Metformin in Gestational Diabetes Mellitus

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As currently diagnosed, gestational diabetes mellitus (GDM) affects 5–9% of all pregnancies in the United States and is growing in prevalence.[1] It is defined as carbohydrate intolerance of variable severity that is first recognized during pregnancy. Although GDM has been recognized for decades, the potential significance of the condition, as well as criteria for screening and diagnosis, remain debatable.[1] Historically, GDM has been treated with lifestyle modifications and insulin, and oral antihyperglycemic agents have been used infrequently because of concerns regarding neonatal hypoglycemia and teratogenicity. Most recent studies suggest that oral hypoglycemic agents, specifically metformin, are safe to use during pregnancy (Table 1).[2–13]

Risk for developing GDM has been noted in women who are overweight before pregnancy, have had GDM in a previous pregnancy, or have a family history of diabetes. Poorer outcomes have been seen in both pregnant women and their developing fetuses, including induction of labor and caesarean delivery in women and death, shoulder dystocia, bone fracture, and nerve palsy in fetuses.[1] Moreover, recent studies show that diagnosis and management of this disorder will have beneficial effects on both maternal and neonatal outcomes.[14,15]

According to the American College of Obstetrics and Gynecology, comprehensive screening techniques have been implemented by > 90% of practices in the United States.[16] Reasons for the implementation of screening programs were developed from the evidence obtained in the Hyperglycemia and Adverse Pregnancy Outcomes study.[17] This large, prospective, observational study found possible adverse effects associated with even mild maternal hyperglycemia. It included a cohort of women with glucose levels at the upper end of the normal range, as well as women with mild GDM. The investigators found a linear correlation between higher levels of maternal glucose and adverse outcomes, including increased birth weight, first-time caesarean delivery, fetal C-peptide levels, and neonatal hypoglycemia.[17] Based on these findings, it has been suggested that screening for undiagnosed type 2 diabetes should occur at the first prenatal visit in women with risk factors for GDM.[1] Women not previously known to have diabetes and who have no risk factors should be screened for GDM at 24–28 weeks of gestation.[1] Because of the increasing prevalence of obesity and diabetes, detection of overt diabetes in early pregnancy has become a vital aspect of care standards.

On diagnosis of GDM, treatment consists of glucose monitoring, dietary modification, and lifestyle interventions.[1] If necessary, pharmacotherapy may be initiated to maintain euglycemia.

First-line treatment for GDM is medical nutritional therapy. Moreover, moderate exercise has been used in the management of GDM.[1] Pharmacotherapy is implemented when medical nutritional therapy and lifestyle measures fail to achieve adequate glucose control, and insulin is the mainstay of pharmacotherapy.[1] Insulin regimens

Table 1. Studies of Metformin Use in GDM

Authors (Year Published)	Study Design	Study Population	No. of Subjects Treated with Metformin (n_1), Insulin (n_2), Diet Only (n_3), or Metformin + Insulin (n_4)	Outcomes Measured	Comments
Moore et al. (2007)[6]	Prospective, randomized	Women with GDM not controlled with diet and exercise	$n_1 = 32$, $n_2 = 31$	Rate of caesarean delivery, neonatal birth weight, Apgar score at 5 minutes, respiratory distress syndrome, hyperbilirubinemia, hypoglycemia, and NICU admission	All outcomes were similar between the groups
Tertti et al. (2008)[11]	Retrospective, case-control	Women with GDM	$n_1 = 45$, $n_2 = 45$, $n_3 = 85$	Maternal total weight gain, hypertension, preeclampsia, and neonatal hypoglycemia	Maternal outcomes were similar in all groups; neonatal hypoglycemia was higher in the insulin-treated group
Rowan et al. (2008)[2]	Multicenter, randomized, open-label	Women with GDM	$n_1 = 249$, $n_2 = 370$	Maternal glycemic control, maternal hypertensive complications, postpartum glucose tolerance, and treatment preference; neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score, preterm birth, and neonatal and anthropometric measures	Metformin group had less hypoglycemia but more preterm births; other outcomes were similar in both groups
Rai et al. (2009)[9]	Prospective, observational	Women with GDM	$n_1 = 30$, $n_2 = 30$	Maternal glycemic control; perinatal deaths, birth weight, and NICU admission	Metformin group had better maternal and fetal outcomes
Balani et al. (2009)[8]	Prospective, nonrandomized	Women with GDM not controlled by diet for metformin group and retrospective cohort of women with GDM for insulin group	$n_1 = 100$, $n_2 = 100$	Maternal weight gain, gestational hypertension, preeclampsia, induction of labor, and rate of caesarean section; neonatal morbidity, premature birth, neonatal jaundice, NICU admission, and macrosomia	Maternal weight gain was higher in the insulin group; other maternal outcomes and macrosomia were similar in both groups; other neonatal outcomes were improved in the metformin group

