

**Comparative Study of Maternal and Fetal Outcomes in Patients with Gestational Diabetes Mellitus Treated with Insulin or Metformin**Tamal Das<sup>1</sup>, Alpana Chhetri<sup>2</sup>, Devwanti Neogi<sup>3</sup><sup>1</sup>Senior Resident, M.S.(Obstetrics & Gynaecology), Department of Obstetrics & Gynaecology, Tamralipto Government Medical College and Hospital, Tamluk, West Bengal 721636<sup>2</sup>Professor and Head of the Department, M.S. (Obstetrics & Gynaecology), Department of Obstetrics & Gynaecology, Tamralipto Government Medical College and Hospital, Tamluk, West Bengal 721636<sup>3</sup>Senior Resident, M.D. (Anaesthesiology), Department of Anaesthesiology, Barasat Government Medical College & Hospital, Kolkata, West Bengal 700124

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Conflict of interest: Nil

**Abstract:****Introduction:** Gestational Diabetes Mellitus (GDM) is increasing globally, linked to obesity, age, and lifestyle changes. While insulin is the standard treatment, metformin is emerging as a safe, effective alternative. It improves insulin sensitivity and may reduce maternal and fetal complications. This study compares outcomes in GDM pregnancies treated with insulin versus metformin.**Aims:** To compare maternal and fetal outcomes in patients with gestational diabetes mellitus treated with Insulin or Metformin.**Materials and Methods:** This prospective observational comparative study was conducted from December 2022 to November 2023 at the OPD, antenatal, and postnatal wards of the Department of Obstetrics and Gynaecology, Chittaranjan Seva Sadan College of Obstetrics, Gynaecology and Child Health. A total of 106 pregnant women diagnosed with Gestational Diabetes Mellitus were included. The study aimed to compare maternal and fetal outcomes between insulin and metformin treatments.**Results:** In this study, insulin and metformin provided similar glycemic control in women with GDM. However, metformin was associated with significantly fewer neonatal complications such as hypoglycaemia ( $p=0.002$ ), NICU admission ( $p=0.019$ ), and respiratory distress ( $p=0.022$ ). Neonatal birth weight was also lower in the metformin group ( $p=0.037$ ), indicating a potentially safer neonatal profile.**Conclusion:** Untreated Gestational Diabetes Mellitus (GDM) can lead to serious maternal and neonatal complications. While insulin is the standard treatment, metformin has emerged as an effective and cost-efficient alternative. Widely accepted in the West and increasingly used in India, metformin effectively controls blood sugar levels in GDM. It is also linked to fewer pregnancy complications and better neonatal outcomes. These findings support metformin as a safe and effective option for GDM management.**Keywords:** Insulin, Metformin, Maternal Outcomes, Fetal Outcomes, Comparative Study, Gestational Diabetes Mellitus (GDM).This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy [1]. It represents one of the most common metabolic disorders complicating pregnancy and is associated with short-term as well as long-term adverse maternal and fetal outcomes. The prevalence of GDM is rising globally, in parallel with increasing rates of obesity, sedentary lifestyles, and advancing maternal age [2]. In India and other Asian countries, the prevalence is particularly high, ranging between 10–20% in different populations, underscoring the urgent need for effective management strategies [3].

The pathophysiology of GDM involves a state of heightened insulin resistance that typically occurs in the second and third trimesters, due to the influence of placental hormones such as human placental lactogen, progesterone, and cortisol. In women with inadequate  $\beta$ -cell reserve or impaired insulin secretion, this physiological insulin resistance results in maternal hyperglycemia [4]. Maternal hyperglycemia, in turn, exposes the fetus to increased glucose load, leading to fetal hyperinsulinemia, excessive growth, and predisposition to metabolic complications at birth and later in life [5]. Uncontrolled or poorly controlled GDM has been linked to maternal complications including preeclampsia,

polyhydramnios, operative delivery, and long-term risk of developing type 2 diabetes mellitus (T2DM). For the fetus and neonate, risks include macrosomia, shoulder dystocia, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress [6]. Moreover, children born to mothers with GDM are at increased risk of obesity, impaired glucose tolerance, and metabolic syndrome in adulthood, suggesting an intergenerational transmission of diabetes risk [7]. Therefore, timely detection and appropriate management of GDM are critical for optimizing outcomes.

