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Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study

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Running Title: Diabetes and the risks of fetal and infant death

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Abstract

Aims

Pre-existing diabetes is associated with an increased risk of stillbirth but few studies have excluded the effect of congenital anomalies. This study used data from a long-standing population-based survey of women with pre-existing diabetes to investigate the risks of fetal and infant death and quantify the contribution of glycaemic control.

Methods

All normally-formed singleton offspring occurring in women with pre-existing diabetes (n=1206 with type 1 diabetes and n=342 with type 2 diabetes) in the North of England during 1996-2008 were identified from the Northern Diabetes in Pregnancy Survey. Relative risks (RRs) of fetal death (≥20 weeks' gestation) and infant death were estimated by comparison with population data from the Northern Perinatal Morbidity and Mortality Survey. Predictors of fetal and infant death in women with pre-existing diabetes were examined by logistic regression.

Results

The prevalence of fetal death in women with diabetes was over four times greater than among those without [RR=4.56 (95% confidence interval, CI: 3.42, 6.07) p<0.0001], while for infant death it was nearly doubled [RR=1.86 (95% CI: 1.00, 3.46) p=0.046]. There was no difference in the prevalence of fetal death (p=0.51) or infant death (p=0.70) between women with type 1 diabetes and women with type 2 diabetes. There was no evidence that the RR of fetal and infant death had changed over time (p=0.95).

Increasing peri-conception HbA_{1c} above 49mmol/mol (6.6%) [adjusted odds ratio, aOR=1.02 (95% CI: 1.00, 1.04) p=0.01], pre-pregnancy retinopathy [aOR=2.05 (95% CI: 1.04, 4.05) p=0.04] and lack of pre-pregnancy folic acid consumption [aOR=2.52 (95% CI: 1.12, 5.65) p=0.03] were all independently associated with increased odds of fetal and infant death.

Conclusions

Pre-existing diabetes is associated with a substantially increased risk of fetal and infant death in normally-formed offspring, the effect of which is largely moderated by glycaemic control.

Keywords

Diabetes mellitus, HbA_{1c}, pregnancy, miscarriage, stillbirth, neonatal death

Abbreviations

aOR	Adjusted odds ratio
CI	Confidence interval
IQR	Interquartile range
HbA_{1c}	Glycated haemoglobin
LOWESS	Locally-weighted scatterplot smoothing
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey
PMMS	Perinatal Morbidity and Mortality Survey
OR	Odds ratio
RR	Relative risk

Introduction

Diabetes is one of the most common pre-existing maternal conditions complicating pregnancy. Affecting 0.5-2% of pregnancies, the prevalence is rising as a consequence of the obesity epidemic and increases in maternal age. This has considerable implications, since pre-existing diabetes (both type 1 and type 2) is associated with a range of pregnancy complications, including increased risks of macrosomia, congenital anomaly, and delivery by caesarean section[1-3]. It has long been observed that pre-existing diabetes is also associated with an increased risk of stillbirth[4], although there is heterogeneity in the estimated relative risk (RR)[5].

Pre-pregnancy care, particularly focussing on optimising glycaemic control, improves birth outcomes in women with pre-existing diabetes[6]. With intensive support, some women with diabetes can achieve similar outcomes to those without[7], an unmet goal of the St Vincent declaration[8]. It is uncertain, however, whether such improvements can be achieved in routine clinical care. Observational studies from the last 20 years have not shown any reduction in the RR of fetal death[9-18], despite guidelines advising women with pre-existing diabetes to achieve good glycaemic control before pregnancy[19, 20].

There is a paucity of data on the risks of fetal and infant death independent of congenital anomaly, and the contribution of glucose control and other clinical and socio-demographic factors are poorly described. We used unique data from several long-standing population-based registers in the North of England to investigate the association between pre-existing diabetes and the risks of fetal and infant death in normally-formed offspring, and to quantify the contribution of glycaemic control.

Methods

The Northern Diabetes in Pregnancy Survey (NorDIP)

The North of England (UK) is a geographically distinct area with a population of three million and approximately 32,000 births per year (see **Supplementary Figure 1**). The NorDIP records details of all pregnancies occurring in women resident in the region and diagnosed with (type 1 or type 2) diabetes at least six months before conception. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. Clinicians working within the region's nine units collect and supply information on a range of clinical and sociodemographic variables, including maternal glycated haemoglobin concentration (HbA_{1c}) pre-conception, in the first trimester, and in the third trimester. For further details see Glinianaia et al[1].

Study sample

This study includes data on all singleton pregnancies occurring in women with pre-existing diabetes delivered at or after 20 completed weeks' of gestation between 01 January 1996 and 31 December 2008. Pregnancies complicated by major congenital anomalies, which have previously been shown to be associated with both pre-existing diabetes and the risk of fetal and infant death[2, 21], were identified from the Northern Congenital Abnormality Survey (NorCAS) and excluded. The NorCAS is a long-standing population-based register of congenital anomaly that collects data on all cases of congenital anomaly occurring in all deliveries in the North of England, irrespective of maternal diabetes status (for further details see Bell et al[2]). The total number of singleton live births and fetal and infant deaths were obtained from the UK Office for National Statistics (www.statistics.gov.uk) and the Northern Perinatal Morbidity and Mortality Survey (PMMS)[22] respectively. The number of normally-formed offspring was determined by subtracting the number of NorCAS registrations.

