systems. Individuals with several anomalies from the same organ system were included within that group but not classified by subtype. A congenital anomaly was classified as isolated if it occurred alone, or if all coexisting anomalies were commonly associated secondary anomalies. Chromosomal anomalies, syndromes (patterns of anomalies arising from a single cause, e.g. genetic disorders [11]), skeletal dysplasias (syndromes of skeletal development [10]), sequences (patterns of anomalies arising from a prior anomaly or mechanical factor [12]), associations (recognised patterns of anomalies of unknown cause [11]) and other microdeletions, were regarded as primary anomalies rather than instances of multiple anomalies.

Statistical analyses Prevalence rates of congenital anomaly, by group and subtype, were determined for women with and without diabetes and compared by calculating the RR, and 95% CIs for prevalence rates were calculated using exact methods. Numbers of cases are presented only for groups and subtypes where there was at least one case in pregnancies with diabetes. Rates and RRs (95% CI) for the subtypes of congenital anomalies are presented if there were three or more cases in pregnancies with diabetes. Heterogeneity of RRs between anomaly groups was examined using Cochran's Q test.

ORs and associated 95% CIs for non-chromosomal congenital anomalies among women with diabetes were estimated for various sociodemographic and clinical variables using logistic regression. Independent effects were estimated from an adjusted model, constructed using backwards stepwise regression. All variables with an unadjusted p value below 0.5 were entered into the model (maternal age at delivery, gestational age at booking, peri-conception HbA_{1c}, type of diabetes, preconception folic acid, nephropathy diagnosed pre-pregnancy, retinopathy diagnosed pre-pregnancy, fetal sex, parity, pre-pregnancy care, index of multiple deprivation, smoking during pregnancy). Variables were then iteratively removed until all remaining had $p<0.1$. The multivariate analysis had at least adequate power ($\beta=0.8$) to detect a medium effect (Cohen's d=0.5, equivalent to OR of 2.47) for any variable with a baseline exposure probability between 5% and 95% (which included type 2 diabetes, non-white ethnicity, preconception folate consumption, pre-pregnancy care, smoking during pregnancy). Greater power was available for the continuous variables (duration of diabetes, maternal age at delivery, maternal BMI at booking, gestational age at booking, and peri-conception HbA_{1c}).

Interaction terms were used to examine whether variables in the adjusted model had the same effect on the risk of congenital anomalies in women with type 2 compared with type 1 diabetes. The relative contributions of variables in the adjusted model were approximated by estimating the standardised β coefficients, which allow the importance of continuous and non-continuous variables to be directly compared [13]. HbA_{1c} was analysed as a single peri-conception variable, using measurement closest to conception (within three months of conception) where available (48.4% of pregnancies) and mean first trimester value (up to 14 weeks gestation) otherwise. BMI, determined from height and weight at booking, was included as a continuous variable, excluding underweight women due to potential curvilinearity [14]. The index of multiple deprivation (IMD), an area-based measure of socioeconomic status, was determined from maternal residential postcode at booking and grouped into tertiles [15]. Locally weighted scatter plot smoothing (LOWESS), with smoothing parameter 0.8, was used to investigate the shape of the relationship between HbA_{1c}, as a continuous variable, and the risk of congenital anomaly. CIs for the LOWESS plot were estimated by bootstrapping (50,000 iterations).

Statistical analyses were performed using SPSS for Windows version 17.0 (IBM Corporation, Somers, NY, USA) and Stata 11.1 (StataCorp, College Station, TX, USA). $P<0.05$ was considered statistically significant.

Ethics approval and research governance NorCAS, as part of the British Isles Network of Congenital Anomaly Registers, has exemption from the UK National Information and Governance Board (PIAG 2-08(e)/2002 20/06/2002) from a requirement for individual consent and has ethics approval (09/H0405/48) to undertake studies using the data. Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993, and data are now obtained and held with informed consent.

Results

Study population Overall, 401,149 singleton live births, stillbirths, late fetal losses, and terminations of pregnancy were recorded during the study period, including 1,677 in women with pre-existing diabetes, giving a prevalence of 4.2 per 1,000 (95% CI 4.0, 4.4) pregnancies.