Dietary modification, physical activity, and lifestyle interventions form the cornerstone of initial therapy for GDM. However, when euglycemia is not achieved with these measures, pharmacological therapy becomes necessary. Traditionally, insulin has been considered the gold standard for treatment, as it does not cross the placenta and provides effective control of maternal glycemia [8]. Despite its proven efficacy, insulin therapy has limitations including the need for multiple daily injections, risk of hypoglycemia, increased maternal weight gain, and high cost, which may reduce compliance among pregnant women.

In recent years, oral hypoglycemic agents, particularly metformin, have emerged as potential alternatives to insulin in GDM management. Metformin acts by reducing hepatic glucose production and improving peripheral insulin sensitivity, and importantly, it is associated with less maternal weight gain and lower risk of hypoglycemia [9]. Unlike insulin, metformin crosses the placenta, raising concerns about possible effects on the fetus. However, growing evidence from randomized controlled trials and meta-analyses suggests that metformin is safe and effective, with comparable maternal and neonatal outcomes to insulin. Some studies even suggest that metformin use is associated with reduced rates of neonatal hypoglycemia, macrosomia, and maternal weight gain [10]. Given the variations in maternal and fetal outcomes reported in different populations, and the ongoing debate over the optimal pharmacologic therapy for GDM, there is a need for comparative studies in diverse clinical settings. While insulin remains widely used, metformin offers a simpler, more acceptable, and potentially cost-effective option, especially in resource-limited settings where patient adherence is crucial. Evaluating the relative effectiveness and safety of insulin and metformin in the Indian con-

text is particularly important, as the prevalence of GDM is high and pregnancy outcomes may be influenced by unique demographic, genetic, and lifestyle factors.

To compare maternal and fetal outcomes in patients with gestational diabetes mellitus treated with Insulin or Metformin.

**Material and Methods**

**Type of Study:** Prospective observational comparative study.

**Place of study:** OPD, antenatal and postnatal ward of Department of Obstetrics and Gynaecology, Chittaranjan Seva Sadan College of Obstetrics Gynaecology and Child Health.

**Study Duration:** December 2022 to November 2023.

**Sample size:** 106 Gestational Diabetes Mellitus-patients.

**Inclusion Criteria:** All patients having gestational diabetes mellitus not controlled by exercise and medical nutrition therapy and treated with Insulin or Metformin

**Exclusion Criteria:** Patients with multifetal gestations, pre-gestational diabetes (type 1 or type 2 diabetes mellitus), GDM patients with chronic hypertension, hypothyroidism, severe pregnancy induced hypertension etc. and first trimester and second trimester pregnancy loss.

**Statistical Analysis:** For statistical analysis, data were first entered into a Microsoft Excel spreadsheet and subsequently analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Continuous numerical variables were summarized as mean ± standard deviation, while categorical variables were expressed as counts and percentages. The Z-test (Standard Normal Deviate) was employed to assess significant differences between proportions. For comparisons involving means, the student’s t-test was used, with the corresponding p-value obtained from the t-distribution table. A p-value ≤ 0.05 was considered statistically significant, indicating rejection of the null hypothesis in favor of the alternative hypothesis.

**Results**

**Table 1: Association between demographic parameters and Age, History of GDM, Parity, Mode of delivery in previous pregnancy, G- AGE, Birth Weight (Gm)**

