Glycosylated Haemoglobin and Adverse Pregnancy Outcomes in Type 1 and Type 2 Diabetes Mellitus: Systematic Review of Observational Studies

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Abstract

Background

Glycaemic control in women with diabetes is critical to satisfactory pregnancy outcome. A systematic review of two randomised trials concluded that there was no clear evidence of benefit from very tight versus tight glycaemic control for pregnant women with diabetes.

Methods

A systematic review of observational studies addressing miscarriage, congenital malformations and perinatal mortality among pregnant women with type 1 and type 2 diabetes was carried out. Literature searches in MEDLINE, EMBASE, CINAHL and Cochrane Library. Observational studies with data on glycosylated haemoglobin levels categorised into poor and optimal control (as defined by the study investigators) were selected. Relative risks and odds ratios were calculated for glycosylated haemoglobin and pregnancy outcomes. Adjusted relative risk estimates per 1-percent decrease in HbA$_1$c were calculated for studies which contained information on mean and standard deviations of HbA$_1$c.

Results

Twelve studies reported the outcome of congenital malformations and there was an increased risk with poor glycaemic control, pooled odds ratio 3.44 (95%CI, 2.30 to 5.15). For four of the ten studies, it was possible to calculate a relative risk reduction of congenital malformation for each 1-percent decrease in HbA$_1$c, these varied from 0.39 to 0.59. In four studies, risk of miscarriage was associated with poor glycaemic control, pooled odds ratio 3.23 (95%CI, 1.64 to 6.36). Increased perinatal mortality
was also associated with poor glycaemic control in four studies, pooled odds ratio 3.03 (95%CI, 1.87 to 4.92).

Conclusions

This analysis quantifies the increase in adverse pregnancy outcomes in women with diabetes who have poor glycaemic control. Relating percentage risk reduction in HbA1c to relative risk of adverse pregnancy events may be useful in motivating women to achieve optimal control prior to conception.
Background

Diabetes is the most common pre-existing medical condition complicating pregnancy in the United Kingdom (approximately four occurrences per 1000 pregnancies).(1) It is known to have a substantial impact on maternal, fetal and neonatal outcomes. The presence of diabetes is said to increase the risk of congenital malformation (by ten-fold), the risk of stillbirth (by five-fold), and the risk of neonatal death (by three-fold).(2-7) These disappointing data are in contrast to the optimism of the 1989 St Vincent’s Declaration that proposed as a five year target that the outcome of pregnancy should approximate that of the non-diabetic pregnancy.(8)

A pivotal part of management is good diabetic control which is believed to reduce the incidence of pregnancy complications. Glycosylated haemoglobin (HbA1c) reflects long-term glycaemic control and is a more accurate and stable measure than fasting blood glucose levels.(9) It tracks well over time in individuals with diabetes and has less variability than fasting blood glucose.

Longer term glycaemic control in women with diabetes is critical to satisfactory pregnancy outcome. As organogenesis takes place in the first trimester of pregnancy, inadequate pre-conceptual glycaemic control is associated with an increased risk of congenital abnormality and spontaneous abortion.(10;11)

Clinical management decisions are limited by a dearth of randomised trial data due to ethical reasons and current practice must rely on the findings of high quality observational studies.

We performed a systematic review of observational studies to investigate and quantify the risk of adverse pregnancy outcomes in pregnant women with diabetes in relation to glycaemic control, whether poor or optimal.
Methods

Study Design:
We systematically reviewed observational studies of glycosylated haemoglobin and pregnancy outcomes in women with diabetes mellitus.

Study Selection:
We searched the MEDLINE database for articles published in English from 1966 to January 2005 by using Medical Subject Heading terms and text words related to pregnancy, diabetes mellitus, glycaemic control and glycosylated haemoglobin (Figure 1 contains the full text of the search strategy). We also searched EMBASE, CINAHL and the Cochrane Library.

We reviewed all abstracts obtained from our search for relevance. We manually reviewed bibliographies and review articles for additional citations and obtained the full text of potentially relevant articles.

Our pre-specified inclusion criteria were as follows: 1) observational studies that examined pregnancy outcomes in women with type 1 and type 2 diabetes and 2) studies that reported a measure of glycosylated haemoglobin and categorised pregnancy outcomes according to poor and optimal glycaemic control. We excluded studies if they included women with gestational diabetes.

