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Risk and recurrence of serious adverse outcomes in the first and second pregnancies of women with pre-existing diabetes

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ABSTRACT

Objective

Women with pre-existing (type 1 or type 2) diabetes experience an increased risk of serious adverse pregnancy outcomes. It is not known, however, how these risks change between the first and second pregnancy, and whether there is an increased risk of recurrence. This study describes the absolute risks and recurrence of serious adverse pregnancy outcomes in 220 women with pre-existing diabetes.

Research Design and Methods

440 pregnancies occurring in 220 women with pre-existing diabetes who delivered successive singleton pregnancies in the North of England during 1996-2008 were identified from the Northern Diabetes in Pregnancy Survey (NorDIP). Predictors of serious adverse outcome were estimated by competing-risks regression.

Results

67 (30.5%) first pregnancies ended in serious adverse outcome, including 14 (6.4%) with congenital anomalies and 54 (24.1%) additional fetal or infant deaths. 37 (16.8%) second pregnancies ended in serious adverse outcome – half the rate among first pregnancies (p=0.0004), including 21 (9.5%) with congenital anomalies and 16 (7.3%) additional fetal or infant deaths. Serious adverse outcomes in the second pregnancy occurred twice as frequently in women who experienced a previous adverse outcome than those who did not (26.9% vs 12.4%, p=0.004), but previous adverse outcome was not associated with preparation for the following pregnancy.

Conclusions

Serious adverse outcomes are less common in the second pregnancies of women with pre-existing diabetes, though the risk is comparable in those whose first pregnancy ends in adverse

outcome. Reducing the risk of recurrence may require more support in the immediate period following an adverse pregnancy outcome.

ABBREVIATIONS

A1C	Glycated haemoglobin
ADA	American Diabetes Association
aSHR	Adjusted Subdistribution hazard ratio
BMI	Body mass index
CI	Confidence interval
IMD	Index of Multiple Deprivation
IQR	Interquartile range
LGA	Large for gestational age
LOWESS	Locally-weighted scatterplot smoothing
NICE	National Institute for Health and Care Excellence
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey
PMS	Perinatal Mortality Survey
PR	Prevalence Ratio
RR	Relative risk
SGA	Small for gestational age
SHR	Subdistribution hazard ratio

Serious adverse pregnancy outcomes, such as miscarriages, stillbirths, and congenital anomalies, are associated with significant psychological distress and parents who experience such events are often very anxious about their chances of recurrence.(1; 2) In the general population, the risks of miscarriage, stillbirth, and congenital anomaly in the second pregnancy are approximately two times greater in women who experienced the same event in their first pregnancy,(3-5) although in the absence of a clear genetic or physiological cause the absolute risks remain low.

Despite significant improvements in pre-conception and antenatal care, women with pre-existing (type 1 or type 2) diabetes still experience substantially increased risks of serious adverse pregnancy outcomes, including higher risks of miscarriages,(6) congenital anomalies,(7) stillbirths,(8) and infant deaths.(8) Little is known, however, about the absolute risks of these outcomes in first and subsequent pregnancies specifically, and whether women with diabetes experience the same patterns of recurrence as the general population. Suboptimal glycemic control at the start of pregnancy has previously been shown to explain a large proportion of the excess risk of congenital anomalies and fetal and infant death.(7; 8) However, the extent that inter-pregnancy changes in glycemic control can modify the risk in subsequent pregnancies has not been demonstrated.

This study used unique data from the UK's longest-running survey of women with pre-existing diabetes to estimate: 1) preparation for, and change in preparatory behavior between, the first and second pregnancies of 220 women with pre-existing diabetes, including the effect of adverse outcome in the first pregnancy 2) risk of, change in risk of, and predictors of, serious adverse outcome in each pregnancy, including the effect of adverse outcome in the first pregnancy.

RESEARCH DESIGN AND METHODS

Population and sample

The North of England is a distinct geographical region of the UK with a stable population of three million and approximately 32,000 births per year (Supplementary Figure 1).

The sample comprises 440 pregnancies occurring in 220 women with pre-existing diabetes who completed two successive singleton pregnancies, at any gestational age - regardless of pregnancy outcome - in the North of England between 01 January 1996 and 31 December 2008.

Definitions

Miscarriages are the spontaneous loss of a fetus at ≤23 weeks' gestation. *Stillbirths* are the delivery of a fetus showing no signs of life at ≥24 completed weeks' gestation. *Spontaneous fetal deaths* comprise miscarriages and stillbirths. *Infant deaths* are the death of a live-born infant aged ≤1 year. *Congenital anomalies* are any major chromosomal, genetic, or structural abnormality, as defined by the European Surveillance of Congenital Anomalies (EUROCAT) criteria.(9) *Terminations of pregnancy* are the induced loss of a fetus for therapeutic or elective reasons. *Serious adverse outcomes* comprise congenital anomalies, spontaneous fetal deaths, and infant deaths.

Data sources

The Northern Diabetes in Pregnancy Survey (NorDIP) records details of all pregnancies occurring in women resident in the region and diagnosed with any type of diabetes at least six months before conception. Pregnancies in women with gestational diabetes are not included. Clinicians working within the region's nine maternity units collect and supply the NorDIP with information on a range of clinical and socio-demographic variables.(10)

All pregnancies affected by congenital anomaly (regardless of pregnancy outcome) were identified from the Northern Congenital Abnormality Survey (NorCAS).(11) All stillbirths and infant deaths were identified from the population-based Northern Perinatal Mortality Survey (PMS).(12)

