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Review

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Metformin in the treatment of gestational diabetes mellitus: is it safe and efficient?

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Abstract

Gestational diabetes mellitus (GDM) typically occurs when maternal glucose metabolism fails to compensate for the gradually increasing insulin resistance which mainly derives from the indigenous production of diabetogenic placental hormones during pregnancy. With its rising prevalence nowadays, GDM constitutes one of the most serious health problems in pregnant women that may result in both maternal and neonatal adverse outcomes if not treated properly. Although most women succeed in controlling their blood glucose levels with diet alone, some require pharmacological treatment in order to achieve adequate glycemic control. For these women, insulin is considered to be the best pharmacological choice for their treatment. However, a growing number of recent studies suggest oral antidiabetic agents to be equivalent if not superior to insulin in terms of safety and efficacy for the treatment of GDM. The objective of this review is to evaluate efficacy and safety of metformin in the treatment of GDM based on the most recent data of the literature.

Key words: Gestational diabetes mellitus, metformin, maternal outcome, neonatal outcome

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of carbohydrate intolerance occurring or recognized for the first time during pregnancy resulting in hyperglycemia of variable severity. This definition includes cases of pre-existing type 2 diabetes mellitus (T2DM) that have been diagnosed for the first time early in pregnancy and true gestational diabetes mellitus (GDM) with onset later in pregnancy that may persist after labor.[1]

Nowadays, the incidence of GDM is estimated at 7-8% of all pregnancies, affecting approximately 200.000 deliveries in the United States each year.[2] This condition is associated with both maternal and neonatal adverse outcomes. Maternal implications include preeclampsia, higher caesarean section rate and development of type 2 diabetes mellitus after

pregnancy. In neonates, GDM may lead to macrosomia, shoulder dystocia, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia and plethora. Finally, the infants of gestational diabetic mothers have an increased risk of developing both obesity and diabetes later in life.[3]

The management of GDM involves lifestyle modifications such as medical nutrition therapy, exercise, weight management and self-monitoring of maternal blood glucose. If the aforementioned measures do not achieve to control the maternal blood sugar levels, then pharmacological treatment is required.[4]

The gold standard for the pharmacological treatment of GDM is subcutaneous insulin, a US FDA category B drug. However, the insulin therapy has its drawbacks; the unfavorable route of administration in combination with the complicated dosing schedule reduces patient compliance with the treatment.[5] During the last decade, a growing number of studies suggest oral antidiabetic agents including metformin and glyburide, as a safe and efficient alternative to insulin in the treatment of GDM.[6, 9-18, 24, 25]

The aim of this review is to evaluate the efficacy and safety of metformin in the treatment of GDM based on the most recent data of the literature.

The role of metformin in gestational diabetes mellitus

Metformin is the most commonly used oral hypoglycemic drug in the treatment of non-insulin dependent diabetes mellitus. Being a part of biguanides, it exerts its hypoglycemic effect by suppressing hepatic gluconeogenesis and reducing glucose absorption from the gastrointestinal tract. Moreover, it has an insulin-sensitizing effect on multiple tissues resulting in a gradual increase in the peripheral uptake and utilization of glucose.[6]

Like insulin, metformin is listed as an US FDA category B drug for use during pregnancy, thereby indicating that animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women. However, most physicians avoid to use metformin in the treatment of GDM due to the fact that it passes through the placenta and may cause potential toxic effects to the fetus. Currently, there are no guidelines regarding the use of metformin during pregnancy. Thus, the dosage of the drug and the duration of the treatment is totally determined by clinicians based on their personal experience and judgement.[7]

As far as breastfeeding is concerned, data seem to conclude that metformin is safe for the neonates of breastfeeding mothers. The concentrations of the drug in the breast milk are generally low to undetectable, whilst the mean infant exposure to the drug is below the 10% level concerning breastfeeding. Nevertheless, every mother should previously take into consideration the risk/benefit ratio for her and her infant before proceeding to breastfeeding.[8]

Data comparing metformin to insulin for the treatment of GDM

During the last decade, the use of metformin as an alternative option for the treatment of gestational diabetes mellitus is gradually gaining popularity among the medical scientific society. An increasing number of studies conducted from both gynecologists and endocrinologists have shown that metformin is superior to insulin in the treatment of GDM resulting in better maternal and neonatal outcomes. However, because of the lack of adequate data, the use of metformin in GDM is currently restricted only to USA, although lately it is increasingly used in Europe and South Africa. The data from the literature seem to support those who suggest the use of this drug for the glycemic control of pregnant women.[9-18]

