NICE’s latest guidelines on diabetes in pregnancy: getting the balance right

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NICE Guideline 3 on diabetes in pregnancy was published in February¹ and auspiciously timed to focus attention on improving pregnancy outcomes following publication of the first National Diabetes in Pregnancy (NDIP) Audit.² The audit has demonstrated disappointingly little improvement in some outcomes of pregnancy for women with diabetes in the 10 years since the Confidential Enquiry into Maternal and Child Health in 2003.³ There is also important new evidence from the landmark Hypoglycemia and Adverse Pregnancy Outcomes (HAPO) study published in 2008,⁴ which has meant the diagnostic criteria for gestational diabetes mellitus (GDM) have been challenged since publication of the last NICE guidance in 2008 (CG63). The priorities identified for review by the Guideline Development Group (GDG) focus on pregnancy planning, diagnostic criteria and intervention for GDM, metabolic management during diabetic pregnancy and follow up for women who have had GDM.

Preparation for pregnancy
The NDIP Audit 2013 has highlighted that perinatal mortality and the risk of congenital abnormalities remain high. Despite widespread recognition of the importance of pregnancy planning, most women with type 1 or type 2 diabetes are entering pregnancy inadequately prepared, with poor glycaemic control, taking insufficient folic acid, or taking potentially harmful medications.

The GDG have considered a number of areas to address the lack of pregnancy planning. Firstly they have carefully examined the data on safety of oral contraceptives for women with diabetes, finding no convincing evidence for increased risk of harm, and stressing instead the importance of avoiding unplanned pregnancy. Oral contraceptives can therefore be used if there are no standard contraindications. The importance of discussing, and documenting, pregnancy planning with women with diabetes at every encounter from adolescence onwards is emphasised, as is the relationship with care providers. This is recognised in specialist diabetes services, but relationships with the community services are paramount to increasing access to preconception counselling for women with type 2 diabetes and are emphasised as an area for priority.

HbA₁c targets prior to pregnancy have been revised based on eight studies of glycaemic control prior to conception. The evidence suggests a linear relationship between glycaemia and congenital abnormality risk above a threshold of 6.3% (45mmol/mol).⁴ However, the recommendation has been brought in line with the Type 1 Diabetes NICE Guideline⁵ and advises women who are planning pregnancy to aim to keep to HbA₁c <6.5% (48mmol/mol) where this can be safely achieved, and women reassured that any reduction towards this target is likely to improve outcome. This is important because even for very motivated women the 2008 target (6.1%) was difficult to achieve, particularly in type 1 diabetes. Women with HbA₁c >10% (86mmol/mol) are strongly advised to avoid pregnancy because of the increased risk of congenital abnormalities.⁶

Diagnostic criteria for GDM
How to diagnose GDM is the most contentious issue the new guidance has tackled. HAPO was an observational study of 25 505 women in nine countries and confirmed a linear relationship between maternal glucose levels and adverse pregnancy outcomes.⁴ The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations⁷ based on this dataset have now been adopted by WHO⁸ and the ADA⁹ and some centres in the UK. In this model the diagnostic thresholds following 75g oral glucose tolerance test at 0, 1 hour and 2 hours (5.1, 10 and 8.5mmol/L respectively) are the glucose thresholds at which risk increases 1.75-fold for the three outcomes (birth weight, cord C-peptide and percent body fat over 90th percentile) in the HAPO study. There is widespread recognition that the IADPSG thresholds would increase the number of women diagnosed with GDM, based on the lower fasting glucose threshold.¹⁰ WHO recognised that the costs of adopting the IADPSG thresholds might be prohibitive.⁸ It is also widely felt that there is insufficient evidence for the benefit of intervention at the lower fasting levels in particular.¹¹ NICE has responded with a mathematical model running to 53 pages, to determine the most cost-effective glucose thresholds based on the available cost–benefit data from the HAPO dataset and from Norwich. Based on this model the new recommended levels are those at which the greatest cost benefit was found, namely fasting glucose of ≥5.6mmol/L and 2-hour glucose ≥7.8mmol/L. It has long been recognised that the 2008 fasting threshold of 7mmol/L was too high and, in a recent survey of current UK practice, around half of responding centres have already dropped their fasting threshold to between 5.0 and 5.5mmol/L.¹² Lowering the fasting threshold further would identify women whose infants are likely to benefit least from intervention.

The recommendations of when and whom to screen are largely unchanged at 24–28 weeks and ethnicity altered to ‘minority ethnic origin with a high prevalence of diabetes’. Women who have had GDM in a previous pregnancy may commence home blood glucose monitoring in the first trimester, partly so that women who have developed type 2 diabetes are diagnosed at the earliest opportunity. Although glycosuria should not be used as a criterion for screening, if it is found to be persistent, testing should take place. Where there is a possibility that a woman may have pre-existing diabetes, HbA₁c should be
measured. Throughout the updated guideline there is emphasis on the importance of not missing opportunities to diagnose overt diabetes.

