Guidelines for the management of gestational diabetes in pregnancy

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Practice Points

- Gestational diabetes mellitus (GDM) has a significant impact on maternal and fetal outcomes.
- There remains a need for further clinical studies to help unify diagnostic and management strategies used for GDM.
- When and how to diagnose GDM: first, the first antenatal visit offers an opportunity to identify women for GDM in early pregnancy. Second, all pregnant women should be offered testing for GDM at 24–28 weeks of gestation.
- Management of GDM during pregnancy: treatment including lifestyle advice and insulin therapy if required should be offered to all women diagnosed with GDM. Although oral hypoglycemia agents are being used more frequently in clinical practice, there remains a need for further studies to validate their risks and benefits.
- Intrapartum management: intrapartum management during labor should aim to maintain target glucose levels, avoid hypoglycemia and avoid unnecessary medicalization of labor in low-risk women.
- Postpartum management: women with GDM require long-term follow-up with regards to the development of Type 2 diabetes.

SUMMARY There is great interest in developing universal guidelines for the diagnosis and treatment of gestational diabetes mellitus (GDM). This stems from the accumulating evidence that GDM is associated with significant risk of adverse outcomes for both mother and neonate. In recent years, the diagnostic thresholds for GDM have been lowered capturing a greater proportion of pregnant women with GDM. The timing and means by which pregnant women should be tested for GDM have not been well studied. Treatment aimed at reducing blood glucose levels appears to be effective in reducing risk of adverse outcomes. The most widely used methods by which to achieve treatment targets are lifestyle modification and insulin. Oral hypoglycemic agents are increasingly being used. There continues to be questions regarding

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SUMMARY (CONT.) treatment targets both during pregnancy and parturition. Given the increased risk of Type 2 diabetes in the future, it is important to educate women with GDM about the ongoing need for periodic testing for diabetes after pregnancy.

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. GDM is one of the most common medical disorders complicating pregnancy and is increasing in prevalence worldwide [2,3]. The increasing prevalence may be related to the rise in maternal age and weight at the time of conception, as well as the increasing number of women from ethnic groups in which Type 2 diabetes is more common.

GDM results from insufficient insulin secretion from the pancreas during a state of insulin resistance created by pregnancy. Insulin resistance arises in pregnancy as a consequence of placental secretion of hormones such as progesterone, growth hormone, corticotropin-releasing hormone and placental lactogen. These hormones drive metabolic changes that ensure the fetus receives sufficient nutrients at all times during confinement. For the majority of women, when the placenta is removed at delivery, the state of insulin resistance responsible for GDM is removed and normoglycemia is restored. Sometimes persistent Type 2 diabetes or impaired glucose tolerance may be discovered, and more rarely Type 1 diabetes, in the postpartum period.

There is consensus that pregnancies of women with Type 1 or Type 2 diabetes are associated with significant risk of adverse maternal and perinatal outcomes when blood sugar levels are not well controlled before and during the pregnancy [4]. Maternal risks include pre-eclampsia, cesarean delivery and increased risk of developing Type 2 diabetes later in life. There are also increased risks for the fetus and newborn such as macrosomia, shoulder dystocia, birth injuries, hyperbilirubinemia, hypoglycemia, respiratory distress syndromes and childhood obesity. The risk of adverse perinatal outcome associated with lesser degrees of hyperglycemia than Type 1 or Type 2 diabetes is controversial but differential effects at varying levels of hyperglycemia are emerging.

In recent years, there has been much debate regarding the ideal approach for diagnosing GDM. Some groups in both USA and Canada (the US Preventive Services Task Force and Canadian Task Force on the Periodic Health Examination) and in Europe (the UK National Health Service) assert that there is still insufficient high-level evidence to recommend identifying and treating GDM [5]. Some have attributed risks of adverse outcomes associated with GDM, such as macrosomia, excess fetal adiposity and higher rate of cesarean section, to confounding characteristics, such as obesity, more advanced maternal age or other medical complications, rather than glucose intolerance [5]. Despite continued controversy, most parts of the world recognize that undiagnosed and untreated GDM is harmful to both the mother and her offspring. Although hyperglycemia and its effects in pregnancy is a continuum, there is a concerted effort led by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) to unify diagnostic criteria and treatment targets for GDM.