Definitions

Late miscarriages are the spontaneous loss of a fetus at 20-23 completed weeks of gestation. Stillbirths are deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation. Late stillbirths are stillbirths at 28 of more completed weeks of gestation. Antepartum stillbirths are stillbirths where the fetus died before the onset of labour. Intrapartum stillbirths are stillbirths where the fetus after the onset of labour. Fetal deaths comprise late miscarriages and stillbirths. Neonatal deaths are deaths, following live birth, within the first

28 days of life. Postneonatal deaths are deaths, following live birth, of an infant aged 28 days or more, but less than one year. Infant deaths comprise neonatal deaths and postneonatal deaths.

Analysis

Prevalence rates were estimated per 1000 births and late miscarriages, for fetal outcomes, and per 1000 live births, for infant outcomes. 95% confidence intervals (CIs) for prevalences were estimated using the Clopper-Pearson (Exact) method. RRs were calculated by comparing the prevalences among women with pre-existing diabetes to the prevalence among the remaining population. To examine whether the RR for fetal and infant death had changed over time, a cross-product interaction between diabetes status and year of delivery was evaluated within a Poisson regression model. RRs for fetal death at specific gestational ages were estimated using the 'fetuses-at-risk' approach[23]. In each period, the proportion of cases from the total number of on-going pregnancies (i.e. containing fetuses 'at risk of fetal death') was compared. The number of on-going pregnancies at each gestational age was estimated from a reference UK population[24].

Odds ratios (ORs) and 95% CIs for all variables with hypothesised influences on fetal and/or infant death were analysed in relation to fetal death, late stillbirth, infant death, fetal and infant death combined, and late stillbirth and infant death combined within a series of logit-linked generalised estimating equations. Between-mother variation was modelled as a random-intercept to account for the non-independence of repeat pregnancies in the same woman. Peri-conception HbA_{1c} was defined as the closest measurement within three months prior to the last menstrual period (available for 48.8% of pregnancies) or mean first trimester measurement (<14 weeks' gestation) (available for 86.0% of pregnancies) for women with no pre-conception measurement. Peri-conception HbA_{1c} was chosen as a reasonable surrogate of pre-conception HbA_{1c}, as first trimester HbA_{1c} was highly correlated with pre-conception HbA_{1c} (Spearman's correlation coefficient=0.76). Third-trimester HbA_{1c} was examined only in relation to deliveries at ≥28 weeks' gestation. Adjusted ORs were estimated using a backwards stepwise approach; all variables were entered into the model and non-significant ones were removed iteratively, by decreasing p-value, until only those with $p<0.1$ remained. Cross-product interaction terms were used to explore whether the effect of each variable with a significant independent association on the risk of fetal and infant death varied by diabetes type. The relationships between peri-conception and third trimester HbA_{1c} with the risks of fetal and infant death were explored by locally-weighted scatterplot smoothing (LOWESS)[25]. LOWESS produces

smoothed estimates of the association between two variables without requiring a priori specification. Since J-shaped associations were observed between both variables and the risk of fetal death, all models of fetal death or fetal and infant death combined were modelled by piecewise linear regression with knots at the lowest LOWESS values [49mmol/mol (6.6%) for peri-conception HbA_{1c} and 43mmol/mol (6.1%) for third trimester HbA_{1c}]. LOWESS was also used to estimate the absolute risks of fetal death, stillbirth, late stillbirth, and infant death for selected categories of peri-conception and third trimester HbA_{1c} by averaging the modelled risk for all values within that category (with CIs being estimated by bootstrapping from 10,000 subsamples). Logit-linked generalised estimating equations were used to estimate the absolute risk of late stillbirth for selected categories of peri-conception and third trimester HbA_{1c} simultaneously by evaluating the model at the category-specific means (with CIs being estimated using the delta method[26]). Due to instability at the LOWESS tails, only categories within the 5^{th} and 95^{th} centile of case values are reported. Participants with missing data were excluded from individual analyses by casewise deletion. 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.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed in this manuscript are entirely those of the authors and do not necessarily those of the funders.

Results

Figure 1 shows the derivation of the study sample. Overall, 397,392 singleton live births, stillbirths and late miscarriages uncomplicated by major congenital anomalies were identified during the study period, including 1,548 in women with pre-existing diabetes, a prevalence of 3.9 (95% CI: 3.7, 4.1) per 1,000 deliveries. Descriptive statistics for pregnancies affected by pre-existing diabetes are shown in **Supplementary Tables 1** and **2**. 53% involved male fetuses, 41% were primiparous, and 94% of women were white. The median maternal age was 30 years (interquartile range, IQR=25-34) and the median body mass index was 27kg/m^2 (IQR=24-32). 24% of women were recorded as smoking during pregnancy and 32% as taking folic acid pre-pregnancy. 78% had type 1 diabetes and 22% type 2. The median peri-conception and third trimester HbA_{1c} values were 62mmol/mol (IQR=51-76) and 50mmol/mol (IQR=43-58) respectively. The median gestational age at delivery was 37 weeks (IQR=36-38) and 38% were delivered preterm (<37 weeks).