The concept of metformin use in pregnancy started with Rowan et al in 2008 with MIG (Metformin vs Insulin for the treatment of Gestational di-

abetes) trial where they reported that the neonates whose mother treated with metformin for GDM suffered less commonly from severe hypoglycemia (glucose level <1.6 mmol per liter) than those whose mother's GDM was treated with insulin. (P= 0.008). However, in this study, preterm birth (labor before the 37th gestational week) was more common in the metformin group (P=0.04) still without being associated with a higher rate of neonatal complications.[9] Later, in 2009, Rai et al published a prospective observational study in which 60 diabetic pregnant women divided in two groups, one treated with metformin whilst the other treated with insulin. The results of this study reported a better glycemic control in the metformin group the first week of the treatment and throughout gestation. (P=0.03-0.007). Additionally, the same study showed a significant increase in neonatal intensive care unit admission and higher cost of therapy in the insulin group.[10] As far as birth weight and neonatal morbidity is concerned, Ijäs et al. randomized controlled study in 2010 showed no statistically significant difference between the two groups in any outcome.[11]

In 2011, Rowan et al. (MIG-TOFU) reviewed those women who had participated in the MIG trial when their children were 2 years old. In an attempt to investigate the long term neonatal outcomes of the treatment, they discovered that the children whose mother belong to the metformin group had larger mid-upper arm circumferences (P =0.002), subscapular (P =0.02) and biceps skinfolds (P =0.04), but overall body fat was the same as in children whose mothers were treated with insulin alone. This implies that exposure to metformin in utero led to further fat storage in subcutaneous tissue rather than in ectopic or visceral sites in these children. Those findings create queries whether the use of metformin in GDM can lead to a more insulin sensitive pattern of growth in the offspring of diabetic mothers or not.[12] At the same time, Goh et al conducted a prospective study in New Zealand which suggested that the treatment of GDM with metformin offered diabetic mothers better glycemic control, improved neonatal outcomes (P=0.004) and resulted in fewer preterm deliveries. (P=0.005).[13] These findings are in line with Rai's et al findings[10] but do not agree with Rowan's et al findings (MIG 2008)[9] that suggested a higher rate of preterm birth in the metformin treated group.

One year later, in 2012, Gandhi's et al randomized controlled study hinted that the incidence of macrosomia (birth weight >4 kg) was significantly lower in the neonates of diabetic mothers treated with metformin[14], whilst Tertti's et al study in 2013 implied no significant differences in birth weight between the neonates of the insulin and metformin group[15]. Meanwhile, Spaulonci's et al in their study reported that diabetic pregnant women who treated with metformin presented less weight gain (P=0.002) and their infants had a lower frequency of neonatal hypoglycemia (P=0.032)[16], exactly as the neonates of the metformin group in MIG trial.[9] However, 26.08% of the patients in the metformin group required additional insulin so as to preserve their glycemic control.

More recently, a randomized controlled study conducted in 2015 in Pakistan by Ainuddin et al suggested that the use of metformin for the treatment of GDM results in less maternal weight gain (P<0.000) and reduces the incidence of maternal preeclampsia and neonatal macrosomia (P<0.01).[17] In this study, the percentage of patients in the metformin group needed supplemental insulin for glycemic control was 42.7%, significantly higher than those in Tertti's et al[15] and Spaulonci's et al[16] studies (20.9% and 26.08% respectively). Patients who required supplemental insulin were more obese with BMI > 30, had higher blood sugar levels on the OGTT and needed pharmacological treatment for GDM at an earlier gestational age compared to women who maintained euglycemia with metformin alone, implying that obesity and high blood sugar levels constitute predictive fac-

