Journal of Biomedical Sciences | ISSN: 2960-9356
Research Article Peer-review, Open Access

Prophylactic Metformin in Obese Non-Diabetic Pregnant Women: Effects on Gestational Weight Gain, Preeclampsia, and Neonatal Outcomes

Melak Ahmed Ghazi*[1], Maysoon Sharief[2], Zaid Nadhim Kadhim[3]

Abstract

Maternal obesity is a major global health problem associated with increased maternal and neonatal morbidity, including gestational diabetes mellitus (GDM), preeclampsia, excessive gestational weight gain, and adverse fetal outcomes. Metformin, an insulin-sensitising agent widely used in type 2 diabetes mellitus and polycystic ovary syndrome (PCOS), has been proposed as a preventive therapy during pregnancy. This randomised, placebo-controlled trial evaluated the effect of prophylactic metformin on gestational weight gain and preeclampsia in obese, non-diabetic pregnant women. A total of 150 women with a body mass index (BMI) ≥ 30 kg/m² were recruited between 12 and 20 weeks of gestation at Basra Maternity and Child Hospital and allocated to receive either metformin 500 mg once daily (n = 75) or a matching placebo (n = 75) from the 12th week of gestation until delivery. Maternal metabolic parameters, gestational weight gain, obstetric complications, and neonatal outcomes were assessed, and data were analysed using SPSS version 21. Metformin significantly reduced mean gestational weight gain compared with placebo (4.6 kg versus 6.3 kg; P = 0.01) and lowered the incidence of preeclampsia (P = 0.01). No significant differences were observed in fasting blood glucose, the homeostatic model assessment of insulin resistance (HOMA-IR) at 36 weeks, caesarean section rate, postpartum haemorrhage, birth weight, Apgar scores, or neonatal intensive care unit (NICU) admissions. Low-dose prophylactic metformin appears to be a safe and effective intervention for reducing excessive gestational weight gain and preeclampsia in obese, non-diabetic pregnancies without adversely affecting neonatal outcomes.

Keywords: Maternal obesity; Metformin; Preeclampsia; Gestational weight gain; Insulin resistance; Pregnancy outcome.

[1] MBChB. Basrah Maternity and Childhood Hospital, Basrah, Iraq.
[2] D.O.G., C.A.B.O.G. Department of Gynecology and Obstetrics, College of Medicine, University of Basrah, Basrah, Iraq.
[3] MBChB, MD, CABR. Al-Mawadda Hospital, Basrah, Iraq.

Corresponding email: melakahmed2225@gmail.com

Introduction

Global obesity rates have risen dramatically over the past four decades and now constitute a worldwide epidemic [1]. International bodies, including the World Health Organization (WHO), the United Nations, and the World Obesity Federation, have emphasized the urgent need for intervention to reduce the obesity burden [2], and in 2013 obesity was formally recognized as a chronic, relapsing disease in which weight-loss interventions frequently fail to achieve sustained reduction [3]. Obesity is most commonly assessed using the body mass index (BMI), defined as weight in kilograms divided by the square of height in meters [4].

The WHO classifies a BMI below 18.5 kg/m² as underweight, 18.5–24.9 kg/m² as normal weight, 25–29.9 kg/m² as overweight, and ≥ 30 kg/m² as obese; obesity is associated with a reduction in life expectancy of 5–20 years . It is a leading risk factor for non-communicable diseases (NCDs), including cardiovascular disease and malignancy, which together account for more than 70% of global mortality [5]. Through its global action plan for the prevention and control of non-communicable diseases 2013–2020, the WHO set a target to halt the rise in obesity prevalence by 2025 . This is of particular importance in developing countries, where healthcare systems are often inadequately equipped to manage the resulting comorbidities [6,7].

Above a BMI of 25 kg/m², each additional 5 kg/m² increases vascular mortality by approximately 40% and diabetes-related mortality by 120%. BMI alone, however, does not capture individual metabolic health, giving rise to the so-called obesity paradox, whereby some individuals with a high BMI remain metabolically healthy; visceral adiposity is considerably more harmful than subcutaneous fat, so parameters such as insulin resistance and lipid distribution are important for characterising metabolic risk [8]. Obesity induces chronic low-grade inflammation, increased pro-inflammatory cytokine secretion, ectopic hepatic lipid deposition, and endocrine disturbances, including elevated leptin, adiponectin, and circulating insulin, establishing it as a major determinant of type 2 diabetes (T2D) [9]. These alterations also increase susceptibility to cholelithiasis, hypertension, cerebrovascular disease, cardiovascular disease, and hormone-related malignancies, while obesity-related conditions such as sleep apnoea and osteoarthritis further reduce quality of life and may worsen outcomes from infection [10].