Data Abstraction:
One investigator reviewed each article that met the selection criteria and abstracted the data by using standardised data abstraction forms. Information was collected on study design, country of study, time-period of study, glycaemic control groups, method of measuring glycosylated haemoglobin, and timing of glycaemic control measurement. Data abstracted were age, parity, smoking, duration of diabetes, pre-pregnancy planning, folic acid consumption, presence of microvascular
complications, pre-pregnancy insulin dose, sample size, type of outcome or outcomes, main results, statistical methods and variables, if any, which were included in the adjusted model or models.

For each study that met our inclusion criteria, we abstracted relative risks and odds ratios for the association between adverse pregnancy outcomes and poor vs. optimal glycaemic control if they were stated. If not, then the relative risks and odds ratios were calculated from information stated in each study.

A range of outcomes were investigated, however due to the quality of data we focussed on congenital malformations, miscarriage and perinatal mortality (which included stillbirths and neonatal deaths).

Quality assessment was modified to suit a meta-analysis of observational studies rather than randomized controlled trials, examining patient selection, data extraction methods, losses to follow up, confounding and bias.

Statistical Analysis:

In the primary analysis, HbA$_1c$ was the principal ‘exposure’ of interest. HbA$_1c$ was categorised into poor and optimal control. Dichotomous outcomes are expressed as odds ratios and 95% confidence intervals are calculated. A test of heterogeneity was performed for each outcome and if no heterogeneity was present, a fixed-effects meta-analysis was performed. If heterogeneity was marked, random effects models were performed.

For studies that reported the mean and SD of glycosylated haemoglobin we estimated the effect of a 1-unit percent change in glycosylated haemoglobin, assuming a normal distribution for glycosylated haemoglobin values. We calculated the 25$^{th}$ and 75$^{th}$ percentiles and divided the log relative risk by the difference of these 2 values to give an estimate of the effect of a 1-percent change in glycosylated haemoglobin.(12) We
did not pool data from individual studies for these analyses as the measurement of
glycosylated haemoglobin differed between centres.

We assessed publication bias where possible by using the Egger test(13) and funnel
plots which graphically display the magnitude of the effect estimate by the inverse
variance of the study. Sensitivity analyses assessed the relative influence of each
study by omitting one study at a time to assess the influence of the single study on the
pooled estimate.

Statistical analyses were conducted using StatsDirect and Stata software.
Results

Search Results:
Our study identified 880 published studies from our search strategy. We retrieved the text of 256 and reviewed them to assess whether they provided information on glycosylated haemoglobin and adverse pregnancy outcome in pregnant women with type 1 and type 2 diabetes. After we applied all exclusion and inclusion criteria, thirteen studies which compared poor vs. optimal glycaemic control in relation to maternal, fetal and neonatal outcomes, were included in this review, (Figure 2 contains the flow diagram of studies). Of these, eight were cohorts, two case-controls, one cross-sectional and two historical reviews.

Qualitative Summary:
Seven studies specifically looked at only women with type 1 diabetes and the remaining six studies included both type 1 and type 2. Table 1 summarises the characteristics of all studies included in the analysis. Study populations were from United States, United Kingdom, Finland, France, Netherlands, Sweden and Poland. Sample sizes ranged from 83 to 2459 participants in the largest study, with a total of 5550 women. Most studies involved patients who were receiving pregnancy care at the study outpatient clinics. All studies described basic inclusion and exclusion criteria for study participants.

The method of measurement of glycosylated haemoglobin varied across all the studies. Five studies used high-performance liquid chromatography. (7;14-17) Other methods used included spectrophotometric absorption,(18) column chromatography,(19) cation exchange method,(20) thiobarbituric acid colorimetric
assay, (21) electrophoresis, (22) and isoelectric focusing. (23) Two of the studies did not give details on their method of measuring glycosylated haemoglobin. (24;25) All studies used different cut-off points for grouping glycosylated haemoglobin into poor and optimal groups, varying from 5.6% to 10.1%. The timing of the glycaemic control measurement varied across the studies, the majority of studies (twelve) measured HbA$_{1c}$ during the first trimester. One study based glycaemic control on measurements taken at the first antenatal visit, 20$^{th}$ and 28$^{th}$ week of gestation, and just before delivery. (25) The data extraction method varied across the studies and very few studies (14;16) adjusted for potential confounding factors in their analysis, (Table 2). Of these, neither stated what specific factors they adjusted for in the analysis.