Evidence for identifying & treating women with GDM

Historically, the diagnostic criteria for GDM were chosen to identify women at high risk for development of diabetes after pregnancy or were derived from the criteria used for nonpregnant individuals. It has become evident that impaired glucose control of lesser severity during pregnancy is associated with poorer maternal and neonatal outcomes [6–9].

The pivotal study was the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study published in 2008 [6]. This was a large, prospective, blinded, multinational study that examined pregnancy outcomes in 23,316 women who did not have pre-existing diabetes based on a 75-g 2-h oral glucose tolerance test (OGTT) performed at 24–32 weeks gestation (fasting plasma glucose levels were ≤5.8 mmol/l and/or 2-h, post-75-g glucose load ≤11.1 mmol/l). Primary outcomes were birth weight above the 90th percentile for gestational age, primary cesarean delivery, clinically diagnosed neonatal hypoglycemia and cord-blood serum C-peptide level above the 90th percentile. Secondary outcomes were pre-eclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia and intensive neonatal care.

The HAPO study reported a strong linear correlation between glycemia at 24–28 weeks gestation and adverse maternal and neonatal outcomes. In particular, maternal hyperglycemia was correlated with birth weight, umbilical cord C-peptide levels and all five secondary outcomes. There did not appear to be an exponential risk at any degree of glycemic control.

The question has also been raised whether treatment of mild GDM offers any outcome advantages. The Australian Carbohydrate Intolerance Study (ACHOIS) conducted in 2005 included 1000 women with mild hyperglycemia based on a 75-g OGTT (fasting plasma glucose level less than 7.8 mmol/l and 2-h value between 7.8 and 11 mmol/l) [7]. The women were randomized to either routine obstetric care or intervention, which consisted of physician review, dietitian advice, daily glucose monitoring and insulin if needed. The primary outcomes were induction of labor, cesarean delivery, neonatal death, shoulder dystocia or birth trauma, neonatal ICU admission and jaundice. Serious neonatal complications were lower in the intervention group as was induction of labor but not cesarean sections.

The second large, multicenter, randomized, controlled trial investigating treatment advantage of mild GDM was the National Institute of Child Health and Human Development Maternal Fetal Medicine Unit (NICHD-MFMU) trial [8]. This study of over 900 women found that treatment including nutritional counseling, diet therapy and insulin when required resulted in lower birth weight, neonatal fat mass, rates of cesarean delivery, shoulder dystocia and gestational hypertension/pre-eclampsia.

There are several more studies that have supported the beneficial effects of treating GDM in terms of both maternal and fetal wellbeing [9,10]. A Cochrane review in 2009 concluded that treatment was associated with less serious perinatal morbidity in the infant including death, shoulder dystocia, nerve palsy and bone fracture [10]. Treatment was associated with reduced incidence of maternal pre-eclampsia and infant macrosomia. However, there was an increased rate of admission to special care units and labor induction. Overall, substantial evidence exists to support the beneficial effects of treating women with GDM.

When & how to diagnose GDM

There have been a variety of methodologies suggested for identifying women with diabetes in pregnancy. Several groups have proposed guidelines for the testing and diagnosis of GDM [4,11]. In 2010, the IADPSG published their guidelines for the testing and diagnosis of GDM, which have subsequently been endorsed by several national organizations including the American Diabetes Association (ADA) [4]. However, these guidelines have not been met with universal support. There remains controversy surrounding when testing should take place and which diagnostic thresholds should be applied [12–14].

A suggested guide for testing and identifying women with GDM is provided in **Figure 1**. This is a suggested model that only is based on the available evidence. Two options for testing in early pregnancy are provided owing to the fact that there is no evidence to guide which approach is better in early pregnancy.