Among women with diabetes, median (interquartile range, IQR) maternal age at delivery was 30 (25–24) years; 649 (40.1%) women were primiparous and the median (IQR) peri-conception HbA_{1c} was 7.9% (6.8–9.2). A total of 1314 (78.4%) women had type 1 and 363 (21.6%) had type 2 diabetes. There were significant differences in the characteristics of women with type 1 and type 2 diabetes (Tables 1 and 2). Overall reported preconception folate consumption was low, but not significantly different in women with type 1 and type 2 diabetes ($p=0.06$).

Risk of congenital anomaly A total of 9,488 singleton pregnancies were affected by at least one major congenital anomaly, including 129 in women with diabetes. The risk of a pregnancy affected by any major congenital anomaly in women with diabetes was over three times higher than the background population (RR 3.3 [95% CI 2.8, 3.9]; Table 3). There was no difference in the proportion of affected pregnancies ending in termination for fetal anomaly in women with and without diabetes: 23 (18%) vs 1,811 (19%); RR 0.9 (95% CI 0.6, 1.3).

The prevalence of major congenital anomaly per 1,000 pregnancies was 82.2 (95% CI 67.9, 98.3) in women with type 1 diabetes and 57.9 (95% CI 36.2, 87.1) in women with type 2. There was no significant difference in risk of congenital anomaly by type of diabetes (RR 1.4 [95% CI 0.9, 2.2] for type 1 vs type 2).

There was no evidence of increased risk of chromosomal anomalies in women with diabetes (RR 1.2 [95% CI 0.6, 2.4]). Excluding chromosomal anomalies, the relative risk of affected pregnancy for women with diabetes was 3.8 (95% CI 3.2, 4.5). There was significant variation in relative risk between different groups of non-chromosomal anomaly ($p=0.05$), attributable to a 12-fold increase for the sequence group (including caudal dysplasia sequence, sirenomelia and partial urorectal septum malformation sequence) among women with diabetes (Table 3).

Among pregnancies in women without diabetes, the rate of non-chromosomal anomaly was significantly higher in

Table 1 Characteristics of mothers with type 1 and type 2 diabetes (continuous variables)[a]

Continuous variable	Type 1 (n=1314)			Type 2 (n=363)			p value
	n	Range	Median (IQR)	n	Range	Median (IQR)	
Duration of diabetes (years)	1,303	0.9–36	2 (6–18)	352	1–19	2 (1–4)	<0.001
Maternal age at delivery (years)	1,314	15–46	29 (24–33)	363	17–46	33 (29–37)	<0.001
BMI at booking (kg/m^2)	1,010	17–52	25.5 (23–29)	283	19–64	34.6 (29–40)	<0.001
Gestational age at booking (weeks)	1,308	1–34	8 (7–11)	358	2–34	9 (7–12)	0.009
Peri-conception HbA_{1c} (%)	1,146	5–16.4	8.1 (7.0–9.3)	291	4.6–15.3	7.0 (6.2–8.2)	<0.001
Peri-conception HbA_{1c} (mmol/mol)	1,146	31.1-155.7	65.0 (53.0-78.1)	291	26.8–143.7	53.0 (44.3-66.1)	<0.001

[a] Includes chromosomal and non-chromosomal anomalies

males (RR 1.2 [95% CI 1.1, 1.2]). This sex difference was not apparent among pregnancies in women with diabetes (RR 0.9 [95% CI 0.6, 1.2] for males vs females), although the risk ratio did not differ significantly from that observed in the general population.

Predictors of non-chromosomal congenital anomalies in women with diabetes Peri-conception HbA_{1c} and presence of pre-pregnancy nephropathy were significant independent predictors of congenital anomaly (Table 4). For each percentage (11 mmol/mol) increase in HbA_{1c}, the odds of a pregnancy being affected by congenital anomaly increased by 30% (adjusted odds ratio (aOR) 1.3 [95% CI 1.2, 1.4]). LOWESS indicated that this was a steadily increasing effect for HbA_{1c} values above 6.3% (45 mmol/mol) (Fig. 1 and Table 5). There was no evidence of risk reduction below this value, although there were very few cases in this range.

Pre-pregnancy nephropathy was associated with greater than two-fold increased risk of congenital anomaly (aOR 2.5 [95% CI 1.1, 5.3]). Gestation at booking in weeks (aOR 1.1 [95% CI 1.0, 1.1]) and parity (aOR 1.6 [95% CI 1.0, 2.5]) were also included in the final adjusted logistic regression model (p<0.1) although the associations did not quite reach the nominated significance level (p<0.05). Of the four variables that were retained in the adjusted model, the highest predictive contribution was attributable to HbA_{1c} (standardised beta coefficient, β=0.41), which was more than twice as important as parity (β=0.19), and over 2.5 times more important than gestational age at booking (β=0.16) and nephropathy (β=0.15).

