Al-Azhar International Medical Journal

Volume 4 | Issue 5 Article 7

2023

Section: Obstetrics and Gynecology

Pregnancy outcomes in pregnant women with diabetes mellitus treated with insulin versus insulin combined with metformin

Abdel Monem Mohammed Zakareya
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Ahmed Mohammed Saeed
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Mostafa Mohammed Rady
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt, mosthamed92@gmail.com

How to Cite This Article

Zakareya, Abdel Monem Mohammed; Saeed, Ahmed Mohammed; and Rady, Mostafa Mohammed (2023) "Pregnancy outcomes in pregnant women with diabetes mellitus treated with insulin versus insulin combined with metformin," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 5, Article 7.
DOI: https://doi.org/10.58675/2682-339X.1805

ORIGINAL ARTICLE

Pregnancy Outcomes in Pregnant Women with Diabetes Mellitus Treated with Insulin Versus Insulin Combined with Metformin

Abdel Monem Mohammed Zakareya, Ahmed Mohammed Saeed, Mostafa Mohammed Rady*

Department of Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Gestational diabetes is any degree of glucose intolerance that occurs or is 1st recognized throughout pregnancy. It is becoming more common around the world, accounting for up to ten percent of all pregnancies.**

Aim, and objectives: **To compare the effect of insulin plus metformin in controlling maternal blood glucose level and pregnancy outcomes compared to insulin in females with DM.**

Subjects and techniques: **This is randomized controlled research of 220 pregnant females with diabetes who attended twenty to forty weeks gestation at Al Hussein hospital from May 2020 to May 2022, which are given informed written consent before enrolment in the study.**

Result: **There were no statistically significant variations among two groups in terms of FPG level or 2 h PG at start of therapy or during the research period. No significant differences in FPG, 2 h PG, or HbA1C were shown among 2 groups during the therapy period till delivery.**

Conclusion: **Diabetes-pregnant females treated with insulin and with similar baseline risk factors for adverse pregnancy results have less weight gain and insulin dosage needed for glycemic control, as well as better neonatal results, such as macrosomia, neonatal hypoglycemia, and special care baby admission when compared to those cured with insulin.**

Keywords: Diabetes mellitus, Gestational diabetes, Pregnancy, Pregnant females

1. Introduction

Gestational diabetes was described as any degree of glucose intolerance that develops and is discovered throughout pregnancy.[1]

It is becoming more common around the world, accounting for up to ten percent of all pregnancies.

GDM is distinguished by insulin resistance and low glucose tolerance that worsens during pregnancy. GDM is linked to poor pregnancy results and can have long-term consequences for both mother and child.[2]

As result, it should be addressed early and appropriately.

GDM is a reason for diabetes throughout pregnancy, accounting for up to ninety percent of diabetes-related complex pregnancies.

Females with diabetes have a forty-sixty percent chance of developing diabetes within five-ten years of giving birth.[3]

More than ten researches have been conducted to evaluate Metformin's safety and efficacy.[4]

Metformin in Gestational Diabetes research, which included 751 pregnant females with GDM, was the largest. Later, some smaller research was conducted.

Metformin has received favorable outcomes across the board.

Accepted 4 December 2022.
Available online 18 August 2023

* Corresponding author at: Resident of Obstetrics and Gynecology at Ghamrah Military Hospital, 3753450, Egypt. Fax: 20225065579.
E-mail address: mosthamed92@gmail.com (M.M. Rady).

https://doi.org/10.58675/2682-339X.1805

Metformin does not differ from insulin in terms of maternal glycemic control, congenital abnormalities, macrosomia, and other maternal or neonatal adverse results.[5]

Furthermore, when compared to insulin regimens, metformin was shown to cause less maternal hypoglycemia.

Metformin is an insulin substitute that is beneficial for treating females with gestational diabetes mellitus.[6]

In females with gestational diabetes mellitus, studies found no significant variations in maternal or neonatal results when oral diabetes factors were used versus insulin.[7]

Metformin appears to be safe in 2nd and 3rd trimester of pregnancy, even though it crosses the placenta.[8]

The goal of the research is to compare impact of Insulin plus Metformin on controlling maternal blood glucose levels and pregnancy results in females with diabetes to the impact of Insulin alone.