Treatment		Insulin	Metformin	Total	P Value
Age	18-20	5(9.43)	2(3.77)	7(6.6)	0.23

	21-25	12(22.64)	19(35.85)	31(29.25)	
	26-30	22(41.51)	21(39.62)	43(40.57)	
	31-35	9(16.98)	10(18.87)	19(17.92)	
	36-40	5(9.43)	1(1.89)	6(5.66)	
	Total	53(100)	53(100)	106(100)	
History of GDM	GDM	7(13.21)	7(13.21)	14(13.21)	1
	No	46(86.79)	46(86.79)	92(86.79)	
	Total	53(100)	53(100)	106(100)	
Parity	Primi	36(67.92)	28(52.83)	64(60.38)	0.112
	Multi	17(32.08)	25(47.17)	42(39.62)	
	Total	53(100)	53(100)	106(100)	
Mode of delivery in previous pregnancy	LSCS	8(50)	6(25)	14(35)	0.104
	VD	8(50)	18(75)	26(65)	
	Total	16(100)	24(100)	40(100)	
G- AGE	32-33	1(1.89)	1(1.89)	2(1.89)	0.264
	33-34	0(0)	1(1.89)	1(0.94)	
	35-36	2(3.77)	0(0)	2(1.89)	
	36-37	7(13.21)	6(11.32)	13(12.26)	
	37-38	22(41.51)	14(26.42)	36(33.96)	
	38-39	19(35.85)	30(56.6)	49(46.23)	
	39-40	2(3.77)	1(1.89)	3(2.83)	
	Total	53(100)	53(100)	106(100)	
Birth Weight (Gm)	≤1.5 kg	0(0)	1(1.89)	1(0.94)	0.007
	1.5-2 kg	4(7.55)	1(1.89)	5(4.72)	
	2-2.5 kg	5(9.43)	5(9.43)	10(9.43)	
	2.5-3 kg	8(15.09)	14(26.42)	22(20.75)	
	3-3.5 kg	17(32.08)	27(50.94)	44(41.51)	
	3.5-4 kg	9(16.98)	5(9.43)	14(13.21)	
	4-4.5 kg	10(18.87)	0(0)	10(9.43)	
	Total	53(100)	53(100)	106(100)	

Table: 2 Distribution of mean Glycemic control parameter

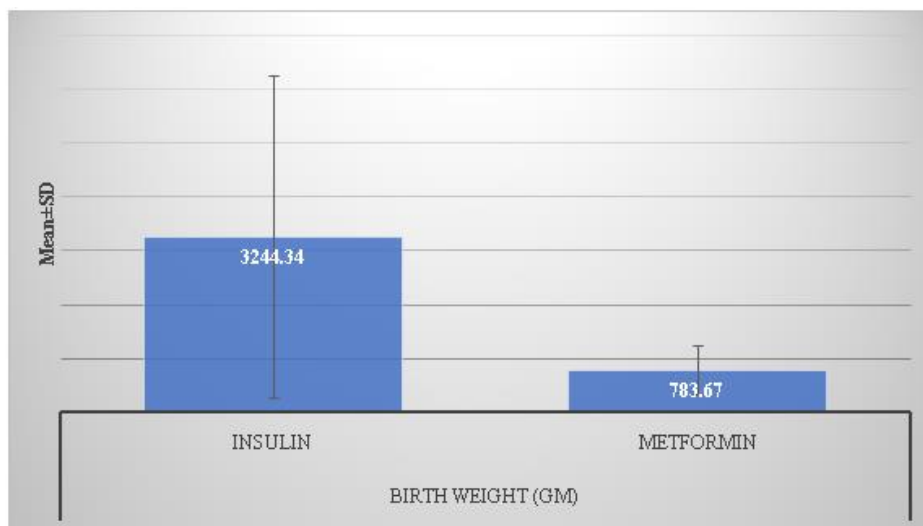
Glycemic control parameter	Group	N	Mean	Std. Deviation	P value	Significance
Pre-treatment FBS (mg/dl)	Insulin	53	101.28	11.84	0.054	Not significant
	Metformin	53	96.68	12.42		
Pre-treatment PPBS (mg/dl)	Insulin	53	160.06	15.86	0.058	Not significant
	Metformin	53	165.66	12.44		
Pre-treatment HbA1c	Insulin	53	5.6	0.64	>0.05	Not significant
	Metformin	53	5.5	0.56		
Post treatment FBS (mg/dl)	Insulin	53	89.77	9.62	0.052	Not significant
	Metformin	53	85.66	6.46		
Post treatment PPBS (mg/dl)	Insulin	53	125.38	8.2	0.082	Not significant
	Metformin	53	105.49	9.48		
PosttreatmentHbA1c	Insulin	53	5.2	0.6	0.051	Not significant
	Metformin	53	5.1	0.58		
Improvement of FBS (mg/dl)	Insulin	53	11.51	12.52	0.824	Not significant
	Metformin	53	11.02	9.99		
Improvement of PPBS (mg/dl)	Insulin	53	23.68	8.16	0.571	Not significant
	Metformin	53	30.17	16.28		
Improvement of HbA1c (%)	Insulin	53	0.42	0.63	0.58	Not significant
	Metformin	53	0.41	0.59		

Table 3: Distribution of mean Birth Weight (Gm)