In univariate analysis, socioeconomic status (OR 2.0 [95% CI 1.2, 3.2]) and lack of folic acid (OR 2.0 [95% CI 1.3, 3.3]) were significant predictors of pregnancy affected by congenital anomaly. However, these effects were attenuated below significance when adjustment was made for HbA_{1c}. There was no evidence that any of the associations between variables in the adjusted model and the risk of congenital anomalies was different in women with type 2 diabetes compared with women with type 1 diabetes.

Type and duration of diabetes, fetal sex, maternal ethnicity, early pregnancy BMI, smoking during pregnancy, pre-pregnancy retinopathy, and neuropathy were not significantly associated with the risk of congenital anomaly in either unadjusted or adjusted models.

Discussion

This population-based cohort study provides robust estimates of the risk of major congenital anomaly among offspring of women with pre-existing diabetes. Overall, one in 13 singleton deliveries (7.7%) was affected, and the rate of non-chromosomal anomaly was almost four times higher than in women without pre-existing diabetes. Peri-conception HbA_{1c} has previously been reported to be associated with congenital anomaly [4], but the association with pre-existing nephropathy is, to our knowledge, previously unreported. The risk of congenital anomaly increased linearly with increasing HbA_{1c} above 6.3% (45 mmol/mol), by nearly 30% for each 1% (11 mmol/mol) increase.

This study linked independently and robustly ascertained congenital anomaly cases with detailed clinical information on pregnancies in women with diabetes, notified to long-standing population-based registers. This minimised potential detection bias between pregnancies in women with and without diabetes, and enabled exploration of the independent effects of a wide range of clinical and sociodemographic risk factors. Ascertainment and coding of anomalies was consistent throughout, standardised according to internationally agreed criteria, and independent of diabetes status. We restricted our analysis to EUROCAT defined major anomalies, because these are consistently ascertained, and have the greatest impact on mortality and morbidity. Pregnancies in women with diabetes are subject to increased antenatal surveillance, leading to the potential for ascertainment bias unless, as in NorCAS, cases are notified whenever diagnosed in childhood (to age 12 years). This is particularly important for cardiovascular anomalies, many of which are only diagnosed in early

Table 2 Characteristics of mothers with type 1 and type 2 diabetes (categorical variables)[a]

Categorical variable	Type 1 (n=1314)		Type 2 (n=363)		p value
	n	%	n	%	
Complicated by a congenital anomaly	108	8.2	21	5.8	0.12
Preconception folic acid					
Yes	424	32.3	98	27.0	0.06
No	810	61.6	223	61.4	
Missing	80	6.1	42	11.6	
Nephropathy (pre-pregnancy)					
Yes	57	4.3	3	0.8	0.002
No	1,257	95.7	360	99.2	
Neuropathy (pre-pregnancy)					
Yes	28	2.1	0	0.0	0.01
No	1,286	97.9	363	100.0	
Retinopathy (pre-pregnancy)					
Yes	263	20.0	16	4.4	<0.001
No	992	75.5	323	89.0	
Missing	59	4.5	24	6.6	
Pre-pregnancy care					
Yes	583	44.4	106	29.2	<0.001
No	731	55.6	257	70.8	
Fetal sex					
Male	707	53.8	179	49.3	0.13
Female	601	45.7	182	50.1	
Uncertain/missing	6	0.5	2	0.6	
Smoking during pregnancy					
Yes	290	22.1	81	22.3	0.92
No	910	69.2	246	67.8	
Missing	114	8.7	36	9.9	
Parity					
Primipara (parity=0)	559	42.5	90	24.8	<0.001
Parity ≥1	710	54.0	243	66.9	
Missing	45	3.4	30	8.3	
Ethnicity					
White	1,278	97.3	286	78.8	<0.001
Other	31	2.4	70	19.3	
Missing	5	0.4	7	1.9	
IMD					
Tertile 1 (most deprived)	385	29.3	171	47.1	<0.001
Tertile 2	442	33.6	115	31.7	
Tertile 3 (least deprived)	481	36.6	76	20.9	
Missing	6	0.5	1	0.3	

[a]Includes chromosomal and non-chromosomal anomalies

childhood. Most previous cohort studies of anomalies in pregnancies complicated by diabetes include only those diagnosed antenatally or apparent shortly after birth, a major methodological limitation [2, 3, 5, 16–19].

