Drug Saf (2015) 38:65–78
DOI 10.1007/s40264-014-0253-9

REVIEW ARTICLE

Safety Considerations with Pharmacological Treatment of Gestational Diabetes Mellitus

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Published online: 27 December 2014

Abstract The number of women with gestational diabetes mellitus (GDM: diabetes first diagnosed in pregnancy) continues to grow, as do the associated risks of antenatal and postnatal complications and the chance of future diabetes and obesity in both mother and offspring. Recent randomised controlled trials have demonstrated clear benefits for intensive management of GDM using lifestyle modification, self blood glucose monitoring, close clinical supervision and, where glycaemia remains inadequately controlled, insulin therapy. More recently, metformin and glibenclamide have been shown to adequately reduce hyperglycaemia as part of a stepped approach to GDM management, with a switch to insulin therapy where necessary. Other oral medications have not been shown to be safe in pregnancy. Human insulin therapy is safe within the limits of hypoglycaemia and weight gain. Most insulin analogues are also now considered safe for use in pregnancy (insulin lispro, aspart and detemir). Metformin therapy is oral, and therefore preferred to insulin, but is associated with more gastrointestinal adverse effects, although not hypoglycaemia or weight gain. Conversely, glibenclamide is also an oral therapy but is associated with hypoglycaemia and weight gain. However, metformin crosses the placenta and it remains unclear whether glibenclamide crosses the placenta or not: long-term risks have not been shown, and are thought to be minimal, but further studies are needed. Metformin is seen by some as the treatment of choice where weight gain is an issue, providing that the unanswered questions over the long-term safety of oral agents have been discussed.

Key Points

Several pregnancy complications, including macrosomia, shoulder dystocia and pre-eclampsia, can be reduced through the treatment of gestational diabetes mellitus (GDM).

Human insulin therapy is safe within the limits of hypoglycaemia and weight gain but some women may prefer oral therapies.

Metformin is increasingly seen as a safe oral therapy for GDM, but as the drug crosses the placenta, the long-term effects on the offspring remain uncertain.

Glibenclamide is associated with weight gain and hypoglycaemia, and there is growing evidence that it crosses the placenta.

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1 Background

There has been a traditional, and understandable, reluctance to prescribe medications before and during pregnancy, and while breastfeeding [1]. The pharmacological treatment of diabetes mellitus in pregnancy has also been beset by concern over the potential teratogenic and long-

term harms from any treatment: 'Primum non nocere' (first, do no harm). However, teratogenesis is not only caused by pharmacological interventions. Glucose is a major cause of 'fuel-mediated teratogenesis' [2], i.e. hyperglycaemia is a major cause of cardiac, neurological and other malformations (and miscarriage) when exposure occurs during the first 8 weeks of pregnancy (and probably before). However, the fuel-mediated teratogenesis theory postulates that exposure to hyperglycaemia not only causes structural malformations, but that exposure at different times during pregnancy is also associated with long-term metabolic harms, including predisposing to future diabetes and obesity. Indeed, maternal third trimester 2-h glucose concentrations directly correlate with the future risk of diabetes in the offspring [3]. Obesity is also more common in the offspring of women with diabetes, including gestational diabetes mellitus (GDM), from a young age [4].

There is currently an epidemic of type 2 diabetes and obesity among children, adolescents, and non-pregnant adults [5], which is associated with growing numbers of women with type 2 diabetes in pregnancy and GDM (including undiagnosed type 2 diabetes) [6–8]. This, in turn, is thought to increase the risk of diabetes and obesity in the offspring and future generations [9–11], amplifying the current epidemic. The prevalence of the metabolic syndrome is also substantially increased by the age of 11 years in the offspring of women with GDM who were large for gestational age, compared with offspring from other women with GDM and women without GDM but a large baby [12]. This observation suggests that perhaps if we can prevent macrosomia, we might be able to prevent, or at least reduce, the current epidemic of type 2 diabetes, obesity and metabolic syndrome. We now have good randomised controlled trial (RCT) evidence from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Maternal-Fetal Medicine Units (MFMU) Network [13, 14, 19] that such macrosomia can be substantially reduced by treating GDM with lifestyle change and/or insulin therapy, and that at least two oral medications used within a treatment algorithm (metformin and glibenclamide/glyburide) can achieve comparable fetal outcomes [15, 16].

Does this lead to long-term benefits in the offspring? This remains speculative. To date, one study has suggested that more intensive treatment of GDM is associated with a reduced risk of adiposity in the offspring by 2 years 8 months [17], and another study showed a reduced risk of childhood obesity and overweight after 5–7 years when comparing treated (with higher antenatal glucose values) and untreated (with lower antenatal glucose values) [18] pregnancies. However, there was no evidence of reduction in body mass index (BMI) by 5 years of age in the offspring of the ACHOIS cohort [19]. Based on prior studies, the authors proposed that differences in lean and fat mass might not be reflected by BMI, and that differences may be undetectable up to 9 years of age.

Other adverse outcomes besides macrosomia and long-term fetal risks are also important, of course, and treatment of GDM reduces the risk of other severe outcomes (ACHOIS used a composite of perinatal mortality, birth trauma and shoulder dystocia), pre-eclampsia and operative delivery [13, 14].