Some women may enter a pregnancy with undiagnosed Type 1 or 2 diabetes or impaired glucose control. These women are at increased risk of maternal and neonatal complications such as those identified in the HAPO study. They are also at increased risk of spontaneous abortion and congenital anomalies as well as diabetes-related complications such as nephropathy and retinopathy, which may require treatment during pregnancy [15,16]. They are clearly a group who require rapid treatment and close follow-up in pregnancy, as well as confirmation and treatment of diabetes after pregnancy. Infants born to a mother with undiagnosed diabetes are at increased risk of developing obesity and diabetes later in life, and may have impaired fine and gross motor functions and higher rates of inattention [17,18]. It is clearly advantageous to identify these women early in pregnancy.

GDM in the absence of undiagnosed diabetes may also be discovered in early pregnancy before the usual testing performed at 24–28 weeks gestation. Risk factors for women at greater risk of early diabetes in pregnancy have been identified and could guide which women should have early testing for GDM [19]. Risk factors that could be used to guide early testing are listed in **Box 1** and are adapted from the ADA and the NICE recommendations [1,19].

No studies have been performed in women diagnosed with diabetes in early pregnancy to guide recommendations regarding early testing. The IADPSG guidelines recommend either fasting plasma glucose, HbA1c or random plasma glucose for early diagnosis of diabetes at the first