This is one of the largest cohort studies to date, including 120 cases of major non-chromosomal anomaly in women with both type 1 and type 2 diabetes, and the only such study to include detailed clinical information. The north of England benefits from a long history of collaborative clinical networking within maternity and neonatal services, and the NorCAS and NorDIP surveys were initiated by pioneering clinicians in the 1980s and 1990s. The surveys are now supported by the Regional Maternity Survey Office (RMSO) which provides a focus for data collection and dissemination

Table 3 Rates (95% CI) of major groups and selected subtypes of congenital anomalies[a] in pregnancies of women with and without pre-existing diabetes per 1000 singleton pregnancies and RR (95% CI%)

Group (subtype)[a]	Pregnancies with diabetes		Pregnancies without diabetes		Relative risk(95% CI)
	n	Rate (95% CI)	*n*	Rate (95% CI)	
Nervous system	16	9.5 (5.4, 15.4)	769	1.9 (1.8, 2.1)	5.0 (3.0, 8.1)
Neural tube defects	10	6.0 (2.9, 10.9)	443	1.1 (1.0, 1.2)	5.4 (2.9, 10.1)
Hydrocephalus		2		115	
Microcephaly		1		55	
Holoprosencephaly		1		31	
Eye	2		98		
Cardiovascular system	44	26.2 (19.1, 35.1)	2919	7.3 (7.0, 7.6)	3.6 (2.7, 4.8)
Transposition of great vessels	3	1.8 (0.4, 5.2)	130	0.3 (0.3, 0.4)	5.5 (1.8, 17.2)
Single ventricle	1		13		
Ventricular septal defect	21	12.5 (7.8, 19.1)	1285	3.2 (3.0, 3.4)	3.9 (2.6, 6.0)
Atrial septal defect	1		217		
Atrioventricular septal defect	2		69		
Tetralogy of Fallot	4	2.4 (0.7 6.0)	95	0.24 (0.2, 0.3)	10.0 (3.7, 27.2)
Pulmonary valve stenosis	3	1.8 (0.4, 5.2)	244	0.6 (0.5, 0.7)	2.9 (0.9, 9.1)
Hypoplastic left heart	1		78		
Coarctation of aorta	2		101		
Total anomalous pulmonary venous return	1		35		
Orofacial clefts	1		437		
Digestive system	10	6.0 (2.9, 10.9)	421	1.05 (0.95, 1.15)	5.7 (3.0, 10.6)
Oesophageal atresia	2		43		
Duodenal atresia or stenosis	1		36		
Hirschprung's disease	1		51		
Atresia of bile ducts	1		15		
Diaphragmatic hernia	2		91		
Urinary	12	7.2 (3.7, 12.5)	974	2.4 (2.3, 2.6)	2.9 (1.7, 5.2)
Cystic kidney disease	2		200		
Congenital hydronephrosis	1		20		
Bladder exstrophy	1		14		
Genital	2		76		
Limb	2		234		
Musculoskeletal	3	1.8 (0.4, 5.2)	55	0.14 (0.1, 0.2)	13.0 (4.1, 41.5)
Syndrome (monogenic or unknown)	11	6.6 (3.2, 11.7)	439	1.1 (1.0, 1.2)	6.0 (3.1, 10.9)
Laterality syndrome (right/left atrial isomerism, situs inversus)	6	3.6 (1.3, 7.8)	25	0.06 (0.04, 0.09)	57.2 (23.5, 139.2)
Angelman syndrome	1		6		
Blepharophimosis-ptosis syndrome	1		3		
Laurence–Moon syndrome	1		2		
Prader–Willi syndrome	1		10		
Incontinentia pigmenti	1		6		
Associations	1		34		
Sequence	7	4.2 (1.6, 8.6)	139	0.35 (0.3, 0.4)	12.0 (5.6, 25.6)
Caudal dysplasia sequence	5	3.0 (0.9, 6.9)	7	0.02 (0.01, 0.03)	170.2 (54.1, 535.6)
Sirenomelia	1		6		
Partial urorectal septum malformation sequence	1		21		
Multiple anomalies	9	5.4 (2.5, 10.2)	440	1.1 (1.0, 1.2)	4.9 (2.5, 9.4)
Total non-chromosomal	120	71.6 (59.6, 84.9)	7613	19.1 (18.6, 19.5)	3.8 (3.2, 4.5)
Chromosomal anomalies	9	5.4 (2.5, 10.2)	1747	4.4 (4.2, 4.6)	1.2 (0.6, 2.4)
Grand total	129	76.9 (64.6, 90.8)	9359	23.4 (23.0, 23.9)	3.3 (2.8, 3.9)

