Global Guideline

Pregnancy
and diabetes

unite for diabetes

International Diabetes Federation

The mission of the International Diabetes Federation is to promote diabetes care, prevention and a cure worldwide

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1. Introduction

Pregnancy is associated with changes in insulin sensitivity which may lead to changes in plasma glucose levels. For women with known diabetes or for women who develop diabetes during the pregnancy, these changes can put outcomes at risk. This guideline deals with the means of identifying women for whom such problems are new, and helping them, as well as women already known to have diabetes, to achieve the desired outcome of a healthy mother and baby.

Within the IDF Global Guideline for Type 2 Diabetes of 2005 [1] there was a section on pregnancy, but this did not address type 1 diabetes and did not consider the wider issues surrounding gestational diabetes mellitus (GDM) and prevention of diabetes. The current guideline includes these additional topics, and attempts to present some of the evidence bearing on areas of controversy.

Since 2005 an evidence-based guideline on diabetes in pregnancy has been published in the UK [2], the Canadian evidence-based diabetes guideline (including pregnancy) has been revised [3], and there have been further deliberations on the implications of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [4]. In preparing the current guideline, a non-formal evidence review was circulated to, and discussed by, a small Writing Group in March 2009, then redrafted before circulation to an Expert Review Committee. The revised draft was referred to IDF member organizations for comments. This document represents the final revision which has taken into consideration comments received from this wide consultation.

The aim was to draw up a set of recommendations for Standard Care as envisaged in the 2005 Global Guideline [1] and which represents current best practice. It is acknowledged that due to limited human and material resources, many countries or health systems will not be able to implement all of the recommendations in this Guideline. The Recommendations are presented together towards the end of the document (section 6). The topics covered in this Guideline have in general been presented in the order encountered before, during, and after pregnancy, except that gestational diabetes is introduced first.

2. Gestational diabetes mellitus (GDM)

2.1 Defining the condition

The widely accepted definition is that given by the American Diabetes Association (ADA) '…any degree of glucose intolerance with onset or first recognition during pregnancy' [5]. The definition is applicable even if 'the condition persists after pregnancy'. 'It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy.' The widespread acceptance of this definition is in no small part due to the fact that it does not mention any specific diagnostic criteria.

Any definition of GDM has to take into account three elements of risk – of perinatal morbidity and mortality in the current pregnancy, of the mother developing type 2 diabetes, and of intra-uterine programming of the developing fetus with subsequent expression of disorders in later life.

2.2 Diagnosis of GDM

There is a continuum of risk for maternal glucose levels and, at least, adverse pregnancy outcomes [6-11]. Currently there is a lack of international consensus regarding the diagnostic criteria for GDM. In most parts of the world the diagnostic criteria are based on either the 100 gram 3-hour test as commonly used in the USA or the 75 gram 2-hour World Health Organization (WHO) test. Many national bodies have derived their own criteria based on local experience and their healthcare delivery systems. This lack of consensus may well be addressed by recommendations arising from the International Association of Diabetes in Pregnancy Study Groups (IADPSG), a working group analysing the results of the HAPO study. Any recommendations from this group will then need to be considered by relevant national bodies and incorporated into the local health service arrangements. This process will take some time. Other than by chance, it is not clear if any diagnostic criteria of GDM based exclusively on pregnancy outcomes will be applicable to the other two elements of risk.

2.3 Rationale for treating GDM

It is generally acknowledged that women with GDM are at increased risk of adverse pregnancy outcomes, particularly relating to perinatal mortality and morbidity. It is also generally acknowledged that treatment of women with GDM, by whatever means, can reduce the risk of these problems. In the developed world an increased perinatal mortality rate is unlikely but can still be demonstrated in a sufficiently large series [12]. However, in settings where obstetric care does not uniformly reach modern quality standards, perinatal mortality is still an important issue [13].

Perinatal morbidity is an ongoing concern. Macrosomic or large-for-gestational-age (LGA) infants are still common, and can be considered a surrogate marker for at least some of the effects of intra-uterine programming.

An earlier prospective controlled trial demonstrated that 'tight' control, with a high rate of insulin use, improved perinatal outcomes [14]. Later, a prospective non-randomized intervention study demonstrated for women with GDM that intensive control (versus conventional control) improved perinatal outcomes to a level that was comparable to a group without GDM [15]. The hazards of a late diagnosis of GDM, and therefore effectively no treatment, have been outlined [16]. The Australian Carbohydrate Intolerance Study in Pregnancy (ACHOIS), a blinded randomized trial including 1000 women, designed to examine whether the treatment of women with GDM would reduce perinatal complications, found a significant reduction in serious perinatal complications in the treated group [17]. Recently the results of the Maternal-Fetal Medicine Unit (MFMU) Network study have become available. Treating women with designated 'mild' GDM lowered the risk for many adverse pregnancy outcomes [18].

