Gestational Diabetes Mellitus

Koning, Saakje; Hoogenberg, Klaas; Lutgers, Helen; Van den Berg, Paul P.; Wolffenbutel, B.H.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Link to publication in University of Groningen/UMCG research database

REVIEW ARTICLE

Gestational Diabetes Mellitus:current knowledge and unmet needs

> **Highlights**
> 1. There is considerable controversy in the literature surrounding the diagnosis and treatment (including diet, insulin therapy, and oral blood glucose lowering agents) of gestational diabetes mellitus, as well as the possible long-term consequences for the offspring.
> 2. Worldwide different diagnostic criteria are used and discussion remains on the efficiency, and safety, of treatment modalities.
> 3. There is clearly more need for GDM research. Gestational diabetes mellitus is a global health concern, because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring.

Sarah H. KONING,[1] Klaas HOOGENBERG,[3] Helen L. LUTGERS,[4] Paul P. VAN DEN BERG[2] and Bruce H.R. WOLFFENBUTTEL[1]

Departments of [1]Endocrinology and [2]Gynecology and Obstetrics, University of Groningen, University Medical Center Groningen, [3]Department of Internal Medicine, Martini Hospital, Groningen, and [4]Department of Endocrinology, Medical Center Leeuwarden, Leeuwarden, The Netherlands

Abstract

Gestational diabetes mellitus (GDM) is a global health concern, not only because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring. Unfortunately, there is considerable controversy in the literature surrounding the diagnosis and treatment of GDM, as well as the possible long-term consequences for the offspring. As a result, worldwide there is a lack of uniformly accepted diagnostic criteria and the advice regarding the treatment of GDM, including diet, insulin therapy, and the use of oral blood glucose-lowering agents, is highly variable. In this review we provide an overview of the important issues in the field of GDM, including diagnostic criteria, different treatment regimens available, and the long-term consequences of GDM in the offspring.

Keywords: diagnosis, diet, gestational diabetes mellitus, insulin, oral blood glucose-lowering agents.

Introduction

Historically, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance with an onset or first recognition during pregnancy. According to the American Diabetes Association (ADA),[1] GDM is diabetes mellitus (DM) diagnosed in the second or third trimester of pregnancy that does not clearly meet the criteria of overt DM. For women diagnosed with GDM in the first trimester of pregnancy, pre-existing DM should be strongly considered.[1] Gestational diabetes mellitus affects up to 14 % of all pregnancies, depending on the diagnostic criteria used and the population studied.[2] Given the fact that both obesity and DM are now worldwide epidemics, the prevalence of GDM is still increasing.[2–4]

Untreated GDM carries a risk for both the mother and child and is associated with serious short- and long-term consequences, including neonatal and obstetric complications during pregnancy and childbirth (e.g. macrosomia, birth injury, cesarean section[5–7]) and a predisposition to obesity and DM in the offspring in later life.[8–10] Fortunately, studies have shown that many of these consequences can be reduced by early detection

and intervention.[11,12] However, worldwide there is still a lack of agreement on the best way to diagnose and treat GDM. Different diagnostic criteria are used, and many countries use their own recommendations. As a result, discussion remains on the efficiency, and safety, of treatment modalities for GDM, including the use of oral blood glucose-lowering agents, as well as the possible short- and long-term consequences for the offspring.

Herein we describe both the current knowledge regarding GDM and the unmet needs of this condition. We review the diagnostic criteria, different treatment regimens available, and the consequences of GDM in the offspring.

Diagnostic criteria

The original diagnostic criteria for GDM were established in 1964 by O'Sullivan and Mahan.[13] Their criteria were based on a 3-h 100-g oral glucose tolerance test (OGTT) and were chosen to identify women at high risk for development of diabetes after pregnancy.[13] In 1979–80, the 2-h 75-g OGTT was introduced as diagnostic test for non-pregnant diabetic individuals, and the World Health Organization (WHO) advised that this be used to diagnose diabetes in pregnant women, with cut-off values for the diagnosis of GDM being fasting plasma glucose (FPG) ≥ 7.8 mmol/L and 2-h glucose levels ≥ 11.1 mmol/L.[14,15] In 1997, the ADA proposed to lower the FPG from 7.8 to 7.0 mmol/L for non-pregnant diabetic individuals.[16] Two years later, the WHO 1999 report on the definition, screening, and diagnosis of GDM was the first step to creating a universal guideline for GDM.[17] In that report, the same fasting glucose values for pregnant women were recommended as proposed by the ADA.[17] These diagnostic criteria were not specifically intended to identify increased risk of adverse neonatal and maternal outcomes.[18]

For decades, the degree of hyperglycemia that was associated with increased risk of adverse neonatal and maternal outcomes remained uncertain. In 2008, the multinational prospective observational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported on the associations between FPG and 1- and 2-h plasma glucose values during an OGTT and the risk of adverse neonatal and maternal outcomes.[19] More than 25 000 non-diabetic women with singleton pregnancies underwent a 75-g OGTT at 24–32 weeks gestation. The study demonstrated a continuous association of maternal glucose levels with increased rates of both the predefined primary adverse pregnancy outcomes (i.e. birth weight > 90th percentile and cord blood serum C-peptide levels >90th percentile) and the secondary outcomes (i.e. premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia,

and pre-eclampsia).[19] As a result of these findings and those from earlier observational studies,[5,20–23] the diagnostic criteria of GDM were reconsidered worldwide, and guidelines were adapted to include these more stringent criteria. In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published new criteria for the diagnosis of GDM, which recommended the following 75-g OGTT glycemic thresholds: fasting value ≥ 5.1 mmol/L (92 mg/dL); 1-h value ≥ 10.0 mmol/L (180 mg/dL); and 2-h value ≥ 8.5 mmol/L (153 mg/dL).[18] These values were chosen because they predict an increased risk of adverse pregnancy outcomes (defined as a 75 % higher chance of adverse outcomes vs normal glucose values). For the other adverse outcomes of the HAPO study, no threshold risk could be identified.[18]