1.1 Targets and Criteria for Gestational Diabetes Mellitus (GDM)

The relationship between maternal glycaemia and adverse maternal and neonatal outcomes is a continuum [20]. Clearly, if there is a relationship between glycaemia and adverse outcomes then the criteria and targets for diagnosing and treating GDM need to be set at thresholds that are maximally effective, while minimising any treatment adverse effects. As a continuum, with no natural inflection point where harm from hyperglycaemia increases rapidly, agreement over criteria has been hard to reach, and consensus approaches have been needed to ascertain the thresholds at which to diagnose GDM using a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks [21]. The latest World Health Organisation (WHO) criteria (fasting glucose $\geq$5.1 mmol/L and/or 1-h post-load glucose $\geq$10.0 mmol/L and/or 2-h post-load glucose $\geq$8.5 mmol/L) have been agreed based upon an odds ratio of 1.75 for key adverse outcomes, compared to the median glucose values in the HAPO (Hyperglycaemia and Pregnancy Outcomes) study population [20]. Most clinical guidelines for GDM recommend targeting pre-prandial levels between 3.9 and 5.3 mmol/L and 1- and 2-h post-prandial levels of $<$7.8 and 6.7 mmol/L, respectively. These targets need to be maintained until the end of pregnancy, even though demand for insulin is increasing, and the glucose trend will be upwards.

The need for medication is currently defined by the glucose concentrations shown by self blood glucose monitoring, an approach associated with reductions in adverse outcomes [13–16]. Partial treatment would be expected to be associated with less benefit. There have also been trials of more versus less tight glycaemic control, such as twice a day insulin therapy versus four times a day therapy [22], and a focus on pre-prandial versus post-prandial glycaemic targets [23], both of which showed benefits with more intensive treatment. There has been one meta-analysis, comparing the outcomes among women with GDM, using less and more intensive management [24], but of the 13 studies accepted, only one [22] had a low probability of bias. Overall, the only significant difference in outcomes was a reduction in shoulder dystocia [0.31 (95 % CI 0.14–0.70)].

Of particular importance is the group of women who were likely to have had diabetes prior to the diagnosis of GDM, called 'overt diabetes' by the International Association of Diabetes in Pregnancy Study Groups [25] and 'diabetes in pregnancy' by the WHO [21]. This group is obviously more likely to require more intensive treatment from early pregnancy, unlike women diagnosed from 24 to 28 weeks. Use of medications in the first trimester is not covered in this review, as GDM is rarely diagnosed and treated within this time period.

Consideration of the outcomes for offspring is paramount in the decision over whether and which agents to use to manage hyperglycaemia in GDM once lifestyle measures have been found to be inadequate. Clearly, any treatment benefits must outweigh treatment harm, and eyes are very much on the long-term risks and benefit for the fetus. Indeed, fetal harm does not only arise from intrauterine exposure to maternal hyperglycaemia or medications, but there is also potential for harm with overtreatment of GDM (i.e. excessive glucose lowering), which can lead to more small for gestational age babies [26]. In the background rests the thrifty phenotype (Barker) hypothesis, which proposes that intrauterine under-nutrition is also associated with increased risk of diabetes, obesity, hypertension and cardiovascular disease [27]. This is also a consideration when setting targets to manage GDM.

1.2 Importance of Weight, Weight Gain and Weight Loss in Pregnancy

Obesity is independently associated with greater adverse pregnancy outcomes, which are additive to those from GDM [28]. A range of studies have also shown that antenatal weight gain is associated with adverse pregnancy outcomes (e.g. macrosomia, caesarean section) among women who are obese [29–36]. As insulin and sulphonylureas (e.g. glibenclamide) are associated with weight gain (unlike metformin and lifestyle change alone), benefits from improved glycaemia might not accrue to the extent required and this has to be taken into account in any management plan. Furthermore, weight gain during pregnancy often remains post-natally [37].

2 Use of Insulin During the Second and Third Trimesters

There have been two major RCTs comparing usual care and contemporary management (including insulin therapy where lifestyle alone was inadequate to control hyperglycaemia) of GDM: the ACHOIS and—MFMU Network studies [13, 14]. Although a systematic review and meta-analysis in 2010 identified and included three other RCTs from between 1966 and 2005 [24], each of these additional studies was flawed [24] and hence the focus is on the ACHOIS and MFMU Network studies.

Both ACHOIS and MFMU Network used a two-step screening approach (50 g glucose challenge then OGTT), with ACHOIS using WHO criteria and MFMU Network using Carpenter/Coustan criteria. ACHOIS excluded women with fasting glucose $\geq$7.8 mmol/L and MFMU Network excluded women with a fasting glucose of $\geq$5.3 mmol/L. Tables 1 and 2 compare the interventions and results in the two major studies. Relatively few women received insulin, particularly in MFMU Network, which had lower targets, more obese and non-European women, and excluded women with fasting glucose above 5.3 mmol/L. Even so, it is clear that a clinical strategy including insulin therapy for those above target is associated with reductions in shoulder dystocia, macrosomia/large for dates and pre-eclampsia and no increase (possibly a decrease) in caesarean section.

2.1 General Safety Considerations with Insulin Therapy in the Pharmacological Treatment of GDM

Although insulin therapy has historically been the pharmacological agent of choice for managing hyperglycaemia in GDM after nutrition and physical activity, it is not without its problems. Insulin management remains a challenge for many pregnant women with difficulties associated with weight management, balancing dosage, food and activity and, for some, the frequency of hypoglycaemic episodes. Many try to avoid 'the needle', although this can frequently be addressed by involving women in self administration before or at the time of insulin use education. For many women with GDM, there is a need to address post-prandial hyperglycaemia, and for others the overall dosage can be so large that administration is best delivered using continuous subcutaneous insulin therapy [38]. Insulin is an expensive therapy and its use in hot climates requires access to refrigeration and safe storage; as a result, some countries have used oral agents for many years [39]. This review included a literature search within the MEDLINE database using the name of each drug and either 'gestational diabetes', 'diabetes' and 'pregnancy' or 'hyperglycaemia' and 'pregnancy'. The search was undertaken for all years up to July 2014.