Table 1. Studies comparing metformin to insulin for the treatment of GDM

Author	Year	Study characteristics	Region	Number of patients	Main outcome	Results
Rowan et al. (MIG)[9]	2008	RCT	Australia/ New Zealand	733	Neonatal outcome	Severe hypoglycemia was less common in the metformin group (P = 0.008); preterm birth (< 37 gesttional week) was more common in the metformin group (P = 0.04); no significant differences between the groups in the neonatal anthropometric measures or umbilical cord/ serum insulin concentrations
Rai et al.[10]	2009	PS	India	60	Glycemic control, maternal complications, perinatal outcomet	Glycemic control was better in he metformin group after 1 week of therapy and also throughout gestation (P = 0.03-0.007). Significant increase in NICU admission and higher cost of therapy in the insulin group.
Ijäs et al.[11]	2010	RCT	Finland	97	LGA, neonatal morbidity	No significant differences between the two groups in any outcome
Rowan et al. (MIG-TOFU)[12]	2011	RCT	Australia/ New Zealand	318	Long-term neonatal outcome	At the age of 2, children whose mother were treated with metformin had larger mid-upper arm circumferences (P = 0.002), subscapular (P = 0.02) and biceps skinfolds (P =0.04).
Goh et al.[13]	2011	PS	New Zealand	1235	Maternal, neonatal outcome	Metformin group had better glycemic control, fewer preterm deliveries (P=0.005), and improved neonatal outcomes (P=0.004)
Gandhi et al.[14]	2012	RS	UK	592	Maternal, neonatal outcome	Women in the metformin group had a significantly lower incidence of macrosomia (birth weight > 4 kg) (8.2% vs. 14.3% (OR 0.56; 95% CI 0.33–0.99)), as well as birth weight >90th centile (14.8% vs. 23.7% (OR 0.56; 95% CI 0.37–0.85)). There were no significant differences in maternal outcome measures between the groups.

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Tertti et al.[15]	2013	RCT	Finland	217	Birth weight	No significant differences in mean birth weight between the metformin and insulin group. 20.9% of the patients in the metformin group needed additional insulin.
Spaulonci et al.[16]	2013	RCT	Brazil	92	Glycemic control	Lower mean glucose levels were observed in the metformin group (P = 0.020), owing to lower levels after dinner (P=0 .042). Mothers in the metformin group presented less weight gain (P=0.002) and a lower frequency of neonatal hypoglycemia (P=0.032). 26.08% of the women in the metformin group required supplemental insulin for glycemic control.
Ainuddin et al.[17]	2015	RCT	Pakistan	150	Maternal, neonatal outcome	Less maternal weight gain was found in the metformin treated groups (P < 0.000) and the incidence of preeclampsia in these groups was significantly lesser in comparison with the insulin treated group. Mean birth weight was significantly less in metformin treated groups (P < 0.01) so as it was neonatal morbidity. 42.7% of patients required supplemental insulin in the metformin group.
Ghomian et al.[18]	2018	RCT	Iran	286	Glycemic control, neonatal outcome	No significant differences in glycemic control or neonatal outcomes between the two groups.

GDM: Gestational diabetes mellitus, MIG: Metformin versus Insulin for the treatment of gestational diabetes, LGA: Large for gestational age, TOFU: The offspring follow–up, NICU: Neonatal intensive care unit, RCT: Randomized controlled trial, PS: Prospective study, RS: Retrospective study.

tors for the failure of the treatment. Finally, Ghomian et al in their study conducted in Iran in 2018 showed that there are no significant differences in glycemic control or neonatal outcomes between diabetic pregnant women treated with metformin and those treated with subcutaneous insulin.[18] In table 1 you can see a summary of studies comparing metformin to insulin for GDM management.

Data comparing metformin to glyburide for the treatment of GDM

Another oral antidiabetic agent that has recently

been studied for the treatment of GDM with good results is glyburide. Glyburide, also known as Glibenclamide, is a sulfonylurea that reduces blood glucose levels by binding to pancreatic β-receptors in order to increase insulin secretion in blood. Moreover, it prevents hyperglycemia by enhancing sensitivity of peripheral tissues to insulin.[19]

In the last few years, a small number of studies attempted to compare the efficacy of metformin with glyburide for the treatment of GDM.[20-23] In 2010, Silva

Table 2. Studies comparing metformin to glyburide for the treatment of GDM.

