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Gestational Diabetes Mellitus Management with Oral Hypoglycemic Agents

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Abstract

Oral hypoglycemic agents such as glyburide (second generation sulfonylurea) and metformin (biguanide) are attractive alternatives to insulin due to lower cost, ease of administration, and better patient adherence. The majority of evidence from retrospective and prospective studies suggests comparable efficacy and safety of oral hypoglycemic agents such as glyburide and metformin as compared to insulin when used in the treatment of women with gestational diabetes mellitus (GDM). Glyburide and metformin have altered pharmacokinetics during pregnancy and both agents cross the placenta. In this article, we review the efficacy, safety and dosage of oral hypoglycemic agents for the treatment of gestational diabetes mellitus. Additional research is needed to evaluate optimal dosage for glyburide and metformin during pregnancy. Comparative studies evaluating the effects of glyburide and metformin on long-term maternal and fetal outcomes are also needed.

Gestational diabetes mellitus (GDM) complicates 2-10 % o.[1] This condition is characterized by increased insulin resistance and the inability of beta cells to compensate for the increasing degree of insulin resistance. GDM is usually diagnosed late in the 2nd trimester (24-28 weeks' gestation). Uncontrolled GDM can contribute to serious adverse pregnancy outcomes for the mother, fetus and neonate. GDM is associated with neonatal hypoglycemia, respiratory distress syndrome, and macrosomia[2]; as well as maternal hyperglycemia, urinary tract or other infections, hypertensive disorders of pregnancy, and polyhydramnios.[2] Some of these women will be diagnosed with type 2 diabetes postpartum,

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and 35-60% of women with GDM will develop type 2 diabetes mellitus over the next 10-20 years.[1]

Historically, insulin has been the drug of choice for the management of women with GDM. However, the use of oral hypoglycemic agents as alternatives to insulin for the treatment of GDM during pregnancy has been increasing. The comparable efficacy, lower cost, ease of administration and better patient adherence to oral hypoglycemic agents compared to insulin makes oral therapy attractive.[3,4,5,6] The most extensively studied oral hypoglycemic agents in pregnancy are glyburide (second generation sulfonylurea) and metformin (biguanide). Although efficacy of oral agents in the treatment of women with GDM is quite good, failure to achieve glycemic control still occurs in ∼20% of women, which creates an opportunity for further optimization of therapy.[3] In this review, we discuss the use of oral hypoglycemic agents focusing on glyburide and metformin for the treatment of women with GDM.

Oral Hypoglycemic Medications

Glyburide

Glyburide is a second-generation sulfonylurea that works primarily by enhancing insulin secretion. Glyburide is FDA approved for the treatment of patients with type 2 diabetes mellitus.[7] Early use of first-generation sulfonylureas such as chlorpropamide[8] and tolbutamide[9] resulted in concerns regarding teratogenicity, neonatal hypoglycemia, and fetal hyperinsulinemia, thus limiting their use during pregnancy. Maternal hyperglycemia as well as moderate to high placental transfer and the prolonged fetal/neonatal half-life of the first-generation sulfonylureas are the likely causes of these adverse events.[8,9] Both chlorpropamide and tolbutamide have been found to have similar umbilical cord and maternal blood concentrations.[10]

Several randomized controlled studies have compared glyburide to insulin for the treatment of GDM.[3,4,11,12] Glyburide was shown to be comparable to insulin in controlling maternal glucose and decreasing the incidence of macrosomia.[4] Langer et al. (n=404) reported that 82% of the subjects achieved glycemic control (self-monitored fasting glucose • 95 mg/dL) with glyburide (n=165) compared to 88% with insulin (n=179).[3] In a later study, the authors compared efficacy of glyburide and insulin for treatment of women with GDM, stratified for severity of disease (fasting plasma glucose • 95 mg/dL vs > 95 mg/dL).[4] The authors found that both glyburide and insulin were equally effective in treating GDM at both severity levels (n=404).[4] smaller randomized study that compared insulin to glyburide in Asian Indian women with GDM (n=23) reported no significant differences in glycemic control (mean 2-hour postprandial glucose concentrations) between insulin and glyburide treatment.[11]