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Table 1. Studies of Metformin Use in GDM, *continued from p. 290*

Authors (Year Published)	Study Design	Study Population	No. of Subjects Treated with Metformin (n_1), Insulin (n_2), Diet Only (n_3), or Metformin + Insulin (n_4)	Outcomes Measured	Comments
Ijas et al. (2010)[10]	Open-label, randomized, controlled, single-center	Women with GDM not controlled with diet	$n_1 = 50$, $n_2 = 50$	Rate of caesarean section; neonatal outcomes such as LGA status, birth weight, cord artery pH, and neonatal morbidity	No difference between the two groups for neonatal outcomes; rate of caesarean section was higher in the metformin group
Goh et al. (2011)[4]	Prospective, nonrandomized	Obese women with GDM	$n_1 = 249$, $n_2 = 399$, $n_3 = 371$, $n_4 = 216$	Rates of caesarean delivery, preterm birth, LGA, NICU admissions, and intravenous dextrose supplementation	Fewer adverse outcomes in metformin than in insulin groups
Rowan et al. (2011)[5]	Multicenter, randomized, open-label	Offspring of women with GDM who had been studied earlier	$n_1 = 154$, $n_2 = 164$	Central fat measures, total fat mass, percentage of body fat, upper arm circumference, and biceps and subcapsular skinfolds	Upper arm outcomes were higher in metformin group; other outcomes were similar in both groups
Hyer et al. (2012)[7]	Open-label, prospective	Women with GDM	$n_1 = 50$, $n_2 = 50$	Maternal weight gain, mode of delivery, and other complications; neonatal birth weight, hypoglycemia, jaundice, and birth injuries	All outcomes were similar in both groups
Spaulonci et al. (2013)[12]	Randomized, controlled, single-blind	Women with GDM not controlled by diet and exercise	$n_1 = 47$, $n_2 = 47$	Maternal weight gain; neonatal hypoglycemia	Metformin group had lower maternal weight gain and neonatal hypoglycemia
Mesdaghinia et al. (2013)[13]	Prospective, randomized	Women with GDM	$n_1 = 100$, $n_2 = 100$	Maternal A1C, weight gain, hypertension, preeclampsia, and caesarean delivery; neonatal birth weight, dystocia, 1- and 5-minute Apgar scores, neonatal sepsis, liver function tests, hypoglycemia, NICU admission, anomaly, and still birth	End of pregnancy A1C, maternal weight gain, preterm labor, neonatal jaundice, respiratory distress, and NICU admission rates were higher in the insulin group; all other outcomes were similar in both groups

can include intermediate- and short-acting insulin such as the regular recombinant insulin analogs aspart, glulisine, and lispro. Although regular insulin is the most time-tested form of short-acting insulin, evidence supports the use of rapid-acting insulin analogs in GDM.[18–20] Although not used as routinely as insulin, metformin has begun to have greater utilization in GDM. As clinicians increase such utilization, it is important to understand the available data on metformin as a treatment for GDM. The remainder of this article will focus on recent studies with metformin in GDM.

Metformin Overview

Metformin appears to be a viable option for use in GDM. This medication with a different mode of action from insulin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes. Its primary mechanism of action is in reducing hepatic glucose production. Secondarily, it decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Glyburide, an oral antihyperglycemic agent in the sulfonylurea class, has also been studied in the treatment of GDM.[21] Unlike glyburide, metformin does not cause either hypoglycemia or hyperinsulinemia.