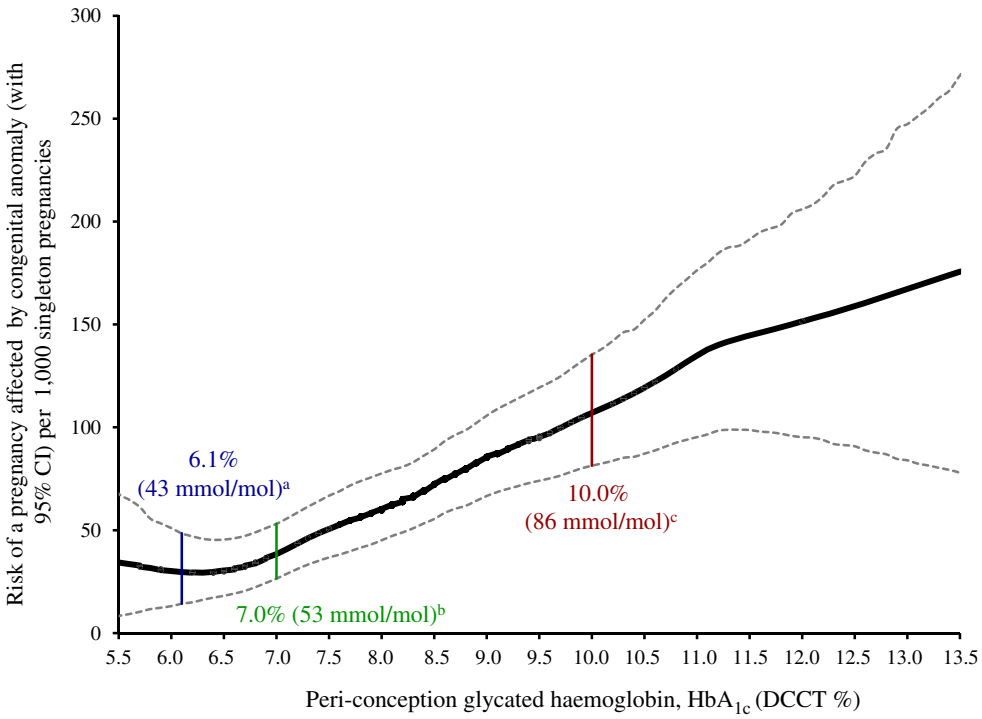
[a] EUROCAT coding

Table 4 Association of maternal and fetal factors with non-chromosomal congenital anomalies in offspring of women with pre-existing diabetes (results of univariate and multivariate logistic regression)

Category	Number (%)			
	Total pregnancies (n=1668)	With congenital anomalies (n=120)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Duration of diabetes (years)[b]	1,646	117	1.00 (0.97, 1.02	
Maternal age at delivery (years)[b]	1,668	120	0.98 (0.95, 1.01)	
BMI at booking (kg/m^2)[b]	1,277	95	1.00 (0.97, 1.03)	
Gestation at booking (weeks)[b]	1,657	120	1.04 (1.00, 1.08)	1.05 (1.00, 1.11)
Peri-conception HbA_{1c} (%)[b]	1,428	96	1.30 (1.18, 1.43)	1.30 (1.18, 1.43)
Type of diabetes				
Type 1	1,306	100 (7.7)	1.42 (0.86, 2.33)	
Type 2	362	20 (5.5)	1.00	
Preconception folate supplement				
Taken	518	22 (4.2)	1.00	
Not taken	1,028	85 (8.3)	2.03 (1.26, 3.29)	
Nephropathy diagnosed pre-preg				
No	1,609	110 (6.8)	1.00	1.00
Yes	59	10 (16.9)	2.78 (1.37, 5.64)	2.45 (1.14, 5.25)
Neuropathy diagnosed pre-preg				
No	1,640	118 (7.2)	1.00	
Yes	28	2 (7.1)	0.99 (0.23, 4.23)	
Retinopathy diagnosed pre-preg				
No	1,308	85 (6.5)	1.00	
Yes	277	24 (8.7)	1.37 (0.85, 2.19)	
Fetal sex				
Female	779	59 (7.6)	1.00	
Male	881	57 (6.5)	0.84 (0.58, 1.23)	
Parity				
Primipara (0)	648	43 (6.6)	1.00	1.00
Multipara (≥1)	945	76 (8.0)	1.23 (0.84, 1.81)	1.56 (1.00, 2.45)
Pre-pregnancy care				
Yes	683	41 (6.0)	1.00	
No	985	79 (8.0)	1.37 (0.92, 2.02)	
IMD (tertiles)				
1 (most deprived)	551	52 (9.4)	1.96 (1.22, 3.16)	
2 (middle)	555	40 (7.2)	1.46 (0.89, 2.41)	
3 (least deprived)	555	28 (5.0)	1.00	
Smoking during pregnancy				
No	11,48	80 (7.0)	1.00	
Yes	370	31 (8.4)	1.22 (0.79, 1.88)	
Ethnicity				
White	1,555	112 (7.2)	1.00	
Other	101	8 (7.9)	1.11 (0.53, 2.34)	
HbA_{1c} measurement recorded				
Pre-pregnancy	807	52 (6.4)	1.00	
1st trimester	621	44 (7.1)	1.11 (0.73, 1.68)	

