The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews, meta-analyses and an economic evaluation

Diane Farrar,[1,2]* Mark Simmonds,[3] Susan Griffin,[4] Ana Duarte,[4] Debbie A Lawlor,[5,6] Mark Sculpher,[4] Lesley Fairley,[1] Su Golder,[2] Derek Tuffnell,[7] Martin Bland,[2] Fidelma Dunne,[8] Donald Whitelaw,[9] John Wright[1] and Trevor A Sheldon[10]

[1]Bradford Institute for Health Research, Bradford Teaching Hospitals, Bradford, UK
[2]Department of Health Sciences, University of York, York, UK
[3]Centre for Reviews and Dissemination, University of York, York, UK
[4]Centre for Health Economics, University of York, York, UK
[5]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK
[6]School of Social and Community Medicine, University of Bristol, Bristol, UK
[7]Bradford Women's and Newborn Unit, Bradford Teaching Hospitals, Bradford, UK
[8]Galway Diabetes Research Centre (GDRC) and School of Medicine, National University of Ireland, Galway, Republic of Ireland
[9]Department of Diabetes & Endocrinology, Bradford Teaching Hospitals, Bradford, UK
[10]Hull York Medical School, University of York, York, UK

*Corresponding author

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Scientific summary

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Background

Gestational diabetes mellitus (GDM) is associated with an increased risk of important adverse perinatal outcomes, including macrosomia and birth injury, and there is limited evidence that longer-term health of women and their offspring may also be compromised.

Over recent years there has been considerable debate about the relative effectiveness of different methods for identifying women with GDM. The identification of a treatment threshold for GDM has proved challenging. In 2010, using data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which reported graded linear associations of fasting and post-load glucose levels with the majority of adverse primary and secondary outcomes, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended new thresholds for diagnosing GDM. The aim of these new glucose thresholds is to identify obesity risk by identifying infants who are large for gestational age (LGA), have more adipose tissue at birth, and who have high cord blood C-peptide levels (as opposed to identifying women at risk of type 2 diabetes). In 2013, the World Health Organization (WHO), whose previous criteria for diagnosing GDM have been widely adopted, endorsed the IADPSG criteria thresholds. The shift in the aim of diagnosing GDM from one of identifying women at risk of type 2 diabetes to one of identifying risk of future offspring obesity is particularly important for South Asian (SA) women, as their infants, in comparison with white Europeans, have markedly lower birthweight (BW) and reduced risk of LGA, but this lower BW masks a propensity to greater adiposity and associated cardiometabolic risk. It is unclear whether the association of glucose levels with perinatal outcomes is the same for SA and white British (WB) women or if the IADPSG criteria for diagnosing GDM should also be the same in SA women, who are at higher risk of GDM than white Europeans. HAPO was a large well designed study; however, it is unclear to what extent the association between glucose levels and adverse outcomes has been investigated by other studies, and, if there are other studies, whether or not these provide additional evidence that can be used to inform criteria.

Changing or lowering diagnostic thresholds will influence the prevalence of GDM in a given population. Prevalence estimates are also influenced by the screening strategy used (selective or universal), and, if selective, the method of selecting women for testing (e.g. the number and/or type of risk factor) and also the characteristics of the population being screened. It is unclear what the prevalence of GDM is in the UK and Ireland when different criteria are applied and whether or not prevalence differs by ethnicity. Certain maternal characteristics/risk factors, including advancing age and obesity, are associated with increased risk of GDM. The performance of these characteristics has been questioned over recent years, with some clinical guidelines recommending universal testing for GDM. Universal testing, however, might incur increased health service costs with little additional health benefit over selective testing, and so it is therefore important to examine the performance of risk factors [the UK National Institute for Health and Care Excellence (NICE) recommended screening strategy] to identify those at increased risk of GDM.

Treatment of GDM aims to reduce associated risks by reducing hyperglycaemia. Treatment seems to reduce the risk of adverse perinatal outcomes, although the effects on longer-term health are more uncertain. There are various treatment options available, including diet modification and pharmacological interventions [metformin (hydrochloride) (Glucophage,® Teva UK Ltd, Eastbourne, UK), glibenclamide (Aurobindo Pharma – Milpharm Ltd, South Ruislip, Middlesex, UK) and insulin], with, currently, no clear indication as to which treatment strategy is most effective. A key issue surrounding GDM is determining the most clinically effective and cost-effective strategy for identification and treatment of hyperglycaemia.

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Aim

The overall aim of this research was to estimate the cost and clinical effectiveness of strategies for identifying and treating women with GDM in order to improve the associated adverse health outcomes for mothers and their infants. Our specific objectives were to determine (1) the risk of adverse outcomes associated with graded increases in maternal glucose level and derive thresholds for diagnosing GDM in SA and WB women; (2) the prevalence of GDM in the UK and Ireland; (3) the effectiveness (sensitivity, specificity, acceptability and costs) of maternal characteristics to accurately identify women at risk of GDM; (4) the most effective treatments for GDM for reducing the risk of adverse perinatal outcomes; and (5) the most cost-effective and clinically effective strategy for identifying and treating GDM.