The IADPSG criteria were adopted by the ADA in 2010[24] and by the WHO in 2013.[14] However, the ADA did not follow the one-step diagnostic approach recommended by the IADPSG and left the door open for the two-step screening strategy based on the National Institutes of Health (NIH) consensus conference report.[24,25] The IADPSG's one-step screening strategy involves the use of a 75-g OGTT, whereby GDM is diagnosed on the basis of one abnormal value for either the fasting or the 2-h glucose level. The two-step screening strategy makes use of a non-fasting 50-g glucose challenge test, whereby an abnormal test result (i.e. 1-h value ≥ 7.8 mmol/L) is followed by a 100-g OGTT. Gestational diabetes mellitus is then diagnosed on the basis of two abnormal values in this 100-g OGTT for the fasting, 1-, 2-, or 3-h glucose levels, using either the Carpenter and Coustan criteria[26] or the National Diabetes and Data Group criteria (Table 1).[27]

Worldwide, there is a lack of uniformly accepted diagnostic criteria. The different criteria used by different expert groups are summarized in Table 1. The main discrepancies in these guidelines relate to the use of FPG values that are higher than those of the IADPSG criteria. However, studies have shown that global adoption of the IADSPG criteria would lead to an increase in the prevalence of GDM, which would result in a higher burden to obstetric healthcare and higher costs.[28–30] Other critics of such a proposed change state that there is only limited evidence for the benefit of treatment of GDM diagnosed according to thresholds proposed by the IADPSG criteria (mild GDM), that the OGTT has poor reproducibility, and that data are lacking on the cost-effectiveness of GDM treatment when diagnosed according to the IADPSG criteria.[31,32]

The differences between the various guidelines in terms of cut-off levels indicate the need for large cost–benefit studies of the treatment of GDM diagnosed according to the

Table 1 Overview of the currently used diagnostic criteria for gestational diabetes mellitus worldwide

	WHO 1999[17]	WHO 2013,[14] IADPSG 2010[18]	ADA 2015[A,24]	NICE 2015[98]	ADIPS[112]	Carpenter and Coustan[26]	NDDG[27]
Glucose levels (mmol/L [mg/dL])							
Fasting	≥7.0 (≥128)	≥5.1 (≥92)	≥5.1 (≥92)	≥5.3 (≥95)	≥5.6 (≥100)	≥5.1 (≥92)	≥5.3 (≥95)	≥5.8 (≥105)
OGTT							
1-h	–	≥10.0 (≥180)	≥10.0 (≥180)	≥10.0 (≥180)		≥10.0 (≥180)	≥10.0 (≥180)	≥10.6 (≥190)
2-h	≥7.8 (≥140)	≥8.5 (≥153)	≥8.5 (≥153)	≥8.6 (≥155)	≥7.8 (≥140)	≥8.5 (≥153)	≥8.6 (≥155)	≥9.2 (≥165)
3-h	–	–	–	≥7.8 (≥140)	–		≥7.8 (≥140)	≥8.0 (≥145)
Total no. abnormal values	≥1[b]	≥1[b]	≥1[b]	≥2[c]	≥1[b]	≥1[b]	≥2[c]	≥2[c]

[a]The American Diabetes Association (ADA) 2015 recommendations leave the option open to use either the one-step International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendation or the two-step strategy, with the option in the two-step strategy of using either the Carpenter and Coustan criteria or the National Diabetes and Data Group (NDDG) criteria.
[b]On a 75-g oral glucose tolerance test (OGTT).
[c]On a 100-g OGTT.
WHO, World Health Organization; NICE, National Institute for Health and Care Excellence; ADIPS, Australasian Diabetes in Pregnancy Society.

IADPSG criteria. Such studies may help overcome reluctance for a broad implementation of strict diagnostic criteria. Because the main reason for this reluctance currently appears to be economic healthcare concerns regarding the burden of obstetric care, such studies will at least provide us with international consensus.

Treatment

Two randomized controlled trials (RCTs) have investigated the benefits of screening and treatment of GDM in terms of pregnancy complications.[11,12] The first was conducted in 2005 by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group.[12] That study randomly assigned 1000 women with GDM between 24 and 34 weeks gestation to receive either dietary advice, self-monitoring of blood glucose (SMBG), and insulin therapy (intervention group) or routine care (control group). Women in the routine care (control) group replicated clinical care in which screening for GDM was not available. The study showed that treatment of GDM reduced the frequency of serious perinatal complications (defined as perinatal death, shoulder dystocia, bone fracture, and nerve palsy) and improved the mother's health-related quality of life.[12] However, the women in the intervention group were more likely to have labor induced than women in the routine group, and more of the neonates in the intervention group were admitted to the neonatal nursery.[12]

The second RCT was conducted in 2009 by Landon et al.[11] and included 958 mild GDM pregnancies (defined as a fasting glucose <5.3 mmol/L) between 24 and 31 weeks gestation. The women were assigned to usual prenatal care (control group) or dietary advice, SMBG, and insulin therapy (intervention group). The study showed that although treatment of mild GDM did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risk of fetal overgrowth, shoulder dystocia, cesarean delivery, and pregnancy hypertensive complications.[11]

Following on from these findings, several systematic reviews and meta-analyses summarized the evidence of the benefits of treatment for women with GDM.[33–37] These reviews included mainly the aforementioned trials, but also additional studies that compared intensive treatment, including diet modification, glucose monitoring, and/or insulin, or any therapeutic intervention of GDM with usual obstetric care in women with GDM. These reviews demonstrated not only that treatment of GDM is effective, but that it also lowers the risk of pre-eclampsia and several neonatal complications, including macrosomia, shoulder dystocia, and neonates born large for gestational age (LGA).[33–37]

Diet

Globally, the primary approach for GDM is dietary advice in combination with SMBG. It is estimated that dietary advice helps 70%–85% of women with GDM to obtain optimal glycemic control.[38] Remarkably, there are no specific guidelines for diet or exercise in GDM. Nevertheless, there is consensus that the goal of dietary advice should be to fulfill nutrient intake for normal neonatal growth and to achieve optimal glycemic control, without inducing weight loss or excessive weight gain.[39] Optimal glycemic control can be achieved by following a diet that includes carbohydrate distribution and a reduction in rapidly digested sugars.