Maternal pre-existing diabetes and the risks of fetal and infant death

46 fetal deaths (including five late miscarriages, 38 antepartum stillbirths and three intrapartum stillbirths) and ten infant deaths (including six neonatal deaths and four post-neonatal deaths) were observed in women with pre-existing diabetes. The prevalence of fetal death in women with pre-existing diabetes was 29.7 (95% CI: 21.8, 39.4) per 1,000 deliveries, over four times greater than among those without [RR=4.56 (95% CI: 3.42, 6.07) p<0.0001] (**Table 1**). The prevalence of fetal death was not significantly different between women with type 1 diabetes [28.2 (19.6, 39.2) per 1,000 deliveries] and women with type 2 diabetes [35.1 (18.3, 60.5) per 1,000 deliveries] (p=0.51). Significantly increased risks were observed for both antepartum stillbirths [RR=6.10, (4.44, 8.38) p<0.0001) and intrapartum stillbirths [RR=3.97 (1.27, 12.41) p=0.042). The estimated RR for a preterm fetal loss [RR=4.95 (3.59, 6.82) p<0.0001] was almost identical to that for a term stillbirth [RR=5.05 (2.62, 9.71) p<0.0001], although the RR for a late miscarriage was significantly smaller [RR=1.61 (0.67, 3.86) p=0.25] (**Table 2**). The prevalence of infant death in women with pre-existing diabetes was 6.7 (3.2, 12.2) per 1,000 live births, almost two times greater than among those without [RR=1.86 (1.00, 3.46) p=0.046] (**Table 1**). The prevalence of infant death was not significantly different between women with type 1 diabetes [7.7 (3.5, 14.5) per 1,000 live births] and women with type 2 diabetes [3.0 (0.8, 16.8) per 1,000 deliveries] (p=0.70).

Although the prevalence of fetal and infant death declined from 11.4 (10.8, 12.0) per 1,000 deliveries in 1996-1999 to 9.3 (8.8, 9.9) per 1,000 deliveries in 2005-2008 (p<0.0001), there was no change in the RR associated with diabetes [in 1996-1999: RR=4.5 (2.8, 7.0), in 2005-2008: RR=4.3 (2.8, 6.4)] (p=0.95).

HbA_{1c} and the odds of fetal and infant death

Increasing peri-conception HbA_{1c} for values above 49mmol/mol (6.6%) [adjusted OR, aOR per mmol/mol=1.02 (95% CI: 1.00, 1.04) p=0.01], pre-pregnancy retinopathy [aOR=2.05 (1.04, 4.05) p=0.04] and lack of pre-pregnancy folic acid consumption [aOR=2.52 (1.12, 5.65) p=0.03] were all independently associated with increased odds of fetal and infant death (**Supplementary Table 3**). Maternal smoking during pregnancy was also crudely associated with the risk of fetal and infant death [OR=1.91 (1.08, 3.36) p=0.03], but the association was not apparent after adjustment for peri-conception HbA_{1c} and folic acid consumption [aOR=1.54 (0.80, 2.94) p=0.19]. There was no evidence that the effects of peri-conception HbA_{1c}, pre-pregnancy retinopathy, or lack of pre-pregnancy folic acid consumption on the risk of fetal and infant death were different in women with type 2 diabetes compared with women with type 1 diabetes (p=0.85, p=0.24, and p=0.74 respectively). In later pregnancy, increasing third-trimester HbA_{1c} for values above 43mmol/mol [aOR=1.06 (1.03, 1.09) p<0.001] and lack of pre-pregnancy folic acid consumption [aOR=3.01 (1.03, 8.79) p=0.04] were the only variables that were significantly associated with the odds of a late stillbirth or infant death (**Supplementary Table 3**).

When fetal and infant death were examined individually, increasing peri-conception HbA_{1c} for values above 49mmol/mol (6.6%) was the only variable that was significantly associated with either fetal death [OR=1.02 (1.01, 1.04) p=0.01] or infant death [OR=1.03 (1.00, 1.06) p=0.01]. The association between peri-conception HbA_{1c} and the odds of fetal death followed a J-shaped pattern (**Figure 2**), although the inverse association for values below 49mmol/mol (6.6%) was not statistically significant [OR=0.95 (0.86, 1.05) p=0.31].

The estimated absolute risks of fetal death, stillbirth, late stillbirth, and infant death (overall and by peri-conception and third trimester HbA_{1c}) are reported in **Table 3**.

Discussion

Principal findings

This large population-based study describes the association between pre-existing diabetes and measures of glycaemic control and the risks of fetal and infant death in normally-formed singleton offspring. The prevalence of fetal death (3%) was over four times greater among women with pre-existing diabetes while the prevalence of infant death (0.7%) was nearly doubled. There was no evidence that the RR of fetal and infant death associated with pre-existing diabetes had reduced over time, nor that the RR of stillbirth varied by gestational age, although the RR was smaller for late miscarriages.

Among women with pre-existing diabetes, increasing peri-conception HbA_{1c} (for values above 45mmol/mol), history of retinopathy and lack of pre-pregnancy folic acid consumption were all associated with increased odds of fetal and infant death. Peri-conception HbA_{1c} was also associated with increased odds of fetal and infant death individually, with each 1mmol/mol increase [above 49mmol/mol (6.6%)] conferring a 2% and 3% relative increase respectively. The association between HbA_{1c} and the odds of fetal death appeared to follow a J-shaped pattern.

There was no difference in the risk of fetal and/or infant death among women with type 1 diabetes compared with those with type 2, nor was there any evidence that the associations with HbA_{1c}, folic acid consumption, or history of retinopathy were different between types.