Methods

Data sources used to address these objectives were:

1. Individual participant data (IPD) from (1) the Born in Bradford (BiB) study, a large cohort of SA and WB women; (2) the Atlantic Diabetes in Pregnancy (Atlantic DIP) study; and (3) Warwick/Coventry hospitals.
2. Summary results from detailed systematic searches of MEDLINE® and MEDLINE In-Process & Other Non-Indexed Citations®, EMBASE, Cumulative Index to Nursing and Allied Health Literature Plus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database, NHS Economic Evaluation Database, Maternity and Infant Care database and the Cochrane Methodology Register, from inception up to October 2014.

Multivariable logistic regression was used to examine potential differences between SA and WB women in the associations of fasting and post-load glucose levels with adverse perinatal outcomes. The IADPSG methods were used to determine diagnostic thresholds in the two groups. Systematic reviews were conducted using standard methods to identify relevant studies examining associations of fasting and post-load glucose levels with adverse perinatal and longer-term outcomes, GDM prevalence, risk factors for GDM, treatments and costs. Meta- and network-analyses were conducted when appropriate.

A decision tree model was developed to evaluate the cost-effectiveness of alternative strategies of combined screening, diagnosis and treatment of hyperglycaemia during pregnancy following the perspective of the UK NHS and Personal and Social Services for both costs and outcomes [quantified as quality-adjusted life-years (QALYs)]. Discounting was not applied to the base-case analysis, given that the time horizon was < 1 year (3 months). Future costs and QALYs accrued after 1 year, included in sensitivity analysis, were discounted at 3.5% annual rate. Probabilistic sensitivity analysis and scenario analysis were performed to characterise and incorporate uncertainty in the analysis. Subgroup analysis was conducted for two subgroups: SA and other ethnicity.

Results

Associations of gestational fasting and post-load glucose levels in women without existing or gestational diabetes with perinatal and longer-term outcomes

Our systematic review identified 58 eligible studies; 38 were included in meta-analyses (including the BiB study and Atlantic DIP study), 28 examined at least three glucose levels and associated risk of adverse perinatal outcomes, 20 examined two glucose level ranges, and five studies reported associations with longer-term outcomes. In analyses from the BiB study alone and the systematic review we found evidence of graded linear associations of fasting and post-load glucose levels with adverse perinatal outcomes. Associations between glucose levels and outcomes were broadly similar for SA and WB women, although the association with LGA appeared stronger in SA than WB women. The frequency of 'LGA' was greater for

WB women than for SA women; however, 'sum of skinfolds > 90th percentile' and 'Caesarean section' were similar. Associations were stronger for fasting glucose levels than for 2-hour post-load glucose levels. For example, from the systematic review (combining fasting glucose results from both the 75-g and 100-g studies), for macrosomia the odds ratio (OR) for every 1-mmol/l increase in fasting glucose level (six studies) was 2.06 [95% confidence interval (CI) 1.86 to 2.28], whereas for the 2-hour glucose level (combining post-load glucose results from both the 75-g and 100-g studies) (seven studies) the OR was 1.21 (95% CI 1.16 to 1.26). There was no robust evidence for a non-linear association between glucose level and log OR of any outcome, and therefore there was no clear threshold below which there was no increased risk. Three published studies examined longer-term infant outcomes: one study, diabetes between the ages of 2 and 24 years (552 participants); one study, childhood obesity between the ages of 5 and 7 years (9439 participants); and one study, overweight and obesity at age 2 years (1165 participants).

In the BiB study, our analyses demonstrated no clear threshold below which there was no increase in risk of an adverse outcome. Using the methods operated by the IADPSG we produced glucose thresholds to identify infants at risk of being LGA or with high levels of adiposity {OR of 1.75 above mean maternal glucose levels [at oral glucose tolerance test (OGTT) for these outcomes]}. Irrespective of ethnicity, these thresholds were as follows: fasting glucose level of 5.3 mmol/l and 2-hour post-load glucose level of 7.5 mmol/l, and corresponding ethnic-specific thresholds of 5.2 and 7.2 mmol/l for SA women, and 5.4 and 7.5 mmol/l for WB women.

Prevalence of gestational diabetes

In the BiB study, we applied six different criteria that have been proposed for diagnosing GDM, including the criteria we derived, those recently suggested by NICE, and the IADPSG criteria. Prevalence varied from 1.2% to 8.7% in WB women and from 4.1% to 24.2% in SA women, prevalence being consistently two to three times higher in SA women than in WB women. Consistent with these findings in the systematic review/meta-analyses the prevalence in UK/Ireland varied between 1% and 24% depending on maternal characteristics (including ethnicity) and the criteria used to define GDM.