Limited observational studies in humans strongly suggest that any pregnancy complicated by hyperglycaemia confers a risk to the offspring of developing type 2 diabetes [19-24], and that improving maternal glycaemic control may reduce this risk. However, the long follow-up necessary makes it unlikely that any randomized controlled trial (RCT) evidence will be forthcoming in the foreseeable future.

3. Before pregnancy

3.1 General issues for different groups of women

All women contemplating a pregnancy should ideally have pre-conception advice from a healthcare professional. This is particularly important for women who currently have diabetes or intermediate degrees of hyperglycaemia (impaired glucose tolerance – IGT, or impaired fasting glucose – IFG), or have experienced GDM in a previous pregnancy.

Women with GDM in a previous pregnancy should have had their glycaemic status clarified in the postpartum period. The probability of developing GDM in a subsequent pregnancy is of the order of 30% to 50% [25]. If more than a year has passed since the postpartum assessment, then these women should have an oral glucose tolerance test (OGTT) prior to conception or at least in the first trimester. If the glycaemic status is then normal, the OGTT should be repeated at around 26 to 28 weeks, or at an earlier time if clinically indicated. These indications may include, but are not limited to, the development of glycosuria, increased amniotic fluid or a suspicion of increased fetal size. Women with previous GDM who are shown to have normal glucose tolerance postpartum, and women with previous GDM who experience a recurrence, do not appear to be at increased risk of first trimester malformations other than the risks associated with obesity.

Women already known to have diabetes (sometimes called 'pre-gestational diabetes' in this context) need to consider how the effects of their pregnancy may impact on the diabetes, and on any of their diabetes-associated problems. Hypoglycaemia is more likely to occur in pregnancy, especially in the first trimester, as a greater effort is made to attain and maintain glycaemic control. A variable dietary intake associated with morning sickness may also increase this tendency towards hypoglycaemia. Women with established diabetic complications, such as retinopathy or nephropathy, may experience a worsening during the pregnancy. These aspects should ideally be assessed prior to any pregnancy and/or at such intervals during the pregnancy as clinically indicated.

3.2 Review of medications

Women with diabetes or previous GDM may be taking medications contra-indicated in pregnancy. These include, but are not limited to, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), calcium channel blockers and lipid lowering agents.

In a large cohort study of pregnancy which excluded women with diabetes, first-trimester exposure to ACE inhibitors was associated with an increased risk of major congenital malformations compared to the use of other anti-hypertensive agents [26]. If ACE inhibitors were being used to treat diabetic nephropathy prior to pregnancy, then a significant deterioration in proteinuria can be anticipated during the course of the pregnancy following discontinuation [27,28]. This aspect will need to be considered when offering advice.

There are theoretical problems potentially associated with the use of ARBs in pregnancy, but only very limited data on this topic. Calcium channel blockers have the potential to cause fetal hypoxia and should be used cautiously if at all.

For statins, congenital malformations have been reported and there is concern that decreased cholesterol synthesis may affect fetal development [29], but evidence on use in pregnancy is very limited. Data on the use of fibrates and niacin are also limited.

These medications need to be stopped as part of preconception planning or as soon as a pregnancy is recognized. Sufficient blood pressure control should be secured by using methyldopa or labetalol.

In common with other women during pregnancy, women with diabetes need to ensure there is an adequate intake of folic acid.

Women with type 2 diabetes who are taking either metformin and/or glyburide (glibenclamide) need to have the potential advantages and disadvantages of these medications outlined and to continue with them if it is in their best interests to do so.

3.3 Pre-conception glycaemic control

Women with diabetes have increased risk of an early miscarriage and are at increased risk of having a baby with malformations. Both of these risks are associated with less than optimal glycaemic control around the time of conception and in the first trimester. The extent of the risk is difficult to quantify, but risks appear to be approximately equivalent for women with type 1 diabetes and type 2 diabetes. Women with type 2 diabetes appear to have a lesser uptake of pre-conception counselling [30].