[a]Adjusted model was constructed using backwards stepwise regression. All variables with an unadjusted p value below 0.5 were entered into the model (maternal age at delivery, gestational age at booking, peri-conception HbA_{1c}, type of diabetes, preconception folic acid, nephropathy diagnosed pre-pregnancy, retinopathy diagnosed pre-pregnancy, fetal sex, parity, pre-pregnancy care, IMD, smoking during pregnancy). Variables were then iteratively removed until all remaining had $p<0.1$, details of which are shown

[b]Continuous variable



HbA_{1c}	5.5–6.4	6.5–7.4	7.5–8.4	8.5–9.4	9.5–10.4	10.5–11.4	11.5–12.4	12.5–13.5
Singleton pregnancies	195	322	346	220	158	70	32	24
Cases	6	10	21	19	17	10	4	5

Fig. 1 Association between peri-conception HbA_{1c} in women with pre-existing diabetes and the risk (with 95% CIs) of a pregnancy affected by major congenital anomaly. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

[a]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.2) 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} below 6.1%. Women should be reassured that any reduction in HbA_{1c} towards the target of 6.1% is likely to reduce the risk of congenital malformations.' [27]

[b]American Diabetes Association (USA), 2011: (VII.B) 'A_{1c} levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.' [26]

[c]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.3) 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.' [27]

across a number of linked surveys of maternal and perinatal health outcome (www.rmso.org.uk).

HbA_{1c} was measured within three months prior to conception in nearly half of cases, and this is likely to reflect peri-conception glycaemia better than first trimester measurements. However, information on covariates such as maternal age and parity was not available for unaffected pregnancies in women without diabetes, and we were therefore unable to adjust our relative risk estimates. Few of the women with diabetes were of non-white ethnicity. Robust information about hypoglycaemic therapy was not available, so we were unable to investigate any potential association with congenital anomaly risk. The study may have lacked power to quantify the relative risk for anomalies with a small effect size, or where very few cases were reported. In the multivariate analyses, we estimated that we had adequate power to detect a medium effect size for almost all variables examined. The study may have missed some associations with smaller effect sizes.

We estimated the relative risk of non-chromosomal congenital anomaly in the offspring of women with existing diabetes to be nearly four-fold higher than the general population. Previously published estimates range from two- to threefold [2, 3, 16, 17, 20] to tenfold [21, 22]. Direct comparison with the current study is difficult due to differences in ascertainment and classification of anomalies, and lack of comparable risk estimates for offspring of women without diabetes. In a large cohort of births to women with diabetes from England, Wales and Northern Ireland (CEMACH enquiry), the prevalence of major non-chromosomal anomaly was 4.6%, compared with 7.2% in the current study. This difference may reflect the fact that CEMACH did not have access to a population-based register and only identified cases apparent within 28 days of delivery. Our study is population-based and draws on multiple sources to identify cases of anomaly diagnosed at any time up to age 12 years. Under-ascertainment is also likely to explain the CEMACH study's low reported prevalence ratio of 2.2 for congenital anomaly in

Table 5 Risk of a pregnancy affected by major congenital anomaly in women with pre-existing diabetes, by peri-conception HbA_{1c}

