

A review of the treatment options for gestational diabetes: The evidence base

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Article points

1. Gestational diabetes is a growing health concern worldwide. In the UK, one in 20 pregnant women are diagnosed with gestational diabetes.
2. Diet and exercise are the first-line management options for gestational diabetes; however, if diet and exercise are not sufficient, drug therapy is introduced.
3. Traditionally, insulin has been the first-line drug therapy, although, over recent years, the use of oral hypoglycaemic agents to treat gestational diabetes is evolving.

Key words

- Gestational diabetes
- Oral hypoglycaemic agents

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Gestational diabetes mellitus (GDM) is glucose intolerance that develops during the second and third trimester of pregnancy. Early diagnosis and effective treatment of GDM are critical because it has the potential to cause serious maternal and fetal complications. Diet and exercise are the first-line management options for GDM, and insulin is generally the first-line pharmaceutical option. An increasing body of evidence is emerging that compares the use of oral hypoglycaemic agents in women with GDM with that of insulin. In this article, we review the latest available recommendations for GDM management and therapy, with specific focus on the use of oral hypoglycaemic agents.

Gestational diabetes mellitus (GDM) is glucose intolerance of varying severity that develops during the second and third trimester of pregnancy, when it can cause serious maternal and fetal complications. Early screening, diagnosis and treatment are imperative to reduce these risks and complications. Diet and exercise are the first-line management options for GDM; however, if diet and exercise are not sufficient, drug therapy is introduced. Traditionally, insulin has been the first-line drug therapy for treating GDM, although, over recent years, the use of oral hypoglycaemic agents to treat it is evolving (Menato et al, 2008; Serlin and Lash, 2009; Niromanesh et al, 2012). The purpose of this article is to review the latest available recommendations in the management and treatment of GDM and to describe the current evidence (within the past 5 years) on the use of oral hypoglycaemic agents.

Epidemiology and pathogenesis

GDM is a growing health concern worldwide. The prevalence of GDM varies in a given

population in direct proportion to the prevalence of type 2 diabetes. In the UK, one in 20 pregnant women are diagnosed with GDM (Diabetes.co.uk, 2014). Furthermore, it is reported that pregnant women with GDM have an at least seven-fold increased risk of

Box 1. Risk factors for developing gestational diabetes mellitus (GDM).

Non-modifiable risk factors

- Age (>25 years)
- Ethnicity
- Genetic background
- Previous history of GDM
- Twin pregnancy
- Polycystic ovary syndrome

Modifiable risk factors

- Obesity
- Lack of exercise
- Smoking
- Increased dietary fat intake
- Drug use
- Alcohol use

developing diabetes later in life (Newson, 2012). A rise in the incidence of GDM is expected given the growing obesity epidemic worldwide and the widespread sedentary lifestyle (American College of Obstetricians and Gynecologists [ACOG], 2013). *Box 1* shows the known risk factors for developing GDM.

Insulin resistance (IR), due to pancreatic beta-cell dysfunction, is the main cause of GDM (Newson, 2012). Metabolic changes that occur during pregnancy can lead to IR. Hyperglycaemia is a major cause of maternal and fetal morbidity associated with GDM (Menato et al, 2008). Maternal complications associated with GDM include higher rates of caesarean delivery, pre-eclampsia and birth defects; fetal and neonatal complications include perinatal mortality, neonatal hypoglycaemia, macrosomia and birth trauma (Turok et al, 2003).

Diagnosis

Early diagnosis and treatment of GDM are essential, as poorly controlled diabetes during pregnancy increases the risk of maternal and neonatal complications during intrapartum and postpartum periods (Turok et al, 2003; Nicholson et al, 2009). Screening for GDM, however, is controversial because the major healthcare bodies concerned endorse different approaches; the NICE guidelines (2008) recommend only screening high-risk women, who make up 30–50% of pregnant women. High-risk women include those who: are obese (have a body mass index ≥ 30 kg/m²); have had a macrosomic baby, weighing 4.5 kg or above; have a history of GDM; have a first-degree relative with diabetes; or who have a family origin that has a high prevalence of diabetes (South Asian, Black Caribbean, Middle Eastern; NICE, 2013). Women with a history of gestational diabetes are offered early self-monitoring of blood glucose or a 2-hour 75 g oral glucose tolerance test (OGTT) at 16–18 weeks’ gestation. An OGTT is offered to the other women with risk factors at 24–28 weeks.