The increased rate of spontaneous miscarriages appears to be low when the HbA_{1c} is modestly raised, and higher with increasingly poor glycaemic control [31-33]. The risks increase rapidly with higher levels of HbA_{1c}. The same pattern is also found with respect to the rate of fetal malformations [34-36]. Women who improve their glycaemic control before conception have a reduced rate of fetal malformation [37]. There appears to be no level of glycaemic control below which no increased risk has been observed [38]. Women with diabetes should be encouraged to obtain the best possible glycaemic control before conception, aiming for, in the absence of confounding variables that may alter the accuracy of the assay, an HbA_{1c} <6.5% (or <7.0% if on insulin). Some consensus opinions advocate a lower value and this is reasonable if it can be safely achieved and maintained. In line with a recent analysis [39], an HbA_{1c} <6.5% might equate with self-monitored capillary plasma glucose values <6.5 mmol/l (<117 mg/dl) before meals and <8.5 mmol/l (<153 mg/dl) after meals. Women with an elevated HbA_{1c} value above 8.0% should be discouraged from becoming pregnant until their control can be improved. There are currently no equivalent data about glucose levels.

Women with diabetes without pre-conception planning, or with an unexpected pregnancy, should have their glycaemic control assessed as soon as practical, and advice on risk should be offered on the basis of this result.

4. During pregnancy

4.1 Testing of all or some women for GDM

There is continuing debate about whether all pregnant women should be tested, or whether testing should be done if risk factors are present, or not done if risk factors are absent. There is general agreement about the major risk factors for GDM. These include but are not limited to increasing maternal age and weight, previous GDM or a macrosomic infant, family history of diabetes among first-degree relatives, and being from an ethnic background with a high prevalence of diabetes. While there is no doubt that women with some or all of these risk factors are more likely to develop GDM, the reality is that any woman can develop this problem. An RCT found that risk-based screening compared with universal screening missed about half the women with GDM (1.45% vs 2.7%) [40].

An earlier observational study of Caucasian women where all were tested with an OGTT found that the prevalence of GDM among women with no risk factors was 2.8%. Excluding this low-risk group of women would still require 80% of the women to be tested and would miss 10% of all cases of GDM [41]. Testing women according to the older age-based American College of Obstetricians and Gynecologists (ACOG) criteria would miss one-third of cases and result in minimal cost savings [42]. A later retrospective study found that testing according to risk factors would require 90% of the population to be tested [43]. A complicated scheme has been suggested for reducing the number of women requiring testing [44], but this was considered unlikely to be practical [45].

There is general consensus that testing should be done at an early stage of pregnancy if risk factors are present, but only poor evidence that interventions initiated at this early stage are helpful.

There is insufficient evidence to come to a definitive opinion on the advantages of selective testing. However, selective testing could be considered:

(a) if there was evidence to show that this process detected the vast majority of women in the population being considered;
(b) if there was evidence that the process of selection based on risk factors could be conducted with accuracy;
(c) if women in the population being considered and not being tested had a more benign outcome to their undiagnosed GDM;
(d) if it was deemed cost-effective, or was the only option, within a particular healthcare arrangement.

The limited evidence so far [46] indicates that a sorting system cannot be conducted in an efficient manner, and that women with GDM without risk factors appear to be no different from women with GDM and risk factors.

4.2 Testing for GDM – a two-stage or one-stage procedure?

A definitive diagnosis of GDM is currently made on the result of an OGTT. Currently, a two-stage diagnostic procedure is conducted in some parts of the world. A two-stage procedure involves a non-fasting glucose challenge test (GCT) followed by a formal OGTT for women who have a positive result. The GCT will inevitably miss some women with GDM. In addition, there has been little systematic examination of:

(a) how many women who are positive on a GCT fail to return for the definitive OGTT;

(b) whether a two-stage procedure delays the diagnosis and treatment of GDM, and what the effect of such a possible delay might be.

A one-stage definitive procedure is preferred, but a two-stage procedure will continue to suit many healthcare arrangements. Potential adoption of a lower glucose load (75 g) and a shorter duration of the testing procedure may lead to a reconsideration about the need for a two-stage procedure.

4.3 Management during pregnancy

4.3.1 Monitoring glucose levels

There is strong evidence of a relationship between elevated maternal glucose levels and macrosomia [15,47,48]. Clinical studies where women were randomized to test either before or after meals have found that treatment decisions based on the postprandial glucose levels resulted in fewer complications, particularly macrosomia [49,50].

One study has found that management based on 1-h rather than 2-h glucose levels resulted in better obstetric outcomes [51]. Women prefer, and are more likely to be compliant with, testing 1 h after a meal [52]. For glucose tolerant women there was a positive correlation between the 1 h postprandial glucose level and the fetal abdominal circumference [53]. Women with type 1 diabetes, who have an LGA infant, are more likely to have an elevated HbA_{1c} than those who do not have an LGA infant [54]. The level of HbA_{1c} in the third trimester has a strong correlation with macrosomia but lacks some sensitivity. A possible explanation is that the postprandial glucose excursions are more important in pregnancy, and this is not always being reflected in the HbA_{1c} level [55]. In one study, women with type 1 diabetes who were tightly controlled, based on fasting and postprandial glucose goals, had no LGA babies [56].