Implementation of metformin should be in conjunction with diet and exercise for glycemic control.[22] The U.S. Food and Drug Administration categorizes this medication as a class B drug in pregnancy; however, it cautions that metformin can cross the placenta and should not be used during pregnancy unless clearly needed.[22] Despite these concerns, metformin appears to be an alternative option for the treatment of GDM.

Clinical Studies

Table 1 provides a summary of key clinical studies involving metformin use in GDM.

The study by Rowan et al.,[2] a landmark randomized, open-label trial of the use of metformin in GDM, suggests no increase in perinatal complications in women treated with metformin. This study differs from those of Moore et al.[6] and Hyer et al.[7] in its robust design and large sample size. The primary outcome, a composite of neonatal complications, shows no difference between women treated with metformin and those treated with insulin.[2] In the insulin group, severe neonatal hypoglycemia (i.e., blood glucose levels < 28.8 mg/dl; $P = 0.008$) was seen more often than in those exposed to metformin. However, preterm births ($P = 0.04$) were different in the metformin group. Secondary neonatal outcomes did not differ significantly between groups in terms of birth weight, birth length, circumference (head, abdominal, and chest), and skin thickness.[2] Approximately 46% of women using metformin at the maximum dose used in the trial (2,500 mg/day) required supplemental insulin. Overall, neonatal and maternal complications were similar in the two groups, indicating that metformin is an acceptable alternative treatment to insulin in GDM.

The Rowan et al. study[2] further assessed glycemic control effects on outcomes from data of the previous Metformin in Gestational Diabetes (MiG) trial.[2,3] Lower fasting capillary glucose values during the treatment for GDM in both treatment groups was strongly associated with a decrease in neonatal complications ($P < 0.001$). Additionally, lower postprandial glucose values were associated with fewer instances of maternal preeclampsia ($P = 0.016$) and large-for-gestational-age (LGA) infants ($P = 0.001$). Interestingly, obesity ($P = 0.08$) did not influence outcomes in this group, nor were the outcomes related to mode of treatment. The large sample size and robust study design of the MiG trial were strengths that lent validity to these findings. Overall, the findings support the importance of glycemic control in preventing neonatal and maternal complications.

The study by Goh et al.[4] reinforces the MiG trial finding that metformin in GDM is associated with fewer adverse complications and better glycemic control than insulin. This study differs from the earlier studies by Rowan et al.[2,3] in its design (a prospective analysis from a single center) and its treatment groups (diet alone, insulin, and metformin).[4] Women treated with insulin had higher rates of caesarean delivery (45.6% with insulin, 37% with metformin, and 34% with diet, $P = 0.02$) and, unlike in the Rowan et al. study,[2] more preterm births (19.2% with insulin, 12.5% with metformin, 12.1% with diet, $P = 0.005$). Rates of impaired glucose tolerance and diabetes were higher among the insulin-treated women ($P < 0.001$). Additionally, higher rates of preterm births ($P = 0.005$), LGA babies ($P = 0.02$), neonatal intensive care unit (NICU) admissions ($P = 0.04$), and requirements for neonatal intravenous dextrose ($P = 0.004$) were found in the insulin-treated group.[4] Women treated with metformin or diet alone did not differ in outcomes.[2,3]

A follow-up study[5] of the body composition of offspring from the MiG trial at 2 years of age assessed differences in adiposity. Baseline characteristics, including age, BMI at recruitment, ethnicity, smoking during pregnancy, chronic hypertension, fasting plasma glucose, 2-hour plasma glucose, and A1C did not differ between women treated with metformin and those treated with insulin. Additionally, there were no differences between groups in pregnancy outcomes, mean fasting capillary glucose, mean postprandial capillary glucose, gestational hypertension, and infant feeding 6–8 weeks postpartum. However, the offspring differed in upper-arm circumference ($P = 0.002$), subscapular skinfold thickness ($P = 0.02$), and biceps skinfold thickness ($P = 0.04$) consistent with increased subcutaneous fat. No differences were found in offsprings' total or percentage of body fat. Unfortunately, only 50% of the initial MiG participants were part of the follow-up study, and a smaller proportion of those of Polynesian ethnicity participated. The overall findings suggested that metformin may lead to more favorable fat distribution, but that further studies are needed to confirm this.