In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) released guidelines, which have been

endorsed by the Royal College of Obstetricians and Gynaecologists in the UK, that recommend screening of all women without diabetes at 24–28 weeks’ gestation using a 75 g OGTT. *Table 1* shows the plasma or serum threshold levels for GDM. The IADPSG guidelines state that diagnosis of GDM is made when the following plasma blood glucose levels are exceeded:

- Fasting: ≥ 92 mg/dL (5.1 mmol/L).
- At 1 hour: ≥ 180 mg/dL (10 mmol/L).
- At 2 hour: ≥ 153 mg/dL (8.5 mmol/L; American Diabetes Association, 2014).

Diagnosis of overt diabetes is made if fasting plasma glucose >7.0 mmol/L (126 mg/dL; IADPSG, 2010).

Management

Non-pharmacologic

The first-line management option for GDM is diet and regular physical activity. The main goals of nutritional therapy include preventing ketosis, achieving normoglycaemia, improving fetal well-being and achieving adequate weight gain (ACOG, 2013). Nutritional therapy modifications are based on individual preferences, ethical considerations, weight changes and blood glucose monitoring. Many programmes involve carbohydrates and calorie counting and exchange systems

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1. Insulin resistance, due to pancreatic beta-cell dysfunction, is the main cause of gestational diabetes. Metabolic changes that occur during pregnancy can lead to insulin resistance. Hyperglycaemia is a major cause of maternal and fetal morbidity associated with gestational diabetes.
2. Early diagnosis and treatment of gestational diabetes are essential, as poorly controlled diabetes during pregnancy increases the risk of maternal and neonatal complications during intrapartum and postpartum periods.
3. The first-line management option for gestational diabetes is diet and regular physical activity. The main goals of nutritional therapy include preventing ketosis, achieving normoglycaemia, improving fetal well-being and achieving adequate weight gain.

Table 1. Plasma or serum glucose threshold levels (adapted from Cheng et al, 2009 and IADPSG, 2010).

Status	Plasma or serum glucose level; Carpenter and Coustan conversion (100 g, 3-hr glucose load) *		Plasma or serum glucose level (75 g, 2-hr glucose load) †		Plasma level National Diabetes Data Group Conversion (100 g, 3-hr glucose load) *	
	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	95	5.3	95	5.3	105	5.8
1 hour	180	10	180	10	190	10.6
2 hours	155	8.6	155	8.6	165	9.2
3 hours	140	7.8	-	-	145	8

*Cheng et al, 2009; †IADPSG, 2010

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1. Drug therapy is introduced when diet and exercise have little effect in controlling gestational diabetes. Traditionally, insulin has been the first-line drug therapy because it does not cross the placental barrier.
2. Insulin therapy can be challenging to use in pregnant women because of weight gain, risk of hypoglycaemia and need for multiple injection sites. Some of these disadvantages related to insulin have prompted research into the use of oral hypoglycaemic agents as an alternative.

(National Institute of Child Health and Human Development, 2006; Serlin and Lash, 2009). The latest recommendations include reducing carbohydrate intake so that the composition of calories consumed is 33–40% from carbohydrates, 20% from protein and 40% from fat (ACOG, 2013). Complex carbohydrates are preferred because their consumption leads to less postprandial hyperglycaemia than simple carbohydrates (ACOG, 2013). During calorie restriction, however, pregnant women with GDM should be carefully monitored for ketone formation because calorie restriction in such women may cause mental and psychomotor deviation in the unborn child (Rizzo et al, 1995).