**Quantitative Summary:**

The most common pregnancy outcome to be investigated was the outcome of congenital malformation, in which twelve out of the thirteen studies reported, (Table 3). All other maternal, fetal and neonatal outcomes were only reported in one, two, three, or four of the studies.

The pooled estimate for patients with poor control and the outcome of congenital malformations was 3.44 (95% CI, 2.30 to 5.15), (Figure 3). Several studies only reported major congenital malformations and the pooled estimate was 5.14 (95% CI, 2.94 to 9.01), (Figure 4). It was possible to calculate a relative risk for each 1-percent point increase in glycosylated haemoglobin for four out of the twelve studies which investigated the outcome of congenital malformations, these are presented in Table 4. The relative risk estimates varied from 1.63 to 2.34 per 1-percent point increase in HbA$_{1c}$. These could be translated to a relative risk reduction per 1-percent point decrease in HbA$_{1c}$ and varied from 0.39 to 0.59.
The pooled estimate for the outcome of miscarriage was 3.23 (95% CI, 1.64 to 6.36), (Figure 5) and for the outcome of perinatal mortality an odds ratio of 3.03 (95% CI, 1.87 to 4.92), (Figure 6).

Sensitivity analyses indicated that three of the studies seemed to contribute more greatly to the analysis. (14;15;24)

**Publication Bias:**

A bias assessment plot for the outcome of congenital malformations is shown in Figure 7. The Egger test was not significant ($P>0.05$) for the congenital malformation subgroup analysis. For the other outcomes however, the small number of studies limits our ability to draw conclusions regarding publication bias and heterogeneity of studies.
Discussion

In our analysis of thirteen published studies, adverse pregnancy outcomes were associated with higher levels of glycosylated haemoglobin in women with type 1 and type 2 diabetes mellitus. These associations were present across different geographic populations and different time periods. A decrease in HbA1c was associated with a clinically important reduction in the risk of fetal congenital malformations. The outcome of congenital malformations was the most commonly reported outcome across the studies. Reasons for this may be because many clinical and epidemiological studies indicate that fetal malformations in pregnancy complicated by diabetes are due to metabolic disturbances affecting the process of organogenesis, which takes place at the early stage of pregnancy. The most common malformations in infants of mothers with diabetes are defects of the cardiovascular system. Studies suggest that these tissues are the most susceptible ones to the destructive action of oxygen-free radicals.(19) Our analysis shows that poor glycaemic control results in a greater than three-fold risk for the outcome of congenital malformations compared to optimal glycaemic control. The rates of miscarriage and perinatal mortality were higher in the poor glycaemic control groups compared with the optimal control groups. Perinatal mortality rates have markedly decreased over the last 25 years, however there still appears to be a higher rate of perinatal mortality with poorer levels of glycaemic control.

There are limited randomised trial data on the impact of different levels of glycaemic control on outcome in diabetic pregnancies.(26) The randomised, prospective Diabetes Control and Complications Trial (DCCT) has shown that timely institution of intensive therapy for blood glucose control is associated with rates of spontaneous abortion and congenital malformations that are similar to those in the non-diabetic
A Cochrane systematic review of randomised trials comparing very tight with tight control of diabetes in pregnancy focused on two trials involving a total of 182 women. The conclusion was that there was no clear evidence of benefit from very tight versus tight glycaemic control for pregnant women with diabetes. (26) Observational studies show much less favourable outcomes in unselected populations. In many studies, adverse outcomes remain more common among the infants of mothers with type 1 diabetes than in the general population. (8;28) The targets of the St. Vincent’s Declaration of 1989 appear not to have been met, thus far. Reasons for persistently poor outcomes in these populations may include unplanned pregnancies, pregnancies in women who have not received pre-conceptual care, or pregnancies in women who fail to achieve optimal control despite adequate pre-conceptual care. The factors that influence women to seek preconception care and counselling and then to actually achieve optimal glycaemic control prior to conception have become important to clinicians. Factors that seem to promote preconception care include higher educational levels, higher incomes, regular employment, and receiving encouragement from their health care providers to avoid unplanned pregnancies. (29) Past pregnancy experience may also play a role through influencing behaviour concerning diabetic control and health habits. (30)