The preliminary study by Moore et al.[6] assessed maternal

outcomes and neonatal characteristics between patients with GDM randomly allocated to metformin or insulin. The mean fasting and 2-hour glucose assessments while on treatment did not differ between the metformin and insulin groups. Also, mode of delivery, incidence of shoulder dystocia, and postpartum hemorrhage did not differ between groups. The neonatal outcomes of birth weight, NICU admission, hypoglycemia, respiratory distress syndrome, and hyperbilirubinemia also did not differ between groups. Unlike the study by Rowan et al.,[2] no supplemental insulin was required for the metformin group, despite the tighter glycemic goals in this study.[6] Additionally, the majority ethnicity in this study was African American, whereas that of the Rowan et al. study was European.[2,6] Lack of sufficient power is a major weakness of the Moore study, but its prospective, randomized design was robust, and preliminary data suggest that metformin is an effective alternative to insulin in GDM.

The prospective, observational study of Hyer et al.[7] assessed the effects of metformin in women with GDM who failed to gain glycemic control through lifestyle changes in a routine practice setting and compared them to a matched control group treated with insulin. The metformin group had less maternal weight gain ($P = 0.04$) and a reduced incidence of neonatal jaundice, were less prone to macrosomia, and had fewer admissions to the special-care baby unit and a lower incidence of neonatal hypoglycemia. These findings reinforce the findings of Rowan et al.[2] and Moore et al.[6] A small sample size and a less-than-robust design were major weaknesses of this study.[7] Overall, however, its findings suggest positive maternal and neonatal outcomes with metformin use.

In a separate publication from the same authors, which expanded the original small study to a larger sample, Balani et al.[8] supported the suggestion that women with GDM may use metformin as an adjunct or an alternative to insulin when the likely benefits from improved glycemic control outweigh the potential for harm. Evidence from this study and the MiG trial suggest potential advantages of metformin over insulin in GDM in terms of less maternal weight gain and lower neonatal birth weight adjusted for gestational age. Both studies also reinforce that there are no increases in adverse perinatal effects for babies exposed to metformin. The findings in this study for maternal outcomes show less weight gain ($P < 0.01$), fewer preterm deliveries ($P < 0.01$), and perhaps less preeclampsia ($P = 0.06$) in patients taking metformin than in those taking insulin.[8,9] Reassuringly, there was no increase in hypertensive complications in the study by Rai et al., or the MiG studies.[2,8,9] Neonatal outcomes showed that birth weight ($P < 0.01$), jaundice rates ($P < 0.01$), and special-care baby unit admissions ($P < 0.01$) were significantly higher in insulin groups. The main strength of this study was the larger sample size compared to previous work by the same authors and some other published studies.[7,8] Overall, neonatal morbidity was improved in the metformin group, and the study supported the use of metformin in GDM.

A small, randomized study by Ijas et al.[10] showed that mean birth weight of newborns did not differ significantly between metformin and insulin groups. The incidence of neonatal hypoglycemia ($P = 0.439$) and hyperbilirubinemia ($P = 0.38$) and the need for treatment in the NICU ($P = 0.37$) showed no difference between the metformin and insulin groups. This study had limited power to detect a difference in variables such as brachial plexus injuries, perinatal mortality, or congenital anomalies because of its small study population. These researchers concluded that metformin might be a safe and effective alternative to insulin in mild GDM cases, especially those involving lean or moderately overweight women in late gestation, whereas insulin might be required in cases involving obese women, high fasting blood glucose levels, and the early need for pharmacological treatment. Like the MiG trial, this study demonstrates that mean birth weight of the newborns did not differ significantly between metformin and insulin groups. However, the sample size was small in this study, and similar studies with larger sample sizes will strengthen the results.