2.2 Safety of Analogue Insulins

There are three rapid-acting insulin analogues: lispro, aspart and subsequently glulisine, which dissociate into monomers upon subcutaneous injection (leading to their

Table 1 Major randomised controlled trials of the management of gestational diabetes mellitus using insulin versus usual care

	ACHOIS: Rx vs. control [13]	MFMU Network: Rx vs. control [14]
N	1,000	958
BMI (kg/m^2)	26.8 vs. 26.0	30.1 ± 5.0 vs. 30.2 ± 5.1
Ethnicity (Europid/Asian/Hispanic/African) (%)	73 vs. 78/19 vs. 14/0 vs. 0/0 vs. 0	25.4 vs. 25.2/0 vs. 0/4.5 vs. 5.9/57.9 vs. 56.0
Primigravida (%)	43 vs. 49	21.4 vs. 26.0
Gestational age at entry (weeks)	29.1 vs. 29.2	28.8 ± 1.6 vs. 28.9 ± 1.5
Fasting/2-h glucose on oral glucose tolerance test	4.8 ± 0.7/8.6 vs. 4.8 ± 0.6/8.5	4.8 ± 0.3/9.7 ± 1.2 vs. 4.8 ± 0.3/9.6 ± 1.1 (100 g)
Intervention	Individualised dietary advice	Individualised dietary advice
	Self blood glucose monitoring 4×/day: fasting and 2-h post-prandial	Self blood glucose monitoring 4×/day: fasting and 2-h post-prandial
Targets	Fasting 3.5–5.5 mmol/L	Fasting <5.3 mmol/L
	Pre-prandial <5.5 mmol/L	2 h Post-prandial <6.7 mmol/L
	2 h post-prandial <7.0 mmol/L	
Insulin therapy if:	2 Tests high: fasting ≥5.5 mmol/L and/or post-prandial ≥7.0 + (to 35 weeks); ≥8.0 + (above 35 weeks)	'Majority' high: fasting ≥5.3 mmol/L
	1 × 9.0 mmol/L anytime	Random blood glucose ≥8.9 mmol/L
Insulin Rx (%)	20 vs. 3	7.7 vs. 0.4
Weight gain		
ACHOIS: from first to last visit	8.1 ± 0.3 vs. 9.8 ± 0.4 kg	1.2 vs. 2.1 kg/m^2 (BMI)
MFMU Network: from enrollment to birth		2.8 ± 4.5 vs. 5.0 ± 3.3 kg
Gestational age at birth (weeks)	39.0 vs. 39.3	39.0 ± 1.8 vs. 38.9 ± 1.8

Values are expressed as mean ± SD

BMI body mass index, *Rx* treatment

'rapid' action), having existed as hexamers in storage. There are three long-acting insulin analogues in use: insulin glargine, insulin levemir and more recently insulin degludec. None of the insulin analogues are thought to cross the placenta either alone or as antibody–insulin complexes in humans. None are known to be excreted into human milk. Insulin glulisine has not been the subject of studies in pregnancy and no reports were found in a literature review in 2009 [40]. Glulisine has been used in four women with type 1 diabetes with no evidence of harm [41]. The literature review found no case reports as yet with degludec in GDM. The pharmacological studies below have largely been undertaken in non-pregnant adults.

2.2.1 *Lispro/Humalog®*

Insulin lispro was the first insulin analogue to enter clinical practice (in 1996). Action reaches a peak after 1 h and lasts 4 h. In comparison with regular insulin, use of insulin lispro is associated with a 1.5–2.5 mmol/L lower post-prandial glucose rise, a consistent reduction in glycosylated haemoglobin (HbA_{1c}) of 0.3–0.5 %, 20–30 % less severe hypoglycaemia (especially nocturnal) and less need for snacks [42, 43].

2.2.2 *Insulin Aspart/NovoRapid®*

Insulin aspart was approved in 1999 with peak action approximately 31–70 min after subcutaneous injection. Action lasts approximately 4 h. In comparison with regular insulin, use of insulin aspart is associated with 1.5 mmol/L lower post-prandial glucose, 0.12 % lower HbA_{1c} and fewer hypoglycaemic episodes needing third-party assistance [44, 45].

2.2.3 *Insulin Glargine*

Insulin glargine was approved for use in 2000; it acts from approximately 90 min after subcutaneous injection and lasts 24 h. It is considered 'peakless'. Insulin glargine is associated with less nocturnal hypoglycaemia, reduced fasting glucose, reduced post-dinner glucose concentrations, less weight gain and a reduced

Table 2 Outcomes of major randomised controlled trials of the management of gestational diabetes mellitus using insulin versus usual care and meta-analysis including other studies