Strengths and limitations

This study, describing one of the largest obstetric cohorts of women with pre-existing diabetes, benefits from the North of England's long history of collaboration between maternity and neonatal services, which created and maintains several complementary population-based registers. Detailed information was collected prospectively on a range of clinical and socio-demographic variables, including multiple measures of HbA_{1c}. All late miscarriages, stillbirths and infant deaths in the region, regardless of whether they occurred in women with diabetes, were obtained from an established register of fetal and infant mortality, minimising the risk of bias from disparities in ascertainment. By excluding all cases with major congenital anomaly derived from an independent and long-standing population-based register (which should again be robust to disparities in ascertainment); this

study is novel in describing the associations in normally-formed offspring. The results 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. Only six neonatal deaths, four post-neonatal deaths and three intrapartum stillbirths were identified, preventing these events from being analysed with precision. For most analyses, fetal and infant deaths were combined, despite likely differences in aetiologies[23]. Due to instability at the tails of our LOWESS models, we only report absolute risks for the middle 90% of values of HbA_{1c}. The primary multivariate analyses had adequate power (β=0.8) to detect a 'medium effect' (Cohen's $d \leq 0.5$, equivalent to an OR of ≥ 2.47) for any variable with a baseline exposure probability of 14%-65%. Weaker associations, or associations in exposures outside this range, may therefore have been missed.

Our LOWESS models, unlike our regression models, made no account for the non-independence of repeat pregnancies occurring within the same woman, introducing a potential source of error. For each regression model, however, the addition of the between-mother intercept did not significantly improve the model and only engendered negligible changes in the other coefficients, suggesting any bias is likely to be trivial.

Pre-conception HbA_{1c} was missing for half the cohort, reflecting low attendance for preconception care. We therefore used a composite measure of peri-conception HbA_{1c} as a proxy for pre-conception HbA_{1c}. Although first trimester values correlate highly with pre-conception, this may have introduced random error. HbA_{1c} itself is an imperfect measure of glycaemic control as it provides no information on glycaemic excursions or hypoglycaemic episodes[27], which may be important in the aetiopathology of fetal and/or infant death[28]. Continuous glucose monitoring provides a more complete record of day to day glycaemic control but is not routinely used in the UK. No information was recorded on pharmacological treatments, so we could not explore their possible contribution. Since the PMMS does not collect information on miscarriages before 20 weeks, we were not able to examine the RR of earlier fetal losses, the risks of which may also be raised in women with diabetes. Finally, although the PMMS records cause of death, over half of all deaths were attributed simply to 'maternal disorder', preventing us from exploring whether diabetes was associated with any particular cause.

Comparison with other studies

Flenady et al conducted an abridged meta-analysis, including just four studies, which estimated that RR of stillbirth was around three times higher in women with diabetes than among those without [OR=2.90 (2.05, 4.09)]. This is smaller than our estimates for both fetal death [OR=4.56 (3.42, 6.07)] and stillbirth [OR=5.87 (4.32, 7.97)][5]. The largest study to examine the RR of fetal death is Mondestrin et al's analyses of data from the US natality and mortality surveys during 1995-1997[9]. Describing 271,691 pregnancies complicated by diabetes and excluding births with recorded congenital anomalies, they reported an RR for fetal death of 2.0 (1.8, 2.2)[9], less than half our estimate. This may be because Mondestrin et al did not distinguish between pre-existing and gestational diabetes or may reflect ascertainment deficiencies inherent in using birth certificate data[9]. Recent data from Ontario describing deliveries from 2005-2006 showed an even smaller RR for stillbirth of 1.53 (0.88, 2.63) for pre-existing diabetes, although they also found an implausible protective effect for gestational diabetes [RR=0.33 (0.12, 0.71)][10]. In a large cohort from Australia including 433,379 deliveries from 1998-2002, Mohsin et al reported a similarly small RR of 1.87 (1.01, 3.48)[11], although it was not indicated how diabetes was defined or ascertained.

There is more agreement between studies from Northern Europe, which typically report RRs of four to five times for stillbirth and two to four times for neonatal/infant death. In a large study of women with type 1 diabetes from Sweden during 1991-2003, Persson et al reported ORs of 4.04 (3.02, 5.40) and 3.08 (2.02, 4.70) for late stillbirth and neonatal death respectively[12], while Jensen et al's study from Denmark during 1993-1999, reported corresponding RRs of 4.72 (3.18, 7.01) and 3.40 (1.91, 6.07)[13]. Eidem et al's study from Norway during 1985-2004 reported smaller, though not statistically inconsistent, ORs of 3.6 (2.5, 5.3) and 1.9 (1.1, 3.2) respectively[14]. Four studies from the UK reported strikingly similar results, possibly reflecting the increased homogeneity of care[15-18]. The four RR estimates for stillbirth ranged between 4.39 (2.22, 8.64) and 4.7 (3.7, 6.0)[15-18], while the two estimates of neonatal death were 2.4 (1.4, 4.1) and 2.6 (1.7, 3.9)[15, 17].

Eidem et al and dos Santos Silva et al examined whether the RR of stillbirth associated with diabetes varied by gestational age, both reporting that the effect was confined to term deliveries[14, 15]. In contrast, we found the RR of stillbirth was uniformly raised for all gestational ages. This discrepancy is due to different methodological approaches. Eidem et al and dos Santos Silva et al used the traditional method of calculating stillbirth rate per deliveries in that period[14, 15], an approach that is highly susceptible to confounding by differences in gestational

age distribution. The rate of induced preterm birth is considerably higher among women with diabetes than among those without.[29] This shift in the denominator produces an artifactually smaller stillbirth rate during preterm (and a larger one during term). By offsetting against the total population of fetuses at risk of fetal death at a particular gestational age, rather than simply the sample of deliveries at that gestational age, our findings are robust to this problem[23].

