



Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study

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Summary

Background Diabetes in pregnancy is associated with preterm delivery, birthweight extremes, and increased rates of congenital anomaly, stillbirth, and neonatal death. We aimed to identify and compare modifiable risk factors associated with adverse pregnancy outcomes in women with type 1 diabetes and those with type 2 diabetes and to identify effective maternity clinics.

Methods In this national population-based cohort study, we used data for pregnancies among women with type 1 or type 2 diabetes collected in the first 5 years of the National Pregnancy in Diabetes audit across 172 maternity clinics in England, Wales, and the Isle of Man, UK. Data for obstetric complications (eg, preterm delivery [<37 weeks' gestation], large for gestational age [LGA] birthweight [>90 th percentile]) and adverse pregnancy outcomes (congenital anomaly, stillbirth, neonatal death) were obtained for pregnancies completed between Jan 1, 2014, and Dec 31, 2018. We assessed associations between modifiable (eg, HbA_{1c}, BMI, pre-pregnancy care, maternity clinic) and non-modifiable risk factors (eg, age, ethnicity, deprivation, duration of type 1 diabetes) with pregnancy outcomes in women with type 1 diabetes compared with those with type 2 diabetes. We calculated associations between maternal factors and perinatal deaths using a regression model, including diabetes type and duration, maternal age, BMI, deprivation quintile, first trimester HbA_{1c}, preconception folic acid, potentially harmful medications, and third trimester HbA_{1c}.

Findings Our dataset included 17 375 pregnancy outcomes in 15 290 pregnant women. 8690 (50·0%) of 17 375 pregnancies were in women with type 1 diabetes (median age at delivery 30 years [10–90th percentile 22–37], median duration of diabetes 13 years [3–25]) and 8685 (50·0%) were in women with type 2 diabetes (median age at delivery 34 years [27–41], median duration of diabetes 3 years [0–10]). The rates of preterm delivery (3325 [42·5%] of 7825 pregnancies among women with type 1 diabetes, 1825 [23·4%] of 7815 with type 2 diabetes; $p<0\cdot0001$), and LGA birthweight (4095 [52·2%] of 7845 with type 1 diabetes, 2065 [26·2%] of 7885 with type 2 diabetes; $p<0\cdot0001$) were higher in type 1 diabetes. The prevalence of congenital anomaly (among women with type 1 diabetes: 44·8 per 1000 livebirths, terminations, and fetal losses; among women with type 2 diabetes: 40·5 per 1000 livebirths, terminations, and fetal losses; $p=0\cdot17$) and stillbirth (type 1 diabetes: 10·4 per 1000 livebirths and stillbirths; type 2 diabetes: 13·5 per 1000 livebirths and stillbirths; $p=0\cdot072$) did not significantly differ between diabetes types, but rates of neonatal death were higher in mothers with type 2 diabetes than in those with type 1 diabetes (type 1 diabetes: 7·4 per 1000 livebirths; type 2 diabetes 11·2 per 1000 livebirths; $p=0\cdot013$). Across the whole study population, independent risk factors for perinatal death (ie, stillbirth or neonatal death) were third trimester HbA_{1c} of 6·5% (48 mmol/mol) or higher (odds ratio 3·06 [95% CI 2·16–4·33] vs HbA_{1c} $<6\cdot5\%$), being in the highest deprivation quintile (2·29 [1·16–4·52] vs the lowest quintile), and having type 2 diabetes (1·65 [1·18–2·31] vs type 1 diabetes). Variations in HbA_{1c} and LGA birthweight were associated with maternal characteristics (age, diabetes duration, deprivation, BMI) without substantial differences between maternity clinics.

Interpretation Our data highlight persistent adverse pregnancy outcomes in women with type 1 or type 2 diabetes. Maternal glycaemia and BMI are the key modifiable risk factors. No maternity clinics were had appreciably better outcomes than any others, suggesting that health-care system changes are needed across all clinics.

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Introduction

As the prevalence of diabetes continues to increase, pregnancies complicated by maternal diabetes are becoming a growing concern. Between 1996 and 2010 the incidence of both gestational diabetes and pregnancies complicated by type 1 or type 2 diabetes doubled,

affecting almost one in ten pregnant women by age 30 years.¹ Increases of 33–44% in pregnancies complicated by type 1 diabetes and of 90–111% in pregnancies complicated by type 2 diabetes have been reported in Sweden and Scotland over a 15-year period since 1998.^{2,3} Pregnancies among women with

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Research in context

Evidence before this study

We searched PubMed for articles published from database inception until July 30, 2020, without language restrictions, using the following search terms: ("diabetes mellitus" OR "diabetes") AND "pregnancy" OR "pregnancy in diabetics" AND "congenital anomaly", AND ("perinatal death") AND ("stillbirth") AND ("neonatal death"). We found that previous studies investigating diabetes in pregnant women had mostly been done 15–20 years ago and had small sample sizes, with especially few women with type 2 diabetes. The UK Confidential Enquiry into Maternal and Child Health was done in 2002–03 and identified a three-times increase in perinatal mortality and a two-times increase in the rate of congenital anomaly in pregnant women with diabetes. The enquiry data included 25 perinatal deaths (19 stillbirths, six neonatal deaths) in 652 women with type 2 diabetes, with similar rates found in women with type 1 diabetes. The researchers noted high levels of ethnic diversity, obesity, deprivation, and poor preparation for pregnancy in women with type 2 diabetes. A Scottish study done of data from 1998–2016 included 37 stillbirths in 1614 women with type 2 diabetes, again highlighting the importance of pre-pregnancy care.

Added value of this study

We compiled a national cohort of 17 375 pregnancies in 15 290 women with diabetes, of whom half had type 2 diabetes, from England, Wales, and the Isle of Man. In pregnant women with type 2 diabetes, we found higher than expected

rates of perinatal death. Third trimester HbA_{1c} of 6.5% (48 mmol/mol) or higher had an odds ratio for perinatal death of 3.93 (95% CI 2.51–6.16). Across all HbA_{1c} levels in the third trimester, pregnant women with type 2 diabetes had higher rates of perinatal death compared with women with type 1 diabetes, suggesting that more vigilant attention to antenatal glucose levels is needed in women with type 2 diabetes. In pregnant women with type 1 diabetes, HbA_{1c} of 6.5% (48 mmol/mol) or higher increased with increasing maternal BMI, and rates of preterm birth and large birthweight babies were high and increased over the 5-year study period. An above-target HbA_{1c} of 6.5% (48 mmol/mol) or higher was associated with maternal BMI and non-modifiable characteristics (maternal age, deprivation, diabetes duration) but not by maternity clinic attended. Thus, after adjustment for confounding factors, we found is no evidence of substantial clinic to clinic variation in maternal glucose levels in type 1 or type 2 diabetes.