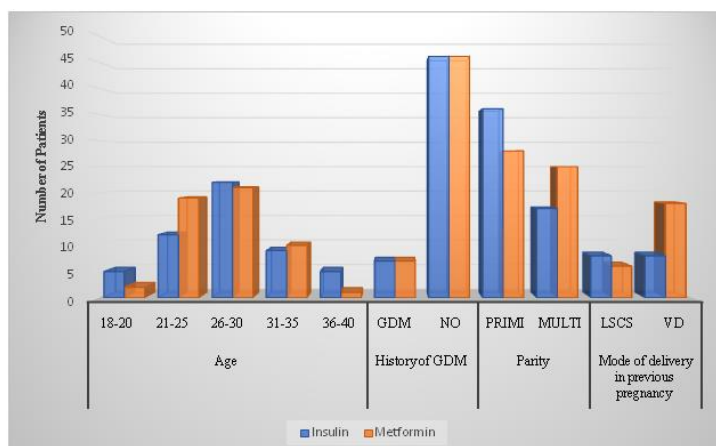
Treatment	Insulin		Metformin		P-value	Significance
	Mean	Std.Deviation	Mean	Std.Deviation		
Birth Weight (gm)	3244.34	783.67	2981.51	452.99	0.037	Significant

**Table 4: Association between demographic parameters and Pregnancy complications, post-partum complications in neonates, Biochemical parameters**

Treatment		Insulin		Metformin		P-value	Significance
		N	Per-cent	N	Per-cent		
Pregnancy complications	PPROM	3	5.66	1	1.89	0.308	Not Significant
	IUGR	5	9.43	3	5.66	0.462	Not Significant
	PIH	7	13.21	6	11.32	0.767	Not Significant
	Breech	1	1.89	0	0	0.315	Not Significant
	PROM	3	5.66	2	3.77	0.647	Not Significant
	Polyhydramnios	3	5.66	1	1.89	0.308	Not Significant
	Oligohydramnios	1	1.89	1	1.89	1	Not Significant
post-partum complications in neonates	Respiratory distress syndrome	11	20.75	3	5.66	0.022	Significant
	NICU admission	13	24.52	4	7.54	0.019	Significant
Biochemical parameters	Hypoglycaemia	11	20.75	1	1.89	0.002	Significant
	Hyperbilirubinemia	2	3.77	1	1.89	0.558	Not significant



**Figure 1: Distribution of mean Birth Weight (Gm)**



**Figure 2: Association between demographic parameters and Age, History of GDM, Parity, Mode of delivery in previous pregnancy, G- AGE, Birth Weight (Gm)**

In this study of 106 women with Gestational Diabetes Mellitus (GDM), there was no statistically significant difference in age distribution between the insulin and metformin groups ( $p = 0.23$ ), with the majority in both groups aged 26–30 years. A history of GDM was present in 13.21% of women in each group ( $p = 1.00$ ), and parity was not significantly different (primigravida: 67.92% in insulin vs. 52.83% in metformin;  $p = 0.112$ ). Among those with previous deliveries, 50% in the insulin group and 25% in the metformin group had a prior cesarean section, while 50% and 75%, respectively, had vaginal deliveries ( $p = 0.104$ ). Gestational age at delivery was comparable between groups, with the majority delivering between 38–39 weeks ( $p = 0.264$ ). A statistically significant difference was observed in neonatal birth weight ( $p = 0.007$ ); notably, 18.87% of neonates in the insulin group weighed between 4–4.5 kg compared to none in the metformin group, while a higher proportion of neonates in the metformin group had weights between 2.5–3.5 kg.

Comparison of glycemic control parameters between the insulin and metformin groups revealed no statistically significant differences. Pretreatment fasting blood sugar (FBS) levels were slightly higher in the insulin group (mean = 101.28 mg/dl) than in the metformin group (mean = 96.68 mg/dl), with  $p = 0.054$ . Similarly, pretreatment postprandial blood sugar (PPBS) levels were 160.06 mg/dl in the insulin group and 165.66 mg/dl in the metformin group ( $p = 0.058$ ). Pretreatment HbA1c was comparable between the groups (5.6 vs. 5.5;  $p > 0.05$ ). After treatment, the mean FBS decreased to 89.77 mg/dl in the insulin group and 85.66 mg/dl in the metformin group ( $p = 0.052$ ), while posttreatment PPBS levels were 125.38 mg/dl and 105.49 mg/dl, respectively ( $p = 0.082$ ). Posttreatment HbA1c values showed slight improvement in both groups (5.2 in insulin vs. 5.1 in metformin;  $p = 0.051$ ). Improvements in FBS (11.51 mg/dl vs. 11.02 mg/dl;  $p = 0.824$ ), PPBS (23.68 mg/dl vs. 30.17 mg/dl;  $p = 0.571$ ), and HbA1c (0.42% vs.