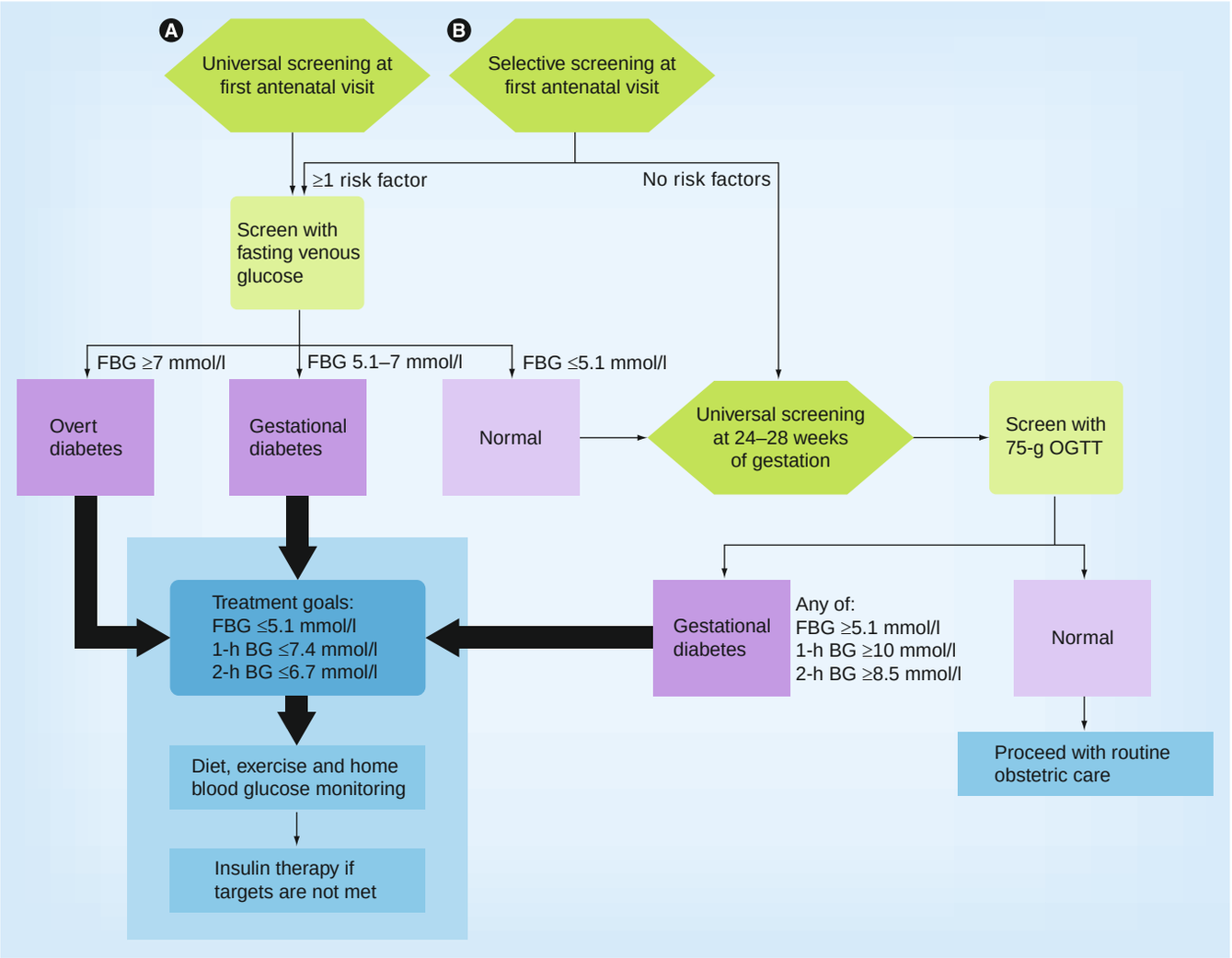

Figure 1. Suggested model for diagnosis and treatment of gestational diabetes mellitus. In early pregnancy, either **(A)** universal testing or **(B)** testing based on risk factor assessment can be applied. There remains no evidence to guide which approach is superior. An OGTT should take place at 24–28 weeks of gestation. The goal of treatment is to achieve BG targets for gestational diabetes mellitus with lifestyle change and insulin when required.
BG: Blood glucose; FBG: Fasting blood glucose; OGTT: Oral glucose tolerance test.

prenatal visit [4]. Some have advocated for an early 75-g, 2-h glucose tolerance test in women with strong risk factors. An OGTT, if performed in early pregnancy, could be interpreted based on reference to an OGTT performed at the usual 24–28 weeks. The measurement of HbA1c is being used in the clinical setting in several countries for assessment of glycemic status in early pregnancy. If HbA1c is to be used as a diagnostic tool then a threshold of 6.5% has been suggested. Its diagnostic use in pregnancy warrants further consideration and study.

Many women will have at least one risk factor for GDM. Therefore, testing all women at their first antenatal visit may be the simplest, most reliable approach [20]. Fasting blood glucose is a useful, cost-effective method to identify those women with impairment of glucose metabolism. Higher first-trimester fasting glucose levels increase the risk of adverse maternal and fetal outcomes including macrosomia and primary cesarean section [21]. At this stage, there is no evidence to guide the methodology used for GDM testing in early gestation. Suggested diagnostic criteria for identification of diabetes in early pregnancy are listed in **Box 2**.

All pregnant women with GDM should be diagnosed by 24–28 weeks of gestation. There

are several methodologies used to identify women with GDM. The IADPSG have based their recommended threshold values on the average glucose values at which the odds ratios for birth weight >90th percentile, cord C-peptide >90th percentile and percentage of neonatal body fat >90th percentile reached 1.75-times the estimated odds ratios of the outcomes at mean glucose values [4]. These odds ratios were based on the HAPO study population using logistic regression models. **Table 1** summarizes the IADPSG guidelines for GDM diagnosis at 24–28 weeks of gestation.

The above recommendations are yet to take effect in many nations, including Australia. Australia, like other nations, is in the process of implementing change. Implementation of these diagnostic guidelines will certainly increase the prevalence of GDM. Already this has been the case in parts of Australia where the IADPSG criteria have been implemented. For example, the prevalence has risen from 9.6 to 13% in Wollongong and is 12.1% in Brisbane [22]. Others have estimated that the IADPSG diagnostic criteria may increase the prevalence in some communities to as high as 18% [4]. This will have significant implications for workload management, resource allocation and public health burden.