Increasing attention is being paid to the effect of different types of dietary intervention on pregnancy outcomes in women with GDM. Such specific dietary approaches include low-glycemic index (GI), energy restriction, and low-carbohydrate (LC) diets. A Cochrane systematic review on the effects of different types of dietary intervention in GDM found no effect for any specific type of dietary intervention in terms of reducing the following outcomes: instrumental deliveries, LGA neonates, or neonates with a birth weight > 4000 g.[40] However, this finding is in contrast with that of a more recent systematic review on the type of dietary interventions on maternal and neonatal outcomes in women with GDM.[41] That review included nine RCTs that had studied different types of dietary advice. The authors performed three meta-analyses according to the three types of dietary intervention: low-GI diets (defined as GI <55); total energy restriction diets (defined as 1600–1800 kcal or ~33 % reduction in caloric intake); and LC diets (<45 % of energy supply coming from carbohydrates). When the dietary interventions were compared with the control diets, only a low-GI diet was associated with beneficial outcomes, such as less frequent insulin use and lower neonatal weight. The study suggested that a low-GI diet reduces the use of insulin because of its ability to reduce postprandial glucose excursions.[41]

Apart from these meta-analyses on dietary interventions, the role of LC diets in GDM has gained considerable attention. Low-carbohydrate diets are currently popular in the general population and are widely used to treat obesity.[42] Evidence has shown that LC diets are also effective in the treatment of diabetes, particularly if the condition is complicated by insulin resistance.[43,44] Consequently, more attention is being paid to the use of an LC diet in GDM. However, evidence is lacking on both the short- and long-term effects of an LC diet in GDM, in terms of both blood glucose values and safety.

According to the National Academy of Medicine, the minimum daily carbohydrate intake should be >130 g for the general population and >175 g for pregnant women.[45] The additional 45 g/day carbohydrates are indicated for neonatal brain development and functioning. A carbohydrate intake <175 g can have negative consequences for the neonate.[46] Furthermore, to compensate for the reduced carbohydrate intake, the intake of other sources of nutrients, such as protein and fat, increases. Because of an LC diet's restricted food choices, there is an increased risk of nutritional deficiencies. Therefore, such diets may theoretically limit the consumption of dietary fiber, vitamins, calcium, potassium, magnesium, and iron.[47]

Two RCTs[48,49] and one non-randomized trial[50] that investigated the short-term effectiveness of an LC diet in GDM reported conflicting results. Two of the studies showed postprandial glucose values were lower in women on an LC diet (ranging from 40 % to 45 % in the intervention group) than in women on a high-carbohydrate diet (ranging from >45 % to 65 % in the control group).[49,50] Although neither of these studies reported a reduction in fasting glucose values, in the study by Major et al.[50] the women with the lowest carbohydrate intake (<42 %) required less additional insulin therapy. However, in the RCT by Moreno-Castilla et al.,[48] an LC diet (intervention 40 % vs control 55 %) did not significantly reduce the need for insulin therapy.

A recent prospective cohort study in women with a history of GDM[51] investigated whether there was an association between an LC diet and the long-term risk of type 2 DM (T2DM). An LC diet with a high intake of protein and fat mainly from animal-based foods was associated with a higher risk of T2DM, whereas an LC diet with a high intake of protein and fat mainly from plant-based foods was not. These findings suggest that women with a history of GDM who follow an LC diet may reduce their future risk of T2DM by consuming plant- rather than animal-based sources of protein and fat.[51]

In summary, there is general agreement on limiting excessive carbohydrate intake and that carbohydrates should be distributed equally throughout the day. Although it is unknown whether carbohydrate restriction is beneficial in GDM, some studies have shown beneficial effects on glucose control and also on the risk of developing T2DM after GDM.

Insulin

Women who receive dietary advice but fail to maintain glycemic control within 1–2 weeks generally receive additional insulin therapy. Insulin therapy is the medication of choice in GDM and is recommended in almost all international guidelines. Insulin is safe in pregnancy because it virtually does not cross the placental barrier and it is not known to have any teratogenic effects. The most frequently used types of insulin are regular insulin (RI) and neutral protamine Hagedorn (NPH) insulin, which are both completely homogeneous with human insulin and therefore considered safe in pregnancy. A major drawback of RI is that its activity profile does not match that of physiological insulin. The onset of action of RI begins between 30 and 60 min after injection, reaching peak activity after 2–3 h and having an effective working duration lasting up to 8–10 h.[52] Not only does it often peak too late to control postprandial blood glucose values, but it also carries an increased risk of hypoglycemia. To overcome this, rapid-acting insulin analogs have been developed in which one of the amino

acids is substituted to improve the pharmacokinetic profile. The action of rapid-acting insulin analogs (i.e. lispro, aspart, and glulisine) begins 5–15 min after injection, reaching peak activity between 30 and 90 min and having an effective working duration of 4–6 h.[52] Rapid-acting insulin analogs can therefore help achieve good postprandial blood glucose values while minimizing the risk of hypoglycemia.[52]

Both insulin aspart and lispro have been shown to be effective in pre-existing DM but have not been studied extensively in GDM.[53–55] To date, few studies have looked specifically at aspart and lispro in GDM.[56–61] A review by Lambert and Holt[62] on the use of insulin analogs in pregnancy showed that compared with RI, the use of aspart and lispro is associated with better maternal glycemic control and a similar fetal outcome. No evidence of increased risk of congenital anomalies has been reported.[63] Because insulin aspart and lispro are licensed for use during pregnancy in Europe, both insulin lispro and insulin aspart can be safely administered in pregnancy.