	ACHOIS intensive vs. control [13]	MFMU Network [14]
Composite[a]	–	32.4 vs. 37.0 %
Any serious perinatal complication	1 vs. 4 %	–
	0.33 (0.14–0.75)	
Death	0 vs. 1 %	0
	0.19 (0.04–0.96)	
Shoulder dystocia	1 vs. 3 %	0.36 (0.15–0.88)
	0.46 (0.19–1.10)	
Bone fracture/nerve palsy	0 vs. 1 %	0.6 vs. 1.3 %
Admission to NICU	71 vs. 61 %	9.0 vs. 11.6 %
	1.13 (1.03–1.23)	0.77 (0.51–1.18)
Induction of labour	39 vs. 29 %	27.3 vs. 26.8 %
	1.36 (1.15–1.62)	1.02 (0.81–1.29)
Caesarean delivery	31 vs. 32 %	26.9 vs. 33.8 %
	0.97 (0.91–1.16)	0.79 (0.64–0.99)
Birth weight >4 kg	10 vs. 21 %	5.9 vs. 14.3 %
	0.47 (0.34–0.64)	0.41 (0.26–0.66)
Large for gestational age	13 vs. 22 %	7.1 vs. 14.5 %
	0.62 (0.47–0.81)	0.49 (0.32–0.76)
Hypoglycaemia	7 vs. 5 %: needing IV glucose	16.3 vs. 15.4 %: any
	1.42 (0.87–2.32)	5.3 vs. 6.8 %: IV glucose
		0.77 (0.44–1.36)
Hyperbilirubinaemia	9 vs. 9 %	9.6 vs. 12.9 %
	0.93 (0.63–1.37)	
Elevated C peptide	–	17.7 vs. 22.8%
Respiratory distress syndrome	5 vs. 4 %	1.9 vs. 2.9 %
	1.52 (0.86–2.71)	0.66 (0.26–1.67)
Antenatal pre-eclampsia	12 vs. 18 %	2.5 vs. 5.5 %
	0.70 (0.51–0.95)	0.46 (0.22–0.97)

Numbers shown are either % or odds ratio (95 % confidence interval)

IV intravenous, *NICU* neonatal intensive care unit

[a] Composite = stillbirth, neonatal death, hypoglycaemia, hyperbilirubinaemia, elevated cordblood C-peptide level and birth trauma

insulin dose with a similar impact on HbA_{1c} than Neutral Protamine Hagedorn (NPH) insulin [46–48]. No RCTs of insulin glargine have taken place in GDM, but there have been a number of prospective, retrospective and case studies of insulin glargine use among women with GDM, and no evidence of harm has been shown [49, 50].

2.2.4 Insulin Detemir

Insulin detemir was approved in 2005 and, following recent trials, has been categorised as a Category B drug [US Food and Drug Administration (FDA) category indicating that no fetal risk has been shown in animal studies and there are no adequate studies in human pregnancy]. Its effect can last up to 24 h, with no peak. More than 50 % of its effect occurs 3–14 h after injection when using doses of between 0.2 and 0.4 Units/kg. Insulin detemir has lower variability in action than either NPH or insulin glargine [51] and comparable glycaemic control but lower hypoglycaemia rates and less weight gain than NPH [52–54]. Although there has been one randomised trial of NPH versus insulin detemir in type 1 diabetes in pregnancy [55], with no significant difference in obstetric outcomes, there have been no RCTs of insulin detemir in GDM.

2.3 When Large Amounts of Insulin are Needed…

Where women with GDM need large amounts of insulin to overcome their insulin resistance, a basal bolus regimen can become increasingly ineffective in maintaining euglycaemia. The addition of metformin can reduce insulin needs [15]. If continuous subcutaneous insulin infusion therapy is not available [38], U500 insulin can also be considered, although safety can be an issue if staff not used to using U500 inadvertently consider it a U100 insulin.

3 Oral Anti-Hyperglycaemic Agents

3.1 Metformin

Metformin has been seen as a logical choice of oral anti-hyperglycaemia agent for the management of GDM to address the pregnancy-associated deterioration in glucose control due to changes in both pre-prandial and post-prandial glucose metabolism and insulin resistance. It has been suggested that control of post-prandial hyperglycaemia is of particular importance during pregnancy, as spikes of higher glucose after meals could lead to a higher concentration of glucose in the amniotic fluid and its subsequent reabsorption/recirculation [56]. Pregnancy outcomes were indeed better when post prandial-rather than pre-prandial glucose was targeted in one RCT [23], although a high proportion of women probably had overt diabetes in pregnancy (likely undiagnosed type 2 diabetes in pregnancy).

The MiG (Metformin in Gestational Diabetes Mellitus) study has provided substantial data about the safety, acceptability and efficacy of metformin treatment in the second and third trimesters [15]. Women ($n = 751$) were randomised to either metformin or insulin therapy at 20–33 weeks. The characteristics at baseline and intervention are described in Table 3 and outcomes in Table 4, alongside the major RCT with glibenclamide [16] for comparison. Among those treated with metformin, 46.3 % required additional insulin therapy. The metformin- and insulin-based strategies had comparable perinatal and obstetric outcomes but metformin treatment was associated with less weight gain in 37/40 from enrolment (−0.4 vs. 2.0 kg) and more weight loss from enrolment to post-partum (−8.1 vs. 6.9 kg). Women randomised to metformin therapy who required supplementary insulin therapy to manage their hyperglycaemia were found to require slightly less insulin. No adverse effects were reported with this combination therapy. Women said they would be more likely to choose metformin therapy if needed in the future (81 % of metformin- vs. 54 % of insulin-treated women would choose insulin therapy) and 59 % of metformin-treated women said that taking the tablet(s) was the easiest part of their management plan.

A case–control study (100 vs. 100) comparing women with GDM treated with metformin versus insulin therapy [57] found that metformin was associated with less pre-eclampsia (2 vs. 9 %), less pre-term delivery (0 vs. 10 %), a lower birthweight centile, less jaundice (8 vs. 30 %), fewer special care baby unit (SCBU) admissions (6 vs. 19%) and similar caesarean section rates. Metformin was stopped in 14 % due to adverse effects (mainly gastrointestinal). There was less weight gain to 37 weeks gestation with metformin (0.94 vs. 2.72 kg). Obviously, there could be confounding with the differential selection of who was to be treated with either insulin or metformin therapy.