Continuous glucose monitoring can add an extra dimension to self-monitoring and may highlight areas of both unexpected hypoglycaemia and hyperglycaemia [57,58].

Whenever it is possible, pregnant women with diabetes should be encouraged to self-monitor blood glucose levels both fasting and postprandial, preferably 1 h after a meal. The target glucose levels should be as low as possible compatible with patient comfort and safety. The conclusions of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [59], in the absence of specific evidence, referred to 'upper boundary' treatment targets for capillary blood glucose levels: fasting 90 to 99

mg/dl (5.0 to 5.5 mmol/l), 1 h after starting a meal <140 mg/dl (<7.8 mmol/l) or 2 h after starting a meal <120 to 127 mg/dl (<6.7 to 7.1 mmol/l). The National Institute for Health and Clinical Excellence (NICE) recommendations for self testing in pregnancy are to have a fasting glucose between 3.5 and 5.9 mmol/l (63 and 106 mg/dl) and a 1-h postprandial glucose <7.8 mmol/l (<140 mg/dl) [2]. The updated Canadian Diabetes Association (CDA) guideline recommends plasma glucose target values during pregnancy as follows: fasting and preprandial 3.8 to 5.2 mmol/l; 1-h postprandial 5.5 to 7.7 mmol/l; 2-h postprandial 5.0 to 6.6 mmol/l [3].

Action points (arbitrary) for treatment adjustment should be easy to remember and therefore may need to be rounded differently depending on which system of units is being used. Exact translation from one system to the other would imply a precision that does not exist. For rounding in the SI, this might mean a fasting glucose ≥5.5 mmol/l, a 1-h postprandial glucose of ≥8.0 mmol/l or a 2-h postprandial glucose level of ≥7.0 mmol/l. Alternatively, it might be a fasting glucose ≥100 mg/dl, 1-h postprandial of ≥140 mg/dl or a 2-h postprandial of ≥120 mg/dl.

The HbA_{1c} level should ideally be measured at regular intervals (4 to 8 weeks), or at such intervals as can be managed, for all women with previously diagnosed diabetes, as an ancillary aid to self-monitoring of blood glucose. For women with gestational diabetes, in whom it is suspected that they may have developed either type 1 diabetes or type 2 diabetes while pregnant, an HbA_{1c} measurement may provide clarification and help with treatment. However, the routine measurement of HbA_{1c} currently has only a minimal role in the management of women with GDM.

4.3.2 Lifestyle management

4.3.2.1 Nutrition

All women in all pregnancies should ideally have advice about the macronutrient and micronutrient intake most suitable for achieving the best possible pregnancy outcome. Women with diabetes require an extra dimension to this advice. Women with pre-existing diabetes have most likely had previous nutritional advice that will need to be revised and reviewed during pregnancy. Women who develop GDM will most likely require this advice for the first time, often towards the end of pregnancy. In some respects the nutrition management advice offered during pregnancy, especially with regard to intake of macronutrients (fats, for instance), may differ slightly from the advice that is applicable before and after the pregnancy. All such advice should be individualized and culturally sensitive, and should be administered by a healthcare professional, ideally someone with specific expertise in medical nutrition therapy (MNT).

Women with pre-existing insulin-treated diabetes should have the type, quality and quantity of their carbohydrate food matched to their insulin type and dose. Quite significant changes may be necessary as efforts are made to improve control, either before pregnancy or after conception is confirmed. Women with intermediate hyperglycaemia (IGT or IFG) and women with type 2 diabetes who are changing

from tablets or electing to be treated with insulin, if diet alone is inadequate, will also need careful advice about their carbohydrate choices. The same observations about carbohydrate regulation apply to women diagnosed with GDM [60,61].

There may be an involuntary decrease in energy intake at the beginning of the pregnancy related to nausea. Later in pregnancy the total energy requirements are likely to increase. For those women who are insulin treated, there is likely to be an increase in the total dose of insulin during the pregnancy related to the physiological decrease in insulin sensitivity. Thus the dietary carbohydrate content and distribution will need to be changing to fulfil nutritional requirements and as the insulin dose and type are changed.

It is possible that maternal obesity could be associated with an increased risk of fetal abnormalities [62,63]. Weight loss diets are in general not recommended during the course of a pregnancy. However, at least for women with GDM who are considerably overweight, reducing energy intake by no more than 30% of habitual intake [64] is not associated with ketosis and does not cause harm [65,66].