The efficacy of glyburide was also reported in prospective and retrospective cohort studies. One prospective observational study (n=64) evaluated glyburide monotherapy (maximum glyburide dose 10 mg twice daily over 1 week) reported a 19% treatment failure rate (fasting blood glucose > 90 mg/dL and 1-hour postprandial glucose > 130 mg/dL) with glyburide.[13] The authors reported gestational age at the time of dietary failure and mean fasting blood glucose prior to initiating glyburide to be the two most significant indicators of glyburide

success. Factors favoring glycemic control with glyburide therapy were mean fasting blood glucose • 110 mg/dL and mean 1-hour postprandial blood sugar • 140 mg/dL before 30 weeks' gestation, or not requiring medication until after 30 weeks (sensitivity 98%, specificity 65%).[13] In a retrospective study of women with GDM (n=75), Conway et al. found that 84% of patients receiving glyburide 2.5-20 mg/day (n=63) achieved glycemic control (overall mean glucose • 105 mg/dL, fasting • 95 mg/dL and 2 hour postprandial • 115 mg/dL) while 16% (n=12) required conversion to insulin.[14] However, among those who could not maintain euglycemia with glyburide therapy, only two patients received the maximum dose before being converted to insulin. The majority of those who achieved glycemic control required low glyburide doses (2.5 – 5 mg/day). This finding may be a result of severity of disease and inadequate dosing or a maximum response effect for glyburide occurring at a relative low dose. Interestingly, 8 out of 12 women who converted to insulin were not in adequate glycemic control by the time of delivery. This study demonstrated that not all patients achieve glycemic control with a single medication, even with insulin. The majority of clinical studies have reported that glyburide is similar to insulin in efficacy and safety when used for the treatment of GDM.[3,4,11,15,16] Such findings along with lower cost and ease of administration have led to the increased utilization of glyburide during pregnancy.

The FDA approved dosage for glyburide in the treatment of non-pregnant patients with type 2 diabetes mellitus is 1.25-20 mg/day (in divided doses)[7]. Optimizing timing of administration of glyburide in pregnancy might allow for lower dosages to be used thereby minimizing risks to the fetus while at the same time maintaining efficacy. Glyburide peak concentrations usually occur 2-3 hours following dosing in pregnant women.[17] Due to induction of metabolism, peak glyburide concentrations are much lower in pregnant women compared to non-pregnant women. Without changing dosage, one way to attempt to optimize glyburide efficacy would be to optimize timing of administration through achieving a simultaneous peak in glyburide concentration with postprandial peak glucose concentration. Oral glyburide administered approximately 1 hour prior to a meal will maximize the effect of glyburide on the pancreas at the time it is most needed.[18]

Another approach to optimizing glyburide efficacy is to consider alternate glyburide dosage strategies. In previously published, randomized, gestational diabetes studies, glyburide dosage has ranged from 1.25 mg to 20 mg/day,[3,4] which is the same range used in the non-pregnant population. However, this dosage range has not been optimized for pregnant women.[17] Glyburide is metabolized by cytochrome P450 (CYP) enzymes (CYP2C9, CYP3A and CYP2C19) in the liver and intestines that are known to have altered activity during pregnancy. In our study[17] evaluating the pharmacokinetics of glyburide in women with GDM, pregnant women had much lower concentrations than in non-pregnant control subjects given the same dose. In order to achieve similar concentrations to those seen in the non-pregnant population, pregnant women would need to take more than twice the dose. Given these results, it is possible that pregnant patients with inadequate glucose control may benefit from higher and more frequent dosing of glyburide. Nevertheless, it is important to be mindful that the safety of doses exceeding 20 mg/day in pregnancy has not been evaluated.