In spite of these equivalent or, indeed, better results, and their inclusion in some national guidelines [58], there remain mixed feelings about the safety of using metformin in pregnancy [56]. A major concern is that there is transplacental passage of metformin [59–61], so a genuine potential exists for risk to the offspring from the use of metformin during pregnancy. One study suggested that metformin might be more concentrated on the fetal side [59]. Such effects could be discovered many years after birth, and many clinicians remain cautious with its use. One Danish study did suggest a greater risk of pre-eclampsia and stillbirth with metformin therapy [62], but this could have been explained by the greater pre-pregnancy BMI (31.2 vs. 22.8–24.8 kg/m^2) and maternal age (32 vs. 28–29 years), and greater proportion with pre-existing type 2 diabetes in the metformin-treated group. Conversely, New Zealand women with metformin-treated type 2 diabetes in pregnancy had similar birthweight, proportion large for gestational age, prematurity (<37 weeks), neonatal unit admission, respiratory support, intravenous dextrose and perinatal loss compared with controls despite having a greater BMI, more chronic hypertension and worse glucose control at baseline [63].

Follow-up in humans with GDM treated with metformin has been limited. In polycystic ovary syndrome (PCOS), pre-conception and antenatal use of metformin has been common and an 18-month follow-up study showed no difference (when compared with controls) in motor–social development, growth or length [64]. The offspring from the MiG study are being followed up [65] and at 2 years the offspring from mothers treated with metformin (vs. those from insulin-treated mothers) had larger subscapular and biceps skinfolds and larger mid–upper arm circumference but no difference in total fat mass or percentage body fat. The implications of these finds are unclear, but follow-up of this cohort remains very important.

A second issue is that how metformin acts on the fetus remains unclear. Metformin acts by reducing hyperglycaemia through suppression of hepatic glucose output (hepatic gluconeogenesis), thereby increasing hepatic insulin sensitivity and enhancing peripheral glucose uptake [66]. As metformin reduces insulin resistance, it could potentially help protect β cell function in the offspring and reduce intergenerational transmission of obesity and type 2 diabetes.

The pharmacokinetics of metformin are altered in pregnancy through enhanced renal elimination, varying food absorption and different gastrointestinal transit times. This may mean that up to 20 % more metformin is required during pregnancy [67]: the MiG study used up to 2.5 g/day. It is not known whether the immediate-release/sustained-

Table 3 Major randomised controlled trials of the management of gestational diabetes mellitus using metformin and glibenclamide

	MiG: metformin [15]	Langer et al. [16]: glibenclamide
N	Metformin: 363	Glibenclamide: 201
	Insulin: 370	Insulin: 203
BMI in early enrolment (kg/m^2)	32.2 ± 58.2 vs. 31.9 ± 7.6	Obese 70 vs. 65
Previous GDM (%)	25.9 vs. 21.9	12 vs. 11
Ethnicity (Europid/Asian/Hispanic/Polynesian) (%)	48.2/24.0/0/20.1 vs. 45.4/24.9/0/22.4	12/0/83/0
Primigravida (%)	31.7 vs. 31.9	28 vs. 29
Gestational age at entry (weeks)	30/40 vs. 30/40	24/40 vs. 25/40
Fasting/2-h glucose on OGTT (100 g Langer et al.) (mmol/L)	5.7 vs. 5.7/9.7 vs. 9.4	5.4 vs. 5.4/9.7 vs. 9.7
Intervention	Clinic visits every 1–2 weeks, diet treatment, 7-point glucose monitoring. Standard protocols (labour, delivery)	Weekly clinic visits, diet treatment, 7-point blood glucose monitoring. Standard protocols (labour, delivery)
	500 mg od or bid increased over 1–2 weeks to maximum 2,500 mg/day to achieve targets	Insulin 0.7 U/kg given tid and increased weekly
	Local insulin guidelines	Glibenclamide 2.5 mg increased to 20 mg maximum and then insulin
Targets above which insulin is started	FBG <5.5 mmol/L	Mean 5.0–5.9 mmol/L
	2-h Post-prandial <7.0 mmol/L	FBG 3.4–5.0 mmol/L
	Some sites had lower levels	Pre-prandial 4.5–5.3 mmol/L
		Post-prandial <6.7 mmol/L
Insulin Rx in oral agent group (%)	46.3	4 %: Switched to insulin
Oral agent stopped (%)	7.4	No information
Maternal hypoglycaemia (%)	Not reported	2.0 vs. 20.2 (all asymptomatic)
Weight gain from enrollment to birth	0.4 vs. 2.0 kg	21 vs. 21 lbs
Gestational age at birth (weeks)	38.3 vs. 38.5	38.7 vs. 38.5

bid twice daily, *BMI* body mass index, *FBG* fasting blood glucose, *GDM* gestational diabetes mellitus, *od* once daily, *OGTT* oral glucose tolerance test, *Rx* treatment, *tid* three times daily

release preparations of metformin have different effects in GDM. It has been suggested that the sustained-release version is less useful than the immediate-release preparation in reducing post-prandial hyperglycaemia among women with PCOS and type 2 diabetes [68, 69].

Metformin use is only very rarely associated with lactic acidosis (0.03 cases/1,000 patients, the same as the background rate [70]) even in those with type 2 diabetes, and even then only in those with significant hepatic, renal or cardiac dysfunction. One possible mechanism for fetal harm from metformin could be in the production of fetal lactic acidosis, e.g. during labour. However, this would be more likely to manifest as stillbirth or fetal distress, rather than long-term complications, and this has not been found in studies to date.

