

Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee

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Executive summary

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Executive summary

Background

Hormonal changes in pregnancy make the body less sensitive to naturally produced insulin. In some women, this can lead to blood glucose (BG) levels being higher than normal. As a result, the baby's BG is higher than normal, and it responds by increasing its own insulin production. This can lead to a number of problems. The baby's higher than normal insulin can lead to overgrowth of fatty tissues, and it may be larger than usual. This can lead to problems at delivery, with shoulders being a particular problem, with occasional fractures of arms and damage to the nerves to the arm. Delivery has to be by caesarean section more often. After birth, the baby's BG may fall too low (neonatal hypoglycaemia) because its own insulin is inappropriately high. Babies are more prone to respiratory problems, and often have to be admitted to neonatal intensive care. Death (perinatal mortality), while rare, is more common than in babies of women who do not have gestational diabetes.

Screening for gestational diabetes has long been a controversial topic. Even the definition of what is gestational diabetes varies. This report is concerned mainly with disorders of glucose regulation which come on in pregnancy and remit afterwards. Some women found to have raised glucose levels in pregnancy will have previously undiagnosed type 2 diabetes mellitus (T2DM).

A previous Health Technology Assessment report reviewed the literature on screening for gestational diabetes mellitus (GDM), published up to the middle of 2000. The main findings were that:

- There were many different definitions.
- The WHO (World Health Organization) criteria for gestational diabetes include a much wider range of hyperglycaemia than in non-gestational diabetes, including impaired glucose tolerance (IGT) as well as diabetes.
- There was almost certainly a continuum of risk, rather than there being two distinct groups of normal and abnormal.
- The key risk factor might be maternal overweight leading to glucose intolerance.
- Diseases should be defined by the harm they do. The early definitions of GDM were based on levels which predicted later diabetes in the mother. Later ones incorporated fetal risk. However that was

often based on 'macrosomia' which was arbitrarily based on birthweight of 4000 g (about 8lbs 11 oz) or 4500 g. Basing it on weight does not distinguish between large healthy babies, and those with the unhealthy insulin-driven overgrowth of adipose tissue.

- There was a need to define GDM more precisely, based not on arbitrary cut-offs of BG, but on the level at which outcomes of pregnancy worsened significantly. Outcomes include neonatal health, caesarean section rates, and maternal anxiety, inconvenience and other disbenefits.
- Universal screening did not appear justified, so the approach might be to screen women with factors known to increase the risk, such as age, ethnicity and obesity.
- Another problem was which measure of BG to use. The leading competitors included fasting plasma glucose (FPG) and the 50-g challenge test.
- The optimum thresholds for positive screening tests were uncertain.
- Treatment options included diet and exercise, and insulin. However it was noted that trials of oral agents such as metformin were under way.
- Screening for GDM failed to meet some of the National Screening Committee (NSC) criteria.

The report noted that a number of relevant studies were under way. These included:

- The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), which was investigating the effect of screening for, and management of, glucose intolerance in pregnancy in approximately 1000 women.
- The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, which was examining the links between the level of BG, and the risk of adverse maternal, fetal and neonatal outcomes, in approximately 25,000 women from the USA, Canada, Europe (including Belfast), Asia and Australia.

What has changed?

The ACHOIS and HAPO studies have now been published, though not all the results of HAPO have yet appeared.

Data on recent trends in maternal age at birth, and on the prevalence of overweight and obesity, indicate that

women are older and heavier when having children, which will increase the prevalence of gestational diabetes.

The key questions for this updating review

1. After HAPO and similar studies, at what level of hyperglycaemia in pregnancy (HGP) should we intervene? At the high end of plasma glucose (PG), there will be definite benefits to the baby and the benefits will outweigh the harms and inconveniences. But at the lower end of the hyperglycaemia distribution (which could be just above the upper limit of normal) the harms and inconveniences may outweigh the benefits.
2. Which BG screening test should be used?
3. Should there be universal PG testing, or selection by risk factors so that only a proportion of women proceed to blood testing?
4. Are oral glucose lowering drugs effective and safe? Should the treatment pathway be lifestyle, then oral agents, then insulin?
5. What are the research needs now?

Methods

For the review of treatment with oral drugs versus insulin, a full systematic review and meta-analysis was carried out.

The results of ACHOIS and HAPO were summarised and their implications discussed. Findings of a selection of other recent studies, relevant to the continuum issue, were summarised.

Some recent screening studies were reviewed, including a particular focus on studies of screening earlier in pregnancy.