The methodology favored by the American College of Obstetricians and Gynaecologists (ACOG) differs from the IADPSG. They recommend a screening process for GDM based on patient history, clinical risk factors or with a 50-g, 1-h glucose challenge test at 24–28 weeks of gestation. If positive screening, they recommend use of the Carpenter–Coustan criteria, which involve a 100-g, 3-h OGTT [23,24]. Their diagnostic criteria for GDM are two or more time points with values greater than or equal to threshold values (fasting 5.3 mmol/l, 1-h 10 mmol/l, 2-h 8.6 mmol/l and 3-h 7.8 mmol/l) [24]. ACOG believes that evidence for the identification and treatment of women based on the IADPSG recommendations is lacking and that their use will result in a significant increase in healthcare costs without benefit in maternal and fetal outcomes.

Management of GDM during pregnancy

Intervention for women with mild hyperglycemia in pregnancy confers benefit for maternal and fetal morbidity as discussed previously [7,8]. The intervention groups in the two large randomized control trials (ACHOIS and NICHD-MFMU) used dietary therapy, home blood glucose monitoring and the administration of insulin if target blood glucose concentrations were not met with diet alone. Although intervention was shown to be effective, it remains unclear whether one particular aspect of the intervention was most effective or indeed whether the study benefit could be explained by reduced weight gain alone. Both trials reported lower pregnancy weight gain in the treated group than in the control group. However, in the NICHD-MFMU trial, there did appear to be a treatment effect independent of weight gain [8].

Box 1. Risk factors for the development of diabetes in pregnancy.

- Previous GDM
- Family history of diabetes (first-degree relative with Type 2 diabetes or sister with GDM)
- BMI >30 kg/m^2
- Ethnicity: Asian (including Indian), Middle Eastern, African–American and Aboriginal/Torres Strait islanders
- Previous macrosomia; birth weight above 4500 g
- Age greater than 25 years

GDM: Gestational diabetes mellitus.
Data taken from [1,19].

Dietary change

Diet advice by a registered dietitian should be offered upon diagnosis of diabetes in pregnancy [25]. It is usually recommended that carbohydrates be distributed throughout the day over three main meals and between-meal snacks. Limiting carbohydrates to 40% of the total caloric intake and having a higher proportion of carbohydrates of lower glycemic index decreases postprandial glucose levels and reduces the need for insulin therapy. Dietary therapy should include the provision of adequate calories and nutrients to meet the needs of pregnancy. For most women, caloric requirement

Box 2. Interpretation of early testing for diabetes in pregnancy.

Pre-existing Type 1 or 2 diabetes
- Fasting venous PG level ≥7.0 mmol/l
- Random or 2-h venous PG level ≥11.1 mmol
- HbA1c ≥6.5%

Gestational diabetes
- Fasting venous PG level 5.1–6.9 mmol/l
- 2-h venous PG ≥8.5 mmol/l

PG: Plasma glucose.
Data taken from [4].

Table 1. Diagnosis of gestational diabetes mellitus on the basis of an abnormal 75-g oral glucose tolerance test.

OGTT	Threshold glucose concentration (mmol/l)
Fasting venous PG	5.1
1-h venous PG	10
2-h venous PG	8.5

Diagnosis of gestational diabetes mellitus can be made on the basis of an abnormal 75-g OGTT where one or more glucose concentrations are above threshold values.
OGTT: Oral glucose tolerance test; PG: Plasma glucose.
Data taken from [4].

is 1800–2500 kcal per day [26]. Fewer calories per kilogram are required for women who are overweight or obese.

Unfortunately, macrosomia may not be prevented by dietary therapy alone. A Cochrane review of four studies involving over 600 women with GDM treated with dietary therapy versus no specific treatment found no difference in birth weight or cesarean section rate [27].

Exercise

Regular moderate intensity physical activity for approximately 30 min per day should be encouraged during pregnancy if there are no medical or obstetric contraindications, and may assist in blunting the postprandial rise in blood glucose [25]. There have been no well-designed studies that have validated the benefit of such advice.