The use of NPH and the long-acting basal insulin analogs has both advantages and disadvantages. A major drawback of NPH insulin is that both its duration of action and peak effect are intermediate. The action of NPH begins 2–4 h after injection, its peak action effect is between 4 and 10 h, and its effective working duration is 12–18 h.[52] Indeed, outside pregnancy, rates of nocturnal hypoglycemia are known to be higher for NPH insulin than for long-acting analogs.[64] The onset of action for long-acting insulin analogs is 2–4 h after injection and their effective duration is 16–20 h, with no peak effect.[52] Insulin detemir has been approved by the US Food and Drug Administration (FDA) for use during pregnancy,[65] and its use has shown no adverse pregnancy outcomes.[66] The data on insulin glargine in pregnancy appear to be insufficient because most of the studies that have included this drug are small and retrospective.[62] Furthermore, insulin glargine has insulin-like growth factor (IGF)-1-binding properties, which could be a disadvantage in pregnancy.[63,67] However, as for RI, insulin glargine does not to cross the placental barrier.[68] There is no evidence to support the use of insulin glargine in GDM.

Oral blood glucose-lowering agents

In recent years, the use of oral blood glucose-lowering agents has gained considerable interest as an alternative for insulin therapy during pregnancy. Oral agents are not only less expensive, but they are also more easy to use, making them more patient friendly than insulin therapy, which requires training in insulin injection technique and demands time of healthcare providers.[69] It has been suggested that the oral blood glucose-lowering agents glyburide and metformin can be used in pregnancy.

Glyburide is a second-generation sulfonylurea (SU) that directly stimulates insulin secretion by binding to the SU receptor on the cell membrane of pancreatic β-cells. The major side effects of glyburide are an increased risk of maternal hypoglycemia and weight gain. There was a long-standing controversy as to whether glyburide can cross the placental barrier. In earlier studies glyburide, was not detected in the cord blood of the neonates,[70,71] but this was rejected by a later study that reported detecting glyburide in the cord blood at concentrations around 70 % of those in maternal blood.[72]

Metformin is a biguanide blood glucose-lowering agent that acts by reducing hepatic gluconeogenesis. In contrast with glyburide, metformin does not carry an increased risk of hypoglycemia and weight gain. Metformin is known to cross the placental barrier, with the fetus being exposed to levels of metformin similar to those in the mother.[73]

Short-term effects of glyburide

The first major RCT to compare glyburide and insulin in GDM was conducted by Langer et al. in 2000.[71] In total, 404 women with GDM between 11 and 33 weeks gestation were randomly assigned to receive glyburide or insulin. The primary endpoint was glycemic control and the secondary endpoints included perinatal complications. Glycemic control and perinatal outcomes were similar in both groups. There was less maternal hypoglycemia in the glyburide group (2 % vs 20 %). In 4 % of women in the glyburide group, this medication failed to produce good glycemic control, and these women needed additional insulin.[71]

Since the RCT by Langer et al., numerous trials and cohort studies have investigated the effects of glyburide in GDM. A recent and well-conducted meta-analysis by Balsells et al.[74] summarized the short-term outcomes of RCTs that compared glyburide or metformin with insulin or with each other. The analysis included seven trials that compared glyburide with insulin and demonstrated that glyburide was associated with a higher birth weight, an almost threefold higher risk of macrosomia, and a twofold higher risk of neonatal hypoglycemia.[74] The findings of Balsells et al.[74] are comparable with those of an earlier meta-analysis conducted by Zeng et al.[75] However, this earlier study concluded that glyburide is as effective as insulin, while also reporting a higher risk of neonatal hypoglycemia, high birth weight, and macrosomia.[75]

Balsells et al.[74] only included two studies that compared metformin with glyburide and found metformin

to be associated with less maternal weight gain, lower birth weight, less macrosomia, and fewer LGA neonates. Metformin was associated with slightly higher fasting blood glucose levels and higher treatment failure compared with glyburide.[74]

In summary, the evidence available from clinical studies does not support the use of glyburide in GDM, especially if metformin or insulin is available.

Short-term effects of metformin
Since 2007, evidence for the efficacy and safety of metformin use in pregnancy has been reinforced by the results of several RCTs and meta-analyses.[74,76–80] In 2013, the first meta-analysis was conducted by Gui et al.[76]; this study included five RCTs[81–85] that compared the effects of metformin with those of insulin therapy in terms of glycemic control and maternal and neonatal outcomes in GDM. Although Gui et al.[76] reported no differences between metformin and insulin in terms of glycemic control and neonatal outcomes (birth weight, LGA neonates, hypoglycemia, shoulder dystocia, and cesarean delivery), rates of preterm birth were found to be increased for metformin. Conversely, compared with insulin therapy, metformin was associated with less maternal weight gain and lower rates of pregnancy-induced hypertension, the latter thought to be explained by insulin-mediated sodium retention.[76]

Recently, five other meta-analyses have been published comparing metformin and insulin therapy in GDM.[74,77–80] The meta-analyses by Poolsup et al.,[77] Balsells et al.,[74] and Gui et al.[76] included the same RCTs and found comparable results. The main difference between these meta-analyses was that Poolsup et al.[77] and Balsells et al.[74] included an additional RCT[86]; they also did not address exactly the same outcomes: Poolsup et al.[77] had no information on maternal weight gain and Balsells et al.[74] added additional outcomes, including severe neonatal hypoglycemia and maternal total weight gain. In this respect, Balsells et al.[74] reported lower occurrence of severe neonatal hypoglycemia and a lower maternal total weight gain in the metformin group. The other three meta-analyses[78–80] included the aforementioned RTCs as well as additional RCTs.[87–89]

On the basis of current evidence, it seems that metformin may have some benefits with short-term neonatal outcomes similar to those for insulin therapy. However, the higher risk of preterm birth in metformin treatment is a point of concern that should be addressed in further studies.