2. Patients and methods

This is prospective randomized controlled research of 220 pregnant females with diabetes who attended twenty to forty weeks gestation at Al Hussein hospital from May 2021 to May 2022 and who are given informed written consent before enrolment in the study.

Two hundred twenty patients were randomized and divided into 2 groups: group I was treated with insulin and metformin, and the group II was treated with insulin only.

2.1. Sample size calculation

According to previous research measuring undesirable perinatal results, the sample size was estimated to be six percent and nineteen percent for groups I and II.[8]

So, based on previously mentioned measures, the estimated sample size in each arm was ninety-eight subjects at type I (α) error 0.05 and type II (β) error 0.2. The estimated sample size was then risen by twenty percent to account for dropouts.

In end, 120 people were recruited for each arm.

Finally, 110 subjects in each arm met inclusion and exclusion criteria and did not drop out.

Inclusion criteria: years old: eighteen to forty-five, gestational age: single foetus at twenty to forty weeks gestation, GDM uncontrolled by diet and exercise for beginning insulin treatment, and pre-gestational diabetes taking insulin.

Exclusion criteria: studied cases with metformin allergies, twin or greater order pregnancy, pregnancy with foetal structural abnormalities, chemical-induced diabetes like glucocorticoid use, after organ transplantation, studied cases with chronic medical disorders like hypertension and kidney or liver diseases.

Absence of lactic acidosis risk factor: 220 patients were randomized and divided into 2 groups: group I was treated with insulin and metformin, and group II was treated with insulin only by blocked randomization, block size and allocation ratio will be specified 110 and subjects are allocated randomly within each block with allocation ratio of (1:1).

All subjects had given written consent before enrolment and patients who did not give consent are excluded. Basic demographic data are recorded like years old, parity, and obstetric history, in addition to recording their weight, and height and calculating BMI. Subjects are followed by their pregnancy by measuring blood pressure, and dose of metformin or insulin required for optimal glycemic control for each studied case.

Obesity and diabetes clinic follow-up to achieve glycemic targets with both soluble and premixed insulin prescribed. There were no brand limitations. Subcutaneously in deltoid region, both premixed insulin and soluble insulin were administered.

Before discharge, all studied cases are educated about disease and how to self-administer correct doses of insulin by nurses and doctors. In group I starting dose of metformin which was same trade name is five hundred mg once a day and raised gradually over 2 weeks to three times a day. Maximum dose allowed per research protocol is 2000 mg per day.

For blood glucose monitoring pregnant females with diabetes were advised to examine their fasting, pre-meal, 2-h postmeal and bedtime blood glucose levels every day until achieving glycemic control during pregnancy.

All studied cases are instructed to return for follow-up appointments every two weeks.

For every test session, that is scheduled every two weeks till the due date, they are advised to come earlier if their plasma glucose levels are unusually great. Studied case recorded data was saved in studied case's record file.

Throughout research time, both groups' therapy monitoring was accomplished through SMBG using a glucometer. Throughout pregnancy, HbA1c levels were checked every three months.

To define level of risk for pregnancy, we measured HbA1c levels in all pregnant females with pre-existing diabetes at start of the research.

We measured HbA1c levels in all females with gestational diabetes at duration of diagnosis to

recognize those who can have pre-existing type 2 diabetes.

Blood glucose control throughout labour and birth: Patients were monitored for capillary plasma glucose every hour throughout labor and birth in females with diabetes, and confirm that it was preserved among 70 and 126 mg/dl. If general anaesthesia is used for birth of diabetic female, blood glucose must be monitored every 30 min from induction of general anaesthesia till baby is born and female is conscious.

Primary outcomes: whether the addition of metformin decreased insulin doses and improved maternal, fetal, and neonatal outcomes in pregnant women with diabetes.

Secondary outcomes: primary maternal results are weight gain from enrollment to delivery, pre-eclampsia, and mode of delivery for pregnancy-induced hypertension. Perinatal results contained perinatal loss, shoulder dystocia, prematurity (<thirty-seven weeks gestation), birth weight, birth weight centile for gestational age, neonatal jaundice, hypoglycemia (glucose< (46.8 mg/dl) within 2 h after birth), and respiratory distress, polyhydramnios, perinatal loss, and special care unit admission.