One aspect of metformin therapy that may need consideration during pregnancy is vitamin B_{12} deficiency [71–73]. Intrauterine exposure to maternal B_{12} deficiency has been raised as a possible risk factor for future insulin resistance [74].

There may be a dose-dependent relationship in older people, with 1 g/day of metformin being associated with a 2.88-fold (95 % CI 2.15–3.87) risk of developing vitamin B_{12} deficiency. However, in GDM the exposure is likely to be short, and it is unclear whether any significant reduction occurs. In pregnant women with PCOS, homocysteine levels (which increase with worsening vitamin B_{12} deficiency) are not altered with metformin therapy [73]. It is therefore unlikely that metformin initiated during pregnancy leads to meaningful vitamin B_{12} deficiency, but measurement of vitamin B_{12} levels prior to commencing metformin may be prudent in those at risk (e.g. vegetarians).

Metformin is thought to be safe to use during breastfeeding [75], as very little is transferred into human milk (<0.4 % of the maternal concentration) [75, 76].

3.2 Sulphonylureas

Unlike metformin, sulphonylureas are insulin secretagogues rather than insulin sensitisers and include acetohexamide, chlorpropamide, tolbutamide, gliclazide,

Table 4 Outcomes of major randomised controlled trials of the management of gestational diabetes mellitus using insulin versus usual care and meta-analysis including other studies

	MiG: metformin vs. insulin [15] (%)	Langer et al. [16]: glibenclamide vs. insulin (%)
Composite[a]	32.0 vs. 32.2	NR
Death	0 (0) vs. 1 (0.3)	1 vs. 1
Shoulder dystocia	1.7 vs. 3.0	NR
Bone fracture/nerve palsy	4.4 vs. 4.6	NR
Admission to NICU	18.7 vs. 21.1	6 vs. 7
Induction of labour	54.0 vs. 56.2	NR
Caesarean delivery	36.1 vs. 38.4	23 vs. 24
Birth weight >4 kg	NR	7 vs. 4
Large for gestational age	19.3 vs. 18.6	12 vs. 13
Hypoglycaemia	15.2 vs. 18.6 (IVG 6.9 vs. 5.9)	9 vs. 6 (IVG 14 vs. 11)
Hyperbilirubinaemia	8.0 vs. 8.4 (phototherapy)	6 vs. 4
Respiratory distress	3.3 vs. 4.3	8 vs. 6
Antenatal pre-eclampsia	5.5 vs. 7.0	6 vs. 6

No statistically significant differences shown

NICU neonatal intensive care unit, *NR* not reported, *IVG* intravenous glucose

[a] Composite = neonatal hypoglycaemia, phototherapy, respiratory distress, birth trauma, 5-min APGAR <7, premature birth <37 weeks

glipizide, glimepiride and glibenclamide. Both chlorpropamide and tolbutamide cross the placenta [77] and use in pregnancy is associated with neonatal hypoglycaemia which can be severe [77]. Both are also excreted into breast milk [78]. It is not known if gliclazide or glimepiride cross the placenta or enter human breast milk. Both are Category C medications (adverse effect on the fetus in animals, no adequate studies in humans; benefits may warrant use in pregnancy despite potential risks). Glipizide does not cross the placenta in clinically significant amounts in in vitro studies [61] and in one study was not found in breast milk [79]. Gliclazide has not undergone trials in GDM, although three case reports showed normal pregnancy outcomes following its use in women with type 2 diabetes in early pregnancy [80, 81] and in *KCNJ11* mutations [82].

There are no glimepiride trials in pregnancy. In animal studies, pregnant and/or lactating rats and rabbits exposed to glimepiride experienced an increase in stillbirths, reduced growth, skeletal deformations and miscarriages. It did not cause any birth defects. Fetotoxicity is thought to be due to hypoglycaemia [83]. There is now one case study in which glimepiride was used up to 20 weeks gestation in a woman with type 2 diabetes and hypertension, also treated with antihypertensive agents (including an angiotensin receptor antagonist), with severe oligohydramnios [84].

Glibenclamide (glyburide) is currently in use during pregnancy and there are a growing number of studies describing its use [85]. Indeed, in a recent international diabetes in pregnancy meeting, 67.4 % of participants reported using glibenclamide in GDM, particularly obstetricians [88.6 vs. 45.9 % (other doctors)] and in the USA [76.1 vs. 35.5 (outside USA)] [86]. As with all sulphonylureas, the major adverse effects are weight gain and hypoglycaemia. It was initially thought that glibenclamide did not cross the placenta [87–89]. More recently, cord plasma concentrations have been shown to be 70–77 % of maternal levels [90, 91]. Plasma concentrations in pregnant women with GDM in the third trimester are approximately 50 % lower than in non-pregnant women [90]. In one study among eight women, glibenclamide was not detected in breast milk and no hypoglycaemia occurred in infants who were wholly breastfed when the glibenclamide was at steady state [79].