Implications of all the available evidence

Our findings reinforce the crucial importance of maternal glycaemia as a key modifiable risk factor and the negative effect of obesity in women with either type 1 or type 2 diabetes. Improving pregnancy outcomes is a shared challenge that will probably require new approaches for optimising glycaemic control and better integration of diabetes health-care systems across primary care, paediatric and young adult clinics, and adult diabetes, obesity, and maternity services.

pre-existing diabetes are associated with preterm delivery, birthweight extremes, and increased rates of congenital anomaly, stillbirth, and neonatal death.^{4–6}

Previous studies have documented pregnancy outcomes associated with type 1 and type 2 diabetes.^{1,2,4–9} Pregnant women with type 1 diabetes tend to have higher glucose concentrations than those with type 2 diabetes and higher associated rates of preterm births and babies with large for gestational age (LGA) birthweight, most likely attributable to both maternal glycaemia and BMI.⁷ Pregnant women with type 2 diabetes tend to be older, with higher rates of obesity, greater ethnic diversity, and greater socioeconomic deprivation than those with type 1 diabetes, but they also have lower glucose concentrations, fewer preterm births, and fewer LGA birthweight babies.^{2,10,11} Nonetheless, adverse pregnancy outcomes (congenital anomaly, stillbirth, neonatal death) have been found to occur at least equivalently in pregnant women with type 1 diabetes and those with type 2 diabetes.^{2,6,12}

The different contributions of risk factors to obstetric complications and adverse pregnancy outcomes in women with type 1 or type 2 diabetes are unclear and have not been fully examined in the National Pregnancy in Diabetes (NPID) annual reports.¹³ Whether some maternity clinics more successfully achieve antenatal

glucose targets and optimal pregnancy outcomes, independent of confounding variables, is also unknown.¹⁰ Here we report an analysis of the first 5 years of data (2014–18) from the NPID audit, including over 17 000 pregnancies in women with diabetes in England, Wales, and the Isle of Man. Our aim was to identify and compare modifiable risk factors associated with pregnancy outcomes in women with type 1 and type 2 diabetes in a large national cohort and to identify particularly effective maternity clinics.

Methods

Study design and data sources

In this national, population-based, cohort study, we used data from the annual NPID audit of 172 maternity clinics across England, Wales, and the Isle of Man for the period Jan 1, 2014, and Dec 31, 2018. All UK National Health Service (NHS) maternity units in England, Wales, and the Isle of Man that provide antenatal diabetes care are expected to participate in the annual NPID audit. Healthcare professionals at each maternity clinic completed web-based manual data entry forms for all pregnant women with pre-existing diabetes (appendix p 2). Remaining data items were collected by data linkage with other systems (Hospital Episodes Statistics data, Patient Episode

For more on the NPID audit see
<http://digital.nhs.uk/npid>

See Online for appendix

	2014	2015	2016	2017	2018
Maternity clinics	150	155	172	166	164
Women	2537	3036	3297	3840	4390
Pregnancies	2553	3044	3304	3855	4400
Total pregnancy outcomes*	2584	3086	3356	3910	4465
Pregnancies ongoing after 24 weeks	2387	2866	3091	3545	4030
Livebirths after 24 weeks	2390	2868	3108	3550	4035
Congenital anomaly	100	120	155	150	180
Congenital anomalies per 1000 livebirths, terminations, and pregnancy losses after 20 weeks	39.7 (32.3–48.3)	39.2 (32.5–46.9)	47.3 (40.2–55.4)	41.7 (35.3–48.9)	44.0 (37.8–50.9)
Stillbirths	28	37	35	40	55
Stillbirths per 1000 livebirths and stillbirths	12.8 (9.6–16.7)	12.2 (8.6–16.8)	10.2 (6.9–14.3)	11.7 (8.4–15.8)	13.7 (10.3–17.8)
Babies born after 24 weeks	2390	2903	3140	3590	4090
Neonatal deaths†	14	30	31	35	40
Neonatal deaths per 1000 livebirths	7.6 (5.1–10.8)	10.0 (6.7–14.3)	10.0 (6.8–14.1)	9.6 (6.6–13.4)	10.4 (7.5–14.0)
Total registered births	2433	2908	3145	3600	4090

Data are n or rate with 95% CI in parentheses. Timelines for annual data submission together with disclosure control procedures result in small differences in numbers between the annual and 5-year dataset. We believe that the data for pregnancies that ended in termination and pregnancy losses before 24 weeks are under-reported. *Total pregnancy outcomes include pregnancy loss before 24 weeks, pregnancy terminations, livebirths, and stillbirths. Each fetus or baby is counted, so a twin pregnancy results in two pregnancy outcomes. †We believe that neonatal deaths were under-represented in type 1 diabetes in 2014 because of the small numbers compared with other years.

Table 1: Numbers of clinics, women, pregnancies, and babies included in the study, by year

Database for Wales, Core National Diabetes Audit, which extracts data from primary care service databases).

The information leaflet and consent forms used for the NPID met the Health Research Authority requirements for clinical audit and research ethics approval was not required. The requirement for individual women to provide written informed consent was removed in England from 2018, because the legal basis for the National Diabetes Audit data collection and linkage in England became a Direction from NHS England to NHS Digital according to section 254 of the Health and Social Care Act for England 2012. Individual written consent was obtained for all women in England who participated in the audit before 2018 and is still required in Wales and the Isle of Man.

Study population and outcome definitions

Our study population included women with pre-existing type 1 or type 2 diabetes who completed a pregnancy during the study period. We defined pre-existing diabetes as diabetes clinically diagnosed before pregnancy and excluded women with monogenic diabetes and those who presented with diabetes first recognised during pregnancy. Ethnicity data were obtained by data linkage with the National Diabetes Audit based on self-identified ethnicity as recorded by the woman's primary care practice. Ethnicity and Lower Super Output Area of residence for deprivation categories were obtained for 98% of participants by linking to the most recent National Diabetes Audit data for the women in the NPID. We defined gestational age according to the estimated date of delivery based on ultrasound assessment at approximately 12 weeks' gestation. We

categorised births before 37 weeks' gestation as preterm. Birthweight was adjusted for maternal BMI, ethnicity, neonatal sex, and gestational age for singleton pregnancies using customised percentiles, with LGA defined as birthweight centile above the 90th percentile and small for gestational age (SGA) defined as below the 10th percentile (Gestation Related Optimal Weight centile tool, version 8.0.4 [Gestation Network, 2019]).

Major and minor congenital anomalies were based on the International Classification of Diseases 10th edition codes identified before hospital discharge. We calculated the rate of congenital anomaly as the number of offspring (including livebirths, terminations, and pregnancy losses after 20 weeks of gestation) with one or more anomalies divided by the number of livebirths, terminations, and pregnancy losses after 20 weeks gestation. We defined stillbirth as fetal loss occurring after 24 weeks' gestation, and neonatal death as death of a liveborn infant up to 28 days after delivery.

Definitions of exposures

Maternal age was grouped as ages 15–24 years, 25–34 years, 35–44 years, and 45 years and older. Self-reported ethnicity was classified as White, Mixed, Asian, Black, unknown, other, or not available. Social deprivation was based on an index of multiple deprivation score for women whose postcode details were recorded in the National Diabetes Audit.¹⁴ Diabetes duration was categorised as less than 1 year, 1–4 years, 5–9 years, 10–14 years, and 15 years or longer. Maternal BMI was based on the first recorded weight in pregnancy and grouped as 18.5 kg/m² or less defined as underweight,

For the Gestation Network website see <https://www.gestation.net/>

For more on International Federation of Clinical Chemistry and Laboratory Medicine standard assays see <https://information.ifcccha1c.org>

18·6–24·9 kg/m² defined as normal weight, 25–29·9 kg/m² defined as overweight, 30–34·9 kg/m² defined as obese class 1, 35–39·9 kg/m² defined as obese class 2, and 40 kg/m² or more defined as obese class 3.

