Original Article

# Maternal and Fetal Outcomes with Metformin Therapy for Obese Pregnant Women A Randomized Control Trial

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## ABSTRACT

**Aim of Work:** To investigate the maternal and neonatal outcomes after using metformin among obese non diabetic Egyptian women.

**Study design:** A case control, open label randomized controlled trial.

**Methods:** A case control, open label randomized controlled trial study was conducted on 178 pregnant – 11 to 16 weeks – obese (Body mass index ≥ 30 kg/m$^2$) non diabetic females. Our populations` cohort were equally randomized into 2 groups, cases – who were subjected to receive metformin from the date of recruitment till termination of pregnancy – and controls – who received nothing – with follow up of the maternal glucose levels and documenting the maternal and fetal outcomes.

**Results:** Metformin appeared to have a good patient acceptability with a less weight gain during enrollment of the trial among the pregnant females with a better glycemic control. There is no difference between the 2 groups regarding incidence of developing GDM, gestational hypertension and fetal macrosomia.

**Conclusion:** Using metformin for obese non diabetic females, from the second trimester of pregnancy can reduce the maternal weight gain during pregnancy and provide a better glycemic control with no increase in perinatal and maternal complications.

**Key Words:** Birth outcomes, fetal macrosomia, maternal weight gain, metformin.

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## INTRODUCTION

Obesity is the feature of the century; nearly its incidence doubled in the last 30 years[1]. Obesity is having abnormal excessive adipose tissue deposition and can be assessed by using Body Mass Index (BMI) equation and its interpretation[2]. Maternal obesity is the most common association with pregnancy; 23% of European women are obese and 50% are overweight[1]. Maternal obesity increases the risk of maternal adverse consequences like postpartum hemorrhage, thromboembolism, surgical wound infection, puerperal sepsis besides anesthesia complications and maternal death[3,4]. Some studies showed that increased maternal BMI is associated with pregnancy induced hypertension, preeclampsia, low gestational weight and increased incidence of caesarian deliveries regardless of maternal glucose levels[5]. Maternal obesity is also adversely affecting the fetal and neonatal life, studies showed increase incidence of congenital malformations by 3 folds; hydrocephaly, omphalocele, fetal distress and still birth. Also, the maternal obesity is associated with neonatal hypoglycemia and neonatal jaundice[6-8]. Metformin is anti-hyperglycemic widely used drug – due to its safety and low cost – with multiple therapeutic benefits. It is mainly used to control blood sugar levels in type II diabetes mellitus (DM) and can be used as adjuvant therapy in many conditions.

Metformin use lowered the maternal weight gain during pregnancy besides decreased incidence of pre-eclampsia and neonatal intensive care unit (NICU) admission[9]. Metformin can be used also for treatment of obese pregnant not diabetic women with improvement of perinatal maternal and fetal outcomes[10].

Moreover, studies clarified using metformin during pregnancy can decrease neonatal hypoglycemia, neonatal macrosomia and decreased caesarian section (C.S) deliveries[9].

To our knowledge, few studies investigated the neonatal and maternal outcomes of using metformin during pregnancy in obese non diabetic Egyptian women.

## AIM OF WORK

This study was to investigate the maternal and neonatal outcomes after using metformin among obese pregnant non diabetic Egyptian women.

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## PATIENTS AND METHODS

### *Type of the study*

A case control, open label randomized controlled trial study was conducted in our hospitals, in the period from February 2021 till July 2022.

### *Subjects*

All pregnant women were recruited from the antenatal care clinic of obstetrics and gynecology department obstetrics and gynecology hospital, Assiut – Egypt.

All pregnant women who were obese with BMI ≥ 30kg/m2, and between 11 and less than complete 16 weeks gestation were recruited in our study.

All pregnant females who had delivered preterm babies during the study duration were excluded from the study.

All females with previous history of gestational diabetes mellitus (GDM), macrosomic baby, preterm labor, or pre-eclampsia were excluded from our study.