The proportion of energy intake derived from carbohydrates will vary depending on the traditional diet and the availability of alternative sources of energy. Regulating and potentially reducing the carbohydrate intake is an effective strategy for helping to control glucose levels [67,68]. Changing the nature of the carbohydrates consumed, particularly with respect to the use of foods with a low glycaemic index (GI), can reduce the postprandial glucose excursions. For women with GDM, postprandial glucose elevations are associated with adverse pregnancy outcomes [49,69]. In normal pregnancies, a low GI diet will result in a reduced rate of LGA babies [70,71]. For women with GDM, a low GI diet can reduce the rate of insulin use, with no compromise of obstetric and fetal outcomes [72].

4.3.2.2 Exercise

A moderate amount of exercise is beneficial for most people most of the time, and pregnancy is no exception. The 'expert opinion' of ACOG was that a minimum of 30 minutes exercise on most days of the week was recommended during a normal pregnancy [73]. There is no indication that this opinion, with common sense precautions, would be any different for pregnant women with diabetes. Women who were exercising before pregnancy should be encouraged to continue this during the pregnancy though the extent and type of exercise may need to be modified. For women with GDM, exercise can be seen as a useful adjunct to treatment [3,64,74]. Exercises that effectively avoid excessive abdominal muscular contraction are preferred [59].

Women who exercise regularly are probably less likely to develop GDM, although this reduced rate appears to be related to the habitual amount of exercise rather than exercise started in the year before the pregnancy [75]. An exercise programme may be an alternative to the use of insulin in women with GDM who have not

responded to diet alone [76,77]. This may come about due to the increased insulin sensitivity associated with exercise therapy [78,79].

Advice on exercise should be tailored to the previous exercise habits of the individual. If they were previously sedentary, then arm exercises may be a good starting point. Inactivity can be expected to result in a further reduction in insulin sensitivity.

In summary, exercise may be useful for preventing GDM and also for improving insulin sensitivity. This is based on limited and diverse clinical studies as well as expert opinion. The prescription of exercise during pregnancy is hindered by lack of evidence regarding the type, frequency and intensity [80].

4.3.3 Insulin use during pregnancy

Insulin has been used in pregnancy since 1922. It is essential for women with type 1 diabetes and is still widely considered the drug of choice for women with either type 2 diabetes or GDM who are not meeting treatment goals with lifestyle modification and/or oral glucose-lowering agents. The clinical experience with insulin use is vast, but the availability of clinical trial evidence is limited. The longer an insulin has been used, the greater is the collective clinical experience but not necessarily the clinical trial evidence. Highly purified animal insulins have been largely replaced by human insulin preparations. These in turn are now being replaced in some markets by insulin analogues, modified to produce either a more rapid action for mealtime use or a longer duration of action for basal use.

Human insulin was shown to achieve improved pregnancy and infant outcomes compared with highly purified animal insulins [81]. Commencing in 1999, the safety and efficacy of the rapid-acting analogue insulin lispro has been demonstrated in pregnancy in pre-existing diabetes and GDM [82,83], and it was found not to cross the placenta [84]. The second rapid-acting analogue, insulin aspart, has also been shown to be safe and effective in pregnancy in type 1 diabetes [85,86] and GDM [87]. The use of these two analogues has been the subject of a systematic review [88]. There are currently no data regarding the rapid-acting analogue insulin glulisine in pregnancy.

For the long-acting insulin analogues, there is limited experience in pregnancy with insulin glargine [89-92] but no data so far for insulin detemir, although a trial is now under way.

The decision about which type of insulin and which insulin regimen to start or continue during pregnancy should be taken after informed discussion. The more limited clinical experience and therefore the theoretical possibility of as yet unknown risks associated with the newer insulin analogues needs to be balanced against patient preference and overall glycaemic control and stability.

4.3.4 Oral glucose-lowering agents in pregnancy

4.3.4.1 General considerations

The majority of women diagnosed with GDM can be managed by modification of lifestyle (including patterns of eating and of physical activity). However, women who exceed predetermined glycaemic goals have been generally advised to commence on insulin. Insulin is expensive, relatively difficult to administer, and also difficult to store if the circumstances are less than optimal. In recent years two clinical trials have examined the effects of the use during pregnancy of glyburide (glibenclamide) [93] and metformin [94]. These studies have stimulated the debate about the use of oral glucose-lowering agents for the treatment of women with GDM.