Few studies have described the continuous association between HbA_{1c} and the risk of fetal and/or infant death. Using LOWESS, Nielsen et al demonstrated an approximately linear association between increasing first-trimester HbA_{1c} above 53mmol/mol and the risk of 'adverse outcome', although this included congenital anomalies and elective terminations[30]. In women with type 1 diabetes, Jensen et al found that the RR of perinatal mortality increased steadily from 2.8 (1.3, 6.1) to 7.3 (2.5, 19.8) as peri-conception HbA_{1c} increased from <52mmol/mol to >90mmol/mol respectively[31]. Neither Nielsen et al nor Jensen et al specifically examined whether low values of HbA_{1c} were potentially harmful[30, 31], although Nielsen et al's LOWESS curve showed evidence of the same J-shape observed in our study[30].

The association between retinopathy, or any microvascular complication, and the risk of fetal or infant death in women with diabetes has not been well described. Contrasting with the current study, Jensen et al found no significant difference (p=0.58) in the rate of 'serious adverse outcome' (perinatal death and/or congenital anomaly) between women with and without retinopathy[13], although the proportion diagnosed with retinopathy was considerably smaller than in our cohort. In a previous study in women with diabetes in the North of England, nephropathy, but not retinopathy, was associated with an increased risk of congenital anomalies[2].

To our knowledge, this is the first study to explore the association between pre-pregnancy folic acid and the risk of fetal and infant death in women with diabetes. However, in a mixed population from England, during 2009-2011, Gardosi et al also identified a lower risk of stillbirth among women who had taken antenatal folic acid[32].

Implications and Conclusions

In England, the National Institute for Health and Clinical Excellence (NICE) recommends that women with pre-existing diabetes aim for a pre-conception HbA_{1c} below 43mmol/mol (6.1%)[19]. The American Diabetes

Association (ADA) suggest 53mmol/mol (7%)[20]. Our results strongly support the attainment and maintenance of good glycaemic control before and throughout pregnancy. If the average peri-conception HbA_{1c} had been 53mmol/mol (the ADA target), rather than 62mmol/mol, then our estimates suggest the prevalence of fetal and infant death would have been 38% lower. However, we found evidence of a J-shaped association between HbA_{1c} and the risk of fetal death. Although implausible that euglycaemic levels of HbA_{1c} are harmful, it is possible that hypoglycaemic episodes, which are more common in women with diabetes and low HbA_{1c}[33], may be[28]. At the least, our results show that for fetal deaths, as for congenital anomalies[2], there appears to be no substantive benefit of achieving peri-conception levels below the ADA target. At the other extreme, NICE discourages pregnancy when the pre-conception HbA_{1c} is above 86mmol/mol (10%)[19]. In demonstrating a clear continuum in risk above 53mmol/mol, our results provide no evidence for this specific threshold.

Even in women with optimal peri-conception HbA_{1c} [with values of 49mmol/mol (6.6%)], we estimated the risk of fetal death to be over twice as high as among women without diabetes [16.6 (8.6, 26.8) vs 6.5 (6.3, 6.8) per 1,000 deliveries]. This may reflect the limitations of HbA_{1c} as a marker of glycaemic control, or it may suggest that other risk factors are operating in women with diabetes.

The rate of fetal and infant death was over two times higher among women who did not take pre-pregnancy folic acid supplements. Women with pre-existing diabetes are advised to take high doses (5mg/day) of folic acid specifically 'to reduce the risk of having a baby with a neural tube defect'[19]. Our results suggest there may be additional benefits for normally-formed offspring, although folic acid use may also simply indicate better preparation for pregnancy.

History of retinopathy was associated with a doubling in the risk of fetal and infant death. It is possible that retinopathy indicates a prolonged history of poor glycaemic control that is not adequately described by HbA_{1c}, or it may signify wider microvascular deficiencies that might impair placental development. These women may warrant additional support when planning their pregnancy.

Over twenty years after the St Vincent declaration, we found that the excess risk of fetal and infant death in women with diabetes has remained stubbornly persistent. In the North of England, less than half of women with pre-

existing diabetes attend pre-conception care, with the proportion declining over time[34]. To achieve any reduction in the RR of stillbirth and infant death in women with pre-existing diabetes, the barriers to uptake of pre-conception care and adequate preparation for pregnancy must be urgently understood and addressed.

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Duality 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 conceived the project and, with JR and SVG, designed the study. PWGT performed the data analysis and drafted the manuscript. RWB was involved in the acquisition of the data. All authors were involved in the interpretation of the data and critically reviewed the manuscript. PWGT had full access to all the data and had final responsibility for the decision to submit for publication.

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Tables

Table 1 Relative risk of a fetal or infant death (in normally-formed singleton offspring) associated with maternal pre-existing diabetes in the North of England during 1996-2008.

Outcome	Without pre-existing diabetes		With pre-existing diabetes		Relative risk (95% CI)	p-value
	Cases (N=395,844[a] / 393,262[b])	Prevalence (95% CI), per 1,000 deliveries[c] / live births[d]	Cases (N=1548[a] / 1502[b])	Prevalence (95% CI), per 1,000 deliveries[c] / live births[d]		
Fetal or infant death	3988	10.1 (9.8, 10.4)	56	36.2 (27.4, 46.7)	3.59 (2.77, 4.65)	p<0.0001
Fetal death[e]	2582	6.5 (6.3, 6.8)	46	29.7 (21.8, 39.4)	4.56 (3.42, 6.07)	p<0.0001
Late miscarriage[f]	796	2.0 (1.9, 2.2)	5	3.2 (1.0, 7.5)	1.61 (0.67, 3.86)	p=0.25[m]
Stillbirth[g]	1786	4.5 (4.3, 4.7)	41	26.5 (19.1, 35.8)	5.87 (4.32, 7.97)	p<0.0001
Antepartum stillbirth[h]	1593	4.0 (3.8, 4.2)	38	24.5 (17.4, 33.5)	6.10 (4.44, 8.38)	p<0.0001
Intrapartum stillbirth[i]	193	0.5 (0.4, 0.6)	3	1.9 (0.4, 5.7)	3.97 (1.27, 12.41)	p=0.042[m]
Infant death[j]	1406	3.6 (3.4, 3.8)	10	6.7 (3.2, 12.2)	1.86 (1.00, 3.46)	P=0.046
Neonatal death[k]	904	2.3 (2.1, 2.5)	6	4.0 (1.5, 8.7)	1.74 (0.78, 3.87)	p=0.17[m]
Post-neonatal death[l]	502	1.3 (1.2, 1.4)	4	2.7 (0.7, 6.8)	2.09 (0.78, 5.57)	p=0.13[m]

