Royal College of Obstetricians & Gynaecologists

Diagnosis and Treatment of Gestational Diabetes

Scientific Impact Paper No. 23

January 2011

Diagnosis and Treatment of Gestational Diabetes

1. Background

Historically, there has been controversy over screening and diagnosis of gestational diabetes. The 2002 National Institute for Health and Clinical Excellence (NICE) Health Technology Assessment concluded that there was insufficient evidence to advocate universal screening in pregnancy while noting that there were clearly women in whom maternal hyperglycaemia caused adverse fetal outcomes including macrosomia, shoulder dystocia and stillbirth.[1] The 2008 NICE guideline on diabetes in pregnancy detailed a screening programme targeting biochemical screening to women with risk factors.[2] There have been several important advances since that report. The multinational Hyperglycaemia and Pregnancy Outcome (HAPO) study[3] defined the relationship of maternal glucose tolerance to neonatal outcomes in over 23 000 women. The results of this large observational study formed the basis of a reconsideration of diagnosis and screening for diabetes in a consensus report published in 2010[4] under the auspices of the International Association of Diabetes and Pregnancy Study Groups (IADPSG). A further major trial examining the effect on pregnancy outcomes of management of gestational diabetes was reported in 2009,[5] while a randomised controlled trial in 2008 examined the efficacy of metformin,[6] adding to the older literature on the use of glibenclamide (glyburide)[7] in gestational diabetes. Collectively, this new evidence clearly demonstrates that there is a continuous linear relationship between maternal glucose and fetal growth and that fetal growth can be modified by glucose-lowering therapies, with diet and lifestyle intervention often being successful. For women requiring pharmacological intervention, treatment strategies starting with oral hypoglycaemic agents (metformin or glibenclamide) but often involving progression to insulin to ensure adequate glycaemic control are as successful but not superior to insulin alone with regard to immediate pregnancy outcomes.

2. New evidence – the relationship of maternal glucose to fetal growth

The HAPO study highlighted the quintessentially important influence of maternal glycaemia on offspring birthweight, demonstrating a linear relationship between maternal fasting plasma glucose and oral glucose tolerance test at 1 hour and 2 hours with birthweight above the 90th percentile.[3] Importantly, infant adiposity as estimated by sum of skin-fold thickness exhibited a similar strong linear relationship with maternal glucose.[8] Furthermore, there was no apparent threshold effect in the HAPO data between maternal glycaemia and pregnancy outcomes that might easily guide precise values at which gestational diabetes should be diagnosed.[3] The likelihood that there would be a linear relationship between maternal glucose and fetal growth had been suggested by a number of previous studies;[9,10] however, the size, blinding to glucose tolerance (with avoidance of treatment effects in the great majority) and international coverage of the HAPO study were important additions.

3. New evidence – efficacy of screening, diagnosing and treating gestational diabetes

Two large randomised controlled trials have investigated the effects of screening, diagnosis and treatment of gestational diabetes. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) established that treatment of gestational diabetes with insulin improved pregnancy outcomes.[11] Specifically, birthweight, macrosomia and birthweight >90th percentile were all significantly reduced. Furthermore, the primary composite outcomes (serious perinatal outcomes: death, shoulder dystocia, bone fracture and nerve palsy) were significantly reduced from 4% to 1%. Notably, this landmark trial used the same definition of gestational diabetes as the current NICE guideline.

The Maternal Fetal Medicines Unit (MFMU) Network trial of treatment of mild gestational diabetes used a similar design and intervention to ACHOIS, but the definition of gestational diabetes was at lower levels of glycaemia (fasting glucose <5.3 mmol/l and two or three postload glucoses above established thresholds).[5] The primary outcome measure did not achieve statistical significance (a composite of

Table 1. Diagnostic criteria for gestational diabetes mellitus for the 75 g oral glucose tolerance test

	WHO/NICE	IADPSG†	Above IADPSG threshold (cumulative %)
Fasting	≥7.0 mmol/l	≥5.1 mmol/l	8.3
1 hour	–	≥10.0 mmol/l	14.0
2 hour	≥7.8 mmol/l	≥8.5 mmol/l	16.1‡