Glucose profiles in women with GDM will show a basal level and postprandial spikes. When considering the glucose crossing from the mother to the fetus, there is a basal consistent amount and the spikes associated with food intake. On a theoretical level, in the process of transfer of the higher postprandial glucose levels, the fetus will tend to recirculate the higher glucose via amniotic fluid reuptake, thus producing a more profound and prolonged effect than the simpler rise and fall of glucose seen in the mother [95]. Thus agents that lower the maternal basal glucose level may not have as great an effect on the fetus as agents that lower the maternal postprandial glucose levels. This concept should be kept in mind when therapeutic choices are being considered.

4.3.4.2 Metformin

There has been extensive clinical experience with the use of metformin in pregnancy over more than a quarter of a century [96,97]. Metformin does cross the placenta, but there appear to have been no teratogenic problems, although this question has not been systematically examined. The recent Metformin in Gestational Diabetes (MiG) study [94] has shown that metformin can be a viable alternative to insulin in a proportion of cases. Both NICE and CDA include metformin as an option for treatment of GDM, and NICE also includes metformin as an option for the treatment of type 2 diabetes in pregnancy, with the proviso that it is not licensed for these indications [2,3].

4.3.4.3 Sulfonylureas

Not all sulfonylureas cross the placenta, and the use of glibenclamide (glyburide) to treat women with GDM was examined prospectively by Langer [93] and has subsequently been the subject of several retrospective reports, as recently reviewed [98]. As with metformin, glibenclamide (glyburide) appears to be an alternative to insulin in some instances, although dose titration can mean that women may be without optimal treatment for some weeks. Both NICE and CDA include glibenclamide (glyburide) as an option for treatment of GDM (although it is not licensed for this indication) [2,3]. However, despite these positives, for women with type 2 diabetes there have been some reports of adverse outcomes associated with the use of glibenclamide (glyburide) in the third trimester [97,99].

4.3.4.4 Other agents

Insulin secretagogues of the meglitinide class might appear to offer theoretical advantages in controlling postprandial glucose levels but have not been subject to either historical usage or prospective studies. The α-glucosidase inhibitors, especially the non-absorbable acarbose, also offer theoretical postprandial advantages and are being examined. The insulin sensitizers of the thiazolidinedione class are contra-indicated in pregnancy.

4.3.4.5 Combination therapy

In the MiG study women taking metformin who had insulin added were found to require a lower dose of insulin [94]. However, the use of metformin with insulin or metformin with glibenclamide (glyburide) has not been systematically examined in pregnancy.

4.3.4.6 Fetal malformations

Women with type 2 diabetes or women treated for polycystic ovary disease may be taking oral glucose-lowering agents at the time of conception. After adjusting for the effects of less than optimal glycaemic control, there does not appear to be any increase in the rate of fetal malformation [100,101]. Clearly a discussion of risks and the option of alternative therapy is needed at the earliest opportunity.

4.3.4.7 Conclusion

The clinical experience with insulin therapy is vast and without problem and it remains the agent of choice whenever possible. There also does not appear to be any clear harm with respect to pregnancy outcomes from using either metformin or glibenclamide (glyburide). The long-term effects of these agents on the developing child have not been systematically examined, but this observation also applies to insulin in general, let alone the different types of insulin. Many countries also have regulatory requirements or non-approval of certain agents in pregnancy.

For women with GDM, who exceed predetermined glycaemic goals, insulin is the preferred treatment. However, if allowable, metformin and glibenclamide (glyburide) can be considered safe and effective alternatives in many instances. In poorly resourced areas of the world, the theoretical disadvantages of using oral glucose-lowering agents for women with GDM and type 2 diabetes are far less than the risks of non-treatment. Where insulin cannot be afforded, or where circumstances make its use hazardous, then oral agents can be the only option.

5. After pregnancy

5.1 Breastfeeding

Unless there is a specific contra-indication or concern, breastfeeding is the preferred option for all women. This general recommendation is also applicable to women whose pregnancy was affected by pre-existing or gestational diabetes. However, it should be noted that it is possible for breastfeeding to have an influence on maternal glycaemic control, and maternal diabetes may in turn influence the composition of breast milk.

Along with nutritional and immunological advantages, breastfeeding has been associated in the general population with a reduction in the rates of childhood obesity. The breast milk of mothers with diabetes has been shown to have a higher glucose and energy content than that of non-diabetic mothers [102,103]. Perhaps because of this, the potential for breastfeeding to be protective against subsequent overweight in the children of women with diabetes has been questioned, and this has been examined without clear conclusions being drawn [104]. In the absence of evidence, it seems advisable to maintain good maternal glycaemic control during the breastfeeding period.

For women with pre-existing insulin-treated diabetes, in limited studies, there was no difference in insulin requirements or in the rate of hypoglycaemia between those women who breastfed compared with those women who did not [105,106]. However, there is recent evidence that type 1 diabetic women have a reduced basal insulin need during lactation [107].