All patients with systemic illnesses like chronic hypertension, chronic DM, heart diseases or patients who had metformin sensitivity were excluded from the study.

All patients on corticosteroids or had had systemic steroids in the past 6 months were excluded from our study.

Females who had acute condition at the time of trial entry with the potential to alter renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock and intravascular administration of contrast agents were excluded from the study.

Any patient with acute or chronic diseases that may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, and/or hepatic insufficiency were excluded from the study.

All pregnant females who were unsure of the date of the last menstrual period and unsure estimate of the date of conception were excluded from the study.

All of the participant had a monthly visit to an endocrinologist to be revised concerning their nutritional states and their OGTT results.

### *Sample size calculation*

According to the G*Power 3 software, the calculated minimum sample was 170 pregnant women needed to detect an effect size of 0.5 in the percentage of change of birth weight at delivery with an error probability of 0.05 and 95 % power on a one-tailed test[11].

### *Data collection*

A total of 178 pregnant females met the inclusion criteria of the study and were randomized equally as 1:1.

The 2 groups were 89 patients and 89 controls, the first group who received metformin (1,1-dimethylbiguanide hydrochloride) 500 mg tablet, known at our country as Glucophage 500mg. tablets by ©Merck & Co., Inc. pharmaceuticals. The second group received nothing during the study period.

The dose regimen of metformin was one tablet per day for the first week of the study, two tablets per day during the second week of the study and three tables per day from the third week of the study till delivery.

**All doses were prescribed with food**

All recruited pregnant females of the two groups were subjected to careful personal, obstetric and gynecological history taking.

All recruits were evaluated by weight, height and BMI calculation by the equation of (BMI=Weight (kg) / Height ($m^2$))[12].

### *Randomization*

Treatment allocation concealment was ensured by participant randomization in a 1:1 ratio through a web-based interface provided by the Edinburgh Clinical Trials Unit and stratified by both study center and BMI band (30 – 34.9 kg/m2 or ≥ 35 kg/$m^2$).

The research information is not withheld from trial participants. In particular, both the researchers and participants know which treatment is being administered.

### *Study procedure*

**First visit**

Women identified as potential participants were seen for an initial screening visit between 11- and 16-weeks' gestation. A written consent from each participant was obtained after explanation of the study process and the potential hazards may be associated with the study.

OGTT was done to all the participant (all of them were of normal values at the time of the first visit as term to be included in our study)

Personal, medical history and maternal anthropometry were recorded at baseline.

**Second visit**

Participants were reviewed at a second visit between 24 – 28 weeks' gestation. Urine analysis, maternal weight, Blood pressure measurement, and a 75-g oral glucose tolerance test (OGTT) was performed in the second visit for all the participants` cohort as a screening for GDM.

**Third visit**

Participants also reviewed at a third visit between 35 – 37 weeks' gestation. All of them were subjected to urine analysis, FBG level, blood pressure, glycosylated hemoglobin A1C (HBA1C), and maternal weight.

**At termination**

At the time of delivery, the participants were also evaluated concerning to (blood pressure at the time of

delivery, FBG, random blood glucose level, blood group and RH, maternal weight, mood of delivery, estimated fetal birth weight (EFBW) and fetal birth weight after delivery also any complication at delivery.

Pregnancy complications were recorded and women were asked about any side effect each visit.

Maternal anthropometry was repeated at 36 weeks' gestation. The OGTT was repeated at 24 - 28 weeks' gestation. The protocol recommended that women who developed GDM be treated with insulin while maintaining their study treatment.

### *Ultrasound assessment*

All study participants were assessed during the antenatal visits by a feto-maternal sonography specialist to detect any associated congenital fetal anomalies may hinder the normal progress of the fetus and maternal weight gain.

### *Statistical analysis*

All statistical analysis were done via Social Package Statistical Sciences software (SPSS) version 22. All data were examined for normality using Shapiro-Wilk testing.

All normally distributed numeric data were described by numbers and percentage and mean ± standard deviation (SD), the not normally distributed data were described using median with range.