Long-term effects of metformin
Unfortunately, little is known about the long-term effects of metformin in GDM. To date, several studies have investigated the long-term effects of metformin use in pregnancy on the subsequent growth and development of the children.[90–93] In 2011, the results of a 2-year follow-up study of offspring were reported by the Metformin in Gestational Diabetes (MiG) Trial. The aim of that study was to compare the results of metformin and insulin treatment in terms of body composition and measures of adiposity in the children of women who participated in the MiG trial.[83,92] Children who were exposed to metformin in utero had larger subscapular and biceps skin folds than the offspring of mothers who received insulin. The study suggests that metformin use is associated with more fat being stored in subcutaneous sites and perhaps less accumulation of ectopic or visceral fat.[92] The study found no difference in total or percentage body fat between the children exposed to metformin or insulin.[92] One other follow-up study found that children exposed to metformin were heavier at the age of 12 months and were both taller and heavier at 18 months.[90] However, in the multivariate regression analysis, maternal body mass index (BMI) was the only risk factor predicting a child being overweight or obese at the age of 18 months. Compared with insulin exposure, the study found no adverse effects of prenatal metformin exposure on motor, linguistic, or social development of the offspring during the first 18 months of life.[90]

Another two follow-up studies of offspring and their mothers were from an RCT conducted in women with polycystic ovary syndrome who had been treated with metformin or placebo during pregnancy.[91,93] The first study,[93] with a 1-year follow-up, showed that women who received a placebo during their pregnancy had lost more weight and had a lower BMI 1 year after delivery than women who received metformin during their pregnancy. However, the women in the metformin group gained less weight during their pregnancy. The offspring exposed to metformin in utero had a higher body weight at 1 year of age than those exposed to placebo.[93] In another study,[91] the same authors performed a small follow-up study of the offspring at the age of 8 years. At that age there were no differences in height, weight, body composition, and insulin resistance. However, the children exposed to metformin in utero had higher fasting glucose levels, higher systolic blood pressure, and lower low-density lipoprotein cholesterol.[91]

There appears to be an urgent need for longer follow-up studies assessing the true effect of metformin in a larger offspring cohort at least until adolescence or adulthood.

Studies on the effects of metformin during pregnancy in humans have reported no harmful effects or teratogenicity.[94,95] However, animal studies have shown that

metformin may harm the male reproductive system. Tartarin et al.[96] investigated both testicular development and function in the offspring of mice administered metformin during pregnancy. As well as analyzing embryonic mice testes in vivo, that study included human and mouse in vitro models. The results showed that, in vitro, metformin reduced testosterone secretion by decreased mRNA expression involved in steroid production. In vivo, the number of Sertoli cells was slightly reduced. The number of Leydig cells, which produce androgens, including testosterone, was diminished in the fetal period. The study showed that metformin has detrimental effects on the developing fetal testis.[96]

Other studies on the possible endocrine-disrupting effects of metformin on male reproduction have been performed in adult male fish. Because metformin is a widely used medication in T2DM patients and is not metabolized by the human body, high amounts are commonly found in wastewater and surface water. The medication is apparently not fully removed by wastewater treatment processes and is thought to be affecting the health of fish populations. Recent studies have shown that metformin can cause intersex in fish and cause male fish to produce eggs.[97] This environmental pollution clearly illustrates that more studies are needed to investigate the possible endocrine-disrupting effects of metformin on vertebrate development and male fertility.

Despite the fact that the use of metformin in GDM is questionable, especially because of the lack of long-term safety data in offspring, metformin has already been incorporated into at least two sets of guidelines. The National Institute for Heath and Care Excellence (NICE) guideline (UK) recommends the use of metformin or insulin if lifestyle interventions fail to control glycemic levels[98]; the American College of Obstetricians and Gynecologists guideline also recommends the use of metformin in GDM.[99]

Long-term effects of GDM

In recent years there has been increasing concern that GDM may also be associated with long-term consequences for the mother and child. Metabolic changes in the mother during pregnancy can lead to structural and functional adaptations during the development of the fetus, with potential consequences for growth and metabolism in the child's later life. This phenomenon is called fetal programming and was first introduced by Hales and Barker.[100] These authors found that babies who grow less well due to starvation in utero were more likely to become overweight and develop T2DM and cardiovascular diseases in adulthood.[100]

To date, several studies have investigated the association between maternal diabetes and the consequences for offspring in later life. These studies have predominantly shown that maternal diabetes is associated with obesity and T2DM in the offspring in later life.[8,101–103] Animal models have also shown that intrauterine exposure to mild maternal DM during pregnancy is associated with T2DM, insulin resistance, and obesity in the offspring.[104] However, in animal studies it is easier to study the precise effect of maternal glucose levels on fetal development than in human studies. It is also easier to control for the main confounders, such as genetic susceptibility and postnatal environmental influences.

Several systematic reviews have summarized evidence from studies on the long-term consequences for offspring of women with GDM. However, in terms of an association between GDM and overweight and obesity in the offspring, the results of the reviews were inconsistent.[105,106] In a recent critical review by Donavan and Cundy,[107] there was no robust evidence found that exposure to hyperglycemia in utero increases the risk of obesity and diabetes in the offspring. These authors suggested that the increased risk of obesity seen in the offspring of women with GDM may be explained by confounding factors, such as parental obesity (Fig. 1).
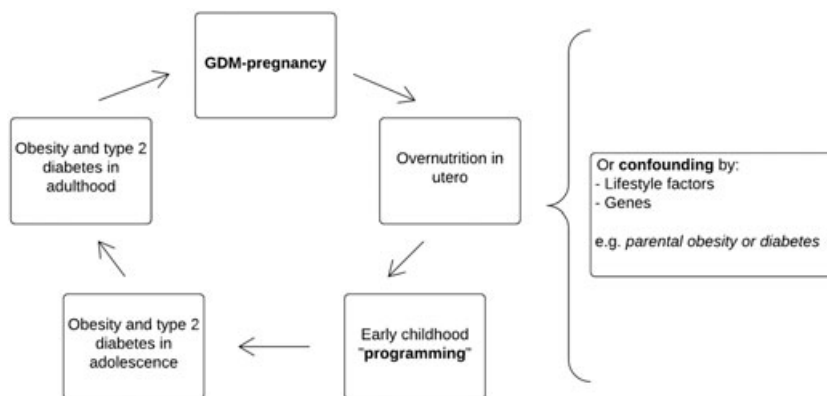
Figure 1 Fetal programming in gestational diabetes mellitus. GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus.

There is a need for more research into GDM, and especially for long-term studies into the programming and development of offspring who have been exposed prenatally to mild or moderate hyperglycemia that include adequate controls for confounding factors.