Values for venous plasma samples.
†Diagnosis of gestational diabetes mellitus made if this value exceeded at any time point.
‡ In addition, 1.7% of participants in the initial cohort were unblinded because of fasting plasma glucose greater than 5.8 mmol/l (105 mg/dl) or 2-hour oral glucose tolerance test values greater than 11.1 mmol/l (200 mg/dl), bringing the total to 17.8%.
IADPSG = International Association of Diabetes and Pregnancy Study Groups; NICE = National Institute for Health and Clinical Excellence; WHO = World Health Organization.

perinatal mortality, hypoglycaemia, hyperbilirubinaemia, neonatal hyperinsulinaemia and birth trauma), but there were significant reductions in mean birthweight (by 106 g), proportion of infants with birthweight greater than 4 kg (5.9% versus 14.3%), proportion of large-for-gestational-age infants (7.1% versus 14.5%) and caesarean section rate (26.9% in the intervention group versus 33.8% in the control group) with treatment of gestational diabetes that improved glycaemic control. Intervention was also associated with benefits in maternal weight gain (2.8±4.5 kg versus 5.0±3.3 kg in the treatment versus the control group), resulting in a small but significant difference in body mass index of 1 kg/m^2 at delivery.

4. New evidence – treatment

Lifestyle advice including dietary modification is the primary intervention in all women diagnosed with gestational diabetes. However, 7–20% of women will fail to achieve adequate glycaemic control with diet and exercise alone: oral hypoglycaemic agents or insulin will be required to control their gestational diabetes.[5,11] Both glibenclamide and metformin are effective treatments for gestational diabetes. Langer et al. demonstrated that a treatment strategy starting with glibenclamide (known in the US as glyburide) and requiring progression to insulin in around 4% of cases was associated with similar birth outcomes to a strategy involving initial treatment with insulin.[7] Since then, multiple studies have shown the need for insulin in about 20–30% of patients who were initially started on glibenclamide and metformin, with those requiring insulin having a higher fasting glucose. More recently, Rowan et al. demonstrated that treatment with metformin resulted in similar outcomes to initial insulin treatment in gestational diabetes, although 46% of women in the metformin arm required supplemental treatment with insulin owing to inadequate glycaemic control. Metformin treatment was also associated with lower maternal weight gain.[6] Finally, Rowan et al. recently reported that women who achieved lower than conventional

Box 1. Risk factors for gestational diabetes

- Body mass index more than 30 kg/m^2
- Previous macrosomic baby weighing 4.5 kg or more
- Previous gestational diabetes
- Family history of diabetes (first-degree relative with diabetes)
- Family origin with a high prevalence of diabetes:
  - South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh)
  - Black Caribbean
  - Middle Eastern (specifically women whose country of family origin is Saudi Arabia,United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt)

Reproduced from the National Institute for Health and Clinical Excellence guideline for diabetes in pregnancy, 2008.2 These at-risk features were also adopted by the Scottish Intercollegiate Guidelines Network: National clinical guideline 166: Management of diabetes. Edinburgh: SIGN; 2010 [http://www.sign.ac.uk/pdf/sign116.pdf].

glycaemic targets with treatment had the lowest risk of complications.[12] The lowest risk of complications – including birthweight greater than 4 kg, prematurity, pre-eclampsia and neonatal hypoglycaemia – occurred with fasting capillary glucose levels ≤4.9 mmol/l and 2-hour postprandial glucose 5.9–6.4 mmol/l. Metformin and glibenclamide cross the placenta and, while no immediate safety concerns for the fetus have been demonstrated, potential long-term effects remain under investigation.