Women with GDM should also take regular moderate physical activity, such as walking, because physical activity enhances the work of insulin in maintaining blood glucose levels (ACOG, 2013). Thirty minutes of physical activity is considered the best type of exercise for pregnant women (Whitelaw and Gayle, 2010). Women are also encouraged to breastfeed because this promotes weight loss, thus decreasing the risk of glucose intolerance and reducing the chance of developing diabetes later in life (Gunderson, 2007).

Pharmacologic treatment

Drug therapy is introduced when diet and exercise have little effect in controlling GDM. Traditionally, insulin has been the first-line drug therapy in treating GDM because it does not cross the placental barrier (Menato et al, 2008; Rai et al, 2009; Serlin and Lash, 2009); however, insulin therapy can be potentially challenging to use in pregnant women because of possible additional weight gain, risk of hypoglycaemia, and need for multiple injection sites (Niromanesh et al, 2012). Some of these disadvantages related to insulin have prompted research into the use of oral hypoglycaemic agents as a pragmatic alternative treatment for GDM (Rai et al, 2009).

Oral hypoglycaemic agents for GDM

Many researchers have been exploring the use of oral hypoglycaemic agents, such as glibenclamide and metformin, as a safe and effective alternative

to insulin for the treatment of GDM. The remainder of this article will present the most current evidence (within the past 5 years) on the use of these two oral hypoglycaemic agents.

Metformin

Metformin belongs to the biguanide class, and is classified by the Food and Drug Administration (FDA) in the US as a category B drug in pregnancy. In the UK, NICE (2008) recommend that metformin is used as an adjunct or alternative to insulin in the preconception period and during pregnancy, when the likely benefits from improved glycaemic control outweigh the potential for harm. Metformin works to lower glucose levels by decreasing peripheral insulin resistance, intestinal absorption and hepatic production of glucose, and decreasing peripheral uptake and utilisation of glucose (Menato et al, 2008). In addition, the drug does not stimulate insulin secretion, cause hypoglycaemia, or stimulate the fetal pancreas to oversecrete insulin (Menato et al, 2008). Metformin, unlike insulin, does not cross the placental barrier, which previously caused concern for its use in pregnant women. Research has since demonstrated, however, that transfer of metformin across the placenta does not have negative effects on the fetus. The starting dose for metformin is 500 mg for the first day and titrated up to 2500 mg as tolerated, depending on the mother's glucose level (Menato et al, 2008; Medicines and Healthcare Products Regulatory Agency, 2007).

Glibenclamide (glyburide)

Glibenclamide (known as glyburide in the US) is a second-generation sulphonylurea medication also categorised as class B in pregnancy by the FDA in the US (Ho et al, 2007). Glibenclamide binds with pancreatic beta-cell receptors, thus increasing insulin secretion and decreasing insulin resistance by reducing glucose toxicity (ACOG, 2013). In contrast to insulin and similar to metformin, glibenclamide also crosses the placenta.

Evidence base for use of metformin in GDM

Several studies have compared glycaemic control achieved using metformin with that achieved

using insulin in women with GDM. Spaulonci and colleagues (2013) conducted a study on 94 Brazilian women (47 randomised to metformin and 47 to insulin) to compare glycaemic control between those receiving metformin and those receiving insulin, and identify factors predicting the need for supplemental insulin. The study showed that metformin was associated with lower glucose levels throughout the day, less weight gain and lower frequency of neonatal hypoglycaemia. Gestational age at diabetes and mean pre-treatment glucose level were predictors of the need for supplemental insulin therapy in those who were initially treated with metformin (Spaulonci et al, 2013).

Two studies were conducted in 2012 comparing the use of metformin and insulin. One study evaluated the effects of metformin and insulin on pregnancy outcomes of 160 Iranian women (Niromanesh et al, 2012) and another compared the effects of metformin and insulin in 28 women with pre-existing type 2 diabetes and early A2 GDM, which is GDM that requires medication rather than being controlled by diet (Hickman et al, 2012). Niromanesh et al (2012) showed that maternal treatment with metformin was associated with neonates with smaller anthropometric measurements, fewer large for gestational age (LGA) babies, and reduced maternal and birth weight. Hickman and colleagues (2012), on the other hand, reported that women in the metformin group had significantly fewer hypoglycaemic episodes and lower glucose values (<60 mg/dL) than women in the insulin group. In addition, women in the metformin group continued to receive the drug up to delivery although 43% required supplemental insulin to control glucose levels (Hickman et al, 2012).