Variables

All available variables with a hypothesized influence on serious adverse pregnancy outcome were obtained from the NorDIP for analyses. Maternal ethnicity, diabetes type, pre-pregnancy history of 'clinically diagnosed' nephropathy, neuropathy, and retinopathy, attendance of pre-conception care, pre-conception folic acid supplementation (self-reported), smoking during pregnancy (self-reported), and whether the first antenatal appointment occurred before ten weeks' gestation were all analyzed as dichotomous variables. Socioeconomic circumstances were estimated from the Index of Multiple Deprivation (IMD, an area-based measure of disadvantage derived from the mother's postcode at birth),(13) and analyzed in tertiles of ranks. Year of delivery, maternal age at delivery, duration of diabetes, maternal body mass index (BMI, derived from height and weight at the first antenatal visit), duration of diabetes, and mean peri-conception glycated hemoglobin concentration (A1C) were analyzed as continuous variables. Peri-conception A1C was defined as the closest measurement within three months prior to the last menstrual period (available for 52.9% of pregnancies) or mean first trimester measurement (<14 weeks' gestation) (available for 82.0% of pregnancies) for women with no pre-conception measurement. Peri-conception A1C was considered a reasonable proxy for pre-conception A1C, as first trimester A1C was highly correlated with pre-conception A1C (Spearman's correlation coefficient=0.73).(14) Gestational age at delivery and at the first antenatal appointment were estimated from information obtained at the first ultrasound examination or (rarely) the date of the last menstrual period. Small-for-gestational-age (SGA, birth weight <10^{th} centile) and large-for-gestational-age (LGA, birth weight >90^{th} centile) offspring were identified from their birth weight standardized for fetal sex, parity, and gestational age using Scottish birth population standards.(15)

Four variables were selected as markers of preparation for pregnancy due to their previously established associations with pregnancy outcome,(16; 17) and their integration within care guidelines for women with pre-existing diabetes in pregnancy:

1) Peri-conception A1C below 53mmol/mol (7.0%) - recommended by the American Diabetes Association (ADA, based in the United States) (18)

2) Self-reported pre-conception folic acid - the National Institute for Health and Care Excellence (NICE, based in England), recommends that women with diabetes take 5mg folic acid per day before conception (19)

3) Attendance at the first antenatal visit before ten weeks' gestation - recommended by NICE (19)

4) Record of attending specialist pre-conception care services - recommended by NICE to be offered to all women with pre-existing diabetes. (19) Regional guidelines advise those responsible for the routine care of women with diabetes to enquire about plans for pregnancy, discuss the benefits of adequate preparation, and refer all those with plans to specialist pre-conception care services.

Analysis (aim 1 - preparation for pregnancy)

The proportion of women achieving each marker of preparation in each pregnancy were calculated per 100 total pregnancies. Changes in prevalence and prevalence ratios (PRs) for repeat preparatory behavior were estimated within Poisson regression models. The association between adverse outcome in the first pregnancy and each marker of preparation in the second were examined by logistic regression, with adjustment for baseline behavior.[REF]

Analysis (aim 2 - prevalence and predictors of serious adverse outcome)

The prevalence of miscarriage, stillbirth, spontaneous fetal death, and congenital anomaly were calculated per 100 pregnancies. The prevalence of infant death, delivery by Caesarean section,

SGA, and LGA, were calculated per 100 total births. Changes in prevalence and relative risks (RRs) of recurrence were estimated within Poisson regression models.

The total probabilities of spontaneous fetal death from 6 weeks, 12 weeks and 24 weeks were estimated using a modified Kaplan-Meier approach. Pregnancies entered the 'at risk' period at the gestational age of their first antenatal appointment; miscarriages and stillbirths then exited as events, and elective terminations of pregnancy were censored, at their gestational age at delivery. Live births were modelled as having survived throughout. This approach is robust to distortions from late stillbirths by offsetting the per-week risk of adverse outcome against the probability of reaching that week of pregnancy.

Predictors of serious adverse outcome in the first and second pregnancy were examined by competing-risks regression.(20) Each pregnancy was modelled to be 'at risk' between the gestational age of the first antenatal appointment and the gestational age of delivery. The primary event was any serious adverse outcome, the competing events were live births or terminations of pregnancy without evidence of congenital anomalies. Unadjusted subdistribution hazard ratios (SHRs, interpreted like hazard ratios) were calculated for each variable in relation to the risk of serious adverse outcome in the first and second pregnancy separately. Adjusted SHRs were estimated within a pair of multivariable models, which were constructed using a backwards stepwise approach. For each pregnancy, variables with unadjusted p-values>0.5 were entered into the model and variables were then removed iteratively (by descending p-value) until only those with $p<0.1$ remained. The shape of association between peri-conception A1C and risk of serious adverse pregnancy outcome was explored by locally-weighted scatterplot smoothing (LOWESS).(21) Since a J-shaped association was observed, peri-conception A1C was modelled by piecewise linear regression with a single knot at the lowest LOWESS value [47mmol/mol (6.5%)]. Differences in associations (i.e. interactions) by type of diabetes were not explored due to the small number of pregnancies with type 2 diabetes. The absolute risks of serious adverse

outcome in the second pregnancy, stratified by outcome in the first pregnancy and categories of peri-conception A1C (evaluating at category-specific means) were estimated by taking marginal values of a simplified logistic regression model (conditioning only for first-pregnancy outcome and peri-conception A1C), estimating 95% confidence intervals (CIs) by the delta method.(22)

Missing data

Missing data were more likely in women who experienced adverse pregnancy outcomes. All calculations were hence evaluated across 100 multiply imputed datasets. Missing values were estimated by multivariate imputation by chained equations (MICE) using the variables described above, with the addition of A1C in the second and third trimesters. Conditional prevalence proportions were estimated by taking marginal values from Poisson regression models, with 95% CIs obtained using the delta method.(22) In the absence of missing data, 95% CIs for prevalence proportions were estimated using the Clopper-Pearson (Exact) method.(23) Missing values were not predicted for gestational age at the first antenatal appointment when required for Cox or competing risk regression. No assumptions were made about the missing data pattern. Analyses were performed using Stata 11.1 (Statacorp, TX, USA). $P<0.05$ was considered statistically significant.