5. Screening and diagnosis of gestational diabetes

The IADPSG is to be applauded for trying to achieve an international consensus for screening and diagnosis of gestational diabetes.[4] The IADPSG document represents a radical redrawing of the diagnosis (Table 1). The consensus recommends a one-step 75 g oral glucose tolerance test for all women not already known to be diabetic at 24–28 weeks of gestation. Diabetes is diagnosed where one or more threshold value is exceeded (fasting ≥5.1 mmol/l, 1-hour ≥10.0 mmol/l, 2-hour ≥8.5 mmol/l). These diagnostic levels are set at the level of maternal blood glucose at which rates of key pregnancy outcomes – large for gestational age, cord C-peptide (a stable marker of fetal insulin) >90th percentile, percentage of newborn body fat >90th percentile – are increased 1.75-fold over the mean for the HAPO study population. The rate of large-for-gestational-age infants in this group was 16.2% in the HAPO population, a rate between those of the ACHOIS and MFMU study control groups (22% and 14.5%, respectively). Application of this system of testing and criteria is predicted to result in a per pregnancy incidence of gestational diabetes of over 16% – a major change in terms of obstetric practice from current levels of 3.5%.

As yet, NICE has not commented on the international consensus, but its 2008 guidelines are markedly different, with screening of high-risk women only (although the risk factors that NICE has defined are found in 30–50% of the pregnant population) and diagnostic levels comprising fasting plasma venous glucose ≥7.0 mmol/l or at 2 hours ≥7.8 mmol/l. Health economic analysis in this area has been limited. After ACHOIS, the NICE group examined the health economics of intervention as per the ACHOIS protocol, finding such a programme to be cost-effective, although notably much of the quality-adjusted life year benefit was generated by a reduction in perinatal mortality, itself based on four events in the control arm of the trial.

In Scotland, the most recent update of the Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of diabetes[13] has adopted the diagnostic levels suggested in the international consensus document based on the arguments presented by the international consensus and the desirability of achieving an internationally agreed definition. However, SIGN has advocated a more selective approach to screening, at present confining the 75 g oral glucose tolerance test to women at high risk (Box 1) and using fasting glucose in other women. This reflects practical concerns from clinicians about the implementation of universal screening with the oral glucose tolerance test and the lack of high-quality health economic analysis of the costs of delivering lifestyle and pharmaceutical interventions and benefits, particularly in women who might be considered at lower risk of gestational diabetes by conventional risk factors (e.g. obesity, prior macrosomia, family history of diabetes, high-risk ethnicity).

6. Opinion and areas for future research

The clinical science of gestational diabetes has seen marked advances in the last 5 years. Taken together, these new data provide conclusive evidence of the relationship of maternal glycaemia to fetal growth and indicate that fetal growth can be modified with glycaemic management. While treatment can have a modest effect on preventing excessive birthweight, there are many unanswered questions, such as can women at risk of gestational diabetes early in pregnancy be identified and its onset prevented, and which endpoints should guideline development and health economic analysis concentrate on? Reductions in birthweight of 100–150 g[5,11] may be important in the short term only if accompanied by reductions in harder endpoints such as perinatal morbidities, caesarean section rates or pre-eclampsia. A reduction in

these 'hard' endpoints was present in the two recent intervention studies, although not completely consistent between them.[5,11]

There is a major challenge for translation of these results into clinical practice. A key advantage of the HAPO, ACHOIS and MFMU trials is that they examined the natural history of maternal hyperglycaemia in largely untreated women (HAPO) or compared against a largely untreated group (ACHOIS and MFMU). Even in these three trials there was a small degree of treatment in the observational or control groups mandated by a higher level of maternal glucose, presumably reducing the observed treatment effect to some degree. Nevertheless, from an ethical perspective it appears unlikely that there will be further trials where it will be acceptable not to diagnose or treat gestational diabetes in a control group other than in women with the mildest degree of hyperglycaemia in pregnancy. Pragmatically, the clinical community will need to translate the evidence we have as further large trials with untreated control groups may not be feasible. There is great logic in basing the level at the point at which benefits of treatment or even cost-effective benefits are found. Advocates of the NICE guidance will note that the diagnostic level at 2 hours (7.8 mmol/l) is in keeping with the level used diagnostically in the ACHOIS trial. Against this view, the MFMU trial used different criteria, and in ACHOIS 93% of women were investigated with an oral glucose tolerance test not on the basis of risk factors (as advocated by NICE) but rather in response to a high level of 1-hour glucose after an oral glucose challenge. The NICE guideline did not advocate use of the oral glucose challenge test. It will be difficult to reconcile these two trials, with different entry criteria and different parts of the population studied, into a single strategy.