Results

The HAPO study showed that there was a continuum of risk with no threshold which could divide women into those with gestational diabetes, and those without. There was a linear relationship between plasma glucose (PG) and adverse outcomes. This makes it inappropriate to classify some women as having gestational diabetes, and the rest not. It is probably better to avoid the dichotomous term gestational diabetes and to talk instead of 'hyperglycaemia in pregnancy' (HGP). In the HAPO study, from results published so far, macrosomia has been defined by birthweight, but head circumference data were also collected.

Other studies published in recent years provided further evidence for the continuum.

Treatment with oral drugs instead of insulin

We identified a total of 27 primary studies, including some published only as conference abstracts. Four randomised controlled trials (RCTs) and 11 observational studies compared glibenclamide with insulin. One RCT also included a group receiving acarbose. Three RCTs and three observational studies compared metformin with insulin.

The RCT evidence showed few differences in results between glibenclamide and insulin. There were no differences in most outcomes. There was less maternal hypoglycaemia with glibenclamide, but less neonatal hypoglycaemia and lower birthweight with insulin.

There were also no differences in most outcomes when comparing metformin with insulin. There was less maternal weight gain with metformin.

Both glibenclamide and metformin are safe and effective, and can be used instead of, or before insulin when diet and physical activity fail. Neither drug has yet been licensed for use during pregnancy. Not surprisingly, there is evidence that women prefer oral agents.

Some factors predicted failure to achieve adequate glycaemic control on oral agents, but the current evidence base is not sufficient to rule out a trial of oral treatment after failure of diet alone. If adequate control is not quickly obtained, a switch could be made to insulin. However, it appears that insulin therapy is not a guarantee of achieving adequate glycaemic control. In studies measuring glucose levels among women receiving insulin, a significant proportion was found to have suboptimal glycaemic control.

One trial compared glibenclamide and metformin and found that failure to achieve glycaemic control was more common among women receiving metformin (41% vs 20%).

However, it appears that insulin therapy is not a guarantee of achieving adequate glycaemic control. In studies measuring glucose levels among women receiving insulin, a significant proportion was found to have suboptimal glycaemic control.

Thresholds for intervention

The continuum of risk by glucose level shown by HAPO creates a problem in that there is no clear clinical threshold for intervention. Most of the adverse

outcomes occur in low risk groups – about half in HAPO categories 2 and 3 – because those groups are much larger. However the numbers needed to treat to avoid an adverse outcome in those groups are much larger (33 and 25, respectively) than in categories 6 and 7 (9 and 6, respectively). However only 12% of the adverse outcomes occur in categories 6 and 7, because the numbers of women in these groups are much smaller.

Screening studies

Early screening

Studies reporting that screening at first antenatal clinic was worthwhile did not all distinguish between early onset of gestational hyperglycaemia and pre-existing T2DM. The rising prevalence of T2DM at younger ages, linked with overweight and obesity, and the older ages of women having pregnancies means that increasing numbers will be diagnosed with T2DM in pregnancy. Glycated haemoglobin may be useful for detecting pre-gestational diabetes, and does not require fasting or glucose loading.

There might be a case for pre-conceptual testing in high risk groups.

Choice of test

In the HAPO study, no one measure of BG came out as being clearly the best, but FPG was as good as any, and has the advantages of being more convenient than the oral glucose tolerance test (OGTT). It might be easier done in general practice in view of the practical difficulties of doing a large number of fasting glucose tests in hospital antenatal clinics. Adherence to fasting might not be universal. However, correlations between the fasting and post-load levels were quite poor, and we need to know how many of the women in the low risk HAPO categories were high risk by post-load levels.

Selective or universal screening

The National Institute for Health and Clinical Excellence (NICE) recommends selective screening based on body mass index (BMI) over 30 kg/m², previous GDM, previous baby over 4500 g, a family history of diabetes, or on high risk ethnicity. This recommendation was based on the probability of being diagnosed with GDM on the basis of the 75-g OGTT, and pre-dates HAPO. It would be useful to have data on the prevalence of risk factors in each of the seven HAPO categories, to see if selective screening would miss many women in the higher risk categories.

Economic studies

Most studies of costs or cost-effectiveness pre-dated HAPO. In brief:

- Costs are about £1833 higher for pregnancies complicated by gestational diabetes, suggesting that prevention would be worthwhile.

- Costs are lower for treatment with oral agents than with insulin.
- The economic analysis of the ACHOIS study found that intervention with more intensive dietary advice, blood monitoring and insulin when required, resulted in a cost per serious perinatal event avoided of £12,688. The (statistically not significant) impact upon perinatal mortality suggested a cost per life-year of £1376.
- Some studies find that screening with the 50-g glucose challenge test and then testing screen-positives with the OGTT, was less costly than going straight to universal OGTT.