0.41%;  $p = 0.58$ ) were also statistically insignificant. Overall, both insulin and metformin achieved comparable glycemic control without significant differences.

The comparison of neonatal birth weights between the two treatment groups showed a statistically significant difference. The mean birth weight in the insulin group was  $3244.34 \pm 783.67$  grams, while in the metformin group it was  $2981.51 \pm 452.99$  grams, with a  $p$ -value of 0.037, indicating a significant difference. Neonates born to mothers treated with insulin had a higher average birth weight compared to those in the metformin group.

The comparison between insulin and metformin treatments in pregnant individuals with respect to maternal and neonatal outcomes revealed that most pregnancy complications—such as PPRM ( $p=0.308$ ), IUGR ( $p=0.462$ ), PIH ( $p=0.767$ ), breech presentation ( $p=0.315$ ), PROM ( $p=0.647$ ), polyhydramnios ( $p=0.308$ ), and oligohydramnios ( $p=1.000$ )—were not significantly different between the two groups. However, significant differences were observed in certain neonatal and biochemical parameters. Respiratory distress syndrome (RDS) was significantly higher in the insulin group compared to metformin (20.75% vs. 5.66%,  $p=0.022$ ), as was NICU admission (24.52% vs. 7.54%,  $p=0.019$ ). Hypoglycaemia was also significantly more frequent in neonates of insulin-treated mothers (20.75% vs. 1.89%,  $p=0.002$ ). Hyperbilirubinemia did not differ significantly between groups ( $p=0.558$ ). These findings suggest that metformin may be associated with fewer neonatal complications compared to insulin therapy.

## Discussion

In this study of 106 women with gestational diabetes mellitus (GDM), both insulin and metformin achieved comparable maternal glycemic control, with no statistically significant differences in fasting blood sugar (FBS), postprandial blood sugar (PPBS), or HbA1c levels before or after treatment.

The mean improvements in FBS (11.51 mg/dl vs. 11.02 mg/dl;  $p = 0.824$ ), PPBS (23.68 mg/dl vs. 30.17 mg/dl;  $p = 0.571$ ), and HbA1c (0.42% vs. 0.41%;  $p = 0.58$ ) were statistically insignificant, indicating that both treatment modalities were equally effective in achieving glycemic targets. These findings align with the results of Rowan et al. [11] and Ijas et al. [12], who reported similar efficacy of metformin and insulin in controlling maternal glucose levels, with metformin offering the added advantage of oral administration and better patient compliance.

Regarding maternal outcomes, most complications—including preterm premature rupture of membranes (PPROM), intrauterine growth restriction (IUGR), pregnancy-induced hypertension (PIH), breech presentation, polyhydramnios, oligohydramnios, and premature rupture of membranes (PROM)—were comparable between groups, reflecting findings from Tertti et al. [13] and El-Badawy et al. [14]. Both studies demonstrated that maternal outcomes are largely influenced by overall glycemic control rather than the choice of pharmacological agent. In contrast, neonatal outcomes exhibited significant differences. Neonates in the insulin group had a higher mean birth weight ( $3244.34 \pm 783.67$  g) compared to those in the metformin group ( $2981.51 \pm 452.99$  g,  $p = 0.037$ ), with a greater proportion of macrosomic infants (18.87% vs. 0%). Additionally, adverse neonatal events such as respiratory distress syndrome (RDS) (20.75% vs. 5.66%,  $p = 0.022$ ), NICU admission (24.52% vs. 7.54%,  $p = 0.019$ ), and hypoglycemia (20.75% vs. 1.89%,  $p = 0.002$ ) were significantly more frequent in the insulin group. Hyperbilirubinemia did not differ significantly between the groups ( $p = 0.558$ ). These results are consistent with the findings of Vanky et al. [15] and Zhang et al. [16], who reported that metformin therapy was associated with lower rates of neonatal hypoglycemia and reduced NICU admissions, likely due to more stable maternal glucose excursions and lower fetal insulin exposure. Other studies have also highlighted the differences in neonatal weight outcomes.