Transfer of metformin to human milk is minimal, at <0.4% of the maternal concentration [108-110]. There is concern that sulfonylureas may cause hypoglycaemia in the baby. Data on sulfonylureas are inadequate, but are discussed in the report of a very small study in which glibenclamide (glyburide) and glipizide could not be detected in the breast milk of nursing mothers [111].

The British National Formulary suggests that enalapril is probably safe with breastfeeding while other ACE inhibitors should probably be avoided [29]. The same cautious advice applies to all of the ARBs and calcium channel blockers. The various statins either appear in the breast milk or have no data available.

5.2 Follow-up of GDM

Unless known to have diabetes, all women who have been treated as GDM should have a postpartum OGTT. The timing of this will depend on the local healthcare arrangements and will vary from being conducted in hospital before discharge to around 6 weeks postpartum [112], ideally as part of other postpartum assessments.

Women with GDM are at increased risk of GDM in a subsequent pregnancy and also of developing type 2 diabetes. Therefore intermediate and long-term follow-up will depend on future pregnancy plans.

If further pregnancies are planned, then a repeat OGTT prior to conception or at least in the first trimester is desirable. If no abnormality is present, then testing should be repeated at the usual time and with the usual indications during pregnancy.

If no further pregnancies are planned, the long-term follow-up arrangements will depend heavily on the perceived risk of developing type 2 diabetes. In a high-risk group there should be an annual OGTT. In a low-risk group there could be fasting glucose every two to three years and an OGTT only if this level is ≥5.5 mmol/l (100 mg/dl).

5.3 Prevention of type 2 diabetes in women who developed GDM

Women with previous GDM are at very high risk of developing type 2 diabetes [113]. The rate of conversion will depend on a mixture of community and genetic factors. The prevention, or at least delay in the development, of type 2 diabetes is an attractive option, as it is likely to reduce the risks associated with having established diabetes.

There are several diabetes prevention studies, all with positive outcomes. Two studies have targeted women with previous GDM. The first was the Troglitazone in Prevention of Diabetes (TRIPOD) study that exclusively enrolled women with previous GDM and showed a 55% risk reduction in the troglitazone treated group compared with placebo [114]. This beneficial effect was substantiated in the follow-on Pioglitazone in Prevention of Diabetes (PIPOD) study when pioglitazone was substituted [115].

The second study was the Diabetes Prevention Program (DPP), where women with previous GDM were included [116]. This study demonstrated a significant reduction in type 2 diabetes for both lifestyle modification and metformin therapy compared with placebo. A subsequent sub-group analysis of the results found that, for women with previous GDM, lifestyle modification and metformin were equally effective [117].

6. Recommendations for Standard Care

These recommendations only address areas of pregnancy care commonly affected by the co-existence of diabetes, and not routine obstetric care such as fetal scanning and monitoring.

Pre-pregnancy counselling

- For all fertile women of child-bearing age with diabetes, identify possibility of pregnancy by direct questioning on every relevant occasion. Provide contraceptive advice where appropriate.

- Offer appropriate pre-pregnancy advice to all women so identified, especially with respect to thyroid status, folic acid supplementation, and the assessment of any diabetes complications that may change during the pregnancy.

- Provide education on the management of pregnancy with diabetes, explaining risks and how they can be minimized.

- Advise optimization of glycaemic control (pre-conception target DCCT-aligned HbA_{1c} <6.5%, or <7.0% if on insulin; self-monitored capillary plasma glucose values <5.5 mmol/l (<100 mg/dl) fasting and <8.0 mmol/l (<145 mg/dl) after meals), actively discouraging women with HbA_{1c} values above 8.0% from becoming pregnant until their control can be improved.

- Discuss the advantages and theoretical risks of oral glucose-lowering agents and start insulin where appropriate.

- Discuss choice of insulin, with possible risks of the most recently introduced insulin analogues to be balanced against individual preference and overall glycaemic control.

- Stop ACE inhibitors and ARBs and use appropriate substitutes.
- Stop statins, fibrates and niacin.
- Assess established diabetes complications, especially of the eyes and kidneys; discuss and manage identified problems.

At first prenatal visit

- For women with diabetes who have had pre-pregnancy counselling, review understanding of management of diabetes in pregnancy, current drug therapy, blood glucose control, diabetes complications, and presence of other medical conditions. Advise as appropriate.
- For women with diabetes who may have missed pre-pregnancy counselling, determine HbA_{1c} as soon as practical, and offer advice on risk on the basis of the result.
- For women who are at high risk of diabetes because of previous GDM, provide healthy lifestyle advice and offer an OGTT as soon as practical. If the result is normal, then offer again at 26 to 28 weeks of gestation. A one-stage definitive procedure is preferred.
- For all other women (unless a selective process based on risk factors is deemed more appropriate), advise that they will be offered testing for GDM at 26 to 28 weeks of gestation.