Ethics approval and research governance

Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993. Data are now obtained and held with informed consent.

RESULTS

Description of population

Of the 220 women with pre-existing diabetes who had two pregnancies recorded during the study period, 89% had type 1 diabetes and 95% were white. The median inter-pregnancy interval (the time between the end of the first pregnancy and the start of the second) was 1.8 years (IQR: 0.9-3.0), although this was significantly shorter in women whose first pregnancy ended in a serious adverse outcome [1.0 years (IQR: 0.4-2.1) vs 2.0 years (IQR: 1.2-3.2), p<0.0001]. Maternal characteristics during the first and second pregnancy are summarized in **Supplementary Tables 1 and 2.**

Preparation for pregnancy

Where not described, hazard ratios, 95% CIs, and p-values can be found in Tables 1-3**.**

A quarter of women achieved a peri-conception A1C below 53mmol/mol (7.0%) before their first and second pregnancies (22.6% and 28.9% respectively), half attended pre-conception care (54.1% and 55.5% respectively) and two thirds made their first antenatal visit before ten weeks' (61.6% and 66.2% respectively) (**Table 1**). The proportion of women who consumed folic acid supplements before pregnancy increased from 27.1% before the first pregnancy to 43.0% before the second pregnancy (p=0.01) (**Table 1**), although this was not significant after adjusting for year of birth (p=0.07). Less than half of women attended both of their first antenatal visits before ten weeks' gestation [43.2% (95% CI: 36.5-49.8)], around a third attended pre-conception care in both pregnancies [35.0% (95% CI: 28.6-41.4)], and less than a fifth achieved a peri-conception A1C below 53mmol/mol or consumed folic acid supplements before both pregnancies [14.4% (95% CI: 9.3-19.4) and 15.9% (95% CI: 10.4-21.5) respectively].

Preparation for pregnancy was correlated between pregnancies. Women who in their first pregnancy achieved a peri-conception A1C below 53mmol/mol, consumed folic acid

supplements, and attended pre-conception care were respectively 3.33 ($p<0.0001$), 1.57 ($p=0.04$), and 1.45 ($p=0.047$) times more likely to do so again in the second pregnancy (**Table 1**).

Experience of a serious adverse outcome in the first pregnancy was not associated with improved preparation going into the second pregnancy. Achieving a peri-conception A1C below 53mmol/mol, attending the first antenatal visit before ten weeks, and attendance of pre-conception care were, if anything, less likely in the second pregnancy among those who had experienced a previous adverse outcome, although none of the associations were significant [A1C: OR adjusted for behavior in the first pregnancy, aOR=0.65 (95% CI: 0.29-1.42, p=0.28); first appointment before ten weeks: aOR=0.74 (95% CI: 0.40-1.37, p=0.34); attendance of preconception care: aOR=0.80 (95% CI: 0.44-1.44, p=0.45)]. There was absolutely no association between outcome in the first pregnancy and folic acid consumption in the second [aOR=1.01 (95% CI: 0.54-1.88, p=0.98)].

Prevalence of serious adverse outcome in either pregnancy

39.1% (95% CI: 32.6-45.9) of women experienced a serious adverse outcome in at least one pregnancy and 8.2% (95% CI: 4.9-12.6) experienced serious adverse outcomes in both pregnancies.

Prevalence and predictors of serious adverse outcome in the first pregnancy

30.5% of first pregnancies were affected by serious adverse outcome. There was no difference in prevalence by diabetes type [type 1 vs type 2: 30.8% (95% CI: 24.4-37.8) vs 28.0% (95% CI: 12.1-49.4), p=0.78]. 17.3% ended in miscarriage, 5.5% in stillbirth, 1.4% in infant death, and 6.4% were affected by congenital anomaly (**Table 1**). Of the 14 first pregnancies affected by congenital anomaly, <5 (<35.7% - the exact count is censored to conform to UK disclosure regulations) ended in termination of pregnancy. The total probability of spontaneous fetal death (from 6 weeks' gestation) was 33.9% (95% CI: 24.7-45.3); from 12 weeks' was 16.1% (95% CI: 11.4-22.4); and from 24 weeks' was 6.3% (95% CI: 3.5-11.0).

178 (80.9%, 95% CI: 75.1-85.9) first pregnancies resulted in a registered birth. Of these, 54.5% were delivered by caesarean section, 4.5% of offspring were small-for-gestational-age, and 42.7% were large-for-gestational-age (**Table 1**).

Non-white ethnicity (p=0.02), pre-pregnancy neuropathy (p<0.0001), increasing maternal age (p=0.03) smoking during pregnancy (p=0.01), and increasing peri-conception A1C ≥47 mmol/mol (p=0.003) were all independently associated with increased risk of serious adverse outcome in the first pregnancy (**Table 2**).

Prevalence and predictors of serious adverse outcome in the second pregnancy

16.8% of second pregnancies were affected by serious adverse outcome, 0.55 (p=0.004) times the rate in the first pregnancy (**Table 1**). There was no difference in prevalence by diabetes type

[type 1 vs type 2: 16.9% (95% CI: 11.9-22.9) vs 16.0% (95% CI: 4.5-36.1), p=0.91]. The proportion of second pregnancies ending in miscarriage (5.5%) and stillbirth (1.4%) respectively were 0.32 (p=0.0005) and 0.25 (p=0.03) times the rate in the first pregnancy (**Table 1**). The proportion of second pregnancies that ended in infant death (0.5%) or were affected by congenital anomaly (9.5%) were not significantly different to the rates observed in the first pregnancy (p=0.28 and p=0.24 respectively) (**Table 1**). Of the 21 second pregnancies affected by congenital anomaly, <5 (<23.8%) ended in termination of pregnancy. The total probability of spontaneous fetal death (from 6 weeks' gestation) was 11.9% (95% CI: 6.1-22.6); from 12 weeks' was 2.7% (95% CI: 1.1-6.4); and from 24 weeks' was 1.5% (95% CI: 0.5-4.6).