Our understanding of glyburide transfer to the fetus has been evolving. *In vivo* studies in pregnant rats have reported high maternal-to-fetal transfer of glyburide resulting in similar fetal and maternal concentrations.[19] In contrast, *in vitro* placental perfusion studies, utilizing placentas from both non-diabetic and diabetic women, reported that glyburide does not cross from the maternal to the fetal circulation in significant amounts.[15,20] In 2005 Langer et al.[3] reported that glyburide concentrations in umbilical cord serum at the time of delivery were below the limit of assay detection (10 ng/mL). Based on the belief that glyburide does not cross the placenta to a significant degree, the use of glyburide in pregnancy increased. However in 2009, utilizing a more sensitive assay, we reported that umbilical cord plasma glyburide concentrations were approximately 70% of the maternal plasma concentrations.[17] It could be argued that even though glyburide does cross the placenta, this level of exposure with doses up to 20 mg/day has resulted in comparable fetal and neonatal outcomes as with insulin[3] and therefore does not raise particular safety concerns. However, any consideration of prescribing higher glyburide doses, particularly exceeding 20 mg/day, to compensate for apparent increases in oral clearance during pregnancy could present as-yet-unknown safety issues for the fetus and neonate.

Neonatal outcomes in the offspring of women with GDM receiving glyburide or insulin were compared in several studies (Table 1a).[3,12,18] Langer et al. found no significant differences in the percentage of infants who were large for gestational age (LGA) (birth weights • 90th percentile), fetal macrosomia (birth weight • 4000 g), neonatal hypoglycemia (two consecutive blood glucose results • 40 mg/dL), neonatal intensive care unit (NICU) admissions, and fetal anomalies.[3] Macrosomia was found in 7% and 4% of patients in the glyburide and insulin treatment groups, respectively (P=0.26). In addition, prospective and retrospective cohort studies have not found significant differences in NICU admissions,[13,21,22] birth weight[13,14,21,22] or gestational age at birth[13,22] when glyburide was compared to insulin. Bertini et al. reported, in a randomized study, a trend toward higher incidence of newborns with macrosomia or LGA in the glyburide group compared to insulin, but statistical significance was not achieved.[12] In a prospective observational study, Chmait et al. found no significant differences in the rate of macrosomia in the offspring of women receiving glyburide for GDM when comparing those that achieved glycemic control (18% of 56 women) to those who did not (15% of 13 women).[13] Two additional studies reported no significant differences in neonatal hyperbilirubinemia when comparing glyburide to insulin in the treatment of GDM.[13,23]

The frequency and definition of neonatal hypoglycemia varies between studies. Langer et al. reported no significant differences in neonatal hypoglycemia (defined as • 2 episodes of blood glucose < 40 mg/dL) between glyburide and insulin treated groups. In contrast, Bertini et al. reported significantly higher rates of neonatal hypoglycemia (blood glucose < 40 mg/dL with blood glucose monitoring performed at 1, 3, and 6 hours after birth) in the glyburide treated group (33%) compared to the insulin treated group (4%, P=0.006).[12] Future research is needed to define optimum glucose targets for women with GDM treated with glyburide that will improve neonatal outcomes.

In the randomized trials, maternal outcomes such as cesarean delivery rate[3,12] and pregnancy induced hypertension[12] were not significantly different between the glyburide

and insulin treated groups (Table 1b).[3,18,24] The most common adverse event with sulfonylureas and insulin is hypoglycemia. In one study, maternal hypoglycemia (blood glucose < 40 mg/dL) was observed in 2% of the subjects on glyburide and 20% on insulin.[4] Two other randomized studies, had no reports of hypoglycemia (definition not provided) in either treatment arm.[11,12]

Metformin

Metformin is a biguanide that decreases hepatic glucose production and intestinal absorption of glucose, while increasing peripheral uptake and utilization of glucose.[25] Through a variety of mechanisms, metformin decreases insulin resistance. Initially, the use of metformin in women was for the treatment of anovulation associated with polycystic ovary syndrome (PCOS).[26] The relative safety of metformin even in the 1st trimester of pregnancy increased its utilization for other indications such as GDM. Like glyburide, metformin alone or in combination with insulin has been reported to have similar safety and efficacy to insulin for the treatment of GDM.[5,24,27] Two advantages of metformin over sulfonylurea agents are that metformin does not cause maternal hypoglycemia or neonatal hyperinsulinemia.[28]