	Pregnancies in women with type 1 diabetes (n=8690)	Pregnancies in women with type 2 diabetes (n=8685)	p value
Age at delivery, years	30 (22–37)	34 (27–41)	..
Duration of diabetes, years	13·0 (3–25)	3·0 (0–10)	..
Weight at first antenatal clinic visit, kg	70·0 (56·3–93·0)	85·6 (62·0–117·0)	..
BMI at first antenatal care visit, kg/m ²	25·9 (21·3–33·8)	32·5 (24·8–43·0)	..
BMI category, kg/m ²			
18·5–24·9	3640/8680 (41·9%)	915/8680 (10·5%)	<0·0001
25–29·9	3060/8680 (35·3%)	2125/8680 (24·5%)	<0·0001
≥30	1975/8680 (22·8%)	5640/8680 (65·0%)	<0·0001
Race or ethnicity*			
White	7370/8645 (85·3%)	3610/8360 (43·2%)	<0·0001
Asian	335/8645 (3·9%)	2980/8360 (35·6%)	<0·0001
Black	185/8645 (2·1%)	805/8360 (9·6%)	<0·0001
Mixed	110/8645 (1·3%)	205/8360 (2·5%)	<0·0001
Other	140/8645 (1·6%)	240/8360 (2·9%)	<0·0001
Not stated or unknown	510/8645 (5·9%)	520/8360 (6·2%)	0·38
Deprivation quintile			
1 (least deprived)	1285/8220 (15·6%)	445/7780 (5·7%)	<0·0001
2	1465/8220 (17·8%)	740/7780 (9·5%)	<0·0001
3	1670/8220 (20·3%)	1315/7780 (16·9%)	<0·0001
4	1790/8220 (21·8%)	2055/7780 (26·4%)	<0·0001
5 (most deprived)	2010/8220 (24·5%)	3225/7780 (41·5%)	<0·0001
Treated hypertension	275/7460 (3·7%)	805/7825 (10·3%)	<0·0001
Markers of pregnancy preparation			
5 mg folic acid before conception	3830/8685 (44·1%)	1930/8680 (22·2%)	<0·0001
ACE inhibitor or ARB	105/8685 (1·2%)	355/8680 (4·1%)	<0·0001
Statin	130/8685 (1·5%)	460/8680 (5·3%)	<0·0001
Gestation at first contact (weeks)	7 (4–12)	9 (5–15)	..
Maternal glycaemia			
First trimester			
n	7135	6265	..
HbA _{1c} , %	7·6% (6·2–10·2)	6·9% (5·7–9·7)	..
HbA _{1c} , mmol/mol	60·0 (44·0–88·0)	51·5 (39·0–83·0)	..
HbA _{1c} <6·5% (48 mmol/mol)	1135/7135 (15·9%)	2285/6265 (36·5%)	<0·0001
Third trimester			
n	6515	5885	..
HbA _{1c} , %	6·7% (5·6–8·2)	6·0 (5·2–7·3)	..
HbA _{1c} , mmol/mol	50 (38–66)	42 (33–56)	..
HbA _{1c} <6·5% (48 mmol/mol)	2715/6515 (41·7%)	4335/5885 (73·7%)	<0·0001
Obstetric outcomes			
n	7825	7815	..
Gestational age at delivery, weeks	37 (34–38)	38 (35–39)	..
Preterm delivery at <37 weeks	3325/7825 (42·5%)	1825/7815 (23·4%)	<0·0001
Preterm delivery at <34 weeks	720/7825 (9·2%)	395/7815 (5·1%)	<0·0001
Infant birthweight percentiles†			
Large for gestational age (>90th percentile)	4095/7845 (52·2%)	2065/7885 (26·2%)	<0·0001
Small for gestational age (<10th percentile)	420/7845 (5·4%)	1115/7885 (14·1%)	<0·0001

(Table 2 continues on next page)

Antenatal glucose measurements were obtained from the first and last HbA_{1c} values recorded during pregnancy. HbA_{1c} was measured in routine care settings using International Federation of Clinical Chemistry and Laboratory Medicine standard assays. Target glycaemic level during pregnancy was defined as HbA_{1c} of less than 6·5% (48 mmol/mol), in accordance with National Institute for Health and Clinical Excellence (NICE) guidelines.¹⁵ We considered 5 mg of folic acid taken before conception, gestational age less than 10 weeks at first antenatal contact, and not taking potentially harmful medications (angiotensin-converting enzyme inhibitor, angiotensin-II receptor blockers, statins) as markers of pre-pregnancy care. Treated hypertension and taking either angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, or statins was categorised as a comorbidity. Total pregnancy outcomes included pregnancy loss before 24 weeks, pregnancy terminations, livebirths, and stillbirths. Each fetus or baby was counted, so a twin pregnancy was counted as two pregnancy outcomes.

Statistical analysis

The statistical analysis plan for this study was agreed at a face-to-face meeting of the NPID advisory group in January, 2020. The plan was outlined in the 2018 NPID methodology report (appendix pp 4–6).^{16,17} We aimed to identify and compare modifiable risk factors associated with adverse pregnancy outcomes in women with type 1 and type 2 diabetes and to identify effective maternity clinics. The hypothesis of interest was to determine the contribution of modifiable risk factors (HbA_{1c} levels, BMI, pre-pregnancy care, maternity clinic attended) to pregnancy outcomes after adjustment for confounding maternal characteristics (age, ethnicity, deprivation, diabetes type and duration, comorbidities). We also explored the effect of clinic-to-clinic variations on glycaemic levels and obstetric complications (preterm delivery, LGA birthweight) to identify whether any maternity clinics were particularly effective.

When examining obstetric complications and adverse pregnancy outcomes (congenital anomaly, stillbirth, neonatal death), we used all data collected during the 5-year study period. We calculated associations between maternal factors and perinatal deaths using a regression model, including factors of diabetes type and duration, maternal age, BMI, deprivation quintile, first trimester HbA_{1c}, folic acid use preconception, use of potentially harmful medications, and third trimester HbA_{1c}. For congenital anomaly, third trimester HbA_{1c} was omitted because anomalies develop during early pregnancy. We ran separate models for pregnancies with type 1 and type 2 diabetes where applicable and we did both univariate and multivariate analyses; only factors that were significant in univariate analyses were retained in multivariate analyses.

On examining the year-to-year data, we noticed that neonatal deaths in 2014 among women with diabetes were

substantially lower than in other years and as such might have been under-reported in 2014. Therefore, we did a post-hoc analysis to compare the rate of neonatal deaths in pregnancies with type 1 and type 2 diabetes during 2015–18.

To explore the effect of maternity clinic attended on first and third trimester target HbA_{1c}, preterm singleton birth and LGA birthweight we used logistic regression models with the model outcomes and odds ratios presented as funnel plots (appendix p 6). The expected number of women with target HbA_{1c}, preterm births, and LGA birthweight babies attending each maternity clinic were obtained from the logistic regression models. We used data collected during 2017–18, when audit participation was stable (166 clinics in 2017, 164 clinics in 2018) to ensure as homogenous a group as possible. We used 5 years of data (2014–18) to build the models and then we ran the models against 2 years of data (2017–18) to predict expected outcomes. We then compared these expected outcomes with the actual outcomes over 2 years to give a standardised ratio. To explore the effect of maternal characteristics on attainment of target glycaemia, we ran separate logistic regression models for type 1 and type 2 diabetes to produce odds ratios indicating any association between maternal age, diabetes duration, BMI, ethnicity and deprivation categories, and markers of pre-pregnancy care (5 mg preconception folic acid, taking potentially harmful medications, gestational age at first antenatal contact). These odds ratios are presented as forest plots (appendix p 6). For data protection of potentially sensitive information in the clinic-to-clinic regression models, we excluded clinics with fewer than five outcome events.