In 2009, Rai and colleagues conducted a prospective observational study, and Balani et al (2009) performed a case-control study, both comparing maternal and neonatal outcomes with the use of metformin versus insulin in women with GDM and type 2 diabetes. The cohorts consisted of 60 Indian women (Rai et al, 2009) and 127 women (Balani et al, 2009). The studies revealed that metformin provided better glycaemic control after one week of therapy and throughout their pregnancy (Rai et al, 2009), and less weight

gain (Balani et al, 2009). Both studies indicated that maternal outcomes were comparable in the metformin and insulin groups, and suggested a decrease in neonatal intensive care admission in the metformin group. In addition, Balani et al (2009) reported significantly improved neonatal outcomes, except for macrosomia, in the metformin group, while Rai and colleagues reported no major complications or perinatal deaths in either group (Balani et al, 2009; Rai et al, 2009).

The Metformin in Gestational Diabetes trial (Rowan et al, 2008) studied 751 women with GDM at 20–33 weeks of pregnancy who were randomly assigned to an open treatment of metformin (with supplemental insulin if required). The study was designed to rule out a 33% increase (from 30–40%) in a composite of perinatal complications in women treated with metformin compared to those treated with insulin. The study showed that women who used metformin (with or without insulin) did not have increased perinatal complications as compared to those treated with insulin. The composite of neonatal complications and anthropometric measurements also did not differ between the two groups. However, Rowan et al (2009) found that women preferred to take metformin to insulin (Rowan et al, 2008).

In a retrospective case-control study (Tertti et al, 2008), neonatal and maternal outcomes were compared among women with GDM who were treated with metformin, insulin or diet alone. The cohort consisted of 45 women treated with metformin, 45 treated with insulin and 83 managed by diet alone. The study showed no difference in maternal outcomes between women in the metformin-treated group and the other two groups. However, 18% of the women in the metformin group required supplemental insulin. Likewise, there was no difference in the neonatal outcomes between the groups. The incidence of neonatal hypoglycaemia, however, was found to be higher in the insulin-treated group compared to the metformin-treated group.

Glibenclamide versus insulin

Two retrospective studies were conducted comparing glibenclamide and insulin in preventing neonatal complications and adverse

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1. Spaulonci et al (2013) conducted a study to compare glycaemic control in women with gestational diabetes mellitus between those receiving metformin and those receiving insulin. The study showed that metformin was associated with lower glucose levels throughout the day, less weight gain and lower frequency of neonatal hypoglycaemia. Gestational age at diabetes and mean pre-treatment glucose level were predictors of the need for supplemental insulin therapy.
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1. Hutchinson et al (2008) conducted a study comparing glycaemic control with glibenclamide/metformin (study group) versus insulin (control group). The study reported no significant difference between the two groups in mean values for gestational age at delivery, birth weight, HbA_{1c}, fructosamine levels and glucose levels.
2. A trial was performed by Silva et al (2012) evaluated perinatal impact of metformin and glibenclamide in 200 women with gestational diabetes. There was no difference found in the number of caesarean deliveries, gestational age at delivery, number of neonates large for gestational age, incidence of neonatal hypoglycaemia, admission to intensive care unit and rate of perinatal death.

perinatal outcomes in women with GDM (Cheng et al, 2012; Mathews et al, 2012). The retrospective cohort study (Cheng et al, 2012) enrolled 10 682 women in the Sweet Success California Diabetes and Pregnancy Program between 2001 and 2004. Cheng et al reported that, compared to insulin, the use of glibenclamide was associated with increased risk of higher birth weight or macrosomia, and admission to the neonatal intensive care nursery. In addition, subsets of higher-risk neonates have an increased incidence of preterm delivery and intrauterine fetal demise (Cheng et al, 2012). A retrospective study of 577 South Indian women with GDM with moderate hyperglycaemia revealed no difference in neonatal outcomes such as hypoglycaemia, hypocalcaemia, macrosomia, polycythaemia, birth trauma and congenital anomalies between women treated with insulin and those assigned to glibenclamide (Mathews et al, 2012). Neonates whose mothers were treated with insulin were more likely to develop hyperbilirubinaemia compared with those who received glibenclamide (Mathews et al, 2012).