2.2. Statistical analysis

Data were entered into computer using 'Microsoft Office Excel Software' program for Windows (2010). Information was then transferred to Statistical Package for Social Science Software, version 23. Statistics will be analyzed. Data is presented quantitatively using range, mean, and standard deviation, and qualitatively using frequency and percentage. The Chi-square test was used to compare qualitative variables, while the independent sample *t*-test was used to compare quantitative variables. Statistical significance was described as *P* values less than 0.05.

3. Results

There was no statistically significant variation among studied cases in groups I and II in terms of years old, BMI, family history of diabetes, parity, and mode of delivery, glycemic state, and type of diabetes with pregnancy (Tables 1 and 2).

Prenatal daily insulin dosage was (67 ± 10.6 units) in group I and was (87 ± 11.296 units) in group II and the difference was greatly different $P =$ zero. Gestational hypertension is 14.5 percent in group I and was 19.1 percent in group II and variation was not significant $P = 0.367$. Pre-eclampsia is 7.27 percent in group I and was 9.09 percent in group II and the difference was not significant $P = 0.622$. Vaginal delivery is 41.8 percent in group I and was 47.3 percent in group II and the difference was not significant $P = 0.416$. FPG after therapy is 89.9 ± 2.2 mg/dl in group I and was 90.2 ± 2.8 mg/dl in group II and variation was not significant $P = 0.444$ (Table 3).

Table 1. Comparison between both groups regarding basic characteristics.

	Group		*P* value
	Group I ($n = 110$)	Group II ($n = 110$)	
Years old			
Range	25–34	23–34	
Mean ± SD	28.8 ± 2.3	29.1 ± 2.5	0.460
BMI			
Range	28–35	27–38	
Mean ± SD	31.1 ± 2.2	30.7 ± 2.6	0.328
Yes	41 (37.3)	42 (38.2)	
No	69 (62.7)	68 (61.8)	
Parity			
Range	Zero–three	Zero–four	0.205
Mean ± SD	1.4 ± 1	1.6 ± 1	
Previous CS			
Yes	46 (41.8)	47 (42.7)	0.891
No	64 (58.2)	63 (57.3)	
Range	5.8–8.3	5.6–8.2	
Mean ± SD	7.1 ± 0.8	7.3 ± 0.6	
DM type			
T1DM	19 (17.3)	25 (22.7)	0.312
T2DM	39 (35.5)	36 (32.7)	0.670
GDM	52 (47.3)	49 (44.5)	0.685

* Group I= Insulin + Metformin, Group II= Insulin only.
**P* value < 0.05 percent significant.

This table shows that neonatal jaundice requiring phototherapy is 13.6 percent in group I studied cases receiving insulin and metformin and was 33.6 percent in group II studied cases receiving insulin and variation is greatly significant $P = 0.000$. Neonatal hypoglycemia is 7.3 percent in group I and was 24.5 percent in group II and the difference was greatly significant $P = 0.000$. Neonatal respiratory distress is 13.6 percent in group I and was thirty percent in group II and the difference was significant $P = 0.003$ (Table 4).

This table shows that neonatal jaundice requiring phototherapy is 17.3% in group I studied cases receiving insulin and metformin and was 36.7% in group II studied cases receiving insulin and variation is significant $P = 0.027$. Neonatal hypoglycemia is 7.7% in group I and was 22.4% in group II and variation was significant $P = 0.037$. Neonatal respiratory distress is 15.4 percent in group I and was 32.7% in group II and the difference was significant $P = 0.042$. Birth weight from 10th to 90th birthweight centile is 65.3% in group I and was 44.8% in group II and variation was significant $P = 0.038$.

Table 2. Comparing both groups regarding maternal outcomes.