To maintain patient confidentiality and the transparency of reporting, we used standard methods of suppression across all National Diabetes Audits. Zeros are reported (0, 1, 20, 40, 50, and so on) and all numbers are rounded to the nearest five, unless the number is one or seven, in which case it is rounded to five. Rounded numbers were used to calculate proportions and at a national level this method leads to almost no difference in the resultant proportions reported.

The audit submission deadlines are in February for pregnancies ending until December 31. Pregnancies which occurred during the calendar year but were submitted after the annual submission deadline are included in the overall 5-year 2014–18 data.

Variables that were not normally distributed are reported as median (IQR or 10–90th percentile) and normally distributed variables are reported as mean (SD). We did univariate analyses comparing the proportions between groups using Z tests and used *t* tests for comparing continuous variables.

We analysed all available data with no imputation of missing data. We defined *p* values of less than 0.05 as significant. We used SAS Enterprise Guide (version 7.1) for all analyses and we used Poisson distribution to obtain 95% CIs for the rate and prevalence ratios.

	Pregnancies in women with type 1 diabetes (n=8690)	Pregnancies in women with type 2 diabetes (n=8685)	<i>p</i> value
(Continued from previous page)			
Neonatal care admission			
Special care unit	2470/8060 (30.6%)	1440/8035 (17.9%)	<0.0001
Intensive care unit	1025/8060 (12.7%)	630/8035 (7.8%)	<0.0001
Adverse pregnancy outcome			
Congenital anomaly‡	..	..	0.17
n (%)	365/8150 (4.5%)	330/8150 (4.0%)	..
Rate per 1000 births	44.8	40.5	..
Stillbirth	..	..	0.072
n (%)	85/8150 (1.0%)	110/8150 (1.3%)	..
Rate per 1000 livebirths and stillbirths	10.4	13.5	..
Neonatal death	..	..	0.013
n (%)	60/8065 (0.7%)	90/8035 (1.1%)	..
Rate per 1000 livebirths	7.4	11.2	..

Data are n (%), n/N (%), rate per 1000 births, or median (10–90th percentile). All *p* values were calculated using a two-sample Z test. All patient-level data are reported to the nearest five patients, and any differences between the total denominator and the summed numerators has been accounted for in our statistical methods. Disclosure control has been applied to mitigate the risk of patient identification so overall values for pregnancies during the 5-year 2014–18 study period might slightly differ from the annual values provided elsewhere in the Article. ACE=angiotensin converting enzyme. ARB=angiotensin-II receptor blockers. *Maternal ethnic groupings used in National Pregnancy in Diabetes analyses were White (British, Irish, White Gypsy/ Irish traveller/White any other background), Mixed (White and Black Caribbean, White and Black African, White and Asian, any other mixed background), Black (Caribbean, African, any other Black background), Asian (Indian, Pakistani, Bangladeshi, any other Asian background), and other (Chinese, Arab, any other ethnic group). †These data are applicable for singleton pregnancies; birthweight was adjusted for maternal BMI, ethnicity, neonatal sex, and gestational age for singleton pregnancies using the Gestation Related Optimal Weight centile tool (version 8.0.4). ‡Includes major and minor congenital anomalies identified on the basis of the international Classification of Diseases 10th edition codes before hospital discharge.

Table 2: Maternal and neonatal characteristics and pregnancy outcome, by diabetes type

Role of the funding source

There was no funding source for this study.

Results

In table 1, we show the annual audit data for 17156 pregnancies over 2014–18, with 17401 pregnancy outcomes (ie, including twin pregnancies, pregnancy losses before 24 weeks, terminations, livebirths, and stillbirths). For this 5-year study, we report data for 17375 pregnancy outcomes among women with type 1 diabetes (8690 [50.0%]) or type 2 diabetes (8685 [50.0%]). Among women with type 1 diabetes, median age at delivery was 30 years (10–90th percentile 22–37) and median duration of diabetes was 13 years (3–25). Among women with type 2 diabetes, median age at delivery was 34 years (27–41) and median duration of diabetes was 3 years (0–10; table 2). Our database included 700 congenital anomalies and 345 perinatal deaths (195 stillbirths, 150 neonatal deaths) among 15 290 pregnant women with diabetes. The number of NHS maternity clinics that participated across the 5-year period ranged from 150 to 172 (table 1). There was some variation in participating clinics, with the mean number of pregnancies per clinic in 2018 being 27. However, 20 of 164 clinics had fewer than ten pregnancies and four clinics had more than 80 pregnancies.

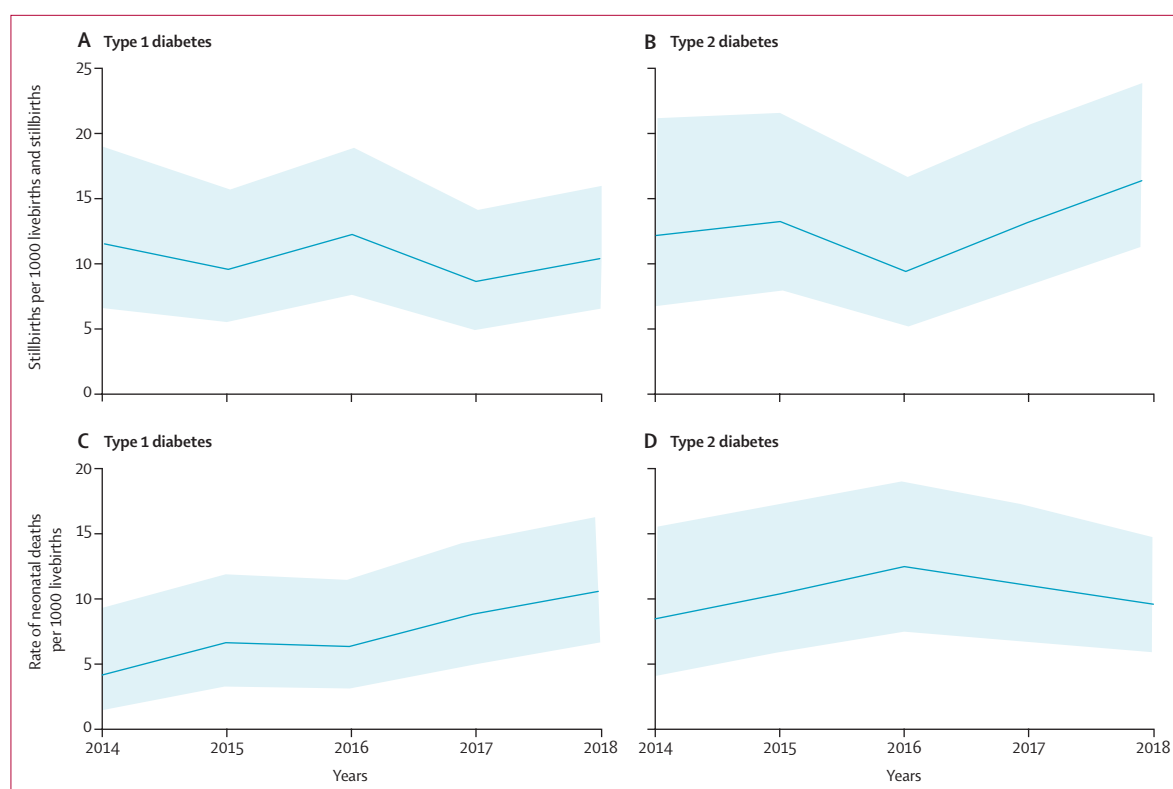


Figure 1: Perinatal death rates in type 1 and type 2 diabetes

Stillbirth rate per 1000 livebirths and stillbirths in pregnant women with type 1 diabetes (A) and in pregnant women with type 2 diabetes (B). Neonatal death rate per 1000 livebirths in pregnant women with type 1 diabetes (C) and in pregnant women with type 2 diabetes (D). The solid line indicates the estimate, with the shaded area showing the 95% CI.