A recent randomized clinical trial of 160 women with GDM reported that metformin monotherapy resulted in comparable maternal glycemic control as with insulin.[29] With a median daily dose of 1500 mg (range 1000-2500 mg), mean fasting blood glucose < 95 mg/dL was achieved in 74% of subjects receiving metformin vs 79% with insulin. Mean postprandial glucose < 120 mg/dL was achieved in 81% of both metformin and insulin treated groups. In this study, 14% of women in the metformin monotherapy group eventually required supplementation with insulin. In another study (n=363), Rowan et al. reported that 46% of patients with GDM receiving metformin monotherapy experienced treatment failure requiring supplemental insulin.[6] However, both fasting blood glucose and mean 2-hour postprandial glucose concentrations were comparable in metformin and insulin treatment groups.[6] A recent randomized trial comparing metformin and insulin did not find glycemic control differences in the first week of therapy (27% vs 21%, respectively). Glycemic control was defined as fewer than 30% of capillary blood glucose concentrations above the reference values for fasting (< 95 mg/dL) and 2-hours postprandial (< 120 mg/dL).[24] In this study, 12 out of 46 subjects receiving metformin required supplemental insulin.

Ten to forty-six percent of women with GDM treated with metformin will require supplemental insulin to achieve glycemic control.[6,24,30,31] The study by Rowan et al. had the highest rate of subjects needing insulin supplementation (46%) compared to the study by Balani et al. (10%), Terrti et al. (18%), and Niromanesh et al. (14%). The variation in the percentage of patients requiring insulin in these studies is attributed to differences in definitions of glycemic control, population characteristics and the population responses. Niromanesh et al. reported that race and BMI may explain some of the differences. The subjects in the study by Rowan et al. were predominantly Caucasian with a mean BMI 32.2, whereas the subjects in the study by Niromanesh et al. were Iranian/Persian with a mean BMI 28.1.

Metformin doses ranging from 500 to 2500 mg/day (in divided doses) have been used to treat women with GDM. Metformin is almost entirely eliminated unchanged in the urine with renal clearance exceeding glomerular filtration rate, consistent with active tubular secretion.[32] Pregnancy is known to increase renal filtration and active drug transport in the kidney.[33] Evaluating the effects of pregnancy on metformin pharmacokinetics is somewhat challenging due to issues related to study design and metformin's unique pharmacokinetic properties. The dose-dependent pharmacokinetics of metformin can mask pregnancy-induced changes. For example, the higher the administered dose of metformin, the lower the bioavailability due to saturable intestinal absorption.[32,34] Therefore, to evaluate the effects of pregnancy on metformin pharmacokinetics, it is necessary to control for the metformin dose, which has not consistently been done in pregnancy studies. Some studies have reported non-significant differences in the pharmacokinetics of metformin when comparing late pregnancy to postpartum[35] or late-pregnancy to non-pregnant controls.[36] In the study by Hughes et al. $AUC_{0\text{-}4h}$ was 20% lower (non-significant change) in late pregnancy compared to postpartum women with type 2 DM (n=7).[35] This study had a small sample size, limited sampling and did not fully report PK parameters. Charles et al. did not find significant changes in systemic clearance or terminal half-life in late-pregnancy (n=12) vs. previously published non-pregnant controls.[36]

In our study (n=35) evaluating pharmacokinetics of metformin during pregnancy, renal clearances in mid- and late-pregnancy were 49 and 29% higher ($P<0.01$), respectively, compared to postpartum.[33] Creatinine clearance correspondingly increased by 29 and 21% and net renal secretion clearance was increased by 45 and 38% in mid- and late-pregnancy compared to postpartum. The correlation between metformin renal clearance and creatinine clearance was strong (r=0.8), suggesting that creatinine clearance can be used as a gross estimate to determine metformin pharmacokinetics. Comparison of the same dosage regimen (500 mg twice daily) revealed increased apparent oral clearance and apparent volume of distribution as well as lower maximum concentration and AUC during pregnancy. In light of this finding, patients with inadequate glycemic control might require higher doses of metformin during pregnancy. However, the impact of doses exceeding 2500 mg/day during pregnancy on maternal, fetal and neonatal safety has not been determined. Of particular interest is the potential impact of higher metformin doses on the risk of metformin-induced lactic acidosis. Current research has not found maternal lactic acidosis in pregnant women,[23] however doses higher than 2500 mg/day have not been studied. Future research studies for optimal metformin dosing in pregnancy and evaluation of fetal and maternal safety are needed.