	Group		*P* value
	Group I (n = 110)	Group II (n = 110)	
Weight gain from enrolment to delivery (kg)			
Range	3.5–5	4.5–7	
Mean ± SD	4.397 ± 0.49	5.905 ± 0.721	**0.0000***
Prenatal daily insulin dosage (unit)			
Range	42–85	55–100	
Mean ± SD	67 ± 10.6	87 ± 11.296	**0.000***
Gestational hypertension			
Yes	16 (14.5)	21 (19.1)	0.367
No	94 (85.5)	89 (80.9)	
Preeclampsia			
Yes	8 (7.27)	10 (9.09)	0.622
No	102 (92.73)	100 (90.91)	
Mode of delivery			
Vaginal delivery	46 (41.8)	52 (47.3)	0.416
Elective CS	43 (39.1)	36 (32.7)	0.325
Emergency CS	21 (19.1)	22 (20)	0.865
Primary CS	18 (16.3)	11 (10)	0.162
Delivery			
Preterm delivery	22 (16.63)	27 (24.55)	0.417
Term delivery	88 (83.64)	83 (75.45)	0.417
FPG (mg/dl)			
Range	86–95	85–95	
Mean ± SD	89.9 ± 2.2	90.2 ± 2.8	0.444
Two Hr PP (mg/dl)			
Range	116–124	114–124	
Mean ± SD	119.9 ± 1.6	120.1 ± 2.2	0.529
HbA1C (percent)			
Range	5.5–7.1	5.6–7.3	
Mean ± SD	6.3 ± 0.4	6.3 ± 0.5	0.587
Perinatal metformin dose mg/dl			
1000	14 (12.7)		
1500	75 (68.2)		
2000	21 (19.1)		

Group I= Insulin + Metformin, Group II= Insulin only. * = *P* value < 0.05 percent significant.

4. Discussion

The research aims to compare the effect of Insulin plus Metformin in controlling maternal blood glucose levels and pregnancy results compared to Insulin in females with DM.

This is prospective randomized controlled research of 220 pregnant females with diabetes who attended 20–40 weeks gestation at Al Hussein hospital and are given informed written consent before enrolment in the study.

Patients were randomized and divided into 2 groups: Group I: 110 pregnant females treated with insulin and metformin. **Group** II:110 pregnant females treated with insulin only.

In the current thesis, our results in studying the Basal characteristics of included subjects found that there is no significant variation between 2 groups in terms of years old, BMI, family history of diabetes, parity, glycemic state, and type of diabetes with pregnancy. Furthermore, no significant variations in FPG level or 2 h PG were noticed among the 2 groups, neither at beginning of cure nor in study duration ($P > 0.05$).

Furthermore, no significant variation in glycemic control was observed among 2 groups, which is consistent with previous research results.

Zhu et al.,[9] but in our research, we reached the glycemic target with less insulin dosage in group I than group II and variation is greatly significant among 2 groups and subgroups.

These researchers concluded that metformin and insulin have similar impact on achieving glycemic control, however, in research, we used metformin as adjunct to the insulin resulting in glycemic control with less insulin dosage.

Although reporting on similar effect of 2 medications, around studies have mentioned essential of supplementary insulin in few studied cases when FPG might not be adequately controlled.[10] However, in research, we did not test metformin alone;

Table 3. Comparing both groups regarding perinatal results.

	Group		*P* value
	Group I (n = 110)	Group II (n = 110)	
Jaundice			
Yes	15 (13.6)	37 (33.6)	**0.000***
No	95 (86.4)	73 (66.4)	
Hypoglycemia			
Yes	8 (7.3)	27 (24.5)	
Polyhydramnios			
Yes	15 (13.6)	36 (32.7)	**0.000***
No	95 (86.4)	74 (67.3)	**0.001***
Birth weight > 90% birthweight centile			
Yes	18 (16.4)	32 (29.1)	**0.024***
No	92 (83.6)	78 (70.9)	
Respiratory distress			
Yes	15 (13.64)	33 (30)	**0.003***
No	95 (86.36)	77 (70)	
Special care baby unit admission			
Yes	27 (24.55)	39 (35.45)	**0.077**
No	83 (75.45)	71 (64.54)	
Birth weight from 10th to 90th birthweight centile	74 (67.2)	53 (48.1)	**0.004***
Birth weight < ten% birthweight centile			
Yes	18 (16.4)	25 (22.7)	0.234
No	92 (83.6)	85 (77.3)	
Shoulder dystocia			
Yes	3 (2.7)	5 (4.5)	0.721
No	107 (97.3)	105 (95.5)	
Perinatal loss			
Yes	3 (2.7)	4 (3.6)	0.701
No	107 (97.3)	106 (96.4)	

Group I= Insulin + Metformin, Group II= Insulin only.* = *P* value < 0.05 percent significant.