Home blood glucose monitoring

Multiple daily self-measurements of blood glucose are recommended for women with GDM. It is generally recommended that four blood glucose measures should be performed each day (fasting and three postprandial blood glucose measures). Postprandial blood glucose checks can be performed at either 1 or 2 h after the beginning of a meal; the optimal time point has not been determined [28]. The accuracy of home blood glucose monitoring is dependent on multiple factors. There is reliance on self-report and the accuracy of glucometers can vary greatly. For instance, in one study there was a variation between glucometer readings up to 1.9 mmol/l [29]. Therefore, this makes judgment based on single readings very unreliable. When considering blood glucose levels in individual women, the patterns of glycemia are more important than individual results. Clinical practice varies in terms of the criteria used to escalate treatment and the criteria for reducing the frequency of home blood glucose monitoring in the setting of well-controlled blood glucose readings. There is no evidence that monitoring for ketonuria is beneficial.

To date, no randomized trial has been conducted using the IADPSG diagnostic criteria for inclusion and no trial has defined the optimal treatment targets. However, extrapolating from the HAPO data has led to the treatment targets suggested in **Box 3** [11]. Treatment outcome studies have yet to be performed in women diagnosed with GDM in early pregnancy, although a benefit can be inferred from treatment outcomes in women treated later in pregnancy.

Third-trimester fetal growth ultrasounds may be useful in guiding strictness of glucose monitoring and targets in women with GDM [30]. Fetal abdominal circumference may be a useful predictor of birth weight. Some research has suggested that if fetal abdominal circumference is greater than the 75th percentile then there is benefit in attempting to achieve even tighter glycemic targets than those suggested by the IADPSG [30]. It is of course important to weigh up the benefit of tight glycemic control with the risk of increased frequency of hypoglycemia. In our center, we recommend a third-trimester ultrasound to estimate fetal size if there is clinical suspicion of large size for gestational age or if the pregnant woman is receiving insulin.

Insulin

Insulin therapy is commenced when glycemic goals cannot be met by dietary adjustment alone. It should also be considered if there is evidence of excessive fetal growth. The type and dose of insulin should be based on the results of frequent home blood glucose monitoring. As compared with regular human insulin, the newer rapid-acting insulin analogs lispro (Humalog) and aspart (NovoRapid) appear to be as safe in pregnancy [31,32]. They are more effective in controlling postprandial hyperglycemia with less hypoglycemia than regular human insulin.

When fasting capillary blood glucose targets are not met, intermediate- or long-acting insulin at bedtime should be considered. Occasionally, a morning dose of intermediate insulin is also required to achieve target blood glucose levels. Historically, longer-acting insulin analogs have generally not been recommended. There are only a few studies investigating the use of

the insulin glargine in pregnancy, which have predominantly been in pregnant women with Type 1 diabetes. A recent review that examined the safety of basal analogs in pregnancy, reported no difference in fetal outcomes when lantus was compared to intermediate-acting NPH [33]. Lapolla *et al.* reported outcomes in ten women with Type 1 diabetes using detemir throughout pregnancy with reassuring results [34]. The subject population was obviously small. The results of a large clinical trial investigating the efficacy and safety in pregnancy of the insulin detemir will soon be published [33].

Oral hypoglycemic agents

The use of metformin in the second and third trimester of pregnancy appears to be safe and prevents at least two-thirds of women with GDM from needing insulin therapy [35–37]. In the Metformin in Gestational Diabetes (MiG) trial, 751 Australian women with GDM at 20–33 weeks of gestation were randomly assigned to receive metformin or insulin therapy [35]. There were no serious adverse effects related to metformin. It was shown to be as effective as insulin in reducing a composite score of neonatal hypoglycemia, respiratory distress, hyperbilirubinemia, birth trauma and prematurity.

Despite the positive effect of metformin in the above study, there remains concern regarding the long-term effects of metformin on offspring. Metformin has been shown to cross the placenta and, in one study, cord arterial levels were twice as high as maternal venous levels [38]. It is not known whether fetal exposure to metformin causes long-term effects, either beneficial or harmful, for the offspring. Current guidelines by the IADPSG, US and Australian advisory groups do not recommend the use of metformin.