201 (91.4%, 95% CI: 87.6-95.1) second pregnancies resulted in a registered birth. Of these, 60.7% were delivered by caesarean section. The proportion of births delivered by Caesarean section in the second pregnancy was 2.81 (p<0.0001) times greater in women whose previous birth had been delivered by Caesarean section (88.6%); 11.4% (95% CI 5.6-19.9) delivered vaginal birth after caesarean (**Table 1**). 3.5% of births in the second pregnancy were SGA and 58.2% were LGA (**Table 1**). The proportion of births in the second pregnancy that were LGA was 1.55 (p=0.045) times greater in women whose first birth was LGA (69.5%) (**Table 1**).

Women whose first pregnancy resulted in a serious adverse outcome experienced over twice the prevalence of a repeat serious adverse outcome in their second pregnancy than those who did not [26.9% vs 12.4%, SHR=2.59 (95% CI: 1.35-4.96), p=0.004] (**Table 1** and **Table 3**). Nearly a third of this effect, however, was explained by other explanatory variables. Non-white ethnicity (p=0.01), pre-pregnancy nephropathy (p=0.01), and increasing peri-conception A1C≥47 mmol/mol (p=0.0005) were all independently associated with increased risk of serious adverse outcome in the second pregnancy while later year of delivery (p=0.006) was associated with decreased risk (**Table 3**). After adjusting for these and other variables with 0.05<p<0.1, the

association between previous adverse outcome and risk in the second pregnancy was no longer statistically significant [adjusted SHR, aSHR=1.83 (95% CI: 0.96-3.47), p=0.07] (**Table 3**).

To establish the relative importance of contemporaneous A1C compared with historical A1C, additional analyses were performed with peri-conception A1C in the previous pregnancy. There was no crude association between first pregnancy A1C and risk of serious adverse outcome in the second [A1C<47mmol/mol: SHR=1.13 (95% CI 0.92-1.40, p=0.25); A1C≥47mmo/mol: SHR=1.00 (95% CI: 0.99-1.02, p=0.46)]. After adjusting for other model variables, however, there was some suggestion of a *lower* conditional risk for increasing values of A1C≥47mmol/mol, although the effect was outside the nominal significance level [A1C<47mmol/mol: aSHR=1.15 (95% CI: 0.9-1.44, p=0.24); A1C≥47mmo/mol: aSHR=0.98 (95% CI: 0.95-1.00, p=0.054)].

The absolute risk of serious adverse outcome in the second pregnancy, stratified by outcome in the first pregnancy and peri-conception A1C are shown in **Table 4**.

CONCLUSIONS

Principal findings

This study describes the preparation for and outcome of the first and second pregnancy in women with pre-existing diabetes. The overall risk of serious adverse outcome fell from 30% in the first pregnancy to 17% in the second pregnancy. This was predominately attributable to a fall from 34% to 12% in the probability of spontaneous fetal death.

Women who experienced a serious adverse outcome in their first pregnancy were over two times more likely to experience another serious adverse outcome in their second pregnancy, although around a third of this was explained by persistent risk factors such as maternal non-white ethnicity and higher peri-conception A1C.

A greater proportion of women achieved a favorable peri-conception A1C and consumed folic acid supplements before their second pregnancy than their first, though both were still minority behaviors. There were no differences in the number who attended pre-conception care, or whose first antenatal visit was before 10 weeks' gestation. Achieving a peri-conception A1C below 53mmol/mol, use of pre-pregnancy folic acid consumption, and attendance of pre-conception care were all more likely in the second pregnancy if they had occurred in the first, but there was no evidence that experiencing an adverse outcome in the first pregnancy was associated with a change in preparation for the second pregnancy.

Strengths and limitations

This study benefitted from the North of England’s unique range of long-running population-based registers. The NorDIP is England's longest running uninterrupted audit of pregnancies occurring in women with pre-existing diabetes and is one of few registers that supports the study of repeated

pregnancies in the same mother. Detailed information is gathered before and during each pregnancy on a range of clinical and socio-demographic variables. Cases of congenital anomaly were identified by the UK's longest running regional register of congenital anomaly, which maintains high ascertainment by receiving information, regardless of pregnancy outcome, from multiple sources at any time up to 12 years after birth. The PMS has been collecting information on all stillbirths and infant deaths within the region since 1981 and cross-references with mortality records from the UK Office for National Statistics. The results of this study are likely to be generalizable to any predominately white population with similar standards of peri-conception and perinatal care.

Several limitations result from low statistical power. Due to the small absolute number of pregnancies ending in any individual outcome specifically, all multivariable analyses used a composite variable, serious adverse pregnancy outcome, despite possible heterogeneity. Only those associations that apply to all constituent outcomes are likely to have been detected. Due to small numbers with type 2 diabetes (n=25), it was not possible to examine whether the identified associations differed by diabetes type, although previous studies have found negligible evidence of effect modification by diabetes type.(7; 8; 14; 17) Several important exposures also had low absolute numbers – most notably maternal ethnicity and the indicators of pre-pregnancy microvascular complications. Although women of non-white ethnicity experienced an increased risk of serious adverse outcome, the numbers were too small to stratify the second pregnancy absolute risks by either ethnicity or pre-pregnancy nephropathy. Lack of statistical significance should not be taken as evidence of no effect, as demonstrated by the biologically implausible disagreement in the influence of smoking during the first and second pregnancies (**Tables 2-3**). Similarly, the inter-pregnancy differences in the contributions of neuropathy and nephropathy are entirely consistent with sampling variation. Data were more likely to be missing in women who experienced serious adverse outcomes. MICE was used to reduce any consequent bias, but requires all predictors of missingness to be known for complete efficacy. Some individuals with

mild microvascular complications may not have been ascertained, since only those who had been 'clinically diagnosed' (regardless of the method) were recognized. Other potentially-relevant exposures, most notably peri-pregnancy medication usage, were not collected.