A systematic review of 14 cohort studies has shown that pre-conception care aiming to achieve tight glycaemic control is associated with a reduction in the rate of major congenital abnormalities – 2.1% in the preconception care recipients versus 6.5% in non recipients, relative risk 0.36, 95% CI 0.22 to 0.59. (31) Patients who frequently monitor and adjust their diabetes regimen are more likely to maintain strict control of their blood glucose levels throughout pregnancy. (32) Our findings support this with a marked increase in congenital malformation in association
with poor glycaemic control. A decremental approach to HbA1c may appeal to women who are overwhelmed at the prospect of achieving a dramatic change in control from poor to optimal. Advising women that there is a potential health gain with each 1% reduction may be a useful motivator in gradual reduction to an optimal level or may provide some reassurance for women who manage a large improvement but do not quite achieve optimal levels.

This review has several limitations. It is unclear to what extent methodologic limitations, such as residual confounding and selection bias, might exist in these studies. The pooled odds ratios have been used to quantify the risks, however the small number of studies meant that statistical analyses for heterogeneity and publication bias were limited. Thus, we cannot exclude the possibility that the observed association is a result of publication bias.

The studies use different definitions of poor and optimal control, ranging from 5.6% to 10.1%. Reasons for this include the use of different methods of measurements for glycosylated haemoglobin and varying reference ranges for the non-diabetic population. Nonetheless, the cut-offs used were appropriate to the method used to measure glycosylated haemoglobin and relevant to the reference range in use for the individual study populations.

Definitions for several of the outcomes varied across the studies, for example, the outcome of congenital malformations included both major and minor malformations in some studies(15;25)while in others only included major malformations. (7;17)

Few studies adjusted for confounding factors in their analysis and there is no certainty that the observed association was caused exclusively by an elevated HbA1c level rather than to some degree by related confounders. In the majority of the studies we do not know how advanced the patients’ diabetes was. Diabetic nephropathy and
retinopathy are the most frequent complications in patients of childbearing age with diabetes and will have an important impact on pregnancy outcome. (33) One possible causal factor for adverse outcome could be women with established diabetes complications, such as microvascular disease. A single unsatisfactory glycosylated haemoglobin value cannot be used as an absolute predictor of fetal outcome, but it indicates a subgroup of pregnancies with substantial fetal risk. (25)

Major advantages of pooling data from observational studies to investigate this important clinical issue are better generalisability because the analyses combine data from heterogeneous populations, and increased sample size.

**Conclusions**

Our systematic review highlights important weaknesses in the literature. Studies to date are based on very small numbers and this systematic review allows more robust estimate of risk. Many important clinical outcomes were not examined in the thirteen studies included in the review. More than a decade after the initial evidence proposing that pregnancy outcome was improved by better glycaemic control, the question of how strict that control should be remains unanswered. There remains an urgent need to address the maternal and perinatal benefits of varying degrees of control of blood sugar for pregnant women with diabetes. Outcome measures should be standardised and include important factors associated with poor perinatal and maternal outcomes, such as pre-eclampsia, macrosomia, caesarean section, shoulder dystocia, perinatal loss, neonatal respiratory and metabolic complications. (26) Future studies also need to investigate the issue of pre-conceptual glycaemic control and post pregnancy outcomes for the mother. We are currently undertaking a study exploring the related issues of pre-conceptual glycaemic control, antenatal care, and mode of delivery in
terms of pregnancy-related, maternal and neonatal outcomes both in the short- and long-term.

We conclude that adverse pregnancy outcomes in women with type 1 and type 2 diabetes mellitus were associated with higher levels of glycosylated haemoglobin. This review summarises the currently available evidence and should be useful to clinicians who are counselling women with type 1 and type 2 diabetes in the reproductive years.

**List of abbreviations used**

Confidence interval (CI); United Kingdom (UK); glycosylated haemoglobin (HbA$_{1c}$); standard deviation (SD); Diabetes Control and Complications Trial (DCCT); Confidential Enquiry into Maternal and Child Health (CEMACH).