[a]Total singleton live births, stillbirths and late miscarriages. [b]Total singleton live births. [c]The prevalence of fetal or infant death, and fetal death and all subsidiary outcomes of fetal death are presented per 1,000 deliveries. [d]The prevalence of infant death and all subsidiary outcomes are presented per 1,000 live births. [e]Late miscarriages and stillbirths. [f]Spontaneous loss of a fetus at 20-23 completed weeks of gestation. [g]Deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation. [h]Stillbirths where the fetus died before the onset of labour. [i]Stillbirths where the fetus died after the onset of labour. [j]Neonatal deaths and post-neonatal deaths. [k]Death, following live birth, within the first 28 days of life. [l]Death, following live birth, of an infant aged 28 days or more, but less than one year. [m]Fisher's exact test.

Table 2 Absolute and relative risks of a fetal death (in normally-formed singleton offspring) associated with maternal pre-existing diabetes, by gestational age.

Gestational age	Fetal deaths		Total deliveries		On-going pregnancies		Risk during given gestational age (95% CI)			
							Absolute risk (per 1,000 deliveries)		Relative risk	Compared with RR at term
Pre-existing diabetes:	With	Without	With	Without	With	Without	With	Without		
Preterm (20-36 weeks)	37	1913	585	34618	1548	395844	23.9 (16.9, 32.8)	4.8 (4.6, 5.1)	4.95 (3.59, 6.82)	0.98 (0.47, 2.04)
20-23 weeks	5	796	6	796[a]	1548	395844	3.2 (1.0, 7.5)	2.0 (1.9, 2.2)	1.61 (0.67, 3.86)	0.32 (0.11, 0.95)
24-27 weeks	10	413	15	4828	1542	395048	6.5 (3.1, 11.9)	1.0 (0.9, 1.2)	6.20 (3.32, 11.59)	1.23 (0.50, 3.05)
28-36 weeks	22	704	564	28994	1527	390220	14.4 (9.1, 21.7)	1.8 (1.7, 1.9)	7.99 (5.24, 12.17)	1.58 (0.72, 3.46)
Term (37-41 weeks)	9	669	963	361226	963	361226	9.3 (4.3, 17.7)	1.9 (1.7, 2.0)	5.05 (2.62, 9.71)	1 (reference)
Total	46	2582	1548	395844	1548	395844	29.7 (21.8, 39.4)	6.5 (6.3, 6.8)	4.56 (3.42, 6.07)	

[a]Bonellie et al[24] provides no estimate of the number of deliveries occurring during 20-23 weeks. This was approximated to be equal to the total number of fetal deaths during the same period.

Table 3 Absolute risk of a fetal or infant death (in normally-formed singleton offspring) in women with pre-existing diabetes, overall and by HbA_{1c} peri-conception and in the third trimester.