Globally, approximately half of all women begin pregnancy overweight or obese [11], a pattern reflected in the United Kingdom, where more than half of pregnant women are overweight or obese [12]. Because excessive gestational weight gain (GWG), particularly in early pregnancy [13]. associated with adverse long-term outcomes for both the mother, such as postpartum weight retention and hypertension [14], and the offspring, such as adiposity and hypertension [15], the National Academy of Medicine has issued BMI-specific GWG recommendations, advising lower gains for overweight (7–11.5 kg) and obese (5–9 kg) women than for those who are underweight (12.5–18 kg) or of normal weight (11.5–16 kg) . Nevertheless, pre-pregnancy BMI remains one of the strongest predictors of adverse obstetric outcomes [16], underscoring the importance of preconception counselling and targeted intervention to mitigate the maternal and fetal consequences of obesity [17].

Maternal obesity is strongly associated with GDM. Maternal lipid profiles, rather than glycaemia, may be the stronger determinant of fetal growth [18], and placental gene-expression changes in GDM occur predominantly in lipid- rather than glucose-metabolic pathways [19]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that maternal BMI, independent of glycaemic status, is associated with fetal adiposity and hyperinsulinaemia [20], with comparable associations reported for raised umbilical-cord C-peptide and macrosomia [21]. Current guidance therefore recommends that obese pregnancies receive the same intensive late-gestation monitoring as those complicated by GDM. Offspring exposed to maternal obesity and GDM are themselves at increased risk of obesity, β-cell dysfunction, and diabetes, perpetuating an intergenerational cycle of metabolic dysfunction [22].

Metformin (1,1-dimethylbiguanide hydrochloride), first described by Jean Sterne in 1957, is now the most widely used oral hypoglycaemic agent for T2D [23]. Its earliest use in pregnancy was incidental, through continued treatment of women with pre-existing diabetes, and was accompanied by reassuring safety data; the first deliberate gestational use, reported in a 1979 South African study, concluded that the drug had an acceptable safety profile in pregnancy [24]. In the late 1990s, metformin was introduced for PCOS, in which periconceptional and gestational treatment reduces first-trimester miscarriage [25]. In 2004, Glueck et al.

reported that metformin throughout pregnancy improved insulin sensitivity, reduced body weight, and lowered GDM incidence in women with PCOS, without adverse effects on infant growth or development during the first 18 months [26]. Longer follow-up of metformin-exposed offspring has, however, raised concerns, with one study reporting higher offspring BMI at 4 and 7 years of age [27]. These observations, together with the established maternal benefits of metformin, have prompted interest in its prophylactic use in obese, non-diabetic pregnancies.

The aim of this study was to evaluate the role of prophylactic metformin administration in obese, non-diabetic pregnant women with regard to maternal gestational weight gain and preeclampsia.

Methods

Study Design and Setting

This randomised, placebo-controlled trial was conducted in the obstetrics clinic of Basra Maternity and Child Hospital, Basrah, Iraq, and enrolled 150 obese, non-diabetic pregnant women recruited between 12 and 20 weeks of gestation.

Participants

Eligible women were aged over 16 years with a singleton pregnancy and a BMI ≥ 30 kg/m². Women were excluded if they had fetal abnormalities, pre-existing impaired glucose tolerance, multiple pregnancy, previous GDM, or any of the following: hypertension, renal failure, known liver disease, corticosteroid use, alcohol dependence, gastrointestinal malabsorption, or a known allergy to metformin. A 2-hour 75 g oral glucose tolerance test (OGTT) was performed between 12 and 16 weeks of gestation; women with impaired glucose tolerance or diabetes, defined as a fasting plasma glucose ≥ 126 mg/dL or a 2-hour OGTT value ≥ 200 mg/dL, were excluded [20–22].

Randomisation and Intervention

The 150 eligible women were allocated in equal numbers to a metformin group (500 mg once daily; n = 75) or a placebo group (n = 75), with treatment commencing at the 12th week of gestation and continuing until delivery [28,29,32,33].Blood glucose was monitored throughout pregnancy; during follow-up, GDM was diagnosed when the fasting blood sugar (FBS) was ≥ 92 mg/dL or the 1-hour post-prandial value was ≥ 180 mg/dL [20,21].

Outcome Measures

The primary maternal outcomes were gestational weight gain and preeclampsia. Additional maternal outcomes included polyhydramnios (amniotic fluid index [AFI] ≥ 25 cm), GDM, mode of delivery and indications for caesarean section, and postpartum haemorrhage. Fasting blood glucose and insulin resistance, estimated by the homeostatic model assessment of insulin resistance (HOMA-IR), were measured at baseline and at 36 weeks. Neonatal outcomes comprised birth weight, Apgar score, gestational age at delivery, neonatal blood glucose, and admission to the neonatal intensive care unit (NICU).