**Competing interests**

All authors have nothing to declare.

**Authors' contributions**

MEI, TPF and DJM conceived the review, MEI reviewed and analysed the data and wrote the review. All authors interpreted the data, contributed to writing the manuscript, and gave critical comments. All authors have given approval of the final version to be published.
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References


<table>
<thead>
<tr>
<th>Author et al, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Time Period</th>
<th>Sample size (n)</th>
<th>Glycaemic Control Groupings (HbA₁c unless stated)</th>
<th>Timing of Glycaemic Control Measurement</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaarasmaki et al, 2000 (25)</td>
<td>Finland</td>
<td>Cohort</td>
<td>1986-1995</td>
<td>84</td>
<td>Optimal &lt; 8.0% Poor &gt; 8.0%</td>
<td>First antenatal visit 20 and 28th week Before delivery</td>
<td>Malformations Caesarean Section Stillbirth NICU Neonatal Hypoglycaemia RDS</td>
</tr>
<tr>
<td>Greene et al, 1989(22)</td>
<td>US</td>
<td>Cohort</td>
<td>Dec.5th 1983-Dec.31st 1987</td>
<td>303</td>
<td>Optimal ≤ 9.3% Poor ≥ 9.4% (Data based on HbA₁c)</td>
<td>1st trimester</td>
<td>Malformations Spontaneous Abortion</td>
</tr>
<tr>
<td>Evers et al, 2004(15)</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>April 1st 1999 - April 1st 2000</td>
<td>261</td>
<td>Optimal ≤ 7.0% Poor ≥ 7.0%</td>
<td>1st trimester</td>
<td>Malformations</td>
</tr>
<tr>
<td>Key et al, 1987(15;18)</td>
<td>US</td>
<td>Cohort</td>
<td>Jan.1st 1979 – Dec.31st 1984</td>
<td>83</td>
<td>Optimal &lt;7.5% Poor ≥ 7.5%</td>
<td>1st trimester</td>
<td>Malformations Spontaneous Abortion</td>
</tr>
<tr>
<td>Kitzmiller et al, 1991(21)</td>
<td>USA</td>
<td>Cohort</td>
<td>1982-1988</td>
<td>194</td>
<td>Optimal ≤ 7.6% Poor &gt; 7.6%</td>
<td>1st trimester booking visit</td>
<td>Malformations</td>
</tr>
<tr>
<td>Ylinen et al, 1984(20)</td>
<td>Finland</td>
<td>Cohort</td>
<td>April 1978-Dec. 1982</td>
<td>142</td>
<td>Optimal ≤ 7.9% Poor &gt;7.9%</td>
<td>Before 16 weeks gestation</td>
<td>Malformations</td>
</tr>
<tr>
<td>CEMACH, 2005(24)</td>
<td>England, Wales &amp; Northern Ireland Descriptive Cohort</td>
<td>March 1st 2002-Feb 28th 2003</td>
<td>2459</td>
<td>Optimal &lt; 7% Poor ≥ 7%</td>
<td>1st trimester</td>
<td>Malformations Stillbirths or neonatal deaths</td>
<td></td>
</tr>
<tr>
<td>Hiilesmaa et al, 2000(16)</td>
<td>Finland</td>
<td>Case-Control</td>
<td>1988 - 1997</td>
<td>664</td>
<td>Optimal ≤ 6.8% Poor &gt; 6.8%</td>
<td>Early pregnancy</td>
<td>Pre-eclampsia PIH</td>
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<td>Hanson et al, 1990(23)</td>
<td>Sweden</td>
<td>Case-Control</td>
<td>1982-1985</td>
<td>532</td>
<td>Optimal &lt;10.1% Poor ≥ 10.1%</td>
<td>1st trimester</td>
<td>Spontaneous abortion Malformation</td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Study Design</td>
<td>Time Period</td>
<td>Sample size (n)</td>
<td>Glycaemic Control Groupings (HbA1c unless stated)</td>
<td>Timing of Glycaemic Control Measurement</td>
<td>Outcomes</td>
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<tr>
<td>Miller et al, 1981(17)</td>
<td>US</td>
<td>Case-series</td>
<td>April 1977 – April 1980</td>
<td>116</td>
<td>Optimal ≤ 8.5% Poor ≥ 8.6%</td>
<td>Initial value</td>
<td>Malformations</td>
</tr>
<tr>
<td>Wender-Ozegowska et al, 2005(19)</td>
<td>Poland</td>
<td>Case-Series</td>
<td>1st Jan. 1994-31st Jan. 1999</td>
<td>119</td>
<td>Optimal ≤ 5.6% Poor &gt; 5.6%</td>
<td>1st trimester</td>
<td>Malformations</td>
</tr>
</tbody>
</table>
Table 2: Methods and statistical analysis of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection of patients</th>
<th>Data Extraction Method</th>
<th>Losses to follow up</th>
<th>Confounding accounted for in analysis</th>
<th>Power calculation</th>
<th>Blinding of outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaarasmaki et al, 2000 (25)</td>
<td>Hospital records from one tertiary university hospital and four central secondary hospitals</td>
<td>Medical records</td>
<td>Not mentioned.</td>
<td>No. Relative Risks not calculated.</td>
<td>No</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Greene et al, 1989 (22)</td>
<td>All patients presenting at the study clinic at 12 weeks gestation or less.</td>
<td>Medical Records and Follow-up Phone Contact</td>
<td>21 patients were excluded from study for insufficient outcome data, 2 patients suffered 1st trimester spontaneous abortions at other hospitals, 9 patients transferred care to other hospitals, and 10 patients were completely lost to follow-up. (12%)</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Evers et al, 2004 (15)</td>
<td>All patients presenting at the study clinics.</td>
<td>Patient and medical professional questionnaires.</td>
<td>One maternal death at 17wks gestation, 4 therapeutic abortions, and 4 spontaneous abortions before 24wks gestation. (3.3%)</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Key et al, 1987 (18)</td>
<td>All patients receiving prenatal care at the study clinic before 15th wk of gestation.</td>
<td>Direct measurement.</td>
<td>11 elective terminations and 12 patients transferred care or were lost to follow-up. (21.7%)</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study ID</td>