Outcome		Risk, per 1,000 (95% CI)									
			By peri-conception HbA_{1c} (mmol/mol, DCCT % in brackets)[a]								
			40 – 49 (5.8 – 6.6)	50 – 59 (6.7 – 7.5)	60 – 69 (7.6 – 8.5)	70 – 79 (8.6 – 9.4)	80 – 89 (9.5 – 10.3)	90 – 99 (10.4 – 11.2)	≤43[c] (≤6.1)	≤53[d] (≤7)	≥86[e] (≥10)	49[f] (6.6)
Fetal death		29.7 (21.8, 39.4)	19.6 (9.6, 33.6)	19.3 (11.9, 29.0)	28.4 (18.2, 40.6)	36.5 (24.2, 50.8)	41.5 (27.0, 58.3)	44.8 (26.4, 67.3)	31.9 (7.2, 64.8)	22.7 (9.5, 39.4)	46.7 (22.4, 79.41)	16.6 (8.6, 26.8)
Stillbirth		26.6[b] (19.1, 35.9)	18.7 (8.6, 31.6)	17.5 (10.3, 26.6)	24.7 (14.9, 36.0)	30.9 (19.3, 44.2)	35.4 (21.8, 51.1)	39.2 (21.6, 60.9)	30.9 (8.0, 64.7)	21.7 (9.3, 38.1)	42.7 (19.0, 74.2)	15.5 (7.8, 25.1)
Late stillbirth		20.3[b] (13.8, 28.7)	13.0 (4.9, 24.8)	12.4 (6.5, 20.3)	17.5 (9.9, 27.2)	23.4 (14.1, 34.9)	28.7 (16.7, 42.9)	33.9 (17.5, 53.6)	21.8 (3.0, 49.3)	15.2 (0.5, 29.0)	38.9 (16.0, 68.9)	10.7 (4.7, 19.0)
By third trimester HbA_{1c} (mmol/mol, DCCT % in brackets)	35 – 44 (5.4 – 6.2)	10.3 (4.3, 18.9)	7.1 (2.1-12.0)	6.4 (1.4-11.4)	8.1 (2.1-14.1)	10.3 (2.6-18.1)	12.3 (2.3-22.3)	14.6 (1.3-27.9)	8.4 (2.2-14.5)	8.4 (3.0, 13.9)	19.2 (2.2, 36.2)	5.6 (0.9, 10.4)
	45 – 54 (6.3 – 7.1)	13.4 (7.0, 21.0)	9.3 (2.6, 15.9)	8.3 (2.4, 14.3)	10.5 (3.8, 17.2)	13.3 (5.0, 21.7)	15.9 (5.1, 26.7)	18.8 (4.2, 33.3)	11.0 (2.2, 19.9)	11.0 (3.7, 18.4)	24.8 (4.2, 45.3)	7.3 (1.5, 13.2)
	55 – 64 (7.2 – 8.0)	22.5 (13.2, 33.4)	16.1 (4.8, 27.5)	14.5 (4.9, 24.1)	18.3 (8.5, 28.2)	23.3 (12.4, 34.2)	27.8 (14.4, 41.2)	32.7 (14.1, 51.4)	19.1 (3.8, 34.5)	19.2 (7.3, 31.1)	45.5 (15.4, 75.6)	12.8 (3.0, 22.6)
	65 – 74 (8.1 – 8.9)	39.8 (21.6, 62.2)	29.1 (5.2, 53.0)	26.2 (6.4, 46.1)	33.1 (13.0, 53.2)	42.0 (21.2, 62.8)	49.9 (27.1, 72.8)	58.6 (29.5, 87.7)	34.4 (3.1, 65.6)	34.5 (9.5, 59.5)	76.6 (27.9, 125.3)	23.2 (3.1, 43.3)
	75 – 84 (9.0–9.8)	72.9 (26.4, 123.4)	54.1 (<0.1, 110.2)	49.2 (1.6, 96.7)	61.9 (10.8, 113.0)	78.3 (23.1, 133.6)	92.8 (33.7, 151.9)	108.4 (41.4, 175.4)	63.3 (<0.1, 133.1)	63.8 (3.9, 123.7)	139.7 (36.1, 243.3)	43.6 (<0.1, 90.2)
	43[f] (6.1)	8.9 (4.2, 15.4)	6.3 (1.2, 11.3)	5.6 (1.0, 10.3)	7.1 (1.5, 12.7)	9.0 (1.8, 16.2)	10.7 (1.5, 20.0)	12.7 (0.5, 24.8)	7.5 (0.9, 14.1)	7.5 (1.7, 13.3)	16.8 (0.2, 33.3)	5.0 (0.6, 9.3)
Infant death		6.7 (3.2-12.2)	No cases[g]	4.3 (1.0, 9.2)	6.6 (2.2, 12.5)	8.8 (3.3, 16.0)	10.7 (4.2, 20.4)	13.3 (4.4, 26.0)	No cases[g]	No cases[g]	17.6 (4.0, 39.1)	No cases[g]

Fetal deaths, stillbirths, and late stillbirths are deliveries of a fetus showing no signs of life at ≥20 weeks of gestation, ≥24 weeks of gestation, and ≥28 weeks of gestation respectively. Infant deaths are deaths, following live birth, within the first year of life. The absolute risks of fetal death, stillbirth, late stillbirth and infant death, overall and by selected values of peri-conception and third trimester HbA_{1c}, were estimated by locally-weighted scatterplot smoothing (LOWESS) while the absolute risks of late stillbirth for selected values of peri-conception and third trimester HbA_{1c} simultaneously, were estimated from logit-linked generalised estimating equations.

[a]Defined as the closest measurement within three months prior to the last menstrual period or mean first trimester measurement (<14 weeks' gestation) for women with no pre-conception measurement. [b]Minor discrepancies from Table 1 are due to very slightly different denominators. Table 1 presents the rates per all deliveries after 20 weeks; these values are per deliveries after 24 weeks (stillbirths) and 28 weeks (late stillbirths) specifically. [c]A pre-pregnancy HbA_{1c} target of ≤43mmol/mol is recommended by the National Institute for Clinical Excellence: 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} *below 6.1%.*'[19] [d]A pre-pregnancy HbA_{1c} target of ≤53mmol/mol is recommended by the American Diabetes Association: *'A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted'*[20] [e]The National Institute for Clinical Excellence advises that women with a pre-pregnancy HbA1c above 86mmol/mol should be advised to avoid

pregnancy: ‘Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.’[19] [f]The peri-conception and third-trimester HbA_{1c} values with the lowest risks of fetal death or late stillbirth were estimated to be 49mmol/mol (6.6%) and 43mmol/mol (6.1%) respectively. LOWESS estimates for these values were obtained by averaging each LOWESS curve within ±1mmol/mol of the target value [g]There were no cases of infant death among women with a peri-conception HbA_{1c} below 53mmol/mol, thus the estimated risk for these categories are not reported.

Figures

Figure 1. Derivation of the study sample.