Statistical Analysis and Ethics

Data were analysed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Quantitative variables were summarised as measures of central tendency and qualitative variables as frequencies; the Student t-test and the chi-square test were used for comparisons, and a P value < 0.05 was considered statistically significant. Ethical approval was obtained from the Ethics Committee of Basra Medical College, and written informed consent was obtained from all participants.

Results

A total of 150 obese pregnant women were enrolled and equally allocated to the metformin and placebo groups. The two groups were comparable at baseline with respect to maternal age, weight, BMI, parity, mode of conception, history of PCOS, fasting blood sugar, and HOMA-IR, with no statistically significant differences (Table 1).

Table 1. Maternal characteristics and obstetrical history of the study groups.

Characteristic	Metformin group (n = 75)	Control group (n = 75)	P value
Mean maternal age, years (range)	31 (21–36)	30 (19–38)	0.6
Mean maternal weight, kg (range)	87 (78–112)	90 (81–110)	0.5
Mean BMI, kg/m² (range)	32 (30–35)	31 (32–37)	0.6
Parity – primigravida	33	32	0.6
Parity – multigravida	42	43	–
Conception – spontaneous	41	46	0.5
Conception – induction	26	29	–
History of PCOS	15	17	0.2
Baseline fasting blood sugar (range)	76–105	73–115	0.4
Baseline HOMA-IR	2.1	2.1	–

BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; PCOS, polycystic ovary syndrome.

Fetal and birth outcomes did not differ significantly between the groups. There were no significant differences in birth weight or in the frequency of miscarriage, stillbirth, neonatal death, preterm delivery, birth trauma, an Apgar score below 7, or NICU admission (Table 2).

Table 2. Fetal and birth outcomes.

Outcome	Metformin group (n = 75)	Placebo group (n = 75)	P value
Birth weight, kg (range)	2.5–4.2	2.9–4.5	0.6
Miscarriage	1	2	0.12
Stillbirth	0	1	0.62
Neonatal death	0	1	0.12
Preterm delivery	5	4	0.12
Birth trauma	0	0	0.7
Apgar score < 7	1	2	0.6
Admission to NICU	4	3	0.7

NICU, neonatal intensive care unit.

Metformin was associated with a significantly lower mean gestational weight gain than placebo (4.6 kg versus 6.3 kg; P = 0.01) and a significantly lower incidence of preeclampsia (2 versus 5 cases; P = 0.01). There were no significant differences between the groups in GDM, caesarean section rate, postpartum haemorrhage, fasting blood glucose at 36 weeks, or HOMA-IR (Table 3).

Table 3. Maternal outcomes.

Outcome	Metformin group (n = 75)	Control group (n = 75)	P value
Maternal weight gain, kg [range (mean)]	2.3–7.2 (4.6)	2.9–9.2 (6.3)	0.01
Gestational diabetes mellitus	0	1	0.7
Preeclampsia	2	5	0.01
Delivery by caesarean section	14	15	0.1
Postpartum haemorrhage	7	6	0.1
Fasting blood glucose at 36 weeks (range)	98 (82–102)	100 (70–110)	0.1
HOMA-IR at 36 weeks	2.85	2.89	0.1

HOMA-IR, homeostatic model assessment of insulin resistance.

Discussion

In this cohort, metformin commenced at the 12th week of gestation significantly reduced mean gestational weight gain (4.6 versus 6.3 kg; P = 0.01) and the incidence of preeclampsia (P = 0.01). Similar findings were reported by Syngelaki et al. in the large MOP trial, in which metformin significantly reduced median gestational weight gain and the incidence of preeclampsia compared with placebo . In contrast, the EMPOWaR trial reported by Chiswick et al. found no significant effect of metformin on preeclampsia or maternal weight gain[28] . These discrepancies may reflect differences in study populations, dietary habits, metformin dosage, or baseline metabolic status [29].

Despite the reductions in weight gain and preeclampsia, fasting blood glucose and HOMA-IR at 36 weeks did not differ significantly between the groups (P = 0.1). This suggests that the protective effects of metformin in this cohort may be mediated by mechanisms other than a major reduction in late-third-trimester systemic insulin resistance [30], such as improvements in placental endothelial function, early-pregnancy metabolic regulation, or lipid metabolism [31]. By contrast, Balani et al. linked the clinical benefits of metformin to a measurable systemic reduction in insulin resistance, reporting lower HOMA-IR at 28 weeks in obese, non-diabetic women [32]. The absence of a significant HOMA-IR difference at 36 weeks in the present study may indicate that the 500 mg daily dose was sufficient to prevent clinical complications such as preeclampsia but insufficient to produce a marked change in late-gestation systemic insulin resistance.