Numeric variables were be tested for association using Pearson correlation coefficient for normally distributed data and Spearman correlation coefficient for not normally distributed data.

All numeric data were tested for mean differences using independent sample t-test for data with normal distribution and Mann-whitney U test for not normally distributed data.

All categorical variables were tested for differences via Chi-square test. *P-value* ≤ 0.05 is considered statistically significant.

## RESULTS

A case control study was conducted on 178 obese with BMI ≥ 30kg/m$^2$ non diabetic pregnant females.

A total of 178 pregnant females were fulfilling all the inclusion criteria and completed the study procedure, they were distributed as 89 cases – who were prescribed metformin – and 89 controls.

The mean age of all cases was 28.6 ± 6.5-year-old, in comparison to 27.62 ± 6.92 years for controls with no significant difference between them (p=0.333). Out of all recruited females, 42 females were primigravida (23.6%). The mean BMI among cases was 32.63 ± 1.97 kg/m$^2$ in comparison to 32.62 ± 2.09 kg/m2 with no significant difference between the two groups.

General and clinical characteristics of the populations` cohort at recruitment are described in (Table 1).

**Table 1:** General and clinical characteristics of the studied groups at recruitment (first antenatal visit) (n =178)

| Variables (Mean ± SD or N & %) | Cases (n =89) | Controls (n =89) | *P-value* |
|---|---|---|---|
| Age (years) | 28.6 ± 6.5 | 27.62 ± 6.92 | 0.333 |
| Gestational age (weeks) | 14.81 ± 1.1 | 14.6 ± 1.35 | 0.255 |
| Parity | | | |
| Primigravida | 18 (20.2%) | 24 (27%) | |
| 1 – 4 | 62 (66.7%) | 59 (66.2%) | 0.630 |
| 4 – 8 | 9 (10.1%) | 6 (6.8%) | |
| Previous abortion | | | |
| 0 | 64 (71.9%) | 70 (78.7%) | |
| 1 | 16 (18%) | 9 (10.1%) | |
| 2 | 6 (6.7%) | 7 (7.9%) | 0.257 |
| 3 | 1 (1.1%) | 3 (3.4%) | |
| 4 | 2 (2.2%) | 0 | |
| Weight (Kg) | 85.39 ± 6.13 | 84.10 ± 6.58 | 0.177 |
| Height (Cm) | 161.78±5.52 | 160.57 ± 5.46 | 0.146 |
| BMI (Kg/m$^2$) | 32.63 ± 1.97 | 32.62 ± 2.09 | 0.970 |
| Urine analysis | | | |
| Pus cells | | | |
| • No pus cells | 41 (46.1%) | 53 (59.6%) | |
| • 8 – 10 cells | 28 (31.5%) | 21 (23.6%) | 0.164 |
| • 10 – 20 cells | 19 (21.3%) | 12 (13.5%) | |
| • 20 – 30 cells | 1 (1.1%) | 3 (3.4%) | |
| Glucose | | | |
| Nil | 87(97.8 %) | 88(98.9%) | 0.560 |
| + | 2(2.2 %) | 1(1.1%) | |

Eleven females missed the second antenatal visit of the study. Three participants were missed in the control group due to miscarriage, on the other hand eight participants were missed from the case group six of them due to miscarriage and the other two we have lost the contact with them. Therefore 167 participants attended the second antenatal visit, distributed as 81 cases and 86 controls. There was no significant difference between the two groups regarding FBG and a statistically significant difference regarding the one- and two-hours blood glucose level (*P*= <0.0001 and 0.007) respectively, (Table 2).