Even though in most women with GDM glucose values normalize after delivery, it is well known that women with a history of GDM are at increased risk for impaired glucose tolerance and for developing T2DM postpartum.[108–110] Studies have shown that the risk of developing T2DM may be as high as 50 % in the 5–10 years after GDM.[108,109] Therefore, it is important that we recognize persistent glucose intolerance and diagnose T2DM as early as possible in these women in order to start early interventions and to prevent long-term DM complications. Prevention strategies, such as lifestyle interventions, could have a considerable positive public health impact.[111]

Future directions and challenges

There is clearly a need for more GDM research. Gestational diabetes mellitus is a global health problem, not only because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring. There is a clear need for a set of globally uniform guidelines on the diagnosis of and treatment strategy for GDM. Currently, guidelines differ with regard to diagnostic cut-off criteria, most likely prompted by the fear of the costs and healthcare efforts that would be attached to any strengthening of diagnostic criteria. Endeavors to adopt the criteria proposed by IADPSG will warrant large cohort studies in GDM in order to provide both medical and economic justifications for such a change.

The treatment of GDM is also accompanied by both certainties and caveats. There is no specific guideline on dietary treatment and studies are scarce, although there is general consensus that excessive carbohydrate intake should limited and distributed over meals to lower glycemic excursions. However, it is unknown whether carbohydrate restriction is actually beneficial in GDM, as has been indicated by a number of studies on this topic. Although these studies showed promising results on glycemic control and the reduced risk of later developing T2DM, there is a clear need for further investigating the benefits and perils of carbohydrate restriction in GDM both during pregnancy and afterwards.

With the exception of specific issues related to the use of insulin in GDM, drug treatment remains contentious and the advice provided in guidelines is highly variable.

In terms of the use of oral blood glucose-lowering agents, the risk of neonatal hypoglycemia and increased neonatal birth weights does not support use of glyburide in GDM. The use of metformin seems promising and has already been incorporated into several guidelines. The uncertainties related to metformin use are a possible risk of premature delivery and concerns of the long-term safety regarding male fertility, and there is a particular need for studies regarding fetal programming and development in the offspring.

Acknowledgements

Disclosure

The authors have nothing to declare.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014; **37**: (Suppl.)S81–90.
2. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. *Obstet Gynecol Clin North Am*. 2007; **34**: 173–99.
3. Ferrara A. Increasing prevalence of gestational diabetes mellitus a public health perspective. *Diabetes Care*. 2007; **30**: S141–S6.
4. Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort. Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care*. 2005; **28**: 579–84.
5. Sermer M, Naylor CD, Gare DJ et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes: The Toronto Tri-Hospital Gestational Diabetes Project. *Am J Obstet Gynecol*. 1995; **173**: 146–56.
6. Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: The consequences of not treating. *Am J Obstet Gynecol*. 2005; **192**: 989–97.
7. Yang X, Hsu-Hage B, Zhang H, Zhang C, Zhang Y, Zhang C. Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. *Diabetes Care*. 2002; **25**: 1619–24.
8. Vohr BR, Boney CM. Gestational diabetes: The forerunner for the development of maternal and childhood obesity and metabolic syndrome? *J Matern Fetal Neonatal Med*. 2008; **21**: 149–57.
9. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles M-A, Pettitt DJ. Childhood obesity and

metabolic imprinting the ongoing effects of maternal hyperglycemia. *Diabetes Care*. 2007; **30**: 2287–92.

10. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: Relationship to fetal hyperinsulinism. *Diabetes Care*. 1995; **18**: 611–7.

11. Landon MB, Spong CY, Thom E et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med*. 2009; **361**: 1339–48.

12. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med*. 2005; **352**: 2477–86.

13. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes*. 1964; **13**: 278–85.

14. World Health Organization. Diagnostic Criteria and Classification of Hypoglycemia First Detected in Pregnancy. 2013. Available from: http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf, accessed 22 September 2015.

15. World Health Organization (WHO). WHO Expert Committee on Diabetes Mellitus. Second Report. Geneva, WHO, 1980.

16. Gabir MM, Hanson RL, Dabelea D et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care*. 2000; **23**: 1108–12.

17. World Health Organization (WHO). Definition and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, WHO, 1999.Department of Noncommunicable Disease Surveillance

18. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010; **33**: 676–82.

19. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008; **358**: 1991–2002.

20. Jensen DM, Korsholm L, Ovesen P, Beck-Nielsen H, Mølsted-Pedersen L, Damm P. Adverse pregnancy outcome in women with mild glucose intolerance: Is there a clinically meaningful threshold value for glucose? *Acta Obstet Gynecol Scand*. 2008; **87**: 59–62.

21. Pettitt DJ, Knowler WC, Baird HR, Bennett PH. Gestational diabetes: Infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. *Diabetes Care*. 1980; **3**: 458–64.

22. Jensen DM, Damm P, Sørensen B et al. Clinical impact of mild carbohydrate intolerance in pregnancy: A study of 2904 nondiabetic Danish women with risk factors for gestational diabetes mellitus. *Am J Obstet Gynecol*. 2001; **185**: 413–9.

23. Ferrara A, Weiss N, Hedderson M et al. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycaemia and hyperbilirubinaemia. *Diabetologia*. 2007; **50**: 298–306.

24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2015; **38**: (Suppl.)S8–S16.

25. Vandorsten J, Dodson W, Espeland M et al. NIH consensus development conference: Diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements*. 2012; **29**: 1–31.

26. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes mellitus. *Am J Obstet Gynecol*. 1982; **144**: 768–73.

27. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979; **28**: 1039–57.

28. Cundy T, Ackermann E, Ryan EA. Gestational diabetes: New criteria may triple the prevalence but effect on outcomes is unclear. *BMJ*. 2014; **348**: g1567.

29. Moses RG, Morris GJ, Petocz P, San Gil F, Garg D. The impact of potential new diagnostic criteria on the prevalence of gestational diabetes mellitus in Australia. *Med J Aust*. 2011; **194**: 338–40.

30. O'Sullivan E, Avalos G, O'Reilly M et al. Atlantic Diabetes in Pregnancy (DIP): The prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. *Diabetologia*. 2011; **54**: 1670–5.

31. Harlass FE, Brady K, Read JA. Reproducibility of the oral glucose tolerance test in pregnancy. *Am J Obstet Gynecol*. 1991; **164**: 564–8.