Maternal characteristics (risk factors) to identify women at increased risk of gestational diabetes

Two IPD cohorts and 29 published studies were included. Studies examined individual risk factors, risk prediction models and guideline recommendations. None of these accurately predicted GDM. Performance varied by risk factor; for example, in the BiB study the sensitivity and specificity of GDM in a previous pregnancy was 6.0% and 99.3%, respectively. However, this risk factor identifies fewer women because the incidence is lower than that in, for example, women from an ethnic group with a high prevalence of GDM (sensitivity and sensitivity using BiB study data 76.3% and 40.6%, respectively). There was some evidence that in some populations characteristics/risk factors could identify low-risk women accurately and in those populations risk factors might be useful for identifying women who do not require diagnostic tests.

Treatments for gestational diabetes

Forty-eight trials were included. Dietary modification (possibly alongside glucose monitoring and supplemental insulin if needed) compared with routine antenatal care was effective in reducing the risk of the majority of reported adverse outcomes. For example, macrosomia (nine trials) relative risk (RR) of 0.46 [95% CI 0.36 to 0.60 ($I^2 = 33\%$)] and Caesarean section (eight trials) RR of 0.86 [CI 0.77 to 0.95 ($I^2 = 3\%$)]. Metformin appeared as effective as insulin at reducing the risk of most adverse outcomes, and for some outcomes, macrosomia for example, was more effective [RR 0.75, 95% CI 0.57 to 0.96 ($I^2 = 0\%$)]. From the network meta-analyses, both insulin and metformin appeared to be more effective than glibenclamide (macrosomia: glibenclamide vs. insulin OR 3.43, 95% CI 1.32 to 8.91; and glibenclamide vs. metformin OR 5.36, 95% CI 1.86 to 15.59), although the small number of trials for these comparisons means that the CIs are wide and include the null value for most effect estimates. We found similar effectiveness when differing insulin preparations were compared. Few trials included reported negative treatment effects, such as satisfaction or side effects.

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Cost-effectiveness of screening, diagnosis and treatment of gestational diabetes

Our economic evaluation showed that for all strategies to identify and treat GDM, the costs exceeded the health benefits. A policy of no screening/testing or treatment offered the maximum expected net monetary benefit (NMB) of –£1184 at a cost-effectiveness threshold of £20,000. The NMB for the three best-performing strategies in each category (screen only then treat; screen, test, then treat; and test all, then treat) ranged between –£1197 and –£1210.

Results were robust to sensitivity analysis. Because longer-term health benefits within the model are estimated with considerable uncertainty, the higher cost-effectiveness threshold of £30,000 might not be applicable.

Limitations

Studies and trials included in our systematic reviews and meta-analyses varied considerably in terms of size, population, inclusion criteria, treatments and outcomes reported and we found evidence of statistical heterogeneity, with the I^2 value varying from 0% to 77% in different meta-analyses. Criteria thresholds used to diagnose GDM varied and therefore trial populations included women with varying degrees of hyperglycaemia, potentially influencing treatment effects, prevalence and risk factor performance estimates. Some comparisons included few trials and/or participants and therefore results may be imprecisely estimated.

Conclusions

There is a graded positive association of glucose level with adverse perinatal outcomes in different populations, including both SA and WB women. Our findings suggest that applying lower thresholds for identifying GDM – particularly in women of SA origin – than those in current practice in the UK will increase prevalence, but would identify more of those at risk of adverse perinatal outcomes. Maternal risk factors do not accurately identify those at risk of GDM, but may be valuable for predicting those at very low risk, who do not require diagnostic testing, in some populations. Treatment of GDM with diet (with glucose monitoring and supplemental insulin if needed) reduces the risk of most adverse outcomes, and metformin or insulin is effective at reducing the risk of most adverse perinatal outcomes. These findings support the 'step-up' approach, for which, in most cases, lifestyle modification is the first-line treatment, with metformin and/or insulin added as required.

The aim of diagnosing GDM has shifted from identifying women at risk of type 2 diabetes to identifying offspring who are at future risk of longer-term greater adiposity and cardiometabolic ill health. Our research shows an absence of evidence to support the assumption that treatment will reduce any longer-term effects.

There is a balance between costs and improved perinatal and any longer-term health impacts from the application of different diagnostic criteria and treatments. We found that at a cost-effectiveness threshold of £20,000 per QALY it is not cost-effective to identify women for treatment for hyperglycaemia, even in the scenario in which longer-term outcomes are incorporated into the model. It is only with the inclusion of longer-term health outcomes and at cost-effectiveness thresholds of > £24,000 per QALY that net health benefits are improved by intervening. Given the uncertainty surrounding the estimation of longer-term outcomes, and that only when these are incorporated into our economic model are health benefits improved, further research in this area would be useful to help determine the potential cost-effectiveness of intervening in GDM.

Study registration

This study is registered as PROSPERO CRD42013004608.

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