At the same time, while diagnosis of gestational diabetes in 16% of the population would be a major increase in the number of women labelled with gestational diabetes, the data suggest that relatively modest dietary and lifestyle interventions are effective in improving pregnancy outcomes. Management of gestational diabetes involved exogenous insulin in only 8% of women in the MFMU study[5] and in 20% of women in the ACHOIS study[11] – so the great majority of women with gestational diabetes were effectively managed by diet, lifestyle and glucose monitoring alone. Thus, the interventions proposed for women with gestational diabetes are relatively noninvasive in most women and have an effect on both newborn weight and maternal weight gain.

Perhaps most pressingly, we need to understand the interactions of maternal glucose with other risk factors, in particular maternal obesity.[14,15] Do these interactions allow identification of particularly high-risk women to target intensive intervention? Conversely, is there a combination of risk factors that identifies women at such low risk of gestational diabetes that biochemical screening does not need to occur? More provocatively, would dietary intervention be of benefit to an even larger proportion of the pregnant population, either to prevent gestational diabetes or to reduce complications?

Finally, all of the endpoints discussed here occur during pregnancy or around the time of birth. Maternal diabetes increases the risk of overweight and obesity in offspring in later life, and it would appear that this effect acts via intrauterine programming. The extent of these long-term effects, particularly at lower levels of maternal glycaemia, need to be defined to allow us to assess in which groups intervention in pregnancy may also be needed to improve health in the next generation.

In conclusion, there is an urgent need for health economic modelling to assess the costs of adoption of the international consensus in the UK. Importantly, it would appear important not to reject the consensus simply on the grounds of the number of women likely to be diagnosed with gestational diabetes, not least as the evidence would suggest that relatively noninvasive treatments, despite their inherent cost implications, may be beneficial in many women in pregnancy.

References

1. Scott DA, Loveman E, McIntyre L, Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2002;6:1–161.

2. National Institute for Health and Clinical Excellence. NICE clinical guideline 63: *Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period*. London: NICE; 2008 [http://www.nice.org.uk/nicemedia/pdf/CG063Guidance.pdf].
3. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002.
4. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676–82.
5. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339–48.
6. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358:2003–15.
7. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343:1134–8.
8. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 2009;58:453–9.
9. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D, et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital Gestational Diabetes Project. *Am J Obstet Gynecol* 1995;173:146–56.
10. Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JF. Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. *Am J Obstet Gynecol* 1995;172:607–14.
11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–86.
12. Rowan JA, Gao W, Hague WM, McIntyre HD. Glycemia and its relationship to outcomes in the metformin in gestational diabetes trial. *Diabetes Care* 2010;33:9–16.
13. Scotish Intercollegiate Guidelines Network. National clinical guideline 116: Management of diabetes. Edinburgh: SIGN; 2010 [http://www.sign.ac.uk/pdf/sign116.pdf].
14. Yogev Y, Catalano PM. Pregnancy and obesity. *Obstet Gynecol Clin North Am* 2009;36:285–300.
15. Nelson SM, Matthews P, Poston L. Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. *Hum Reprod Update* 2010;16:255–75.

This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
RS Lindsay MBChB, Glasgow Cardiovascular Research Centre, Faculty of Medicine, University of Glasgow, Scotland; Professor PM Catalano MD, Department of Reproductive Biology, Case Western Reserve University, Cleveland, Ohio, USA; Professor SM Nelson MRCOG, Glasgow, Scotland

and peer-reviewed by:
Mr RB Fraser FRCOG, Sheffield; Dr H Murphy, Cambridge; Mr SA Walkinshaw FRCOG, Liverpool; RCOG Consumers' Forum.

The Scientific Advisory Committee lead reviewer is: Ms SM Quenby FRCOG.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2014 unless otherwise indicated.