Additionally, 13 clinics submitted data for the first time in 2017–18 and an increase in pregnancies was reported in 2017 and 2018, both before and after the requirement for written consent was removed in England. Furthermore, we noted a small number of medically implausible combinations of values present in the data, such as 110 (1.3%) of 8585 women being recorded as having type 1 diabetes not being on insulin.

As expected, pregnant women with type 2 diabetes were older and had a shorter duration of diabetes compared with women with type 1 diabetes (table 2). More pregnant women with type 2 diabetes lived in areas of deprivation, were of Asian or Black ethnicity, and were overweight or obese than those with type 1 diabetes. Among women with type 1 diabetes, about 20% more pregnancies than expected (according to general population conception statistics¹⁸) occurred in women with greater deprivation. The socioeconomic gradient in pregnancies was particularly pronounced in women with type 2 diabetes, with more than 40% living in the most deprived quintile and less than 6% in the least deprived quintile. Among those with available ethnicity and deprivation quintile data, women of Asian or Black ethnicity comprised 65 (5%) of 1175 pregnancies among women with type 1 diabetes in deprivation

quintile 1 (least deprived) and 255 (14%) of 1595 in quintile 5 (most deprived); by contrast, the proportions of pregnant women of Asian or Black ethnicity with type 2 diabetes were 160 (38%) of 420 in the least deprived quintile and 1770 (58%) of 3050 in the most deprived (appendix p 7). Notably, the proportion of missing data for ethnicity and deprivation was approximately 0.5–5% in women with type 1 diabetes and 5–10% in women with type 2 diabetes.

Pregnant women with type 2 diabetes presented for antenatal care approximately 2 weeks later than women with type 1 diabetes, and had higher rates of treatment with antihypertensive and lipid-lowering medications and lower rates of use of 5 mg preconception folic acid (table 2). They also had lower HbA_{1c} levels and were more likely than women with type 1 diabetes to achieve the NICE glycaemic target of HbA_{1c} of less than 6.5% (48 mmol/mol) both early and late in the pregnancy. Before pregnancy, 5580 (64.9%) of 8595 women with type 2 diabetes were taking metformin and only 1590 (18.5%) of 8595 women with type 2 diabetes were taking insulin (appendix p 8). No changes in folic acid use were seen in women with either type of diabetes over the 5-year study period but a reduction was seen in potentially harmful medication use in women with type 2 diabetes but not in those with type 1 diabetes

(appendix p 9). Insulin pump therapy was used by 1890 (22.4%) of 8440 women with type 1 diabetes, increasing from 250 (19.3%) of 1295 in 2014 to 505 (24.8%) of 2035 in 2018 (appendix p 10). No changes were seen in maternal glycaemia over the 5-year study period in women with type 1 or those with type 2 diabetes (appendix p 11).

Overall, rates of preterm births, LGA babies, and neonatal care admissions were all higher in women with type 1 diabetes, whereas rates of SGA babies were higher in women with type 2 diabetes (table 2). In pregnant women with type 1 diabetes, the rates of preterm births and LGA babies increased over the 5-year study period. No changes were seen in the rates of preterm births or LGA babies in women with type 2 diabetes (appendix p 12).

Pregnant women with type 2 diabetes had a similar rate of stillbirth to pregnant women with type 1 diabetes, and a significantly higher rate of neonatal death (table 2, figure 1). Overall, an increase in the number of stillbirths was seen from 2014–18, but there was no significant change in the overall stillbirth rate (data not shown). The rates of stillbirth in pregnant women with type 1 diabetes were unchanged during 2014–18, but rates of stillbirth in pregnant women with type 2 diabetes appeared to increase from 2016 to 2018). In a post-hoc analysis, the increased rate of neonatal death in pregnant women with type 2 diabetes compared with women with type 1 diabetes persisted after exclusion of data from 2014 (in 2015–18: 8.1 per 1000 livebirths in type 1 diabetes vs 11.7 per 1000 livebirths in type 2 diabetes; $p=0.036$). No difference was seen in the prevalence of congenital anomaly between women with type 1 versus type 2 diabetes (table 2). Cardiac anomalies were the most common type of congenital malformation in women with both diabetes types, with more digestive system and chromosomal anomalies in pregnant women with type 2 diabetes (appendix p 13). Pregnant women with type 2 diabetes had higher rates of perinatal death across all third trimester HbA_{1c} categories below 10% (86 mmol/mol; figure 2).

Among the entire cohort, independent risk factors for perinatal death were third trimester HbA_{1c} level of 6.5% (48 mmol/mol) or higher (odds ratio [OR] 3.06, 95% CI 2.16–4.33), living in the highest deprivation quintile (2.29, 1.16–4.52), and having type 2 diabetes rather than type 1 diabetes (1.65, 1.18–2.31; appendix p 14). When examined according to type of diabetes, only third trimester HbA_{1c} level of 6.5% (48 mmol/mol) or higher remained significantly associated with perinatal death in both pregnant women with type 1 (OR 2.47, 1.49–4.08) or type 2 diabetes (3.93, 2.51–6.16).

For congenital anomaly, only first trimester HbA_{1c} level of 6.5% (48 mmol/mol) or higher (OR 1.70, 95% CI 1.35–2.14) and not taking 5 mg folic acid preconception (1.31, 1.08–1.58) were significant independent risk factors among the entire cohort (appendix p 15). When examined by type of diabetes, an HbA_{1c} level of 6.5% (48 mmol/mol) or higher remained significantly associated with congenital

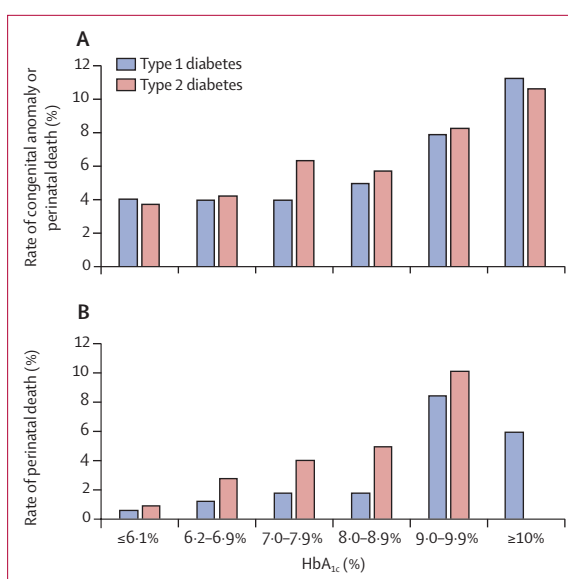


Figure 2: Adverse pregnancy outcome by early (A) and late (B) maternal HbA_{1c} level, in pregnancies among women with type 1 or type 2 diabetes. Rate of congenital anomaly or perinatal death (stillbirth and neonatal death) by first trimester HbA_{1c} level (A) and rate of perinatal death (stillbirth and neonatal death) by third trimester HbA_{1c} level (B). The HbA_{1c} categories are 6.1% (43 mmol/mol) or less, 6.2–6.9% (44–52 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol), 9.0–9.9% (75–85 mmol/mol), and 10% (86 mmol/mol) or higher.

anomaly in pregnant women with type 1 (OR 1.79, 95% CI 1.2–2.7) and those with type 2 diabetes (1.64, 1.23–2.21), and the association with not taking folic acid preconception was also significant for pregnant women with type 1 diabetes (1.30, 1.02–1.65; appendix p 15).