Author	Year	Study characteristics	Region	Number of patients	Main outcome	Results
Silva et al.[20]	2010	RCT	Brazil	72	Glycemic control, neonatal outcome	No significant differences in any outcome except maternal weight gain during pregnancy was less in the metformin group (P=0.02).
Moore et al.[21]	2010	RCT	US	149	Glycemic control	No significant differences in glycemic control between the two groups. However, the percentage of women required supplemental insulin was 2.1 times higher in the metformin group than in the glyburide group, suggesting a higher rate of failure with metformin compared to glyburide (P=0.01).
Silva et al.[22]	2012	RCT	Brazil	198	Neonatal outcome	No significant differences between the two groups except neonatal weight (P=0.01) and ponderal index (P=0.05) were lower in the metformin group. Glucose levels at 1st and 3rd hour after birth were lower in glyburide group (P=0.01 for both). Maternal weight gain was lower in the metformin group (P=0.04)
George et al.[23]	2015	RCT	India	159	Maternal,	Women in the metformin group had significantly higher fasting triglyceride levels than those in the glyburide group (P =0.05). The incidence of neonatal hypoglycemia was higher in the glyburide group (P=0.001) Secondary outcomes in both groups were similar.

GDM: Gestational diabetes mellitus, RCT: Randomized controlled trial

et al in Brazil published a randomized controlled trial of 72 patients in order to evaluate glycemic control and neonatal outcomes in the treatment of GDM with metformin or glyburide. The study showed that there were no significant differences in any outcome but for maternal weight gain, which was less in the metformin treated group (7.6 kg vs 10.3kg, P=0.02).[20] At the same time, Moore et al in United States reported in their study that the percentage of women with GDM that were treated with oral antidiabetic agents and required supplemental insulin for adequate glycemic control was 2.1 times higher in the metformin group (34.7% vs 16.2%), indicating a higher rate of success with glyburide in comparison with metformin as far as glycemic control is concerned (P= 0.01).[21]

Two years later, Silva et al, in their randomized controlled trial conducted in Brazil tried to evaluate the perinatal impact of metformin and glyburide in the treatment of GDM. The results of the trial hinted that metformin was associated with lower maternal weight gain (P = 0.04) and lower neonatal weight (P=0.01) and ponderal index (P=0.05), whilst glyburide resulted in lower glucose levels at 1st and 3rd hour after birth (P=0.01 for both).[22] The aforementioned result seems to be in line with George's et al randomized control trial (India, 2015), that showed a higher incidence of neonatal hypoglycemia in the glyburide group.[23] In table 2 we summarize the studies comparing metformin to glyburide.

Conclusion

The studies of the literature seem to advocate the use of metformin in diabetic pregnant women indicating that metformin is a safe and efficient alternative to insulin for the treatment of GDM.[9-18]

It is listed as an US FDA category B drug for use during pregnancy and is considered to be safe for breastfeeding mothers and their neonates.[7, 8]

Currently there are no guidelines regarding the use of metformin during pregnancy. Most studies suggest an initial dose of 500mg once or twice a day with food [9,14,15,17,18,20,22,23] and a gradual increase of the dosage every week until adequate glycemic control is achieved or a maximum dose of 2000-2550mg/day divided in two or three doses is reached.[9,10,14-17,20-23] If metformin alone do not achieve to meet glycemic targets then supplemental insulin should be added.[9,11,14-17] Moreover, metformin should be stopped and replaced by insulin treatment if maternal contraindications (such as renal or liver impairment) develop.[9,11,14,15]

Except for metformin, glyburide, a sulfonylurea with hypoglycemic effect can also be used as an oral anti-diabetic agent in the treatment of GDM.[6,20-25] However, metformin seems to be a more efficient drug associated with less maternal weight gain and a lower incidence of neonatal hypoglycemia compared to glyburide.[20,22,23]

As far as the treatment of GDM is concerned, metformin compared to insulin, is associated with less maternal weight gain[16,17], lower incidence of preeclampsia[17], better maternal glycemic control[10,13], lower frequency of neonatal hypoglycemia[9,16] and macrosomia[14,17]. The incidence of preterm birth in the metformin group compared to the insulin group seems to be higher in one study[9] and lower in another[13]. Those results seem to be attributed to differences regarding the indication for preterm birth (iatrogenic or spontaneous labor, preterm rapture membranes) in each study. One study showed that insulin therapy is more expensive and associated with a significant increase in neonatal intensive care unit admission.[10]

The MIG-TOFU trial showed that children exposed to metformin had larger measures of subcutaneous fat, but overall body fat was the same as in children whose mothers were treated with insulin alone. This suggest that in-utero exposure to metformin may lead to a more insulin sensitive pattern of growth in the offspring of diabetic mothers. However, these

findings require further examination and clinical research in order to prove their value.[12]

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