**Table 2:** General and clinical characteristics of the studied groups at second antenatal visit) (n =167)

| Variables (Mean±SD or N & %) | Cases (n =81) | Controls (n =86) | *P-value* |
|---|---|---|---|
| Gestational age (weeks) | 25.84±1.3 | 25.62 ± 1.34 | 0.276 |
| Weight (Kg) | 88.10±5.59 | 88.21±6.22 | 0.904 |
| Fasting blood glucose (mg/dl) | 82.93±21.27 | 86.35±18.25 | 0.265 |
| 1-Hr postprandial blood glucose (mg/dl) | 132.86±19.01 | 142.67±16.25 | <0.0001* |
| 2-Hr postprandial blood glucose (mg/dl) | 115.88±17.49 | 122.72±15.13 | 0.007* |
| Hemoglobin (gm/dl) | 10.79±1.0 | 10.82±1.02 | 0.808 |
| Systolic blood pressure (mmHg) | 115.31±12.36 | 113.72±12.65 | 0.414 |
| Diastolic blood pressure (mmHg) | 73.7±8.28 | 72.21±8.1 | 0.267 |
| Urine analysis | | | |
| • Pus cells | | | |
| No pus cells | 49 (60.5%) | 54 (62.8%) | |
| 8 – 10 cells | 3 (3.7%) | 0 | |
| 10 – 20 cells | 13 (16%) | 22 (25.6%) | |
| 20 – 30 cells | 4 (4.9%) | 5 (5.8%) | 0.075 |
| 30 – 40 cells | 4 (4.9%) | 0 | |
| 40 – 50 cells | 7 (8.6) | 3 (3.5%) | |
| >50 cells | 1 (1.2%) | 2 (2.3%) | |
| • Glucose | | | |
| Nil | 76 (93.8%) | 83 (96.5%) | |
| + | 3 (3.7%) | 2 (2.3%) | 0.707 |
| ++ | 2 (2.5%) | 1 (1.2%) | |
| • Albumin | | | |
| Nil | 75 (92.6%) | 75 (87.2%) | |
| + | 4 (4.9%) | 5 (5.8%) | 0.209 |
| ++ | 1 (1.2%) | 6 (7%) | |
| +++ | 1 (1.2%) | 0 | |

A number of five females missed the third antenatal visit one from the control group due to loss of contact with her and four from the case group one of them was a case of intrauterine fetal death and the other three due to loss of contact with them. Therefore 162 participants attended, distributed as 77 cases and 85 controls. There was no difference regarding RBS nor hemoglobin level nor blood pressure between the two groups. The glycosylated hemoglobin was statically lower among cases in comparison to controls (*P*= 0.001), (Table 3).

**Table 3**: General and clinical characteristics of the studied groups at third antenatal visit) (n =162)

| Variables (Mean ± SD or N & %) | Cases (n =77) | Controls (n =85) | *P-value* |
|---|---|---|---|
| Gestational age (weeks) | 36 ± 0.16 | 36 ± 0.15 | 0.999 |
| Weight (Kg) | 91.7 ± 5.2 | 92.69 ± 6.29 | 0.278 |
| Random blood sugar (mg/dl) | 105.31 ± 23.29 | 108.14 ± 26.65 | 0.475 |
| Hemoglobin A1C | 5.38 ± 0.61 | 5.66 ± 0.99 | 0.001* |
| Hemoglobin (gm/dl) | 10.84 ± 1.0 | 10.91 ± 1.01 | 0.679 |
| Systolic blood pressure (mmHg) | 118.96 ± 13.14 | 120.94±13.94 | 0.355 |
| Diastolic blood pressure (mmHg) | 74.94 ± 7.88 | 75.88 ± 8.49 | 0.464 |
| Urine analysis | | | |
| • Pus cells | | | |
| No pus cells | 46 (59.7%) | 57 (67.1%) | |
| 8 – 10 cells | 7 (9.1%) | 11 (12.9%) | |
| 10 – 20 cells | 19 (24.7%) | 9 (10.6%) | 0.307 |
| 20 – 30 cells | 2 (2.6%) | 3 (3.5%) | |
| 30 – 40 cells | 2 (2.6%) | 3 (3.5%) | |
| 40 – 50 cells | 1 (1.3) | 2 (2.4%) | |
| • Glucose | | | |
| Nil | 75 (100%) | 83 (97.6%) | |
| + | 1 (1.3%) | 1 (1.2%) | 0.995 |
| ++ | 1 (1.3%) | 1 (1.2%) | |
| • Albumin | | | |
| Nil | 68 (88.3%) | 72 (84.7%) | |
| + | 7 (9.1%) | 8 (9.4%) | 0.584 |
| ++ | 2 (2.6%) | 2 (5.9%) | |

