Does treatment of mild gestational diabetes reduce the risk of adverse outcomes?

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of a US-based study investigating whether treating gestational diabetes is necessary to improve pregnancy outcomes for mother and child.

Tristan Richardson, Consultant Physician, Bournemouth

Despite recent trial evidence (Crowther et al, 2005; HAPO [Hyperglycaemia and Adverse Pregnancy Outcomes] Study Cooperative Research Group, 2008), there remains uncertainty regarding the treatment and management of gestational diabetes. Landon et al (summarised alongside) have looked at the treatment of "mild" gestational diabetes and a variety of pregnancy outcomes.

There was no significant difference between groups in the frequency of the composite outcome, but there were significant reductions in many secondary outcomes with treatment – results similar to other recent publications.

The lack of a significant benefit with regard to the composite outcome of perinatal death could be explained by the numbers within each group – there were no perinatal deaths in either arm. Whether this is enough to satisfy the more steadfast among us remains to be seen.

There may be difficulties with interpretation of US versus European screening criteria, as in this latest study. However, we now have three recent publications indicating a benefit of aggressively treating gestational diabetes. The benefits may not be clear to the most feared outcome – perinatal death – but they are now clearer regarding other outcomes, such as rates of fetal overgrowth, caesarean delivery, and pre-eclampsia.

This latest addition to our knowledge base is important in light of the ever-increasing number of women with gestational diabetes in the diabetes antenatal clinic each week. The burden on delivery of mothers to be with gestational diabetes, let alone resources and manpower, is perhaps yet to be seen.

Crowther CA, Hiller JE, Moss JR et al (2005) Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* **352**: 2477–86

HAPO Study Cooperative Research Group (2008) Hyperglycaemia and adverse pregnancy outcomes. *N Engl J Med* **358**: 1991–2002

Richard Holt, Professor in Diabetes & Endocrinology, University of Southampton

Although gestational diabetes affects between 1% and 14% of pregnancies in the US, there is no international consensus on its diagnosis and management. It is generally accepted that degrees of hyperglycaemia that would fulfil the diagnostic criteria for diabetes outside pregnancy should be treated, but there is more uncertainty about lesser degrees of elevated glucose. The controversy arises because, while it is known that hyperglycaemia affects fetal development and growth, the relationship between maternal glucose and pregnancy outcomes is continuous with no obvious threshold. Consequently, different diagnostic tests, cut-offs and targets for treatment are used.

The Australian Carbohydrate Intolerance Study (Crowther et al, 2005) was the first to show that treating mild hyperglycaemia reduces serious perinatal complications, and was used to inform the NICE (2008) guidelines. Gestational diabetes was diagnosed by the World Health Organization criteria, and women with fasting glucose <7.0 mmol/L and 2-hour glucose tolerance of between 7.8 and 11.0 mmol/L were randomised to receive intensive glycaemic management or routine management. A composite outcome (in the fetus), including death, shoulder dystocia, bone fracture, and nerve palsy was reduced from 4% in the control group to 1% in women in the intensive group. These findings have now been replicated in the US by Landon et al (2009; summarised alongside).

A total of 958 women whose fasting glucose was <5.3 mmol/L but who had an abnormal result during a 100 g oral glucose tolerance test were randomised to an intensive glycaemic management group that included dietary intervention, self-monitoring of blood glucose, and insulin therapy if necessary, or a control group. Although there was no difference in the primary outcome (a composite of fetal death and neonatal complications), there were clinically meaningful reductions in birth weight, frequency of macrosomia, shoulder dystocia and caesarean birth with active treatment. Furthermore, pre-eclampsia and gestational hypertension were also reduced with active treatment.

Although this study is probably less relevant to UK practice because the diagnostic criteria were different from those recommended by NICE, the study provides further evidence that even mild levels of hyperglycaemia may be harmful to the fetus and active treatment will reduce adverse pregnancy outcomes.

Conflict of Interest: Richard Holt was an author of the NICE diabetes in pregnancy guidelines.

Crowther CA, Hiller JE, Moss JR et al (2005) Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* **352**: 2477–86

NICE (2008) *Diabetes in Pregnancy: Management of Diabetes and its Complications from Preconception to the Postnatal Period.* NICE, London

A multicenter, randomized trial of treatment for mild gestational diabetes.

Landon MB, Spong CY, Thom E et al (2009) *N Engl J Med* **361**: 1339–48

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Treatment of mild gestational diabetes does not reduce risk of stillbirth and several neonatal complications

1 Gestational diabetes occurs in 1–14% of all pregnancies in the US, and is defined as glucose intolerance that first occurs or is first identified during pregnancy.

2 Women were invited to take part in this study if they had a blood glucose level of between 135 and 200 mg/dL (7.5–11.1 mmol/L) 1 hour after a 50 g glucose loading test, between 24 and 30 weeks of gestation.

3 Exclusion criteria were pre-existing diabetes, abnormal blood glucose levels before 24 weeks of gestation, history of gestational diabetes or stillbirth, multi-fetal gestation, asthma, or chronic hypertension, corticosteroid therapy, known fetal anomaly, or likelihood of pre-term delivery.

4 Women who met the inclusion criteria then had further glucose tests, with the definition of mild gestational diabetes being a fasting glucose level below 95 mg/dL (5.3 mmol/L).

5 Women classified with mild gestational diabetes were randomly assigned to usual prenatal care (n=473) or dietary intervention, self-monitoring of blood glucose, and insulin if the majority of fasting values or postprandial values between study visits were elevated (n=485).