Given metformin's chemical properties, active transport is necessary for it to cross membranes including the placenta. Maternal-to-fetal transfer of metformin across *ex vivo* placentas was reported to be 10-16%.[20,37] However, metformin readily crossed the placenta via active transport in vivo. [20,33,37,38] Vanky et al. reported that umbilical cord serum concentrations were similar or even exceeded maternal concentrations at the time of delivery.[38] Our study has also found significant placental transfer.[33] Of note, in a single cotyledon human placenta study, metformin did not increase placental glucose transport rates or uptake.[5] Despite the high placental transfer of metformin, Rowan et al. (n=363) did

not find significant increases in neonatal adverse outcomes (such as hypoglycemia or respiratory distress) as compared with insulin (Table 2a).[6] The study by Niromanesh et al. reported that NICU admission, hyperbilirubinemia, neonatal hypoglycemia, and birth defects were not significantly different between metformin and insulin in the treatment of GDM.[29] In addition, no significant differences were seen in the rates of macrosomia which occurred in 4% of the offspring in the metformin exposed and 10% of the insulin exposed groups. The percent of infants that were large for gestational age (LGA) was significantly higher in the insulin group (35% of 80 women) than the metformin group (18% of 80 women). In this study, cases of small ventricular septal defect (VSD), atrial septal defect, talipes equinovarus, and unilateral cleft lip were reported in the metformin group. The insulin group reported single cases of ventricular septal defect (VSD), talipes equinovarus, and a moderate bilateral hydronephrosis. Since subjects were enrolled in the study to treat GDM with therapy initiating between 20 and 34 weeks gestation (post-organogenesis), the congenital anomalies are possibly due to poorly controlled diabetes during the early gestation rather than from the metformin.[39] In a recent randomized study of 92 subjects with GDM, macrosomia was not found in the metformin treatment arm (n=46), but there were 3 cases in the insulin treatment group (n=46).[24] A higher frequency of neonatal hypoglycemia was observed with insulin (22%) than with metformin (13%) (P=0.03).

The most common maternal side effects of metformin are gastrointestinal in nature (9%), such as nausea, vomiting and diarrhea.[6] Metformin-induced gastrointestinal side effects decrease with time and can be lessened by dose reduction and taking the metformin with food. Most maternal adverse events were not significantly different between metformin and insulin treatment groups (Table 2b). [6,25,29] Niromanesh et al. reported pregnancy induced hypertension in 5% and 14% as well as cesarean delivery in 43% and 46% of pregnant women with GDM receiving metformin or insulin, respectively. The study by Rowan et al. also did not find differences between metformin and insulin treatment groups for pregnancy-induced hypertension (4% vs 6%, respectively) or cesarean delivery (36% vs 38%, respectively). The high rate of cesarean delivery appeared to be influenced by the geographic location and the patient's pregnancy histories.

Data regarding metformin and risk of preterm delivery is conflicting. Rowan et al. reported higher incidence of preterm birth in women with GDM receiving metformin as compared to insulin (P=0.04).[6] In contrast, Balani et al. found preterm birth to be more common in the women with GDM receiving insulin than in those receiving metformin. [30] Of note, Niromanesh et al. reported a non-significant, but 2-fold higher rate of preterm birth in women with GDM treated with metformin than in those treated with insulin.[29]

Glyburide vs Metformin

Two studies have compared glycemic control with glyburide monotherapy vs. metformin monotherapy for the treatment of GDM.[27,40] In one study (n=149), 35% of women receiving metformin monotherapy failed therapy compared to 16% on glyburide monotherapy (P=0.01).[27] Treatment failure was defined as “two or more glucose values in the same meal exceeding target glucose values by 10 mg/dL or greater for 2 consecutive weeks…”.[27] In contrast, in a recent randomized clinical trial comparing glyburide to metformin for the

treatment of women with GDM (n=200),[40] no differences were found with regard to glycemic control or therapeutic failure. Glycemic control was achieved in 71% of patients with GDM treated with glyburide compared to 79% in the metformin group. No significant differences were found in fasting or mean postprandial glucose concentrations during late pregnancy. Therapeutic failure was not defined in this study.