As with any population-based study, it is unlikely that all pregnancies ending in miscarriage were ascertained. Losses before six weeks' are typically undetected,(24) while later losses may be recognized but not reported. The earliest recorded miscarriage in a registered pregnancy occurred at six weeks', by which time approximately a quarter of women had attended their first antenatal appointment. Kaplan Meier scales the denominator to account for differential entry and exit times,(25) thus this study should provide an accurate estimate of the risks of spontaneous intrauterine death in each pregnancy from six weeks onwards. The total risk of miscarriage from conception, however, may be underestimated.

Around half of women in the North of England with pre-existing diabetes do not seek pre-conception care before getting pregnant.(17) For most of these women, we used first trimester A1C values to approximate their pre-conception A1C. Although the two are highly correlated, this will have introduced random variation and biased our estimates towards the null. A1C provides an incomplete profile of overall glycemic control as it provides no information on potentially salient glycemic excursions or hypoglycemic episodes.(26) Unfortunately, continuous glucose monitoring, which might permit such investigations, is not yet routinely available in the UK.

Comparison with other studies

This study is the first to explore the risk of recurrence of adverse pregnancy outcomes in women with pre-existing diabetes, and to describe the absolute risks in first and second pregnancies specifically. Nevertheless, there are analogous observations in the general population. The relative risks of recurrence for both congenital anomalies (at 1.55, 95% CI 0.40-5.99) and fetal or infant death (at 2.45, 95% CI 0.96-6.26), for example, were highly consistent with the doubling of

risk seen in the general population.(3-5) Across both pregnancies, the prevalence of congenital anomaly [8.0% (95% CI: 5.4-10.5)], stillbirth [3.4% (1.7-5.1)], and infant death [1.2% (<0.1-2.4)] were all consistent with previous observations in larger samples from the same population [7.7% (95% CI: 6.5-9.1), 2.7% (1.9-3.6), and 0.7% (0.3-1.2) respectively].(7; 8) The proportion of pregnancies ending in miscarriages [11.4% (8.4-14.3)] was consistent with the 5-20% that is typically reported in women with diabetes.(27-29)

Comparisons are more problematic for the change in risk between the first and second pregnancy, due to large differences in the profile of primiparous and multiparous women.(30) This likely explains the discrepancy between the current study, and a previous cross-sectional analysis, in which no association was found between parity and the risk of stillbirth.(8) Even in longitudinal studies, the true attributable risk of parity may be masked by changes in other risk factors (such as maternal age and BMI) between the first and subsequent pregnancy.(31) Nevertheless, it is broadly recognized that the prevalence of serious adverse pregnancy is greater among first pregnancies than subsequent. In the general population, Flenady et al's meta-analysis estimated that the risk of stillbirth was 1.40 (95% CI: 1.33-1.42) times higher among primiparous women than multiparous.(32) Though apparently much smaller than we observed (RR, for primiparity vs multiparity: 4.02, 95% CI: 1.15-14.04), the difference is consistent with normal sampling variation (p=0.10). A similar pattern was apparent for miscarriage, with the crude RR for the current study (3.17, 95% CI: 1.70-5.90) being higher, but not significantly (p=0.07), than in a UK sample of women of reproductive age (1.75, 95% CI: 1.42-2.14 comparing first and second pregnancies specifically). We did not find a relationship between pregnancy order and the risk of congenital anomalies, despite it previously having been observed in the general population.(33) This may reflect our modest sample size, or the aforementioned complications of comparing longitudinal with cross-sectional data.

Implications and Conclusions

Women with pre-existing diabetes continue to experience very high risks of serious adverse pregnancy outcomes. In the first pregnancy, nearly a third [30.5% (95% CI: 24.4-37.0)] were affected. In the second, as in the general population, pregnancy outcomes were more favorable, with a much lower risk among those who had not experienced an adverse outcome in their first [12.4% (7.6-18.7]. This was not explained by changes in any of the known risk factors, and may instead reflect constitutionally higher risks in the first pregnancy, such as pregnancy-induced hypertension and intrauterine growth restriction.[REF] Among those whose first pregnancy was affected by serious adverse outcome, the risk in the second pregnancy remained very high [26.9% (16.8-39.1)]. Around a third of this was explained by persistent, and known, risk factors. Adverse outcomes were more common in both pregnancies among women from minority ethnic groups, consistent with previous observations in pregnant women with pre-existing diabetes.(34) This may reflect genetic factors or it may represent enduring environmental or behavioral influences. Preparation for pregnancy is particularly poor in non-white women in the North of England,(17) indicating these women urgently require additional or alternative methods of support, such as community-based approaches.(35) We observed the same J-shaped association between peri-conception A1C and adverse outcome that has been identified before,(36) with a steep increase in risk of 2-3% per mmol/mol from 47mmol/mol (equivalent to a doubling per 25-35mmol/mol).This reinforces the benefits of good, though not overly strict, glycemic control before conception.(8) Notably, while peri-conception A1C levels were correlated across both pregnancies, only current values were associated with outcome, suggesting this may be a causal, and therefore reversible, association. However, after adjusting for current values, there was some suggestion of a residual *protective* effect of A1C in the previous pregnancy, indicating the highest risk may be in women whose glycemic control deteriorates substantially between pregnancies.