<td>Selection of patients</td>
<td>Data Extraction Method</td>
<td>Losses to follow up</td>
<td>Confounding accounted for</td>
<td>Power calculation</td>
<td>Blinding</td>
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<tr>
<td>Temple et al, 2002 (7)</td>
<td>Women delivering at a single centre in Norwich.</td>
<td>Not mentioned.</td>
<td>Not stated.</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kitzmiller et al, 1991(21)</td>
<td>Patients recruited for preconception education and patients already pregnant who registered for education and intensive management.</td>
<td>Direct measurement</td>
<td>14 spontaneous abortions and 3 elective abortions in preconception group. 9 elective and 12 spontaneous abortions in postconception group.</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ylinen et al, 1984 (20)</td>
<td>Patients referred to study hospital between 6th and 15th weeks gestation.</td>
<td>Direct measurement</td>
<td>N/A</td>
<td>Not stated.</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>CEMACH, 2005(24)</td>
<td>Patients presenting at one of the 231 maternity units in the study</td>
<td>Questionnaire</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Study ID</td>
<td>Selection of patients</td>
<td>Data Extraction Method</td>
<td>Losses to follow up</td>
<td>Confounding accounted for</td>
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<tr>
<td>Hiilesmaa <em>et al</em>, 2000 (16)</td>
<td>Women were selected from outpatients attending the Dept. of Obs &amp; Gyn. at study centre.</td>
<td>Direct measurement</td>
<td>N/A</td>
<td>Multiple logistic regression was used to assess the main effects of variables independently associated with the outcome. Don’t know what these variables are – Possibly adjusted for age, educational level, hypertension, twin pregnancy, BMI, pre-pregnancy insulin dose, insulin dose increment during pregnancy, smoking, participation in pre-pregnancy planning.</td>
<td>To detect a doubling of the frequency of pre-eclampsia (6 vs 3%) was 81% at a p-value of 0.05.</td>
<td>N/A</td>
</tr>
<tr>
<td>Hanson <em>et al</em>, 1990(23)</td>
<td>Patients presenting at one of the study clinics</td>
<td>Direct measurement and Medical records</td>
<td>20 patients excluded because of incomplete data. 5 pregnancies excluded because of legal termination.</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes and Pregnancy Group, France, 2003 (14)</td>
<td>Patients delivering in one of 12 tertiary perinatal centres were recruited.</td>
<td>Prospective. Direct measurement.</td>
<td>N/A</td>
<td>Logistic regression model was used to assess the role of independent variables on pregnancy outcomes. Not stated what independent variables were used.</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Miller <em>et al</em>, 1981(17)</td>
<td>All pregnant insulin-requiring women who were followed at the prenatal clinics of the study centres.</td>
<td>Medical Records and Phone Contact</td>
<td>N/A</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study ID</td>
<td>Selection of patients</td>
<td>Data Extraction Method</td>
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</tr>
<tr>
<td>Wender-Ozegowska et al, 2005 (19)</td>
<td>Case note review of patients delivering at study centre.</td>
<td>Medical records</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 3: Pregnancy outcomes and number of studies included in review reporting outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies reporting outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
<td>12</td>
</tr>
<tr>
<td>Spontaneous abortions</td>
<td>4</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>4</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>1</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1</td>
</tr>
<tr>
<td>Neonatal hypoglycaemia</td>
<td>1</td>
</tr>
<tr>
<td>Neonatal Intensive Care Unit Admission</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Distress Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Caesarean Section</td>
<td>1</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 4: Relative risk estimates per 1-percentage point increase in glycosylated haemoglobin and the outcome of congenital malformation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Mean</th>
<th>SD</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>δ</th>
<th>InRR</th>
<th>RR per 1% point increase</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller(17)</td>
<td>8.54</td>
<td>1.54</td>
<td>7.50</td>
<td>9.58</td>
<td>2.08</td>
<td>1.87</td>
<td>2.34</td>
<td>0.59</td>
</tr>
<tr>
<td>Greene (22)</td>
<td>10.10</td>
<td>1.99</td>
<td>8.76</td>
<td>11.44</td>
<td>2.68</td>
<td>1.31</td>
<td>1.63</td>
<td>0.39</td>
</tr>
<tr>
<td>Evers (15)</td>
<td>6.5</td>
<td>0.70</td>
<td>6.03</td>
<td>6.97</td>
<td>0.94</td>
<td>0.65</td>
<td>1.99</td>
<td>0.50</td>
</tr>
<tr>
<td>Key (18)</td>
<td>10.99</td>
<td>1.10</td>
<td>10.25</td>
<td>11.73</td>
<td>1.48</td>
<td>1.0</td>
<td>1.95</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Additional files
Additional file 1 – QUORUM Statement
QUORUM statement included as a pdf file.
Figure 1 - Search strategy