32. Visser GH, de Valk HW. Is the evidence strong enough to change the diagnostic criteria for gestational diabetes now? *Am J Obstet Gynecol*. 2013; **208**: 260–4.

33. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: A systematic review and meta-analysis for the US Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med*. 2013; **159**: 123–9.

34. Falavigna M, Schmidt MI, Trujillo J et al. Effectiveness of gestational diabetes treatment: A systematic review with quality of evidence assessment. *Diabetes Res Clin Pract*. 2012; **98**: 396–405.

35. Poolsup N, Suksomboon N, Amin M. Effect of treatment of gestational diabetes mellitus: A systematic review and meta-analysis. *PLoS One*. 2014; **9**: e92485.

36. Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database Syst Rev*. 2009; **3**: CD003395.

37. Horvath K, Koch K, Jeitler K et al. Effects of treatment in women with gestational diabetes mellitus: Systematic review and meta-analysis. *BMJ*. 2010; **340**: c1395.

38. American Diabetes Association. Management of diabetes in pregnancy. *Diabetes Care*. 2015; **38**: (Suppl.)S77–S9.

39. Metzger BE, Buchanan TA, Coustan DR et al. Summary and recommendations of the Fifth International Workshop Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007; **30**: (Suppl.)S251–60.

40. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. *Cochrane Database Syst Rev*. 2013; **3**: CD009275.

41. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: A systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. *Diabetes Care*. 2014; **37**: 3345–55.

42. Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev*. 2009; **10**: 36–50.

43. Yancy WS Jr, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab (Lond)*. 2005; **2**: –34.

44. Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: Stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutr Metab (Lond)*. 2008; **5**: 14.

45. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002; **102**: 1621–30.

46. Uplinger N. The controversy continues: Nutritional management of the pregnancy complicated by diabetes. *Curr Diab Rep*. 2009; **9**: 291–5.

47. Adam-Perrot A, Clifton P, Brouns F. Low-carbohydrate diets: Nutritional and physiological aspects. *Obes Rev*. 2006; **7**: 49–58.

48. Moreno-Castilla C, Hernandez M, Bergua M et al. Low-carbohydrate diet for the treatment of gestational diabetes mellitus: A randomized controlled trial. *Diabetes Care*. 2013; **36**: 2233–8.

49. Cypryk K, Kamińska P, Kosiński M, Pertyńska-Marczewska M, Lewiński A. A comparison of the effectiveness, tolerability and safety of high and low carbohydrate diets in women with gestational diabetes. *Endokrynol Pol*. 2007; **58**: 313–20.

50. Major CA, Henry MJ, de Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. *Obstet Gynecol*. 1998; **91**: 600–4.

51. Bao W, Li S, Chavarro JE et al. Low-carbohydrate-diet scores and long-term risk of type 2 diabetes among women with a history of gestational diabetes: A prospective cohort study. *Diabetes Care*. 2016; **39**: 43–9.

52. Hirsch IB. Insulin analogues. *N Engl J Med*. 2005; **352**: 174–83.

53. Hod M, Damm P, Kaaja R et al. Fetal and perinatal outcomes in type 1 diabetes pregnancy: A randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol*. 2008; **198**: e1–7.186

54. Mathiesen ER, Kinsley B, Amiel SA et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: A randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care*. 2007; **30**: 771–6.

55. Blanco CG, Ballesteros AC, Saladich IG, Pla RC. Glycemic control and pregnancy outcomes in women with type 1 diabetes mellitus using lispro versus regular insulin: A systematic review and meta-analysis. *Diabetes Technol Ther*. 2011; **13**: 907–11.

56. Pettitt DJ, Ospina P, Kolaczynski JW, Jovanovic L. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care*. 2003; **26**: 183–6.

57. Pettitt D, Ospina P, Howard C, Zisser H, Jovanovic L. Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med*. 2007; **24**: 1129–35.

58. Di Cianni G, Volpe L, Ghio A et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes mellitus treated with lispro or aspart insulin: Comparison with regular insulin. *Diabetes Care*. 2007; **30**: e11.

59. Bhattacharyya A, Brown S, Hughes S, Vice P. Insulin lispro and regular insulin in pregnancy. *QJM*. 2001; **94**: 255–60.

60. Mecacci F, Carignani L, Cioni R et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: Comparison with non-diabetic pregnant women. *Eur J Obstet Gynecol Reprod Biol*. 2003; **111**: 19–24.

61. Jovanovic L, Ilic S, Pettitt DJ et al. Metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care*. 1999; **22**: 1422–7.

62. Lambert K, Holt R. The use of insulin analogues in pregnancy. *Diabetes Obes Metab*. 2013; **15**: 888–900.

63. Jong J, Garne E, Wender-Ozegowska E, Morgan M. Jong-van den Berg LT, Wang H. Insulin analogues in pregnancy and specific congenital anomalies: A literature review. *Diabetes Metab Res Rev*. 2016; **32**: 366–75.

64. Horvath K, Jeitler K, Berghold A et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007; **2**: CD005613.

65. Blumer I, Hadar E, Hadden DR et al. Diabetes and pregnancy: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013; **98**: 4227–49.

66. Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: A meta-analysis. *Arch Gynecol Obstet*. 2015; **292**: 749–56.

67. Woolderink JM, Van Loon AJ, Storms F, de Heide L, Hoogenberg K. Use of insulin glargine during

pregnancy in seven type 1 diabetic women. *Diabetes Care*. 2005; **28**: 2594–5.

68. Kovo M, Golan A, Wainstein J, Matas Z, Haroutiunian S, Hoffman A. Placental transfer of the insulin analog glargine in the ex vivo perfused placental cotyledon model. *Endocr Res*. 2011; **36**: 19–24.

69. Norman RJ, Wang JX, Hague W. Should we continue or stop insulin sensitizing drugs during pregnancy? *Curr Opin Obstet Gynecol*. 2004; **16**: 245–50.

70. Elliott BD, Schenker S, Langer O, Johnson R, Prihoda T. Comparative placental transport of oral hypoglycemic agents in humans: A model of human placental drug transfer. *Am J Obstet Gynecol*. 1994; **171**: 653–60.