Neonatal adverse events such as LGA, macrosomia, neonatal hypoglycemia, NICU admissions, and perinatal death were not significantly different between glyburide and metformin treatment groups (Table 1a).[27,40] In the study by Moore et al. the rate of macrosomia (5% vs 1%), neonatal hypoglycemia (0% vs 1%), and NICU admission (1% vs 5%) did not differ between glyburide (n=74) and metformin (n=75) treatment groups, respectively.[27] In a study comparing glyburide (n=96) to metformin (n=104), investigators did not find significant differences in incidence of LGA infants (20% vs 9%), neonatal glucose < 40 mg/dL (14% vs 11%), NICU admissions (7% vs 9%), or perinatal death (1 patient from each group).[40] Maternal outcomes such as preeclampsia[27] and preterm delivery[40] were not significantly different between glyburide and metformin treatment groups (Table 1b). Interestingly, Moore et al. found significantly higher incidences of non-elective cesarean deliveries in the metformin group compared to glyburide group (11 vs 2).[29] However the reason for this remains unclear. The number of non-elective cesarean delivery in women taking metformin or glyburide has not been reported previously. In the study by Silva et al. the rate of cesarean delivery (not specified elective or non-elective) was high in both treatment groups (glyburide 68% vs metformin 66%), however there was no difference between the two groups.[40]

Other Oral Hypoglycemics

Acarbose decreases glucose absorption by inhibiting enzymes (pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolases) that break down complex starches to oligosaccharides as well as oligosaccharides, trisaccharides, and disaccharides to glucose. This in turn slows the increase in postprandial glucose concentrations. When used to treat GDM, a randomized prospective study (n=70) found no significant differences in fasting or postprandial glucose concentrations with acarbose compared to glyburide and insulin.[12] The study also reported no difference in average newborn weight when compared to glyburide and insulin. In this study, the rate of LGA was 11% with acarbose, 4% with glyburide, and 25% with insulin. Macrosomia only occurred in four newborns (16%) who received glyburide treatment. Failure to achieve glycemic control was more frequent with acarbose (42%) than glyburide (21%). The incidence of neonatal hypoglycemia occurred in 1 subject on acarbose, 1 with insulin, and 8 with glyburide treatment. Although failure to achieve glycemic control with acarbose was higher than with glyburide in this small study, the lower incidence of hypoglycemia and macrosomia makes acarbose an interesting agent to consider in future GDM treatment investigations.

Conclusions

The findings from randomized trials have provided evidence that glyburide and metformin have comparable efficacy and safety to insulin for the treatment of women with GDM. The

research thus far provides support for prescribing oral hypoglycemic agents as alternatives to insulin for the initial approach to pharmacotherapy for GDM. However, glyburide and metformin dosage regimens have yet to be optimized. Timing of administration may affect the efficacy and tolerability of these agents. Whereas glyburide should be taken 1 hour before a meal to improve efficacy, metformin should be taken simultaneously with food to minimize its gastrointestinal side effects. Clinical studies to evaluate safety with higher dosages to account for pregnancy-induced changes in pharmacokinetics, maternal and fetal complications, and long-term glyburide versus metformin comparative studies evaluating maternal, fetal and neonatal outcomes are needed. As pointed out in this review, not all patients will achieve successful glycemic control with monotherapy, even with insulin. Some patients may need oral treatment regimens to be supplemented with insulin. Differences in population characteristics, patient adherence, dosing regimens, initiation and length of therapy, and dietary intake all influence the success of GDM treatment.

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Table 1a

Neonatal Outcomes in randomized controlled trials – Glyburide

Author Ref	Drug	LGA	Macrosomia	Hypoglycemia	NICU admission	Perinatal mortality
Langer et al.[3]	Glyburide (n=201)	12	7	9	6	0.5
	Insulin (n=203)	13	4	6	7	0.5
Bertini et al.[12]	Glyburide (n=24)	25	16	33**	ND	0
	Insulin (n=27)	4	0	4**	ND	0
	Acarbose (n=19)	11	0	5**	ND	0
Moore et al.[27]	Glyburide (n=74)	ND	5	0	1	ND
	Metformin (n=75)	ND	1	1	5	ND
Silva et al.[40]	Glyburide (n=96)	20	ND	14	7	1
	Metformin (n=104)	9	ND	11	9	1

Data is presented as %.