Neonatal outcomes, including birth weight, Apgar scores, and NICU admission, did not differ significantly between the groups, indicating that metformin influenced maternal metabolism and weight control without adversely affecting the neonate. Comparable findings were reported in a Cochrane systematic review by Dodd et al., which concluded that metformin makes little or no difference to infant birth weight [33], and by Syngelaki et al., who found no significant difference in neonatal birth weight despite maternal benefits. In contrast, Feig et al., in the MiTy trial, reported reduced neonatal adiposity and macrosomia with metformin; however, that trial enrolled women with pre-existing T2D, suggesting that the effect of metformin on excessive fetal growth may become apparent only in the presence of significant maternal hyperglycaemia [34].

Conclusion and Recommendations

Low-dose prophylactic metformin is a safe and effective intervention for reducing excessive gestational weight gain and the incidence of preeclampsia in obese, non-diabetic pregnancies, while late-gestation systemic insulin resistance remained largely unchanged and neonatal outcomes were unaffected. Based on these findings, the following recommendations are made:

Firstly obstetricians may consider low-dose prophylactic metformin as an adjunct to standard lifestyle and dietary measures for obese, non-diabetic women at increased risk of vascular complications; also future dose-response trials are needed to determine whether higher doses confer broader systemic metabolic benefit without compromising neonatal safety; and mechanistic studies of localised placental and endothelial biomarkers are warranted to clarify the pathways underlying the protective effects of metformin; and long-term follow-up of exposed offspring is recommended to monitor metabolic and developmental outcomes.

Acknowledgements

The authors thank the staff of Al-Basrah Maternity and Children Teaching Hospital and the women who participated in the study for their cooperation.

Reference

[1] NCD Risk Factor Collaboration, "Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants," *Lancet*, vol. 387, no. 10026, pp. 1377–1396, 2016.

[2] World Health Organization, *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020*. Geneva, Switzerland: World Health Organization, 2013.

[3] G. A. Bray, K. K. Kim, and J. P. H. Wilding, "Obesity: A chronic relapsing progressive disease process. A position statement of the World Obesity Federation," *Obes. Rev.*, vol. 18, no. 7, pp. 715–723, 2017.

[4] Prospective Studies Collaboration, "Body-mass index and cause-specific mortality in 900,000 adults: Collaborative analyses of 57 prospective studies," *Lancet*, vol. 373, no. 9669, pp. 1083–1096, 2009.

[5] World Health Organization, *Global Status Report on Noncommunicable Diseases 2014*. Geneva, Switzerland: World Health Organization, 2014.

[6] E. A. Finkelstein, J. G. Trogdon, J. W. Cohen, and W. Dietz, "Annual medical spending attributable to obesity: Payer- and service-specific estimates," *Health Aff. (Millwood)*, vol. 28, no. 5, pp. w822–w831, 2009.

[7] B. M. Popkin, L. S. Adair, and S. W. Ng, "Global nutrition transition and the pandemic of obesity in developing countries," *Nutr. Rev.*, vol. 70, no. 1, pp. 3–21, 2012.

[8] N. Stefan, H. U. Häring, F. B. Hu, and M. B. Schulze, "Metabolically healthy obesity: Epidemiology, mechanisms, and clinical implications," *Lancet Diabetes Endocrinol.*, vol. 1, no. 2, pp. 152–162, 2013.

[9] G. S. Hotamisligil, "Inflammation and metabolic disorders," *Nature*, vol. 444, no. 7121, pp. 860–867, 2006.

[10] B. M. Popkin *et al*., "Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships," *Obes. Rev.*, vol. 21, no. 11, Art. no. e13128, 2020.

[11] L. Poston *et al*., "Preconceptional and maternal obesity: Epidemiology and health consequences," *Lancet Diabetes Endocrinol.*, vol. 4, no. 12, pp. 1025–1036, 2016.

[12] Chief Medical Officer, *Annual Report of the Chief Medical Officer, 2014: The Health of the 51%: Women*. London, U.K.: Department of Health, 2015.

[13] Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC, USA: National Academies Press, 2009.

[14] A. A. Mamun, M. Kinarivala, M. J. O'Callaghan, G. M. Williams, J. M. Najman, and L. K. Callaway, "Associations of excess weight gain during pregnancy with long-term maternal overweight and obesity: Evidence from 21 y postpartum follow-up," *Am. J. Clin. Nutr.*, vol. 91, no. 5, pp. 1336–1341, 2010.