Peri-conception glycated haemoglobin (HbA_{1c})		Risk of a pregnancy affected by congenital anomaly (95% CI)	
DCCT (%)	IFCC (mmol/mol)	Per 1,000 singleton pregnancies	For individual singleton pregnancy
5.5	37	34.3 (8.3, 67.6)	1 in 29 (15, 121)
6.0	42	30.2 (13.1, 51.0)	1 in 33 (20, 76)
6.1[a]	43[a]	29.7 (14.3, 48.5)	1 in 34 (21, 70)
6.5	48	30.3 (18.1, 45.5)	1 in 33 (22, 55)
7.0[b]	53[b]	38.4 (26.5, 53.1)	1 in 26 (19, 38)
7.5	58	50.6 (36.8, 66.8)	1 in 20 (15, 27)
8.0	64	60.1 (45.1, 77.6)	1 in 17 (13, 22)
8.5	69	72.3 (55.5, 89.3)	1 in 14 (11, 18)
9.0	75	85.5 (66.7, 105.7)	1 in 12 (9, 15)
9.5	80	95.3 (74.1, 119.4)	1 in 10 (8, 13)
10.0[c]	86[c]	107.1 (81.4, 135.4)	1 in 9 (7, 12)
10.5	91	119.3 (87.2, 152.3)	1 in 8 (7, 11)
11.0	97	134.9 (95.3, 176.4)	1 in 7 (6, 10)
11.5	102	144.7 (98.7, 191.4)	1 in 7 (5, 10)
12.0	108	151.5 (95.2, 206.1)	1 in 7 (5, 11)
12.5	113	158.9 (90.8, 222.2)	1 in 6 (5, 11)
13.0	119	167.2 (84.0, 247.4)	1 in 6 (4, 12)
13.5	124	175.7 (77.8, 271.0)	1 in 6 (4, 13)

[a,b,c]For further explanation see Fig. 1

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine

women with and without diabetes, as the comparison was with age-adjusted prevalence rates from the EUROCAT network of population-based registries [2]. The current study estimated a 3.8-fold increase, based on a direct comparison of the congenital anomaly rates in women with and without diabetes from the same source population, indentified independently of diabetes status.

Only two variables, higher peri-conception HbA_{1c} and pre-existing nephropathy, were significant independent predictors in multivariate analysis. Parity and gestational age at booking were retained in the multivariate model but the associations did not reach statistical significance. There was no evidence of an independent effect of maternal age, smoking, ethnicity and early pregnancy BMI, which have been associated with congenital anomaly risk in the general population. A higher rate of congenital anomaly was observed in women resident in more deprived areas; this was largely attributable to higher peri-conception HbA_{1c} in these women. We found no evidence that the increased risk of anomaly in women with diabetes was specific to males, in contrast with an earlier report [23], although we confirmed the increased risk for males in the general population [24, 25]. There was no evidence that any of the identified predictors of congenital anomaly were different in type 1 and type 2 diabetes.

Peri-conception HbA_{1c} was the most important independent predictor of congenital anomaly risk, confirming previous reports [4–6]. The current study identified a linear relationship with HbA_{1c} for values between 6.3% and 11% (45 and 97 mmol/mol). The odds were lowest for HbA_{1c}= 6.3% (45 mmol/mol), although still above background population levels, and increased by approximately 2% in absolute terms for each 1% (11 mmol/mol) increase, slightly lower than previous reports [5, 6]. We found no evidence of further reduction for values below 6.3% (45 mmol/mol), although there were few individuals in this range.

Current guidance from the American Diabetes Association recommends a target HbA_{1c} <7% (53 mmol/mol) prior to pregnancy [26]. In England, the National Institute for Health and Clinical Excellence (NICE) suggests a target for preconception HbA_{1c} <6.1% (43 mmol/mol), if safely achievable, and strongly discourages pregnancy at levels >10% (86 mmol/mol) [27]. Our results indicate that there appears to be no specific threshold for change in congenital anomaly risk, and hence do not provide support for particular peri-conception HbA_{1c} targets, but rather provide risk estimates across a range of HbA_{1c} levels. Our results further suggest that even achieving near normal levels of HbA_{1c} does not eliminate the increased risk of congenital anomaly attributable to diabetes. All women with diabetes should be encouraged to achieve as great a reduction in HbA_{1c} as possible prior to conception.