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp cohort studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. Cohort analys$.tw.
7. (Follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. Longitudinal.tw.
10. Retrospective.tw.
12. Cross-sectional studies/
13. Or/1-12
14. Diabetes Mellitus/ or Diabetes Mellitus, Type I/
15. Pregnancy in Diabetics/
17. Pregnancy outcome$/
18. Pregnancy complication$/
19. Infant, Newborn/
20. Fetus/
21. Foetus.mp.
22. Fetal.mp.
23. Foetal.mp.
24. Embryo.mp. and Fetal Development/
25. Newborn.mp.
27. Childbirth.mp.
28. Labour.mp.
29. Labor, Obstetric/
30. Delivery, Obstetric/
32. Miscarriage.mp.
33. abortion, spontaneous/
34. Abortion.mp.
35. abortion, induced/
36. termination.mp.
37. stillbirth.mp.
38. perinatal mortality.mp.
39. infant mortality/
40. Abnormalities/
41. congenital abnormalit$.mp.
42. congenital malformatio$.mp.
43. congenital anomal$.mp.
44. Birth defect$.mp.
45. neonatal trauma.mp.
46. birth injur$.mp.
47. neonatal hypoglycaemia.mp.
48. fetal macrosomia/
49. fetal distress/
50. intensive care, neonatal/
51. antepart$.mp.
52. prenatal.mp.
53. antenatal.mp.
54. perinatal.mp.
55. postnatal.mp.
56. postpart$.mp.
57. obstetrics/
58. preeclamps$./
59. Hypertensi$./
60. Diabetic nephropath$./
61. Diabetic retinopath$./
62. Haemoglobin A, Glycosylated
63. Hemoglobin A, Glycosylated
64. Or/16-63
65. 14 and 64
66. 15 and 64
67. 13 and 65
68. 13 and 66
69. 67 and 68
Figure 2 - Flow of studies in the review

Potentially relevant articles identified and screened for retrieval (n=880)

Studies excluded following review of abstract (n=624)

Studies retrieved for more detailed evaluation (n=256)

Studies excluded: (n=219)
Reasons: No categorisation of glycaemic control; Study population includes gestational diabetics; Study carried out on diabetic population with substantial diabetic complications thus not representative of general diabetic population; Patients on intensive insulin treatment; No relevant outcomes; Patients involved in trial; Review.