Tobias et al. [17] observed that insulin-treated mothers had a higher incidence of large-for-gestational-age infants, whereas metformin-treated mothers more often delivered infants with birth weights within the normal range. Similarly, a meta-analysis by Balsells et al. [18] confirmed that metformin use was linked to a modest reduction in birth weight and decreased risk of neonatal hypoglycemia, without compromising maternal glycemic control. These findings suggest that while both insulin and metformin are effective in controlling maternal glucose, metformin may confer an additional advantage in minimizing neonatal complications.

Furthermore, long-term follow-up studies indicate that children exposed to metformin in utero do not exhibit adverse metabolic effects compared to those exposed to insulin [19,20]. Collectively, these observations support the consideration of metformin as a first-line pharmacologic therapy for GDM in appropriate candidates, particularly when aiming to reduce neonatal morbidity while maintaining effective maternal glycemic control.

### Conclusion

Untreated Gestational Diabetes Mellitus (GDM) during pregnancy can lead to serious maternal complications and affect neonatal outcomes. While subcutaneous insulin administration is the gold standard for managing GDM, the introduction of metformin has provided an alternative treatment option. Metformin, as a cost-effective oral hypoglycemic agent, has been well accepted for GDM treatment in Western countries. In India, clinicians have started prescribing metformin for managing GDM pharmacologically. Metformin has been found to be effective as compared to insulin in controlling elevated blood sugar levels in women with GDM. Additionally, metformin has been associated with fewer complications throughout pregnancy and improved neonatal outcomes compared to insulin. These findings suggest that metformin can be considered an effective alternative to insulin in managing GDM, helping to maintain blood sugar within normal limits and reduce further complications in pregnancy.

### References

1. American Diabetes Association. Standards of Medical Care in Diabetes—2023. *Diabetes Care*. 2023;46(Suppl 1):S254-S263.
2. International Diabetes Federation. *IDF Diabetes Atlas, 10th edition*. Brussels, Belgium: IDF; 2021.
3. Seshiah V, Balaji V, Balaji MS, Paneerselvam A, Arthi T, Thamizharasi M, et al. Prevalence of gestational diabetes mellitus in South India (Tamil Nadu): a community-based study. *J Assoc Physicians India*. 2008;56:329–33.
4. Buchanan TA, Xiang AH. A clinical update on gestational diabetes mellitus. *Endocr Rev*. 2005;26(6): 697–733.
5. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358(19):1991–2002.
6. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol*. 2011;118(6):1379–93.
7. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia*. 2016;59(7):1396–9.

8. American College of Obstetricians and Gynecologists. Gestational diabetes mellitus: ACOG Practice Bulletin No. 190. *Obstet Gynecol*. 2018;131(2):e49–64.
9. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358(19):2003–15.
10. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One*. 2013;8(5):e64585.
11. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358(19):2003–15.
12. Ijas H, Vainio M, Ronnema T, et al. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin. *Diabetes Care*. 2015;38(2):222–7.
13. Terti K, Ekblad U, Koskela P, Hiilesmaa V. Comparison of metformin and insulin in the treatment of gestational diabetes. *Diabet Med*. 2008;25(4):427–31.
14. El-Badawy A, Al-Shehri H, Shalaby H. Maternal and neonatal outcomes in gestational diabetes mellitus treated with insulin versus metformin. *J ObstetGynaecol Res*. 2013;39(5):1000–6.
15. Vanky E, Frosli K, Stridsklev S, et al. Metformin versus insulin in gestational diabetes: effects on maternal and fetal outcomes. *Diabet Med*. 2010;27(5):498–505.
16. Zhang C, Li M, Yang P, et al. Efficacy and safety of metformin compared with insulin in gestational diabetes: a meta-analysis. *Diabetes Res ClinPract*. 2016;120:40–50.
17. Tobias DK, Hu FB, Chavarro JE, et al. Maternal glucose-lowering therapy and birth weight in gestational diabetes: a cohort study. *BJOG*. 2014;121(9):1157–64.
18. Balsells M, Garcia-Patterson A, Solà I, et al. Pharmacological interventions for gestational diabetes: systematic review and meta-analysis. *BMJ*. 2015;350:h102.
19. Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: long-term outcomes in children at 2 years. *Diabetes Care*. 2011;34(10):2277–82.
20. Glueck CJ, Goldenberg N, Wang P, et al. Follow-up of offspring exposed to metformin in gestational diabetes: metabolic and growth outcomes. *J Clin Endocrinol Metab*. 2013;98(9):E1457–63.