Glibenclamide/metformin versus insulin

Hutchinson and colleagues (2008) conducted a study comparing glycaemic control with glibenclamide/metformin (study group) versus insulin (control group). One hundred and seventy-two women with type 2 diabetes or GDM pregnancies were included in the study. The study reported no significant difference between the two groups in mean values for gestational age at delivery, birth weight, HbA_{1c}, fructosamine levels and glucose levels.

Metformin versus glibenclamide

A randomised controlled trial was performed by Silva and colleagues (2012) to evaluate perinatal impact of metformin and glibenclamide in 200 women with GDM. There was no difference found in the number of caesarean deliveries, gestational age at delivery, number of neonates LGA, incidence of neonatal hypoglycaemia, admission to intensive care unit and rate of perinatal death. The differences found were in the weight and ponderal index, which were lower

in the metformin group, while blood glucose levels at the first and third hour after birth were lower in the glibenclamide group (Silva et al, 2012). Studies were conducted by Moore et al (2010) and Silva et al (2010) to compare the efficacy of metformin and glibenclamide for glycaemic control and neonatal outcomes. Moore and colleagues studied 149 women with GDM and reported no significant difference in the mean fasting and 2-hour postprandial blood glucose levels among those who achieved glycaemic control through metformin and glibenclamide therapy. This finding was similar with that found in the study by Silva and colleagues, which also found significantly less weight gain among women in the metformin group.

The study by Moore et al, however, revealed that 34.7% women in the metformin group and 16.2% of those in the glibenclamide group required insulin supplementation. It was also reported that the rate of failure to achieve glycaemic control was 2.1 times higher in the metformin group than the glibenclamide group. Neonatal outcomes were similar between the groups in both studies (Moore et al, 2010; Silva et al, 2010).

Metformin versus non-pharmacologic treatment

Gandhi and colleagues (2012) conducted a retrospective review of 592 case records of women with a diagnosis of GDM. The review was to compare pregnancy outcomes in women with GDM treated with metformin, lifestyle advice ± subcutaneous insulin injection versus lifestyle advice ± subcutaneous insulin injection.

The review found no significant difference in maternal and neonatal outcomes between the two groups; however, those in the metformin group had a significantly lower incidence of macrosomic and LGA babies (Gandhi et al, 2012).

Conclusion and practice implications

An estimated 5–10% of pregnancies are complicated by GDM, which has short- and long-term implications for both the mother and the child. To reduce this morbidity, it is imperative to target maintenance of adequate blood glucose levels during pregnancy. When

diet and exercise are not sufficient to control blood glucose levels, drug therapy is the next option. While insulin remains the treatment of choice for GDM, evidence is emerging that supports the use of oral hypoglycaemic agents, such as metformin and glibenclamide, as alternatives to insulin for treatment of GDM.

Insulin treatment is an effective therapy for controlling maternal glycaemia; however, it requires sufficient education and skills on the part of the woman with GDM to be properly managed, and may cause hypoglycaemia, fear and anxiety. Oral treatment is generally a more user-friendly treatment option than insulin and, thus, may facilitate the control of GDM in some women (Maymone et al, 2011).

Further studies are needed in a larger population to establish the safety of metformin and glibenclamide. Proving the safety and effectiveness of oral hypoglycaemic agents may improve women's adherence, which may prevent further complications of GDM.

As nurses caring for women with GDM, we should be up-to-date with the latest information regarding screening and treatment options. High morbidity and mortality risks associated with the condition means it is essential to educate women at increased risk about early screening, as well as the treatment options available. ■

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