A high quality cost-effectiveness analysis was provided for the NICE Guideline Development Group. Full details are available on the NICE website. It found that two screening strategies dominated:

- selection by the American Diabetes Association (ADA) criteria followed by the 75-g OGTT [incremental cost-effectiveness ratio (ICER) £3678]
- selection by high-risk ethnicity followed by the 75-g OGTT (ICER £21,739).

However, the economics studies do not yet resolve the most difficult issue – at what level of BG does intervention become cost-effective? One study addresses that issue, but is only available as an abstract. It uses US costs, and concludes that lowering the threshold for intervention from HAPO category 5 to category 4, based on the 2-hour glucose results, would not be cost-effective. No similar analysis has yet been done for the UK.

Revisiting the National Screening Committee criteria

Some of the criteria that were not met in the last HTA review have now been met:

- Criterion 1: importance of problem. Met. The condition has become more important, because of rising prevalence, and the HAPO demonstration of adverse outcomes over a much wider range of BG.
- Criterion 3: primary prevention. Debatable. Public health campaigns have not prevented the rise in general population obesity, but primary prevention has not been tried specifically in women planning pregnancy.
- Criterion 5: cut-off level defined. Not yet met, pending further cost-effectiveness analysis post-HAPO.
- Criterion 7: Partially met. HAPO has shown that a single measure of BG is highly predictive.
- Criteria 8 and 9: treatment. Met. The ACHOIS trial has shown that intervention at lower levels is

cost-effective. Trials of oral drugs have shown they are safe and effective, as well as being cheaper and preferred by patients.

- Criterion 11: not met – still no RCTs of screening versus no screening.
- Criterion 13: overall benefits and harms. Partially met. The balance has swung towards easier testing and easier treatment, coupled with increasing prevalence.
- Criterion 14: met for some groups following the economic analyses by the ACHOIS group and for the NICE Guideline Development Groups, but still some uncertainties to be resolved.

Research needs

1. Could we use FPG for screening? We need further analysis of the HAPO data to determine how many women in categories 1–4 by FPG are in categories 5–7 by post-load PG.
2. What are the true rates of macrosomia within the HAPO categories, as assessed by both birthweight and head circumference?
3. Is glycated haemoglobin (HbA_{1c}) a useful test at booking clinic for detecting pre-gestational diabetes, and also pre-gestational insulin resistance likely to be followed by HGP?
4. Can risk factors, in conjunction with HbA_{1c}, identify a group of women whose risk of adverse outcomes is very low and who need not be screened? HAPO data could be used to address the question of selective or universal screening, by comparing risk factors and different thresholds in each category. The hypothesis might be that women with risk factors are more likely to be in the higher categories.
5. What is the most cost-effective screening and treatment strategy, in the light of the new evidence? At which HAPO category does treatment become cost-effective, taking into account infant and maternal outcomes, and treatment with the cheaper oral agents when lifestyle measures fail, with insulin being used only when the oral drugs fail? Resources in this mini-review did not permit new modelling. We recommend that the team which did the modelling for the NICE Guideline Development Group should be asked to update their analysis. One of the issues in modelling is the relative weight given to each of the adverse outcomes.

6. Could public health interventions reduce the prevalence of obesity among women becoming pregnant in the UK, and therefore reduce the problem at source?
7. Given the increasing age and weight of mothers-to-be, should screening start earlier? Screening is usually done at 24–28 weeks. Several commentators have noted that there can be delays between screening, diagnostic testing and treatment, and that these can occur during the 'therapeutic window' and hence result in poorer outcomes. There is a need for studies which report the prevalence of HGP by week of gestation, perhaps at 2-week intervals. Such studies could identify the optimum time to screen, perhaps depending on age and BMI.

Conclusions and recommendation

Despite advances in knowledge following the ACHOIS and HAPO studies, some key uncertainties remain to be resolved. Some of these could be resolved by, firstly, further analysis of the already collected HAPO data, and, secondly, by updated modelling using the UK model used in developing the NICE guidelines, and for each of the seven HAPO categories.

We recommend that the NSC should ask for, and await, additional analyses before revising its policy. It would be wrong to make firm recommendations now given the knowledge gaps and the fact that data will be available from the HAPO study which can fill some of the gaps. The uncertainty about the level at which intervention is justified may come out of the recommended modelling.

There is also a need for interventions aimed at prevention of HGP, firstly by persuading women to achieve normal weight before becoming pregnant, and secondly by physical activity and appropriate diets in pregnancy.

Publication

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