Variation in attainment of target HbA_{1c} level (ie, <6.5% [48 mmol/mol]) in early pregnancy was more dependent on maternal characteristics than maternity clinic attended. Specifically, after adjustment for maternal age, ethnicity, deprivation, BMI, and type and duration of diabetes, we found minimal variation between clinics, with most being within the expected distribution (figure 3). In pregnant women with type 1 diabetes, those who had HbA_{1c} levels within the target range were generally older (35–44 years) and had shorter diabetes duration (figure 4). Among pregnant women with type 1 diabetes, younger women (≤24 years), those with higher deprivation, those with longer diabetes durations, and those with higher BMI were less likely to have target HbA_{1c} levels. In women with type 2 diabetes, longer diabetes duration, higher BMI, highest level of deprivation, and Black or Asian ethnicity were associated with not achieving target HbA_{1c} levels (figure 4).

Likewise, HbA_{1c} in the third trimester was more strongly associated with maternal characteristics than maternity clinic attended (figure 3). First trimester HbA_{1c} was the key predictor for third trimester HbA_{1c} in both type 1 and type 2 diabetes (appendix p 16), with diabetes duration also contributing. We found a direct association between

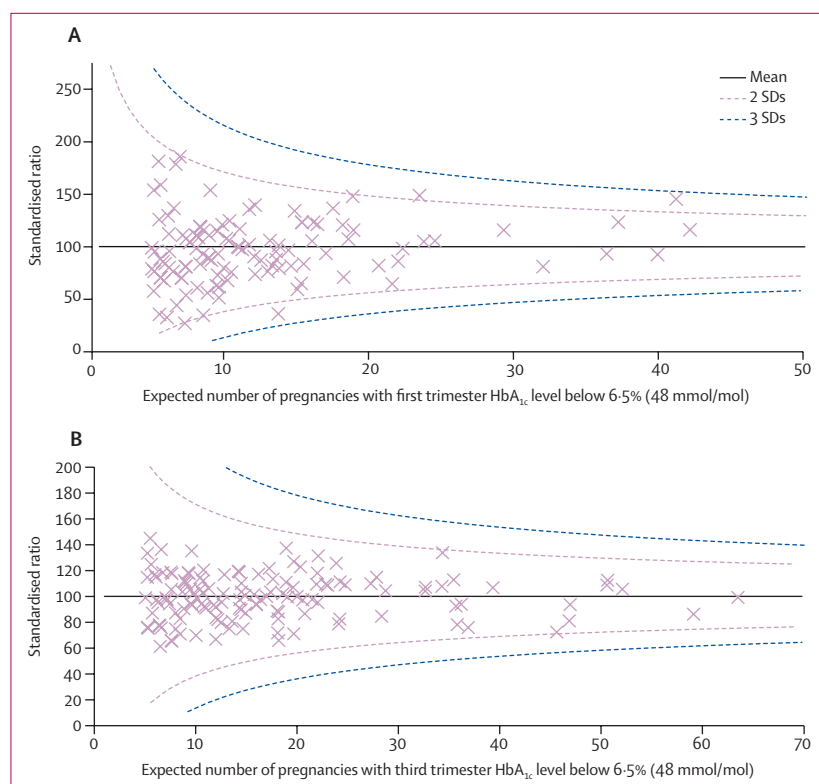


Figure 3: Variation between clinics in attainment of the target glycaemic level

(A) Proportion of women with target HbA_{1c} in the first trimester; model c statistic is 0.70. (B) Proportion of women with target HbA_{1c} in the third trimester; model c statistic is 0.82. The funnel plots show the standardised ratio for HbA_{1c} levels below 6.5% (48 mmol/mol) during 2017–18, adjusted for maternal age, diabetes type, duration of diabetes, ethnicity, deprivation, and HbA_{1c} and BMI at the first antenatal appointment. Crosses show the number of pregnancies with HbA_{1c} below 6.5% (48 mmol/mol) for each clinic. Clinics with an expected number of outcomes of five or fewer were excluded.

maternal BMI in the overweight (BMI 25–29.9 kg/m²) and obese class 1 (30–34.9 kg/m²) and third trimester HbA_{1c} levels above the target range in women with type 1 diabetes. Maternal BMI did not improve the fit of the model for type 2 diabetes (appendix p 16).

We identified some differences across maternity clinics in the rate of preterm births (before 37 weeks' gestation), with six clinics being two SDs above the expected average rate (figure 5). Factors associated with preterm birth in pregnant women with type 1 diabetes were younger maternal age (≤ 24 years), higher deprivation, longer diabetes duration, and higher first and third trimester HbA_{1c} (appendix pp 17–18). Higher first and third trimester HbA_{1c} and longer diabetes duration were also associated with preterm birth among pregnant women with type 2 diabetes. Among women with type 2 diabetes, Black and Asian women were less likely to have preterm births than those of other ethnicities.

Variation in LGA birthweight was strongly associated with maternal characteristics, with no evidence for substantial variation between maternity clinics (figure 5). Factors associated with having an LGA birthweight baby

in pregnant women with type 1 diabetes were not taking potentially harmful medications (reflecting less maternal comorbidity) and higher first and third trimester HbA_{1c} levels (appendix p 19). Also for pregnant women with type 1 diabetes, being aged 35–44 years and presenting for antenatal care after 10 weeks' gestation were associated with reduced risk for LGA birthweight. For pregnant women with type 2 diabetes, an HbA_{1c} level of 6.5% (48 mmol/mol) or higher, especially during the third trimester, was associated with LGA birthweight, with those aged 35–44 years less likely to have an LGA birthweight baby compared with younger women. Presenting for antenatal care after 10 weeks' gestation did not improve the fit of the model for type 2 diabetes.

Discussion

In pregnant women with type 2 diabetes, we found higher than expected rates of perinatal death. HbA_{1c} level of 6.5% (48 mmol/mol) or higher in the third trimester was the dominant risk factor for perinatal death, both in women with type 1 diabetes and those with type 2 diabetes. In pregnant women with type 1 diabetes, above-target HbA_{1c} was common and increased with maternal overweight and obesity. The rates of preterm birth and LGA birthweight babies were increased in type 1 diabetes compared with type 2 diabetes and continued to increase over the 5-year study period. We did not identify any clinics that were significantly more effective in achieving optimal glycaemic or neonatal birthweight outcomes.

To our knowledge, this is the largest and most detailed contemporary dataset of pregnant women with diabetes. We included 200 pregnancies that resulted in perinatal deaths among pregnant women with type 2 diabetes (110 stillbirths, 90 neonatal deaths) and 145 among pregnant women with type 1 diabetes (85 stillbirths, 60 neonatal deaths). Previous studies included fewer pregnant women, especially those with type 2 diabetes.⁶ Investigators of a Scottish study reported pre-pregnancy HbA_{1c} and BMI as key risk factors associated with stillbirth in women with type 2 diabetes.¹¹ We found that after adjusting for these and other risk factors, an above target HbA_{1c} level during the third trimester was associated with an OR for perinatal death in pregnant mothers with type 2 diabetes of 3.93 (95% CI 2.51–6.16). We also found that across all third trimester HbA_{1c} categories, pregnant women with type 2 diabetes had higher rates of perinatal death than those with type 1 diabetes.