LGA: Large for gestational age; NICU: neonatal intensive care unit; ND: Not determined;

Large for gestational age was defined as birth weight > 90th percentile.

Hypoglycemia was defined as blood sugar < 40 mg/dL unless noted.

** Significance was tested by Microsoft Excel ANOVA, with 95% significance rate.

Table 1b

Maternal Outcomes in Randomized Controlled Trials - Glyburide

Author Ref	Drug	Preeclampsia	PIH	Cesarean Delivery	Preterm Delivery
Langer et al.[3]	Glyburide (n=201)	6	ND	23	ND
	Insulin (n=203)	6	ND	24	ND
Bertini et al.[12]	Glyburide (n=24)	ND	ND	50	0
	Insulin (n=27)	ND	ND	44	0
	Acarbose (n=19)	ND	ND	52	0
Moore et al.[27]*a*	Glyburide (n=74)	4	ND	3**	ND
	Metformin (n=75)	3	ND	15	ND
Silva et al.[40]	Glyburide (n=96)	ND	ND	68	4
	Metformin (n=104)	ND	ND	66	5

Data is presented as %.

PIH: Pregnancy-Induced Hypertension; ND: Not Determined; Preterm delivery defined as birth < 37 weeks;

** P < 0.05 compared with metformin

a Percentage of non-elective cesarean delivery.

Table 2a

Neonatal Outcomes in randomized controlled trials – Metformin

Author Ref	Drug	LGA	Macrosomia	Hypoglycemia	NICU admission	Perinatal mortality
Rowan et al.[6]	Metformin (n=363)	19	ND	3*	19	0
	Insulin (n=370)	19	ND	8*	21	0.3
Spaulonci et al.[24]	Metformin (n= 46)	ND	0	13**	ND	ND
	Insulin (n= 46)	ND	7	22	ND	ND
Niromanesh et al.[29]	Metformin (n= 80)	18**	4	4	6	0
	Insulin (n= 80)	35	10	3	3	0
Moore et al.[27]	Glyburide (n=74)	ND	5	0	1	ND
	Metformin (n=75)	ND	1	1	5	ND
Silva et al.[40]	Glyburide (n=96)	20	ND	14	7	1
	Metformin (n=104)	9	ND	11	9	1

Data is presented as %.

LGA: Large for gestational age; NICU: neonatal intensive care unit; ND: Not Determined;

Large for gestational age was defined as birth weight > 90th percentile.

Hypoglycemia was defined as blood sugar <40 mg/dL unless noted.

* Blood glucose < 28.8 mg/dL

** P<0.05 compared with insulin.

Table 2b

Maternal Outcomes in Randomized Controlled Trials - Metformin

Author Ref	Drug	Preeclampsia	PIH	Cesarean Delivery	Preterm Delivery
Rowan et al.[6]	Metformin (n=363)	6	4*	36	12
	Insulin (n=370)	7	6*	38	8**
Spaulonci et al.[24]	Metformin (n=46)	22	ND	72	11
	Insulin (n= 46)	15	ND	65	11
Niromanesh et al.[29]	Metformin (n= 80)	6	5	43	11
	Insulin (n= 80)	9	14	46	5
Moore et al.[27]*a*	Glyburide (n=74)	4	ND	3**	ND
	Metformin (n=75)	3	ND	15	ND
Silva et al.[40]	Glyburide (n=96)	ND	ND	68	4
	Metformin (n=104)	ND	ND	66	5

Data is presented as %.

PIH: Pregnancy-Induced Hypertension; ND: Not Determined; Preterm delivery defined as birth < 37 weeks;

*PIH defined by Australasian Hypertension in Pregnancy Guidelines (Blood pressure • 140 mmHg systolic and/or 90 mmHg diastolic).[41]

**P < 0.05 compared with metformin.

*a*Percentage of non-elective cesarean delivery.