Preparation for pregnancy among our sample of women with diabetes was poor. Only a quarter managed the pre-conception A1C target or took folic acid supplements before their first pregnancy, and only just over a half attended pre-conception care or had their first antenatal

appointment before ten weeks'. Although favorable preparation in the first pregnancy was broadly predictive of repeat behavior in the second pregnancy, this exposes a disheartening converse. Women whose first pregnancy ended in a serious adverse pregnancy outcome did not appear to change their preparatory behavior for the subsequent pregnancy. Given the short inter-pregnancy interval [1.0 years (IQR: 0.4-2.1)] there is clearly a narrow period for intervention and many of the circumstances that inhibited planning and preparation for the first pregnancy are likely to remain for the second. This motivates need for a change in approach, such as providing intensive postnatal support after an adverse event, covering various aspects of care such as control, contraception use, and general well-being.(35) Such an intervention, however, would have to be carefully balanced against the family's psychological needs, given the negative impact of discussing future pregnancies during a period of grief.(37) Regardless, since pre-conception care was equally poor across both pregnancies, changes (or greater choice) may be needed in the style and setting of support for all women with diabetes.(35) The barriers to improved pregnancy planning and preparation are multifaceted and complex,(38) but further progress is urgently needed to reduce the risk of recurrent tragedy in women with diabetes.

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Conflicts of interest

All authors declare that they have no duality of interest.

Contributions Statement

All authors declare that they read and approved the final version of the manuscript before submission. RB and RWB conceived the project and, with PWGT, designed the study. RWB was involved in the acquisition of the data. SP was involved in preparing the data and performing preliminary analyses. PWGT performed the primary analysis and drafted the manuscript. All authors were involved in the interpretation of the data and critically reviewed the manuscript. PWGT (guarantor) had full access to the data and takes responsibility for the conduct of the research, the contents of the article, and the decision to submit and publish the manuscript.

FIGURE LEGENDS

Supplemental Figure 1: The North of England, UK

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Table 1: Pregnancy preparation and outcome in first and second pregnancies, and prevalence ratios/relative risks for repeat behavior/recurrence of adverse outcomes

Variable	Prevalence proportion (95% CI) [n/N]		Relative change in summary prevalence (95% CI) [p-value]	Conditional prevalence in second pregnancy (95% CI) [n/N]		Prevalence ratio/ relative risk (95% CI) [p-value]
	First pregnancy	Second pregnancy		Also in first pregnancy	Only in second pregnancy	
Preparation for pregnancy						
Peri-conception A1C <53mmol/mol (7.0%)	22.6% (16.5-28.6) [50/220]*	28.9% (22.6-35.2) [64/220]*	1.32 (0.89-1.95) [p=0.17]	63.2% (40.4-86.1) [32/50]*	18.8% (11.8-25.8) [32/170]*	3.33 (1.97-5.65) [<0.0001]*
Pre-conception folic acid	27.1% (20.4-33.8) [60/220]*	43.0% (36.2-49.9) [95/220]*	1.55 (1.11-2.18) [p=0.01]	58.7% (38.6-78.8) [35/60]*	37.4% (27.5-47.2) [60/160]*	1.57 (1.01-2.43) [p=0.04]*
First antenatal visit <10 weeks'	61.6% (55.1-68.2) [136/220]*	66.2% (59.9-72.5) [146/220]*	1.08 (0.85-1.36) [p=0.53]	70.0% (55.9-84.2) [95/136]*	60.1% (43.4-76.7) [50/84]*	1.17 (0.83-1.64) [p=0.38]*
Attended pre-conception care	54.1% (47.3-60.8) [119/220]	55.5% (48.6-62.1) [122/220]	1.03 (0.80-1.32) [p=0.85]	64.7% (50.3-79.2) [77/119]	44.6% (31.5-57.6) [45/101]	1.45 (1.01-2.10) [p=0.047]
Serious adverse outcome						
Any serious adverse outcome	30.5% (24.4-37.0) [67/220]	16.8% (12.1-22.4) [37/220]	0.55 (0.37-0.83) [p=0.004]	26.9% (16.8-39.1) [18/67]	12.4% (7.6-18.7) [19/153]	2.16 (1.14-4.12) [p=0.02]
Congenital anomaly	6.4% (3.5-10.4) [14/220]	9.5% (6.0-14.2) [21/220]	1.50 (0.76-2.95) [p=0.24]	14.3% (1.8-42.8) [2/14]	9.2% (5.6-14.0) [19/206]	1.55 (0.36-6.65) [p=0.56]
Spontaneous fetal deaths, infant deaths, or terminations of pregnancy for fetal anomaly	25.5% (19.8-31.7) [56/220]	10.5% (6.7-15.3) [23/220]	0.41 (0.25-0.67) [p=0.0003]	19.6% (10.2-32.4) [11/56]	7.3% (3.8-12.4) [12/164]	2.68 (1.26-5.74) [p=0.009]

Fetal or infant death in normally-formed offspring†	24.1% (18.6-30.3) [53/220]	7.3% (4.2-11.5) [16/220]	0.30 (0.17-0.53) [p<0.0001]	13.2% (5.5-25.3) [7/53]	5.4% (2.5-10.0) [9/167]	2.45 (0.91-6.58) [p=0.08]
Spontaneous fetal death†	23.7% (17.4-28.8) [50/220]	6.8% (3.9-11.0) [15/220]	0.30 (0.17-0.53) [p<0.0001]	14.0% (5.8-26.7) [7/50]	4.7% (2.1-9.1) [8/170]	2.98 (1.08-8.20) [p=0.04]
Miscarriage†	17.3% (12.5-22.9) [38/220]	5.5% (2.8-9.3) [12/220]	0.32 (0.17-0.60) [p=0.0005]	5.3% (0.6-17.7) [2/38]	5.3% (2.7-9.9) [10/182]	0.96 (0.21-4.37) [p=0.96]
Stillbirth†	5.5% (2.8-9.3) [12/220]	1.4% (0.3-3.9) [3/220]	0.25 (0.07-0.89) [p=0.03]	0.0% (0.0-26.5) [0/12]	1.4% (0.3-4.2) [3/208]	-
Infant death†	1.4% (0.3-3.9) [3/220]	0.5% (0.1-2.5) [1/220]	0.29 (0.03-2.74) [p=0.28]	0.0% (0.0-70.8) [0/3]	0.5% (0.0-2.5) [1/217]	-
Other outcomes (births only)‡						
Delivery by Caesarean section‡	54.5% (46.9-62.0) [97/178]	60.7% (53.6-67.5) [122/201]	1.05 (0.79-1.41) [p=0.71]	88.6% (80.1-94.4) [78/88]§	31.6% (21.4-43.3) [24/76]§	2.81 (1.78-4.44) [p<0.0001]§
Small for gestational age‡	4.5% (2.0-8.7) [8/178]	3.5% (1.4-7.0) [7/201]	0.86 (0.29-2.55) [p=0.78]	14.3% (0.4-57.9) [1/7]§	2.5% (0.7-6.4) [4/157]§	5.61 (0.63-50.17) [p=0.12]§
Large for gestational age‡	42.7% (35.3-50.3) [76/178]	58.2% (51.1-65.1) [117/201]	1.04 (0.78-1.39) [p=0.77]	69.5% (59.2-78.5) [66/95]§	44.9% (32.9-57.4) [31/69]§	1.55 (1.01-2.37) [p=0.045]§