Potentially appropriate studies to be included in the meta-analysis (n=37)

Studies excluded from the meta-analysis (n=25)
Reasons: Glycaemic control groupings not related to outcomes; Measurement of glycaemic control not based on glycosylated haemoglobin.

Studies included in meta-analysis (n=13)

Studies withdrawn, by outcome (n=0)

Studies with usable information by outcomes (n=13)
Figure 3: Risk of congenital malformation for poor versus optimal glycaemic control.

Odds ratio meta-analysis plot [random effects]

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaarasmaki</td>
<td>11.88 (0.69, infinity)</td>
</tr>
<tr>
<td>Greene</td>
<td>4.06 (1.12, 22.12)</td>
</tr>
<tr>
<td>Evers</td>
<td>2.05 (0.74, 5.37)</td>
</tr>
<tr>
<td>Key</td>
<td>3.07 (0.14, 67.26)</td>
</tr>
<tr>
<td>Temple</td>
<td>9.91 (0.93, 492.32)</td>
</tr>
<tr>
<td>Ylinen</td>
<td>4.31 (1.11, 24.30)</td>
</tr>
<tr>
<td>Kitzmiller</td>
<td>3.83 (1.05, 14.24)</td>
</tr>
<tr>
<td>DPG</td>
<td>3.49 (1.20, 10.42)</td>
</tr>
<tr>
<td>Miller</td>
<td>6.77 (0.56, 299.00)</td>
</tr>
<tr>
<td>Wender-Ozegowska</td>
<td>2.04 (0.50, 11.97)</td>
</tr>
<tr>
<td>CEMACH</td>
<td>1.90 (1.19, 3.11)</td>
</tr>
<tr>
<td>Hanson</td>
<td>10.86 (3.72, 30.18)</td>
</tr>
<tr>
<td>Combined [random]</td>
<td>3.44 (2.30, 5.15)</td>
</tr>
</tbody>
</table>

Pooled odds ratio = 3.44 (95% CI = 3.00 to 5.15)
Chi² (test odds ratio differs from 1) = 36.2 (df = 1) P < 0.001
Figure 4: Risk of major congenital malformation for poor versus optimal glycaemic control.

Pooled odds ratio = 5.14 (95% CI = 3.00 to 9.01)
Chi² (test odds ratio differs from 1) = 32.8 (df = 1) P < 0.001
Figure 5: Risk of miscarriage for poor versus optimal glycaemic control.

Pooled odds ratio = 3.23 (95% CI = 1.64 to 6.36)
Chi² (test odds ratio differs from 1) = 11.48 (df = 1)  P = 0.001
Figure 6: Risk of perinatal mortality for poor versus optimal glycaemic control.

Odds ratio meta-analysis plot [random effects]

Temple 4.52 (1.07, 21.98)
Greene 1.77 (0.88, 3.72)
Key 2.91 (0.34, 136.82)
Hanson 5.44 (2.23, 12.45)
combined [random] 3.23 (1.64, 6.36)

Pooled odds ratio = 3.23 (95% CI = 1.64 to 6.36)
Chi² (test odds ratio differs from 1) = 11.5 (df = 1) P = 0.001
Figure 7: Bias assessment plot for the outcome of congenital malformations.

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.33  P = 0.15
Egger: bias = 1.27 (95% CI = -0.01 to 2.56)  P = 0.05
Horbold-Egger: bias = 2.19 (95% CI = 0.53 to 3.84)  P = 0.03
Additional files provided with this submission:

Additional file 1: M.Inkster - QUOROM.pdf : 23Kb
http://www.biomedcentral.com/midea/1811719603984135/sup1.PDF