Sulfonylureas for the treatment of GDM are not generally recommended by most advisory bodies including the ADA and ACOG. The most studied sulfonylurea is glyburide. In one study involving over 400 pregnant women with GDM, glyburide was found to be noninferior to insulin in terms of outcomes such as macrosomia and neonatal hypoglycemia [39]. When compared with metformin, glyburide was more effective at achieving target glycemic ranges without the need for insulin therapy [40]. Metformin was associated with less weight gain than glyburide [41]. There still remains concern regarding the effects of oral agents on long-term wellbeing of offspring. Insulin remains the most studied and safe treatment for management of diabetes complicating pregnancy.

Intrapartum management of GDM

The aim of management during labor is to maintain target glucose levels, avoid hypoglycemia and avoid unnecessary medicalization of labor in low-risk women with GDM. The best approach to maintain normoglycemia is unclear and has been poorly studied. There is insufficient evidence derived from intrapartum management of women with Type 1 diabetes [42–45]. Blood glucose levels above 10 mmol/l have been consistently associated with neonatal hypoglycemia. However, there are at least three studies suggesting that blood glucose levels up to 7–8 mmol/l are safe [42,43,46]. The frequency of blood glucose monitoring and the route by which insulin is administered have not been well studied. Intrapartum management in women with Type 1 diabetes can be effectively achieved with an insulin infusion [44,45,47]. Insulin requirements up until active labor are unchanged from the requirements of pregnancy [45]. However, active labor is a glucose-consuming activity that requires extra glucose if insulin doses are unaltered. Some authors have suggested titrating the glucose-containing fluid infusion rate to blood sugar levels or assuming an increased glucose infusion during active labor [45,47]. There is a paucity of evidence regarding the best form of intrapartum management in women with GDM compared with Type 1 diabetes. In our center, we monitor blood glucose levels each 2 h during labor and administer subcutaneous insulin if the blood glucose level is above 7 mmol/l. If blood glucose is below 4 mmol/l then a dextrose infusion is commenced.

Postpartum management

Women who have had GDM are advised to have an OGTT in the postpartum period to ensure resumption of normoglycemia. An annual OGTT thereafter has been suggested. A

Box 3. Treatment targets suggested for home glucose monitoring.

- Fasting capillary BG ≤5.3 mmol/l,
- 1-h postprandial BG ≤7.8 mmol/l
- 2-h postprandial BG ≤6.7 mmol/l

BG: Blood glucose.
Data taken from [11].

postpartum OGTT has particular relevance for a woman who intends on a future pregnancy to exclude pre-conception diabetes. Women with GDM have a 50% chance of developing Type 2 diabetes later in life [48]. There also appears to be increased risk of cardiovascular disease in the long term [49]. All women should be counselled about the importance of a healthy diet, regular exercise, weight control and the ongoing need for follow-up.

Conclusion

Over the past decade, there has been significant change in diagnostic and therapeutic strategies for GDM. In particular, the HAPO study provided clear evidence that mild hyperglycemia in pregnancy is associated with maternal and neonatal morbidity. This has lowered the diagnostic criteria for GDM and, although there remains some contention regarding thresholds, unified recommendations for diagnosis are emerging. Treatment for GDM consists of lifestyle advice and insulin if target blood glucose levels are not achieved with lifestyle advice alone. Metformin and sulfonylureas are likely to be utilized more frequently in clinical practice when there is further evidence regarding the long-term effects on children exposed to them *in utero*. Pregnant women with GDM have the opportunity to gain insight into diabetes and apply lifestyle changes that may potentially alter the long-term outcome for themselves and their offspring.

Future perspective

Additional well-designed randomized controlled trials and other clinical studies are needed to determine the benefits of diagnostic and therapeutic strategies currently suggested. There is also a need to validate the various treatment strategies for GDM including simple lifestyle advice, various insulin therapies and oral hypoglycemic agents. Significant questions remain regarding the implications on healthcare costs. There are further studies required to address many questions including the psychosocial effect of diagnosis and treatment of GDM, its impact upon obstetric interventions in pregnancy, and whether treatment of GDM using current guidelines will improve meaningful maternal and neonatal outcomes. From a public health perspective, there is a definite need for primary prevention strategies to reduce modifiable risk factors for GDM, the most obvious of which is obesity.

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