*Prevalence proportions were estimated over 100 multiply imputed datasets with confidence intervals determined from the analytically derived variance estimator. Counts represent the rounded average across the 100 datasets and should be considered indicative. †Cases exclude offspring with congenital anomalies ‡Sample restricted to pregnancies resulting in registered births (i.e. live-birth or stillbirths) and includes pregnancies complicated by congenital anomaly §Rates calculated from sample of 164 women with two successive births

Table 2: Predictors of serious adverse outcome in the first pregnancy

Variable	Unadjusted SHR (95% CI)	p-value (overall)	Adjusted SHR (95% CI)	p-value (overall)
Non-modifiable variable				
Type of diabetes				
Type 1	Reference		Not entered (p>0.5)	
Type 2	1.01 (0.45-2.26)	0.98		
Maternal ethnic origin				
White	Reference		Reference	
Non-white	3.23 (1.25-8.37)	0.02	3.18 (1.19-8.47)	0.02
Index of Deprivation				
Tertile 1 (most deprived)	1.14 (0.63-2.06)	0.67	Not entered (p>0.5)	
Tertile 2	Reference	(0.52)		
Tertile 3 (least deprived)	0.79 (0.42-1.49)	0.47		
Pre-pregnancy nephropathy				
Yes	1.02 (0.24-4.32)	0.98	Not entered (p>0.5)	
No	Reference			
Pre-pregnancy neuropathy				
Yes	2.77 (1.83-4.20)	<0.0001	4.65 (2.23-9.68)	<0.0001
No	Reference		Reference	
Pre-pregnancy retinopathy				
Yes	0.57 (0.23-1.41)	0.22	Eliminated (p<0.1)	
No	Reference			
Year of delivery (year)	0.94 (0.86-1.02)	0.16	0.93 (0.85-1.01)	0.08
Duration of diabetes (years)	0.97 (0.93-1.01)	0.11	Eliminated (p<0.1)	
Maternal age (years)	1.04 (0.98-1.09)	0.20	1.07 (1.01-1.13)	0.03
Potentially modifiable variable				
Smoked during pregnancy				
Yes	1.78 (1.02-3.11)	0.042	2.25 (1.18-4.29)	0.01
No	Reference		Reference	
Pre-conception folic acid				
Yes	0.75 (0.35-1.60)	0.45	Eliminated (p<0.1)	
No	Reference			
First antenatal visit < 10 weeks				
Yes	0.98 (0.53-1.81)	0.94	Not entered (p>0.5)	
No	Reference			
Attended pre-conception care				
Yes	1.09 (0.66-1.81)	0.73	Not entered (p>0.5)	
No	Reference			
Body mass index (Kg/m^2)	1.02 (0.97-1.06)	0.49	Eliminated (p<0.1)	
Peri-conception A1C (mmol/mol)		(0.04)		(0.02)
<47mmol/mol (<6.5%)	1.00 (0.91-1.09)	0.95	1.00 (0.92-1.09)	0.93
≥47mmol/mol (≥6.5%)	1.01 (1.00-1.02)	0.01	1.02 (1.01-1.03)	0.003

Table 3: Predictors of serious adverse outcome in the second pregnancy

Variable	Unadjusted SHR (95% CI)	p-value (overall)	Adjusted SHR (95% CI)	p-value (overall)
Non-modifiable variable				
Outcome in the first pregnancy				
Normally-formed live birth	Reference		Reference	
Miscarriage, stillbirth or CA	2.59 (1.35-4.96)	0.004	1.83 (0.96-3.47)	0.07
Type of diabetes				
Type 1	Reference		Not entered (p>0.5)	
Type 2	0.89 (0.31-2.52)	0.83		
Maternal ethnic origin				
White	Reference		Reference	
Non-white	2.84 (1.00-8.08)	0.0498	3.38 (1.19-9.61)	0.02
Index of Deprivation				
Tertile 1 (most deprived)	1.10 (0.49-2.50)	0.81	Not entered (p>0.5)	
Tertile 2	Reference	(0.96)		
Tertile 3 (least deprived)	1.12 (0.50-2.51)	0.78		
Pre-pregnancy nephropathy				
Yes	2.76 (1.08-7.10)	0.03	3.37 (1.23-9.26)	0.02
No	Reference		Reference	
Pre-pregnancy neuropathy				
Yes	1.35 (0.20-9.05)	0.76	Not entered (p>0.5)	
No	Reference			
Pre-pregnancy retinopathy				
Yes	1.23 (0.55-2.78)	0.62	Not entered (p>0.5)	
No	Reference			
Year of delivery (year)	0.87 (0.78-0.96)	0.007	0.84 (0.76-0.94)	0.002
Duration of diabetes (years)	0.97 (0.93-1.02)	0.28	Eliminated (p<0.1)	
Maternal age (years)	0.98 (0.92-1.03)	0.39	Eliminated (p<0.1)	
Potentially modifiable variable				
Smoked during pregnancy				
Yes	1.24 (0.55-2.76)	0.61	Not entered (p>0.5)	
No	Reference			
Pre-conception folic acid				
Yes	1.14 (0.56-2.32)	0.72	Not entered (p>0.5)	
No	Reference			
First antenatal visit < 10 weeks				
Yes	0.66 (0.32-1.35)	0.25	Eliminated (p<0.1)	
No	Reference			
Attended pre-conception care				
Yes	1.76 (0.88-3.53)	0.11	1.83 (0.92-3.64)	0.09
No	Reference		Reference	
Inter-pregnancy interval (years)	0.93 (0.74-1.17)	0.55	Not entered (p>0.5)	
Body mass index (Kg/m^2)	0.95 (0.88-1.03)	0.21	Eliminated (p<0.1)	
Peri-conception A1C (mmol/mol)		(0.0005)		(0.003)
<47mmol/mol (<6.5%)	0.94 (0.80-1.11)	0.47	0.94 (0.79-1.11)	0.45
≥47mmol/mol (≥6.5%)	1.03 (1.01-1.04)	0.0001	1.03 (1.01-1.04)	0.0008