71. Langer O, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med*. 2000; **343**: 1134–8.

72. Hebert M, Ma X, Naraharisetti S et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther*. 2009; **85**: 607–14.

73. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril*. 2005; **83**: 1575–8.

74. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: A systematic review and meta-analysis. *BMJ*. 2015; **350**: h102.

75. Zeng Y-C, Li M-J, Chen Y et al. The use of glyburide in the management of gestational diabetes mellitus: A meta-analysis. *Adv Med Sci*. 2014; **59**: 95–101.

76. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: A meta-analysis. *PLoS One*. 2013; **8**: e64585.

77. Poolsup N, Suksomboon N, Amin M. Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: A meta-analysis. *PLoS One*. 2014; **9**: e109985.

78. Su D, Wang X. Metformin vs insulin in the management of gestational diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2014; **104**: 353–7.

79. Kitwitee P, Limwattananon S, Limwattananon C et al. Metformin for the treatment of gestational diabetes: An updated meta-analysis. *Diabetes Res Clin Pract*. 2015; **109**: 521–32.

80. Zhao L, Sheng X, Zhou S et al. Metformin versus insulin for gestational diabetes mellitus: A meta-analysis. *Br J Clin Pharmacol*. 2015; **80**: 1224–34.

81. Moore LE, Briery CM, Clokey D et al. Metformin and insulin in the management of gestational diabetes mellitus: Preliminary results of a comparison. *J Reprod Med*. 2007; **52**: 1011–5.

82. Ijäs H, Vääräsmäki M, Morin-Papunen L et al. Metformin should be considered in the treatment of gestational diabetes: A prospective randomised study. *BJOG*. 2011; **118**: 880–5.

83. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008; **358**: 2003–15.

84. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial. *Diabetes Res Clin Pract*. 2012; **98**: 422–9.

85. Tertti K, Ekblad U, Koskinen P, Vahlberg T, Rönnemaa T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab*. 2013; **15**: 246–51.

86. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol*. 2013; **209**: e1–7.34

87. Hasan JA, Karim N, Sheikh Z. Metformin prevents macrosomia and neonatal morbidity in gestational diabetes. *Pak J Med Sci*. 2012; **28**: 384–9.

88. Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SGA, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: A randomised blinded trial. *Int J Prev Med*. 2013; **4**: 327–33.

89. Hague W, Davoren P, Oliver J, Rowan J. Contraindications to use of metformin: Metformin may be useful in gestational diabetes. *BMJ*. 2003; **326**: 762–3.

90. Ijäs H, Vääräsmäki M, Saarela T, Keravuo R, Raudaskoski T. A follow-up of a randomised study of metformin and insulin in gestational diabetes mellitus: Growth and development of the children at the age of 18 months. *BJOG*. 2015; **122**: 994–1000.

91. Rø TB, Ludvigsen HV, Carlsen SM, Vanky E. Growth, body composition and metabolic profile of 8-year-old children exposed to metformin in utero. *Scand J Clin Lab Invest*. 2012; **72**: 570–5.

92. Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: The offspring follow-up (MiG TOFU): Body composition at 2 years of age. *Diabetes Care*. 2011; **34**: 2279–84.

93. Carlsen SM, Martinussen MP, Vanky E. Metformin's effect on first-year weight gain: A follow-up study. *Pediatrics*. 2012; **130**: e1222–6.

94. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod*. 2002; **17**: 2858–64.

95. Lautatzis M-E, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: A systematic review. *Metabolism*. 2013; **62**: 1522–34.

96. Tartarin P, Moison D, Guibert E et al. Metformin exposure affects human and mouse fetal testicular cells. *Hum Reprod*. 2012; **27**: 3304–14.

97. Niemuth NJ, Klaper RD. Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish. *Chemosphere*. 2015; **135**: 38–45.

98. National Institute for Health and Care Excellence. Diabetes in Pregnancy: Management of Diabetes and

its Complications from Pre-conception to the Postnatal Period. Clinical Guideline NG3. 2015. Available from: http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021, accessed 22 September 2015.

99. Brown HL. ACOG guidelines at a glance: Gestational diabetes mellitus. *Obstet Gynecol*. 2013; **122**: 406–16.

100. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia*. 1992; **35**: 595–601.

101. Dabelea D, Crume T. Maternal environment and the transgenerational cycle of obesity and diabetes. *Diabetes*. 2011; **60**: 1849–55.

102. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. *J Matern Fetal Neonatal Med*. 2010; **23**: 199–203.

103. Fetita L-S, Sobngwi E, Serradas P, Calvo F, Gautier J-F. Consequences of fetal exposure to maternal diabetes in offspring. *J Clin Endocrinol Metab*. 2006; **91**: 3718–24.

104. Aerts L, Van Assche FA. Animal evidence for the transgenerational development of diabetes mellitus. *Int J Biochem Cell Biol*. 2006; **38**: 894–903.

105. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: A systematic review. *Exp Diabesity Res*. 2011; **2011**: 541308.

106. Philipps L, Santhakumaran S, Gale C et al. The diabetic pregnancy and offspring BMI in childhood: A systematic review and meta-analysis. *Diabetologia*. 2011; **54**: 1957–66.

107. Donovan L, Cundy T. Does exposure to hyperglycaemia in utero increase the risk of obesity and diabetes in the offspring? A critical reappraisal. *Diabet Med*. 2015; **32**: 295–304.

108. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. *Lancet*. 2009; **373**: 1773–9.

109. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: A systematic review. *Diabetes Care*. 2002; **25**: 1862–8.

110. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med*. 2004; **21**: 103–13.

111. Cheung NW, Byth K. Population health significance of gestational diabetes. *Diabetes Care*. 2003; **26**: 2005–9.

112. Nankervis A, McIntyre HD, Moses R, et al.. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia. Australasian diabetes in pregnancy society. Available from: http://adips.org/downloads/ADIPSConsensusGuidelines GDM-03.05.13VersionACCEPTEDFINAL.pdf, accessed 10 May 2016. (2012)