Table 4. Comparison between both groups regarding perinatal outcomes for GDM only.

	GDM		*P* value
	Group		
	Group I ($n = 52$)	Group II ($n = 49$)	
Jaundice			
Yes	9 (17.3)	18 (36.7)	**0.027***
No	43 (82.7)	31 (63.3)	
Hypoglycemia			
Yes	4 (7.7)	11 (22.4)	**0.037***
No	48 (92.3)	38 (77.6)	
Respiratory distress			
Yes	8 (15.4)	16 (32.7)	**0.042***
No	44 (84.6)	33 (67.3)	
Yes	13 (25)	19 (38.78)	
No	39 (75)	30 (61.22)	
Shoulder dystocia			
Yes	2 (3.8)	0 (0)	0.495
No	50 (96.2)	49 (100)	
Perinatal loss			
Yes	0 (0)	2 (4.1)	0.233
No	52 (100)	47 (95.9)	
Polyhydramnios			
Yes	6 (11.5)	12 (24.5)	0.120
No	46 (88.5)	37 (75.5)	

Group I= Insulin + Metformin, Group II= Insulin only.* = *P* value < 0.05 percent significant.

instead, we used it in combination with insulin in Group I.

Our results according to perinatal outcomes observed that patients receiving insulin (group II) were significantly higher than patients receiving insulin and metformin (group I) as regards Neonatal hypoglycemia, Neonatal respiratory distress, Birth weight >90th birth weight centile and Polyhydramnios but lower birth weight from 10th to 90th birth weight centile.

Results of research done by **Goh** et al.,[11] research, that included 1269 females, revealed macrosomia in 18.5 percent of neonates in insulin group vs. 12.5percent of neonates in the metformin group, with no significant variation because of a larger sample size in the latter research.

Ghomian et al.,[12] found that measurement of birth weight in both groups insulin versus metformin indicated that mean weight of neonates from both groups is normal, and that there is no variation among 2 groups in this regard, however in contrast to research, there is no combined treatment of insulin and metformin, and only GDM patients were enrolled in that research, that is consistent with results of research by **Mesdaghinia *et al.***[13]

These results were most probably due to its small sample size that can be explained by perinatal complication of large for gestational age newborn and prematurity which is increased in group II, between perinatal problems of LGA newborn, meconium aspiration, clavicle fracture, perinatal hypoxia, hyperbilirubinemia, transient tachypnea, brachial plexus injury, shoulder dystocia, and even neonatal death are noteworthy.[14]

The great incidence of polyhydramnios in group II, that demonstrated variation, may be attributed to macrosomia and foetal hyperinsulinemia in that group. In contrast to the findings, **Saleh** et al.,[15] found great incidence in the metformin group but did not reach significant value, which was explained by enrolling only GDM-studied cases and comparing insulin vs metformin groups in which research dislike research.

Rowan et al.,[16] compared 2 groups of subjects and found significant variation in the incidence rate of severe hypoglycemia in metformin group.

Spaulonci et al.,[17] desirable efficacy of metformin in reducing blood glucose of involved mothers was reflected in lower incidence rate of hypoglycemia. **Ghomian** et al.,[12] showed, metformin group have lower incidence rate of hypoglycemia, but it did not reach statistical significance.

In research, the GDM subgroup shows an increased incidence of gestational hypertension in group I with decreased incidence of pre-eclampsia but both values did not reach statistically significant levels agreeing with us **Goh** et al.,[11] that included 406 patients with GDM taking insulin vs. 218 patients taking insulin and metformin.

In terms of glycosylated hemoglobin testing throughout pregnancy, results revealed levels of HbA1c in both groups I and II (6.3 ± 0.4 vs. 6.3 ± 0.5), with no significant variation. Findings of research conducted by **Mesdaghinia** et al.,[13] Lower levels of HbA1c in metformin group could be attributed to research in pregnant females with gestational diabetes taking metformin alone versus females taking insulin.

In terms of gestational age, no significant variation was observed among the 2 groups in terms of preterm births, despite raised incidence in group II, that can be explained by a higher rate of polyhydramnios in that group.