There was a greater than twofold increased risk of congenital anomaly in the offspring of women with pre-existing nephropathy. This group is known to be at increased risk of adverse pregnancy outcome [28, 29], but this is the first

study to suggest a specific increased risk of occurrence of congenital anomaly. This finding requires confirmation in other studies. Nephropathy may reflect a history of prolonged poor glycaemic control, including high variability in glucose levels, which may not be reflected by HbA_{1c} [30]; however, neither retinopathy nor neuropathy conferred increased risks of congenital anomaly. Women with nephropathy usually require antihypertensive medication and are often treated with ACE inhibitors, which have been associated with congenital anomaly risk [31]. Current guidance suggests that these and other potentially teratogenic medications should be discontinued prior to conception [27, 32] but many pregnancies are unplanned and the extent of peri-conception exposure to potentially teratogenic medications is unknown. We were unable to investigate this issue as the registers do not record details of peri-conception medications. There is evidence for a genetic influence on diabetic nephropathy, and it is possible that an association with congenital anomaly may have a genetic basis [33]. Oxidative stress is thought to play a role in the development of nephropathy as well as in congenital anomaly [34]. These potential shared mechanisms merit further research.

Type of diabetes was not independently associated with risk of congenital anomaly, and did not modify the association with other variables. There was a slightly higher unadjusted risk of non-chromosomal anomaly among women with type 1 diabetes (RR 1.4 [95% CI 0.9, 2.2]), which may have been significant with a larger sample size; however the effect was heavily attenuated by adjustment for HbA_{1c}, suggesting that this is the main driver for any difference in risk between type 1 and type 2. Women with type 2 diabetes had lower peri-conception HbA_{1c}, but were less likely to attend for preconception care, and had markedly different clinical and sociodemographic characteristics compared with women with type 1 diabetes, in line with previous reports [35, 36]. Specific approaches to improve pregnancy planning in women with type 2 diabetes may be required. Reported rates of preconception folate supplementation were generally low, suggesting poor awareness among women and/or low rates of planned pregnancies.

This study confirms the association of pre-existing diabetes with a wide range of non-chromosomal anomalies affecting most major organ systems [20, 37] and with the risk of anomalies affecting multiple systems [37, 38] Cardiovascular anomalies were the most common, reflecting their high frequency in the general population, and were not proportionally more frequent in women with diabetes. However, we confirmed very high relative risks for caudal regression sequence and laterality syndrome [38, 39], suggesting a specific effect of diabetes in the aetiology of these rare anomalies.

Given the diverse range of congenital anomalies associated with maternal diabetes, mechanisms that have a general effect on early organogenesis are likely [40, 41]. Hyperglycaemia may be directly implicated through induction of oxidative stress within the embryo [42]. Disruption of specific genetic pathways in this way has been described in animal models for neural tube and cardiac outflow tract development [43].

Blood glucose levels may fluctuate widely, even in the presence of apparently 'optimal' HbA_{1c} [30]. Multiple anomalies may arise from multiple episodes of hyperglycaemia during the critical windows of development for different organ systems. Hence, approaches to reducing peri-conception glucose variability using insulin pump therapy and continuous glucose monitoring may be valuable in the prevention of congenital anomaly and should be evaluated in this regard [44].

Implications Women with diabetes remain at greatly increased risk of offspring affected by major congenital anomaly. Achieving optimal glycaemic control prior to conception remains the most important modifiable risk factor, but is unlikely to eliminate the excess risk. Guidelines emphasise the provision of specialist preconception care to improve preparation and planning for pregnancy, but uptake remains low, and women from ethnic minority groups, socially deprived areas and with type 2 diabetes are less likely to attend. Awareness of the need for preparation for pregnancy should be incorporated into the routine care of young women with diabetes. Further research is needed to evaluate new approaches to improve the number of women with diabetes who are adequately prepared for pregnancy, and to reduce sociodemographic inequalities in outcome.

We found that women with pre-existing nephropathy were at particularly high risk of congenital anomaly. These women require specific care and support to achieve a planned pregnancy with a good outcome. Further investigation of the extent and consequences of exposure to potentially teratogenic factors in these women, including medications, is required. Interventions to reduce glucose variability and anti-oxidant therapies merit further assessment of their potential to reduce congenital anomaly risk in women with diabetes.

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Contribution statement RB and JR developed the study concept and supervised the research. SVG prepared the database and PWGT coded the anomalies. SVG and PWGT analysed the data, and with RWB, RB and JR, interpreted the findings. RB wrote the first draft of the report; all co-authors contributed to writing and agreed the final draft.

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