The major RCT comparing glibenclamide with insulin therapy in GDM ($n = 404$) [16] was powered to detect a 4.8 % absolute difference (80 % power) in adverse outcomes. Diagnosis of GDM required a 50 g glucose challenge test with a 1-h post-load glucose of ≥7.3 mmol/L, followed by a 100 g OGTT using the Carpenter/Coustan criteria. Women were randomised if the fasting glucose was ≥5.3 mmol/L or the 2-h post-prandial glucose was >6.7 mmol/L following dietary therapy and only women with an initial fasting glucose of 5.3–7.7 mmol/L were included. Pregnancies were between 11 and 33 weeks gestation on entry. Tables 3 and 4 describe the study, cohort and outcomes in more detail and compared with the MiG study. There has been no follow-up of the offspring. Generally, outcomes were similar, although hypoglycaemia was non-significantly higher. Weight gain was comparable with insulin use (unlike with metformin), with very little need for additional insulin. Since this time, there have been a number of other trials and cohort studies among women with GDM. A meta-analysis in 2008 comparing the use of glibenclamide with insulin therapy in GDM included 745 glibenclamide-exposed pregnancies and 637 insulin-treated pregnancies across nine studies. The use of glibenclamide was not associated with increased macrosomia, large for gestational age, intensive care admission or neonatal hypoglycaemia [92].

In spite of this experience, there remains doubt over whether glibenclamide should be used in GDM. A review of the evidence in 2007 described a higher failure rate than in the original trial (approximately 20 %), particularly if the fasting glucose is above 6.4 mmol/L [93]. The review also queried whether neonatal hypoglycaemia and hyperbilirubinaemia occurred more frequently with glibenclamide than with insulin. The most recent study [94] supports these concerns over the use of glibenclamide. Among 10,682 women with GDM needing pharmacological intervention, 2,073 (19.4 %) received glibenclamide and the remainder used insulin. Glibenclamide use was associated with 29 (3–64) % more babies with a birthweight >4,000 g and 46 (7–100) % more admissions to the intensive care nursery.

3.3 Insulin Versus Metformin Versus Glibenclamide

Table 5 compares the benefits and disbenefits for insulin, metformin and glibenclamide [95]. As metformin is the only treatment with no effect on weight, it is described within the context of for/against metformin. There have been two head-to-head comparisons between metformin and glibenclamide [96]. The key finding was that in one study babies from mothers treated with glibenclamide were 200 g heavier than those from metformin-treated mothers.

Combining oral therapies (metformin and glibenclamide) is not recommended, with one 10-year retrospective review suggesting greater problems with combined therapy (than metformin alone or switching to insulin) [97].

3.4 Meglitinides

There are two meglitinides, repaglinide and nateglinide, approved in adults, but neither are approved for use in pregnancy. They are insulin secretagogues working through a different binding site to sulphonylureas. Adverse effects are hypoglycaemia and weight gain. There are few reports of their use in pregnancy. One report covers use up to 7 weeks' gestation resulting in a normal pregnancy [98]. Meglitinides are not recommended in the management of GDM.

3.5 Thiazolidinediones

Thiazolidinediones (TZDs) were introduced in the late 1990s, initially troglitazone and then rosiglitazone and pioglitazone, and reduce peripheral insulin resistance [99]. They seem to play a role in placental maturation and endometrial attachment by the embryo [100, 101]. Inactivation of peroxisome proliferator-activated receptor (PPAR)-γ results in the death of the embryo in animals. PPAR-γ is expressed in human placental cytotrophoblast and syncytiotrophoblast, and is associated with trophoblast differentiation [102]. In humans, placental PPAR-γ activation is associated with an increase in placental hormone secretion, including human placental growth hormone and leptin [103].

Severe hepatic adverse effects (drug-induced hepatitis) led to the withdrawal of troglitazone, and an increased risk of cardiovascular disease led to the temporary withdrawal of rosiglitazone. Pioglitazone, the remaining TZD, is associated with weight gain (especially when compared with metformin [103]) but not hypoglycaemia. TZDs do cross the placenta [104] and pioglitazone is a Category C drug. Animal studies suggest that TZDs are not teratogenic [105]; however, their use has been associated with fetal death and growth retardation. It is not known if TZDs cross into human breast milk.

No studies using TZDs in GDM have been reported, although there are two case reports associated with normal pregnancies in women with type 2 diabetes [106]. TZDs have been used in PCOS, with improvements in ovulation, pregnancy rate and menstrual patterns [107, 108]. High rates of miscarriage have been shown in PCOS-associated infertility, but this would be expected in this group of patients. Use is not recommended in GDM. There has been growing interest in the use of TZDs in complicated pregnancies [including those with certain PPAR-γ polymorphisms (Pro12Ala and C 1431 T)] [109].

3.6 α-Glucosidase Inhibitors

Acarbose is the major α-glucosidase inhibitor in use outside of pregnancy. It is weight neutral and does not cause hypoglycaemia in monotherapy. Its use is frequently associated with gastrointestinal side effects. Very little acarbose (2 %) is absorbed as active drug, although 34 % of the metabolites are found in the systemic circulation. Liver enzyme abnormalities and hepatic failure have been reported with its use. High doses are not teratogenic in animals. There has been a suggestion that the greater carbohydrate breakdown by gut flora could increase butyrate production, which could increase prostaglandin E secretion and induce labour. One Mexican study of acarbose given three times a day before meals among six women was associated with improved fasting and postprandial glucose levels and uneventful pregnancies. Intestinal discomfort was present throughout pregnancy [110]. An RCT among 91 women with GDM needing medication reported, in an abstract, a low need for insulin (6 %) but very little other information was provided [111]. A case series among six women with GDM showed no adverse outcomes [110].

Acarbose is not recommended in the management of GDM.