Frequency of subsequent visits

- Visits should be as frequently as required, depending on achievement of glycaemic targets and management of other diabetes-associated or obstetric problems. This may be monthly in the first two trimesters and more frequently thereafter.

Ongoing management of diabetes during pregnancy

Lifestyle management

- Offer nutritional management and education. Advice should be individualized and culturally sensitive, and should be administered by a healthcare professional, ideally someone with specific expertise in medical nutrition therapy (MNT).

- Offer general instruction about nutrition and specific advice about carbohydrate intake, which wherever possible should include foods with a low glycaemic index. If insulin is being used, then the choice, quantity and distribution of carbohydrate will need to be coordinated with the amount, type and distribution of the varying insulin requirements of pregnancy.

- Encourage physical activity, tailoring advice to the previous exercise habits of the individual. Explain that exercise can counter the decline in insulin sensitivity that occurs during pregnancy and that resting will have the opposite effect.

Glucose control

- Use HbA_{1c} as an ancillary aid to self-monitoring. Aim for an HbA_{1c} <6.0%, or lower if safe and acceptable.

- If at all possible, self-monitoring of blood glucose (SMBG) should be done frequently. For women with pre-existing diabetes this will relate to their previous pattern of testing and the type of insulin regimen they are using.

- Adjust the dose of oral glucose-lowering agents or insulin on the basis of self-monitoring results, HbA_{1c} and experience of hypoglycaemia, and be prepared to change from oral glucose-lowering agents to insulin if required.

Other diabetes-associated problems

- Examine eyes at first prenatal visit and each trimester.

- Monitor blood pressure and advise/treat accordingly, avoiding ACE inhibitors and ARBs.

Management of gestational diabetes

- Advise on risks of adverse pregnancy outcome and how these may be reduced.

- Instruct in self-monitoring of blood glucose (to be used four times daily, fasting and 1 h after each meal), and advise on lifestyle modification.

- If agreed glucose control targets are not met within 1 to 2 weeks of initiation of lifestyle management, offer glucose-lowering medication. Insulin has been, and is likely to remain, the treatment of choice but there is now adequate evidence to consider the use of metformin and glibenclamide (glyburide) as treatment options for women who have been informed of the possible risks. Combination therapy has not been specifically studied.

- Do not use routine measurement of HbA_{1c} for management.

After delivery

- Anticipate changed insulin requirements (immediate reduction), and thus the need for more frequent glucose monitoring, if continuing insulin postpartum and during breastfeeding.

- For women who developed GDM, stop glucose-lowering therapy. At discharge, reinforce lifestyle management advice.

Breastfeeding

- Encourage breastfeeding (nutritional and immunological benefits to the baby). Advise women with type 1 diabetes or type 2 diabetes that self-monitoring should continue and good glycaemic control should be maintained during this period.

- Insulin requirements drop immediately after delivery, and a dose adjustment will be needed to allow for the eating patterns of the breastfeeding mother.

- Review medications, taking into consideration the potential risks associated with any transfer into the milk. Metformin and possibly glibenclamide (glyburide) may be used. Statins should be avoided, and consideration should be given to the choice of anti-hypertensive agents.

Follow-up within 6 weeks

- At a convenient time, from 0 to 6 weeks after pregnancy, ideally together with other postpartum assessments, check for diabetes in women who developed GDM. If then non-diabetic, advise on high risk of future diabetes and on preventative lifestyle measures. Advise check for diabetes every one to three years. If further pregnancies are planned, advise on the risk of developing GDM again, and the need for pre-pregnancy counselling.

7. Implementation

Implementation of these recommendations will require liaison between healthcare professionals involved in diabetes, obstetric and neonatal care, such that joint protocols can be devised for pregnancy and post-pregnancy management. Local decisions will be required as to means of testing for GDM and whether a selective or universal approach will be used.

Healthcare professionals will need to be trained on pregnancy-specific lifestyle adaptation, insulin use, screening for complications. Availability of such staff needs to be assured. Self-monitoring equipment and insulin supply need to be assured. Laboratory resources should be provided for clinical monitoring of glucose control and assessment of renal damage. Pre-pregnancy services may need to be organized separately.

8. Evaluation

Delivery weight of the infant and achieved maternal HbA_{1c} each trimester may be useful surrogate outcomes for quality assurance. Structural review should be of the existence of joint management protocols addressing the above recommendations, and appropriate availability of staff.

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