The small, prospective observational study by Rai et al.[9] assessed metformin as an alternative to insulin in pregnant women with diabetes. Unlike in the studies mentioned above, both women with GDM and those with type 2 diabetes were included in this study. Glycemic control and the number of women attaining glycemic goals ($P = 0.024$) were better in the metformin group, with results usually attained within 1 week. Also, dose adjustments were required less often with metformin than with insulin. Maternal weight gain in the metformin group was less than in the insulin group ($P = 0.02$). There was also one case of gastritis in the metformin group that improved after reducing the metformin dose. Two cases of symptomatic hypoglycemia were seen in the insulin group. Neonatal outcomes did not differ between the two groups except that NICU stays > 24 hours were 27.1% more frequent in the insulin group ($P = 0.02$). This has serious implications for neonates, increasing the chances of comorbidities and infections such as methicillin-resistant Staphylococcus aureus. These findings support metformin as an affordable and safe alternative to insulin in the treatment of GDM and type 2 diabetes.

A small, retrospective study of Tertti et al.[11] comparing merformin to insulin in the management of women with GDM showed no difference in maternal outcomes between the two groups, although the degree of initial maternal hyperglycemia was higher in the insulin group. This may account for the increase in neonatal hypoglycemia seen in this arm and the associated increased need for admission to the NICU. Overall neonatal outcomes results did not show significant differences between the groups. The metformin group had favorable outcomes compared to the insulin group; thus, this study also supports the use of metformin in GDM.

A small, randomized, controlled trial by Spaulonci et al.[12] comparing the glycemic control of women with GDM randomized to either metformin or insulin showed better control in the metformin group. Maternal and neonatal outcomes were also better in the metformin group than in the insulin group, with less weight gain and no differences in other maternal outcomes such as preeclampsia, prematurity, and caesarean section. The frequency of neonatal hypoglycemia was lower in the metformin group ($P = 0.03$), but there were no differences in neonatal outcomes such as gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, and birth weight. However, the sample size was small, and similar studies with larger sample sizes may strengthen the results.

Another randomized, controlled trial by Mesdaghinia et al.[13] comparing neonatal outcomes between women randomized to either metformin or insulin was flawed because of the post-randomization exclusion of women who failed to maintain glycemia with metformin. Thus, although no significant differences were observed between the metformin and insulin groups related to birth weight, LGA status, macrosomia, Apgar scores, shoulder dystocia, neonatal hypoglycemia, or sepsis, the fact that neonatal respiratory distress ($P = 0.038$), neonatal jaundice, and hyperbilirubinemia ($P = 0.02$) were seen more commonly in the insulin group may reflect the poor study design. Similarly, a higher NICU admission rate in the insulin group ($P = 0.002$) may have resulted from the poor design. Although A1C at the time of delivery was lower in those taking metformin, this again may reflect a less severely affected group. The metformin-treated subjects and their neonates did not have any adverse effects. Umbilical blood was tested for aspartate aminotransferase, alanine transaminase, and alkaline phosphatase levels in both groups for analyses of liver function, and no significant differences were seen.

Summary and Conclusion

GDM is growing in prevalence and, if left untreated, is associated with poor maternal and fetal outcomes. For this reason, prenatal testing of pregnant women at high risk for GDM or type 2 diabetes is recommended at the first prenatal visit. Women who are not at high risk should be tested for GDM at 24–48 weeks' gestation. In women with GDM, initial treatment consists of glucose monitoring, medical nutrition therapy, and lifestyle interventions, including moderate exercise. When these treatment options fail, insulin therapy is the next step and remains the mainstay of pharmacotherapy.

However, the use of insulin often requires multiple daily injections and results in increased risks for hypoglycemia and excess weight gain. Although insulin remains a popular, reliable treatment option, the use of metformin as an alternative is gaining popularity. Metformin improves glucose tolerance and insulin sensitivity without risky side effects such as hypoglycemia and hyperinsulinemia.

Several studies have documented similar outcomes in subjects taking metformin compared to those taking insulin.[2,6,10,12] Those in insulin treatment groups have been found to have increases in neonatal hypoglycemia,[2,11,13] higher NICU admissions rates,[4,8,9,13] higher birth weights,[8,9] and more maternal weight gain.[8,12,13] In the MiG follow-up trial,[11] fat distribution and additional measures of fat were found to be similar between subjects treated with insulin and those taking metformin.

Although insulin remains the mainstay of therapy for GDM, the use of metformin is a safe alternative supported by clinical research showing no change or even improved outcomes with the use of metformin compared to insulin. Metformin therapy should be considered a viable alternative to insulin in the treatment of GDM.

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