Numerous randomized controlled trials have found that studied cases taking metformin had higher rate of preterm birth than those receiving insulin **Kitwitee** et al.,[18] **Rowan** et al.,[16] compared to the insulin group, there was a greater prevalence of preterm delivery between metformin-treated studied cases (12.1 percent vs. 7.6 percent). This conflict may be because, in our research, we combined the use of metformin and insulin.

In terms of caesarean section rates, current research compared 2 groups and observed no significant

variations. Similarly, randomized controlled trial conducted in 2016 found no variations in several caesarean section cases among metformin and insulin groups.[16] Research of **Moor** et al.,[19] on thirty-two studied cases in metformin group and thirty-one subjects in insulin group, there was no variation in incidence of caesarean section among 2 groups.

4.1. Conclusion

Based on our findings, diabetic pregnant females treated with insulin and metformin and with similar baseline risk factors for adverse pregnancy results have less weight gain and insulin dosage needed for glycemic control, as well as enhanced neonatal results such as macrosomia, neonatal hypoglycemia, respiratory distress, and special care baby admission when compared to those treated with insulin.

Consent for publication

I verify that all authors have agreed to submit the manuscript.

Availability of data and material

Available.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declared that there were no conflicts of interest.

References

1. Mpondo BC, Ernest A, Dee HE. Gestational diabetes mellitus: challenges in diagnosis and management. *J Diabetes Metab Disord*. 2015;14:1–7.
2. Allard C, Sahyouni E, Menard J, Houde G, Pesant MH, Perron P, et al. Gestational diabetes mellitus identification based on self-monitoring of blood glucose. *Can J Diabetes*. 2015;39:162–168.
3. Coustan DR. Gestational diabetes mellitus. *Clin Chem*. 2013; 59:1310–1321.
4. Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial. *Diabetes Res Clin Pract*. 2015;107:290–299.
5. Gamal HE, Elaleem MA, Sadek S, Elhadary MR. Insulin versus metformin in treatment of gestational diabetes mellitus (randomized controlled clinical trial). *Egyptian J Hospital Med*. 2018;72:438–451.
6. Tertti K, Ekblad U, Koskinen P, Vahlberg T, Rönnemaa T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metabol*. 2013;15:246–251.
7. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358:2003–2015.
8. Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case–control study. *Diabet Med*. 2009;26:798–802.
9. Zhu X, Wu YB, Zhou J, Kang DM. Upregulation of lncRNA MEG3 promotes hepatic insulin resistance via increasing FoxO 1 expression. *Biochem Biophys Res Commun*. 2016;469: 319–325.
10. Niromanesh S, Shirazi M, Dastgerdy E, Sharbaf FR, Shirazi M, Khazaeipour Z. Association of hypertriglyceridaemia with pre-eclampsia, preterm birth, gestational diabetes and uterine artery pulsatility index. *Natl Med J India*. 2012;25:265–267.
11. Goh KL, Chan WK, Shiota S, Yamaoka Y. Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter*. 2011;16:1–9.
12. Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebbi M, Sahebkar A. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: a randomized clinical trial. *J Cell Physiol*. 2018;234:4695–4701.
13. Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SGA, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomised blinded trial. *Int J Prev Med*. 2013;4:327.
14. Berntorp K, Anderberg E, Claesson R, Ignell C, Källén K. The relative importance of maternal body mass index and glucose levels for prediction of large-for-gestational-age births. *BMC Pregnancy Childbirth*. 2015;15:1–8.
15. Saleh HS, Abdelsalam WA, Mowafy HE, Abd ElHameid AA. Could metformin manage gestational diabetes mellitus instead of insulin? *Int J Reprod Med*. 2016;2016:3480629. https://doi.org/10.1155/2016/3480629. Epub 2016 Aug 14. PMID: 27597988; PMCID: PMC5002295.
16. Rowan JA, Haque WJVI, Gao W. Metformin vs insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358: 2003–2015.
17. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol*. 2013;209, 34–e1.
18. Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, et al. Metformin for the treatment of gestational diabetes: an updated meta-analysis. *Diabetes Res Clin Pract*. 2015;109: 521–532.
19. Van Herpe T, Haverbeke N, Pluymers B, Van den Berghe G, De Moor B. The application of model predictive control to normalize glycemia of critically ill patients. In: *2007 European Control Conference (ECC). Kos, Greece,* 2007:3116–3123. https://doi.org/10.23919/ECC.2007.7068484.