6 The primary outcome was a composite of stillbirth or perinatal death and neonatal complications, including hyperbilirubinaemia, hypoglycaemia, hyperinsulinaemia, and birth trauma.

7 Secondary neonatal outcome measures included birth weight >4000 g, large or small size for gestational age, and admission.

8 Secondary maternal outcomes included weight gain from the time of enrolment to delivery, gestational hypertension, pre-eclampsia, caesarean delivery, labour induction and shoulder dystocia.

9 The authors found no significant difference between the usual care and treatment groups in the frequency of the primary outcome (37.0% and 32.4% in the control and treatment groups, respectively; P=0.14).

10 Significant reductions with treatment were observed regarding secondary outcomes, including mean birth weight, neonatal fat mass, large size at of child, birth weight <4000 g, shoulder dystocia, and risk of caesarean delivery.

11 Treatment for gestational diabetes was also associated with reduced rates of pre-eclampsia and gestational hypertension (P=0.01).

12 The authors concluded that, while primary outcomes measures were unaffected by treatment, several risk factors can be reduced by addressing glycaemia in women with mild gestational diabetes.

Henrietta Mulnier, DSN, Haslemere, Surrey

The article by Landon et al (2009; summarised alongside) throws another spanner in the works for the current definition and treatment of gestational diabetes. The diagnostic criteria for gestational diabetes assumes that below this level the risk or harm caused is insignificant. What we do not know is at what level does intervention improve outcome?

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study set out to identify a level of hyperglycaemia above which there was a significant risk, but they were unable to identify such a level but noted linearity in risks with increasing hyperglycaemia (HAPO Study Cooperative Research Group, 2008).

In this well-controlled study, the data highlight that hyperglycaemia, even at levels below those diagnostic for gestational diabetes, produce poor outcomes. The primary perinatal outcomes, such as stillbirth and neonatal hypoglycaemia, were not different between the treatment and the control groups. However, there was a statistically significant 59% risk reduction for a birth weight over 4 kg, a 51% risk reduction in large for gestational age, a 63% risk reduction in shoulder dystocia and a 54% reduction in pre-eclampsia risk.

The authors felt that the composite primary outcome may be more likely to occur in more severe hyperglycaemia, and was, therefore, not seen in this study of mild gestational diabetes. These findings are consistent with those seen in the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and corroborate the outcome data of those with high fasting levels in the HAPO study (Crowther et al, 2005; HAPO, 2008).

To be selected for the study the women had a fasting blood glucose level of <5.3 mmol/L and a 1-hour post 50 g carbohydrate load of 7.5–11.1 mmol/L. These results highlight that we cannot rely on fasting glucose levels to define gestational diabetes, and that perhaps we should be offering an oral glucose tolerance test to all women between 24 and 28 weeks' gestation.

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Helen Murphy, Honorary Consultant, University of Cambridge

While many obstetricians and diabetologists intuitively advocate a goal of "near normoglycaemia" during pregnancies complicated by gestational diabetes, evidence regarding the contribution of hyperglycaemia to poor pregnancy outcome has only recently become available.

The landmark Hyperglycaemia and Adverse Pregnancy Outcomes study (HAPO Study Cooperative Research Group, 2008), suggests an additive effect of hyperglycaemia above and beyond that of maternal obesity, but, of course, does not provide evidence that treating hyperglycaemia or maternal obesity improves pregnancy outcomes.

That vital gap has now been addressed by two large scale rigorously conducted randomised controlled trials. First, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS; Crowther et al, 2005), and more recently the multicentre, randomised trial of treatment for mild gestational diabetes (Landon et al, 2009; summarised alongside).

The ACHOIS study showed that women treated with dietary advice and insulin had a reduced rate of serious perinatal complications (a composite primary outcome measure comprising infant death, shoulder dystocia, bone fracture and nerve palsy). However, the rates of serious complications were low (1% treatment vs. 4% control group) and, therefore, much attention was focused on the secondary outcomes, showing reduced maternal weight gain, reduced pre-eclampsia, reduced infant birth weight and improved health-related quality of life for women in the treatment group. However, in the post-HAPO era, the ACHOIS cohort may be considered as relatively hyperglycaemic (fasting glucose <7.8 mmol/L and median glucose 8.8 mmol/L following a 75 g oral glucose tolerance test [OGTT]).

By contrast, Landon et al found no difference in the rates of serious perinatal complications (again a composite of stillbirth, perinatal death and perinatal morbidity). What they did find was significant reduction in the pre-specified secondary outcomes – infant birth weight, neonatal fat mass, shoulder dystocia, delivery by caesarean section, pre-eclampsia, pregnancy-induced hypertension and maternal weight gain. Notably, this cohort were predominantly multiparous (75%), of mixed ethnicity (25% White) and overweight or obese at entry (mean BMI 30±5 kg/m^2), but had only "mild" gestational diabetes (fasting glucose <5.3 mmol/L and median glucose 8.2 mmol/L following a 100 g OGTT).

It is perhaps not too surprising that there were few serious perinatal complications and no fetal deaths in this cohort. However, the benefits of treatment on limiting maternal weight gain and fetal growth acceleration are striking, in particular the effects of nutritional advice in limiting maternal weight gain (2.5±4.5 kg vs. 5.0±3.3 kg in treatment vs. control groups). This provides compelling evidence regarding the benefits of intensive multidisciplinary management of gestational diabetes – not to prevent the rare occurrences of fetal demise, but to halt the growing epidemic of obesity, both in these mothers and their infants.

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