**Antenatal care**
The GDG have specified that antenatal care for women with diabetes should be delivered by a multidisciplinary team comprising obstetrician, diabetes physician, diabetes specialist nurse, midwife and dietitian.

**HbA1c measurement**
Previous NICE guidance was not to measure HbA1c, which is lower in pregnancy and affected by red cell turnover and iron status. The new guidelines advise that HbA1c should be measured at booking to determine the level of risk for the pregnancy, and in the second and third trimesters for women who are testing insufficiently, or if confirmation is needed that targets are being achieved. There were insufficient data to recommend specific targets however.

**Blood glucose targets**
The new targets are for women with pre-existing diabetes and GDM, and are based on data for pregnant women without diabetes. Fasting blood glucose target is <5.3 mmol/L, postprandial at 1 hour <7.8 mmol/L or at 2 hours <6.4 mmol/L. There is widespread confusion about whether to test at 1 hour or 2 hours, and whether this means from the beginning or end of a meal. The peak glucose probably occurs at around 90 minutes, and the important message is to choose a convenient time and to minimise glucose excursion. These values are difficult for women with type 1 diabetes to achieve without hypoglycaemia, and the recommendation of individual targets is really important here.

**Safety of medicines before and during pregnancy**
The data remain insufficient for NICE to recommend long-acting analogues over isophane insulin. Achieving the recommended targets without hypoglycaemia in type 1 diabetes using isophane insulin is extremely difficult. Although there have previously been safety concerns raised, data from three studies, the largest involving 127 pregnancies in 22 centres in the UK, did not show any adverse outcomes associated with the use of insulin glargine.

Metformin is accepted as first-line management in GDM and there is widespread acceptance that although it does cross the placenta there is no evidence of harm to the developing fetus, and the GDG found extensive evidence of benefit. Metformin remains off-licence, however, and NICE has emphasised that this should be made explicit to women, and consent documented. While recognising that NICE is in a difficult position regarding the use of unlicensed use of medications, the consent process is difficult in this context. The GDG advise metformin can be used prior to conception and in the first trimester if benefits clearly outweigh risk.

For women presenting with fasting blood glucose level ≥7 mmol/L, immediate treatment with insulin or metformin is recommended, otherwise one to two weeks of diet and exercise can be tried first, and women should see a dietitian. Glibenclamide remains an option for those intolerant of metformin or declining insulin, but is also off-licence.

**New technologies**

**Blood ketone testing**
Risk of developing ketoacidosis with a relatively normal blood glucose has been recognised and it is recommended that women with type 1 diabetes are provided with blood ketone strips and meter; also that ketoacidosis can rarely occur in women with type 2 diabetes and GDM, and should be urgently excluded in any pregnant woman with diabetes who becomes unwell.

**Insulin pumps and continuous glucose monitoring**
The GDG have not found any evidence yet in favour of insulin pump use over multiple daily injections of insulin, but recognise the increasing place for pump technology, particularly for women with disabling hypoglycaemia, and studies are ongoing.

Five studies of continuous glucose monitoring (CGM) technology were reviewed. No significant differences in maternal or fetal outcomes were reported but the data were limited. There was recognition that there are specific circumstances when CGM with real-time technology can be useful.

**Timing of elective birth**
The optimal timing of delivery is early enough to minimise the risk of still birth, shoulder dystocia, macrosomia and caesarian section, but not so early as to risk failed induction of labour and fetal immaturity. Evidence from six studies demonstrated a u-shaped curve for mortality in babies delivered between 36 and 41 weeks. Elective delivery should therefore be offered between 37 +0 and 38 +6 weeks in pre-existing diabetes, and for GDM by 40 +0 weeks, or earlier if there are complications.

**Testing for diabetes post GDM**
The recommended test to exclude diabetes is a fasting glucose <6 mmol/L at 6–13 weeks. Uptake of HbA1c may be better, and should be <5.7% (39 mmol/mol) after 13 weeks post-delivery. Women with fasting glucose 6–7 mmol/L, or HbA1c 5.7–6.4% (39–47 mmol/mol), should be counselled that they are at high risk of developing diabetes. Yearly screening thereafter is recommended, and may help to reduce the number of metabolically unprepared women who have developed diabetes entering pregnancy.

**Summary**
This NICE guideline for the management of diabetes in pregnancy is timely and considered. Some areas are controversial, particularly the diagnostic criteria for GDM. However, in this area and most others the GDG have made a good job of reviewing the extensive literature to produce a guideline which is cost effective but is also pragmatic and emphasises the importance of treating women as individuals.

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**References**
References are available in Practical Diabetes online at www.practicaldiabetes.com.
References