[15] A. Fraser *et al*., "Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood," *Circulation*, vol. 121, no. 23, pp. 2557–2564, 2010.

[16] P. M. Catalano and K. Shankar, "Obesity and pregnancy: Mechanisms of short term and long term adverse consequences for mother and child," *BMJ*, vol. 356, Art. no. j1, 2017.

[17] R. F. Goldstein *et al*., "Association of gestational weight gain with maternal and infant outcomes: A systematic review and meta-analysis," *JAMA*, vol. 317, no. 21, pp. 2207–2225, 2017.

[18] U. M. Schaefer-Graf *et al*., "Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus," *Diabetes Care*, vol. 31, no. 9, pp. 1858–1863, 2008.

[19] G. Desoye and S. Hauguel-de Mouzon, "The human placenta in gestational diabetes mellitus: The estrogen and cytokine systems," *Diabetes Care*, vol. 30, suppl. 2, pp. S120–S126, 2007.

[20] HAPO Study Cooperative Research Group, "Hyperglycemia and adverse pregnancy outcomes," *N. Engl. J. Med.*, vol. 358, no. 19, pp. 1991–2002, 2008.

[21] P. M. Catalano *et al*., "The Hyperglycemia and Adverse Pregnancy Outcome study: Associations of GDM and obesity with pregnancy outcomes," *Diabetes Care*, vol. 35, no. 4, pp. 780–786, 2012.

[22] L. Bellamy, J. P. Casas, A. D. Hingorani, and D. Williams, "Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis," *Lancet*, vol. 373, no. 9677, pp. 1773–1779, 2009.

[23] J. Sterne, "Du nouveau dans les antidiabétiques. La NN diméthylguanylguanidine (N.N.D.G.)," *Maroc Med.*, vol. 36, pp. 1295–1298, 1957.

[24] E. J. Coetzee and W. P. Jackson, "Metformin in management of pregnant insulin-independent diabetics," *Diabetologia*, vol. 16, no. 4, pp. 241–245, 1979.

[25] J. E. Nestler, D. J. Jakubowicz, W. S. Evans, and R. Pasquali, "Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome," *N. Engl. J. Med.*, vol. 338, no. 26, pp. 1876–1880, 1998.

[26] C. J. Glueck, P. Wang, N. Goldenberg, and L. Nix, "Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome," *Fertil. Steril.*, vol. 81, no. 3, pp. 520–525, 2004.

[27] L. G. E. Hanem, S. Stridsklev, P. B. Júlíusson, Ø. Salvesen, M. Roelants, S. M. Carlsen, and E. Vanky, "Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: Follow-up of two RCTs," *J. Clin. Endocrinol. Metab.*, vol. 103, no. 4, pp. 1612–1621, 2018.

[28] A. Syngelaki *et al*., "Metformin versus placebo in obese pregnant women without diabetes mellitus," *N. Engl. J. Med.*, vol. 374, no. 5, pp. 434–443, 2016.

[29] C. Chiswick *et al*., "Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): A randomised, double-blind, placebo-controlled trial," *Lancet Diabetes Endocrinol.*, vol. 3, no. 10, pp. 778–786, 2015.

[30] Y. He, J. Zhang, *et al*., "Protective role of metformin in preeclampsia via the regulation of NF-κB/sFlt-1 and Nrf2/HO-1 signaling pathways by activating AMPK," *Placenta*, vol. 143, pp. 7–15, 2023.

[31] R. Romero *et al*., "Metformin, the aspirin of the 21st century: Its role in gestational diabetes, prevention of preeclampsia and cancer, and the promotion of longevity," *Am. J. Obstet. Gynecol.*, vol. 217, no. 3, pp. 282–302, 2017.

[32] J. Balani, S. L. Hyer, A. Johnson, and H. Shehata, "Metformin in pregnancies complicated by obesity," *Curr. Diab. Rep.*, vol. 17, no. 3, Art. no. 16, 2017.

[33] J. M. Dodd, R. M. Grivell, P. T. Depping, and A. J. McPhee, "Metformin for women who are obese during pregnancy for improving maternal and infant outcomes," *Cochrane Database Syst. Rev.*, vol. 7, no. 7, Art. no. CD010564, 2018.

[34] D. S. Feig *et al*., "Metformin in women with type 2 diabetes in pregnancy (MiTy): A multicentre, international, randomised, placebo-controlled trial," *Lancet Diabetes Endocrinol.*, vol. 8, no. 10, pp. 834–844, 2020.