Studies in general maternity populations have showed that rates of stillbirth are increased at birthweight extremes, and that growth-restricted pregnancies have the highest risk.^{19–21} Scottish data confirmed these findings in pregnancies among women with diabetes, showing a six-times increased risk of stillbirth in small birthweight babies and a two-times increased risk in large birthweight babies.¹¹ The higher rates of SGA

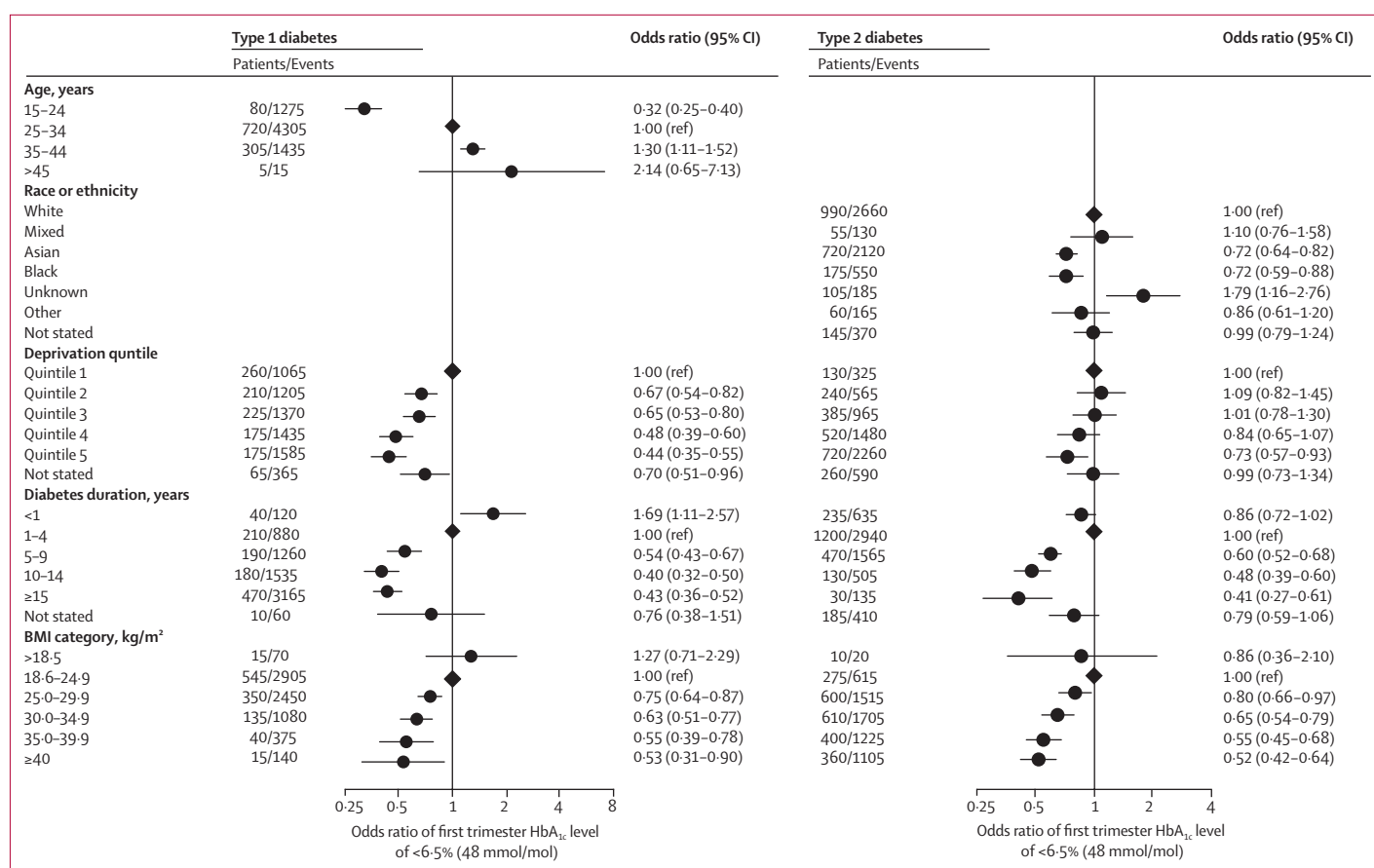


Figure 4: Effect of maternal characteristics on attainment of target glycaemic control

Data are for participants who had HbA_{1c} levels of less than 6.5% (48 mmol/mol) in the first trimester. Separate multivariate analyses were run for type 1 and type 2 diabetes. Only factors that were significant in univariate analyses were retained in the multivariate analyses; maternal age category did not improve the model fit in type 2 diabetes; ethnicity did not improve the model fit in type 1 diabetes.

babies among mothers with type 2 diabetes probably contributed to the higher odds of perinatal death in our cohort.

LGA birthweight remains the most common complication of pregnancy in women with type 1 or type 2 diabetes. Consistent with Scottish data, where the rate of LGA birthweight babies increased among pregnant women with type 1 diabetes during 1998–2013,² we also found a temporal increase over the 5-year study period (2014–18). The reasons for this increasing trend in LGA birthweight are unclear. Although our findings support the known association with higher HbA_{1c} levels, we found no association between LGA babies and maternal obesity, possibly because we used customised growth percentiles and because of the interaction between higher BMI and glycaemia. Interestingly, we found no deterioration in maternal glycaemia over the study period, unlike what has been reported in other cohorts.²² Women not taking antihypertensive or lipid-lowering treatments had an increased risk of LGA birthweight babies, suggesting that in addition to glycaemia, maternal comorbidities

that affect placental vascular function are important. We also found that no maternity clinics were significantly more effective with respect to achievement of optimal birthweight outcomes.

Surprisingly few women with type 2 diabetes were taking insulin (18.5%) or 5 mg folic acid (22%) before pregnancy, suggesting that despite the increased risk of adverse pregnancy outcomes associated with type 2 diabetes having been known for two decades,⁶ type 2 diabetes is still considered a less serious condition than type 1 diabetes. Almost two-thirds of women with type 2 diabetes were taking metformin, showing health-care engagement but missed opportunities for improving pregnancy preparation. Previous studies have confirmed that pre-pregnancy programmes are effective, but that women with type 2 diabetes are less likely than women with type 1 diabetes to attend these programmes.^{23,24} Qualitative studies suggest that unhelpful beliefs about age, obesity, and fertility need to be addressed for more effective implementation of pre-pregnancy care in women with type 2 diabetes.²⁵

High HbA_{1c} was associated with increased rates of adverse outcome in both pregnant women with type 1