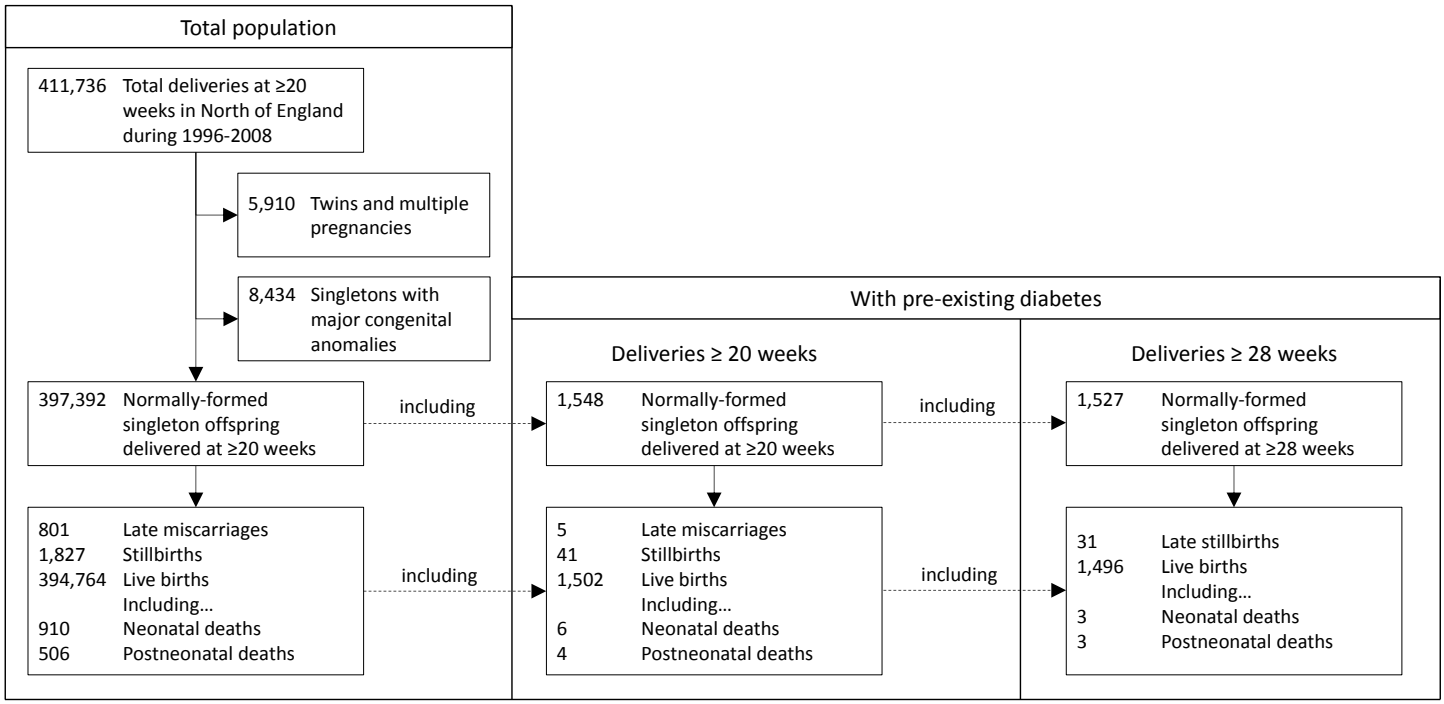
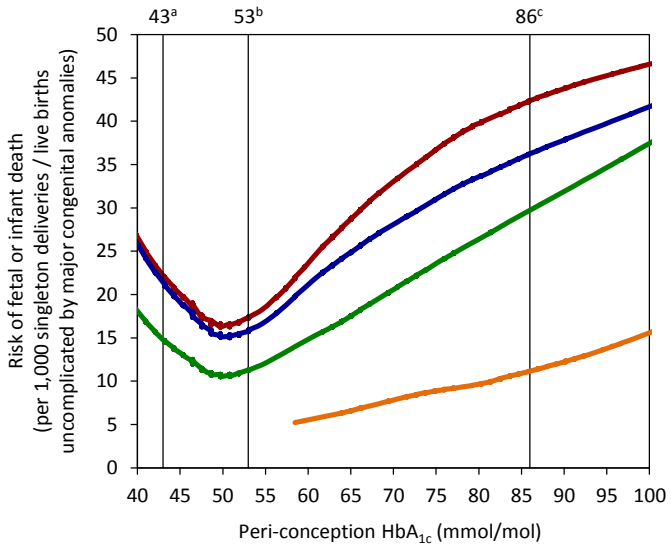


Figure 2. Peri-conception glycated haemoglobin (HbA_{1c}) and risk of fetal or infant death in women with pre-existing diabetes.



HbA_{1c}	40 – 49	50 – 59	60 – 69	70 – 79	80 – 89	90 – 99
Pregnancies	236	289	272	183	123	66
Fetal deaths	3	4	8	9	6	2
Infant deaths	0	2	2	1	1	2

Fetal deaths (red), **stillbirths (blue)**, and **late stillbirths (green)** are deliveries of a fetus showing no signs of life at ≥20 weeks of gestation, ≥24 weeks of gestation, and ≥28 weeks of gestation respectively. **Infant deaths (orange)** are deaths, following live birth, within the first year of life. [a]A pre-pregnancy HbA_{1c} target of ≤43mmol/mol is recommended by the National Institute for Clinical Excellence: 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} *below 6.1%.'*[19] [b]A pre-pregnancy HbA_{1c} target of ≤53mmol/mol is recommended by the American Diabetes Association: *'A1C levels should be as close to normal as possible (<7%) in an* individual patient before conceptio*n is attempted'*[20] [c]The National Institute for Clinical Excellence advises that women with a pre-pregnancy HbA1c above 86mmol/mol should be advised to avoid pregnancy: 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.'[19]