Table 4: Absolute risk of serious adverse outcome in the second pregnancy, stratified by outcome in the first pregnancy, and peri-conception A1C

Outcome in first pregnancy	Peri-conception A1C		Risk of serious adverse outcome in the second pregnancy (95% CI)	
	mmol/mol	DCCT %	Percentage	As fraction
Live birth and infant alive at aged one year	*Total prevalence →*		*12.4 (7.6-18.7)*	*1 in 8 (5-13)*
	<53	<7.0	6.5 (2.1-10.9)	1 in 15 (9-47)
	53-63	7.0-7.9	8.3 (3.6-13.0)	1 in 12 (8-28)
	64-74	8.0-8.9	11.1 (5.8-16.4)	1 in 9 (6-17)
	75-85	9.0-9.9	14.9 (8.2-21.6)	1 in 7 (5-12)
	≥86	≥10	25.9 (11.8-40.1)	1 in 4 (2½-8)
Spontaneous fetal death, infant death, or congenital anomaly	*Total prevalence →*		*26.9 (16.8-39.1)*	*1 in 4 (2½-6)*
	<53	<7.0	15.2 (5.3-25.0)	1 in 7 (4-19)
	53-63	7.0-7.9	18.9 (8.6-29.2)	1 in 5 (3-12)
	64-74	8.0-8.9	24.3 (13.3-35.2)	1 in 4 (3-8)
	75-85	9.0-9.9	31.1 (18.6-43.6)	1 in 3 (*2½-5*)
	≥86	≥10	47.3 (28.0-66.6)	1 in 2 (*1½*-4)

Supplemental Table 1: Descriptive statistics for study participants (continuous variables)

Continuous variable	First pregnancy (N=220)			Second pregnancy (N=220)		
	n	Range	Median (IQR)	n	Range	Median (IQR)
Gestation at first antenatal visit (weeks)	213	1-34	9 (7-11)	219	3-22	8 (6-11)
Gestation at delivery (weeks)	220	4-40	36 (32-38)	220	6-41	37 (35-38)
Duration of diabetes (years)	219	1-27	9 (4-15)	219	2-30	12 (7-18)
Maternal age at delivery (years)	220	15-40	26 (21-30)	220	17-46	29 (24-33)
Maternal body mass index (kg/m^2)	157	17-60	26 (23-29)	172	18-58	26 (23-30)
Peri-conception A1C (mmol/mol)	187	25-187	65 (54-83)	190	29-143	62 (51-77)
Peri-conception A1C (%)	187	4.4-19.3	8.1 (7.1-9.7)	190	4.8-15.2	7.8 (6.8-9.2)
Both pregnancies (N=220)						
Inter-pregnancy interval (years)	220	<0.1-10.1	1.8 (0.9-3.0)			

Supplementary Table 2: Descriptive statistics for study participants (categorical variables)

Categorical variable	First pregnancy (N=220)		Second pregnancy (N=220)	
	n	%	n	%
Index of Deprivation				
Tertile 1 (most deprived)	69	31.4	69	31.4
Tertile 2	72	32.7	73	33.2
Tertile 3 (least deprived)	79	35.9	78	35.5
Pre-pregnancy nephropathy				
Yes	7	3.2	10	4.6
No	213	96.8	210	95.5
Pre-pregnancy neuropathy				
Yes	1	0.5	4	1.8
No	219	99.6	216	98.2
Pre-pregnancy retinopathy				
Yes	26	11.8	47	73.6
No	186	84.6	162	21.4
Missing	*8*	*3.6*	*11*	*5.0*
Smoked during pregnancy				
Yes	46	20.9	47	21.4
No	152	69.1	156	70.9
Missing	*22*	*10.0*	*17*	*7.7*
Pre-conception folic acid				
Yes	51	23.2	89	40.5
No	138	62.7	117	53.2
Missing	*31*	*14.1*	*14*	*6.4*
First antenatal visit < 10 weeks				
Yes	131	59.6	145	65.9
No	82	37.3	74	33.6
Missing	*7*	*3.2*	*1*	*0.5*
Attended pre-conception care				
Yes	119	54.1	122	55.5
No	101	45.9	98	44.6
Year of delivery*				
1996-1999	79	35.9	30	13.6
2000-2004	105	47.7	77	35.0
2005-2008	36	16.4	113	51.4
	Both pregnancies (N=220)			
Diabetes type				
Type 1	195	88.6		
Type 2	25	11.4		
Ethnicity				
White	209	95.0		
Non-white	11	5.0		

*Year of delivery was analyzed as a continuous variable, but is presented in categories to aid comprehension