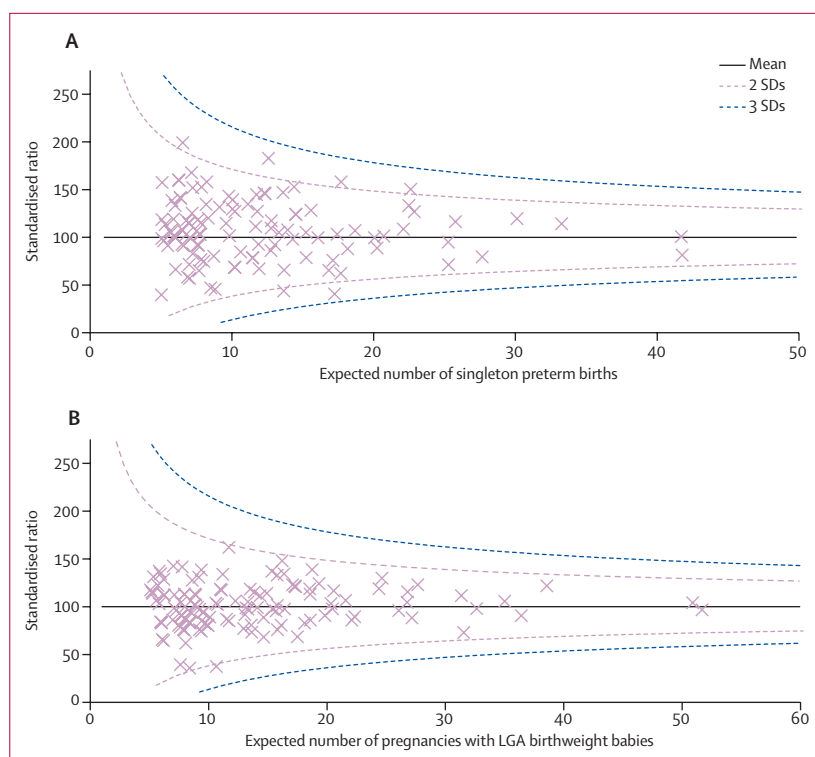


Figure 5: Variation between maternity clinics in rates of singleton preterm births (A) and LGA babies (B)
 (A) Funnel plot of the range of standardised ratios for the rate of singleton preterm births during 2017–18, adjusted for type and duration of diabetes, maternal age, deprivation, ethnicity, gestational age at first contact, first and third trimester HbA_{1c}, congenital anomaly, and presence of LGA birthweight. Six clinics had standardised ratios that were outside the 2 SDs. Clinics with an expected number of outcomes of five or fewer were excluded. Model c statistic is 0.71. (B) Funnel plot of the range of standardised ratios for the rate of LGA birthweight babies (>90th percentile) during 2017–18, adjusted for maternal age, diabetes type, duration of diabetes, first and third trimester HbA_{1c}, medications at conception, and gestational age at first contact. Maternal BMI was not retained in the regression model as it did not add sufficient statistical power. Crosses show number of pregnancies with singleton preterm birth or LGA birthweight babies for each clinic. Clinics with an expected number of outcomes of five or fewer were excluded. Model c statistic is 0.71. LGA=large for gestational age.

diabetes and those with type 2 diabetes. A third of women with type 1 diabetes were overweight and almost a quarter were obese, which was adversely associated with attainment of target HbA_{1c}. Women with type 1 diabetes might require additional dietary and psychosocial support to optimise their weight to achieve glucose targets during pregnancy. Younger women with type 1 diabetes (aged 15–24 years) were most at risk for entering pregnancy with high HbA_{1c}, suggesting unplanned pregnancies and implying that increased attention to contraception provision across paediatric and young adult diabetes services might be beneficial.

The women in our study had a median duration of type 2 diabetes of 3 years, suggesting that potential for diabetes remission with intensive weight management.^{26,27} Many women with type 2 diabetes (between a third and half) will have had at least one previous pregnancy complicated by gestational diabetes.²⁸ An urgent need exists to accelerate diabetes prevention programmes that proactively engage women with gestational diabetes.²⁹

The paucity of clinic-to-clinic variation in attainment of target glycaemic levels suggests that changes to maternity diabetes care are required for all clinics to achieve optimal glycaemic control across a broader range of women. Interventions such as the introduction of continuous glucose monitoring might improve antenatal glucose concentrations and neonatal health outcomes in mothers with type 1 diabetes.³⁰ Many maternal characteristics (younger age, higher deprivation, longer diabetes duration) associated with higher HbA_{1c} among pregnant women with type 1 diabetes are not modifiable, so targeting dietary, educational, and technological resources, such as automated insulin delivery, towards women with the highest risk profiles might be needed.³¹ Women with type 2 diabetes need culturally appropriate pre-pregnancy and antenatal care. Additionally, input from multidisciplinary obesity services and tighter glucose targets, which are potentially achievable using continuous glucose monitoring systems, might be applicable.³² Further evaluation of the effect of metformin on SGA birthweight and stillbirth is needed.³³

A major strength of our study is the use of a detailed, national cohort of pregnant women with diabetes with high case ascertainment across maternity units. The large sample, which included 345 perinatal deaths, yielded robust estimates for serious adverse pregnancy outcomes. Additionally, data from more than 150 maternity clinics allowed a depth of analysis not previously possible, including the development of national average rates for attainment of glycaemic targets in pregnancy and obstetric complications.

The limitations of our study include that our list of dataset variables was limited to key pregnancy outcomes and does not include data for diabetes complications. We acknowledge data quality issues of real-world clinical data, especially for diabetes diagnosis and medication use, and the risk of data entry error especially for diabetes diagnosis and medication use; however these issues only affected a small number (1.3%) of pregnancies and are unlikely to affect our results. Also, we cannot determine the effect of the continued requirement for participant consent to be included in the NPID in Wales and the Isle of Man, but do not expect it to affect our findings. Other limitations include data missingness, with fewer HbA_{1c} measurements in women with type 2 diabetes than in women with type 1 diabetes, and the absence of information on gestational weight gain. The observational nature of our analyses precludes causal inferences.

Our findings have implications for research, health-care policy, and clinical practice. Our results can serve as a reference point from which to judge the effectiveness of future interventions to optimise pregnancy outcomes in women with type 1 or type 2 diabetes. They highlight ongoing, unchanged, adverse pregnancy outcomes in women type 1 diabetes and increased perinatal deaths in women type 2 diabetes. Improving pregnancy outcomes

is a shared challenge that requires better integration of diabetes health-care systems across primary care, paediatric and young adult clinics, and adult diabetes, obesity, and maternity services.

Contributors

HRM, CH, and JO'K developed the study concept and design. JO'K and PK analysed the data. HRM drafted the report with key input from JO'K and BY. All authors critically reviewed the report for important intellectual content and approved the submitted version. HRM, KOK, and PK accessed and verified the underlying study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

National Pregnancy in Diabetes (NPID) advisory group

Emily Angiolini, Emma Barron, Ruth Bell, Alex Berry, Cher Cartwright, Sophie Colling, Matt Curley, Anna Duggan, Laura Fargher, Melissa Flanagan, Angela Pinnock, Lucy Shonegeval, Nickey Tomkins, Liz Draper, Jenny Kurinczuk, Jane Hawdon, Richard Holt, Di Todd, and Mike Maresh.

Declaration of interests

HRM sits on a scientific advisory board for Medtronic (insulin pump manufacturer). EMS reports personal fees from Abbott Diabetes Care and Lilly Diabetes, unrelated to the present work. JV is National Clinical Director for Diabetes and Obesity at NHS England and NHS Improvement. BY is clinical lead for the National Diabetes Audit and a trustee of Diabetes UK. All other authors declare no competing interests.

Data sharing

De-identified participant data will be made available for clinical research purposes following approval of a data access request submission. Inquiries can be directed to the NPID team at npid@nhs.net.

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