Table 5 Reasons for and against choosing metformin therapy over glibenclamide and insulin therapy in the management of type 2 diabetes mellitus in pregnancy [94]

	Insulin	Metformin	Glibenclamide
For metformin			
Weight control	Potential for weight gain associated with adverse fetal outcomes	No weight gain	Potential for weight gain associated with adverse fetal outcomes
Hypoglycaemia (asymptomatic or symptomatic)	Significant risk	No risk unless due to other agents in use	Risk
Complexity of regimen	Complex: needs subcutaneous delivery equipment	Simple: up to 3 times a day oral treatment	Very simple: once a day oral treatment
Injection-site issues	Injection-site infection, bruising	Not an issue	Not an issue
Inconvenience of the regimen	Very inconvenient	Easy	Easy
Psychological insulin resistance, needle phobia	In some women	Not an issue	Not an issue
Cost	More expensive, including need for more blood glucose monitoring	Less expensive	Less expensive but potential need for more blood glucose monitoring than metformin
Against metformin			
Crosses the placenta	If bound to antibodies	Yes: might be concentrated in fetus	Yes: exact proportion uncertain
Known intrauterine effects	Generally considered, but some uncertainty over some analogues	Probably OK: some uncertainty	Probably OK: some uncertainty
Known long-term effect on offspring	Generally known, but some uncertainty over some analogues	Not known	Not known
Efficacy	High	May need insulin as well	May need insulin instead
Do not want to take tablets	Not an issue	In some women	In some women
Gastrointestinal adverse effects	Not an issue	Can be significant: sustained-release version available (no studies in pregnancy)	Not usually an issue

3.7 Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase-4 (*DPP4*) gene encodes for an enzyme expressed on the surface of many cells associated with immune regulation, signal transduction and apoptosis. Two of the peptides that are metabolised by DPP4 are the incretins GLP-1 (glucagon-like peptide 1) and GIP (gastric inhibitory polypeptide). The incretins are released from the small intestine in association with meals and stimulate insulin biosynthesis, inhibit glucagon secretion, slow gastric emptying, reduce appetite and stimulate regeneration of islet β cells. These incretins are inactivated very quickly by DPP4, and DPP4 inhibitors prolong the incretin effects.

There are a growing number of DPP4 inhibitors or 'gliptins', including sitagliptin (October 2006), saxagliptin, vildagliptin, linagliptin, alogliptin, anagliptin, gemigliptin and teneligliptin. Gliptins are weight neutral and do not cause hypoglycaemia on their own. They are associated with increased nasopharyngeal infections. None of the gliptins are approved for use in pregnancy and are pregnancy Category B antidiabetic agents. Passage through placenta and to milk in humans is unknown.

3.8 Glucagon-Like Peptide 1 Receptor Agonists

While gliptins inhibit the breakdown of the incretins GLP-1 and GIP by DPP4, the GLP-1 receptor agonists are largely resistant to DPP4 action, thereby prolonging the incretin effect. There are several GLP-1 receptor agonists currently available (all injectables): exenatide, liraglutide, lixisenatide, abiglutide and dulaglutide. Exenatide also has an extended-release version. Adverse effects are nausea, vomiting, diarrhoea and, rarely, pancreatitis. Hypoglycaemia is rare unless used with other anti-diabetes drugs and the GLP-1 receptor agonists are associated with weight loss. It is not known if these drugs cross the placenta or

enter human milk. An ex vivo human placental perfusion study detected low levels on the fetal side (fetal:maternal ratio of 0.017) [112]. There is a case report of exenatide use in early pregnancy up to 16 weeks with no evidence of harm [113]. These drugs are pregnancy Category C and not recommended for use in pregnancy.

3.9 Sodium–Glucose-Linked Transporter-2 Inhibitors

The sodium–glucose-linked transporter-2 (SGLT-2) inhibitors dapagliflozin, canagliflozin, empagliglozin, ipragliflozin and luseogliflozin inhibit reuptake of glucose from the proximal tubule from the nephron and therefore reduce hyperglycaemia through increased glycosuria. Other SGLT-2 inhibitors are also in the pipeline. The most important and frequent adverse effects are of urinary tract infections and vulvovaginal candidiasis. None are approved in pregnancy and there are no case reports of their use in pregnancy. The FDA have an extensive programme to monitor how dapagliflozin affects pregnancy (http://www.warondiabetes.org/2014/01/08/farxiga). There is particular interest in any fetal renal effects.

4 Conclusion

All women with GDM should be managed with patient education, diet, physical activity and glucose monitoring. Should these be insufficient to achieve glycaemic targets, then medication is required. Many women harbour concerns about oral therapy if there is a potential risk to their baby from placental transfer and so insulin therapy remains the default. Metformin has substantial advantages in view of it being an oral therapy and the lower weight gain associated with it. Obviously, women need to be advised that metformin crosses the placenta and might achieve greater concentrations in the fetus, and that while there has been no harm found, there remains uncertainty over the very long term. Many clinics use an information sheet to form the basis of these discussions. The weight gain with glibenclamide, and the mixed evidence over placental transfer and neonatal hypoglycaemia, are a concern and hence many sites use it sparingly, if at all. If insulin is needed, a quick-acting insulin analogue is used to cover meals and/or an isophane insulin is used to cover nocturnal hyperglycaemia, with morning isophane insulin if need be. Insulin detemir is also safe in pregnancy, and is useful in those who experience hypoglycaemia with isophane insulin. Women on large amounts of insulin have the options of adding metformin and/or using U500 insulin or continuous subcutaneous insulin infusion.

Funding and conflicts of interest No sources of funding were used to assist in the preparation of this review. David Simmons has received consulting fees from Novo Nordisk and travel support from Novo Nordisk, Sanofi and Eli Lilly. He has no other conflicts of interest that are directly relevant to the content of this review.

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