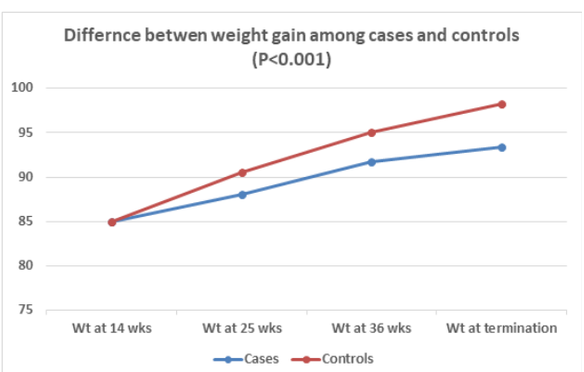
At termination the total of 162 females attended at labor ward, and the women in the cases group had statistically significant lower weight gain during pregnancy and experienced diarrhea more than those in the control group (*p-value* <0.0001 for both). The fetal body weight of the studied groups was 3.47 ± 0.51 kg in comparison to 3.44 ± 0.50 kg with no difference between the two groups (*p*=0.981), (Table 4).

The difference between the two groups regarding weight gain during the study period is showed in (Graph 1).

**Table 4:** General and clinical characteristics of the studied groups at termination (n =162)

| Variables (Mean ± SD or N & %) | Cases (n =77) | Controls (n =85) | *P-value* |
|---|---|---|---|
| Gestational age (weeks) | 36.7 ± 5.8 | 37.9 ± 3.8 | 0.096 |
| EFBW (Kg) | 3.47 ± 0.51 | 3.44 ± 0.50 | 0.634 |
| Weight (Kg) | 93.1 ± 5.3 | 94.4 ± 6.8 | 0.157 |
| Weight gain during pregnancy | 7.7 ± 2.5 | 10.4 ± 2.9 | < 0.0001* |
| Fetal body weight (Kg) | 3.35 ± 0.45 | 3.35 ± 0.45 | 0.981 |
| Mode of delivery | | | |
| Normal vaginal delivery | 56 (72.7%) | 58 (68.2%) | |
| Caesarian section | 21 (27.3%) | 27 (31.8%) | 0.610 |
| Post-partum hemorrhage | | | |
| Yes | 11 (12.4%) | 12 (13.5%) | 0.823 |
| No | 78 (87.6%) | 77 (86.5%) | |
| Gestational diabetes | | | |
| Yes | 5 (6.5%) | 4 (4.7%) | |
| No | 72 (93.5%) | 81 (95.3%) | |
| Gestational hypertension | | | |
| Yes | 5 (6.5%) | 8 (9.4%) | |
| No | 72 (93.5%) | 77 (90.6%) | |
| NICU | | | |
| Yes | 8 (9%) | 11 (12.5%) | 0.451 |
| No | 81 (91%) | 77 (87.5%) | |
| Diarrhea | | | |
| Yes | 38 (42.7%) | 16 (18%) | < |
| No | 51 (57.3%) | 73 (82%) | 0.0001* |
| Nausea | | | |
| Yes | 36 (40.4%) | 39 (43.8%) | 0.649 |
| No | 53 (59.6%) | 50 (56.2%) | |
| Vomiting | | | |
| Yes | 25 (28.1%) | 18 (20.2%) | 0.220 |
| No | 64 (71.9%) | 71 (79.8%) | |

*EFBW: Estimated fetal birth weight, NICU: Neonatal intensive care unit




**Graph 1:** The differences between weight gain of cases and controls

## DISCUSSION

Metformin use during pregnancy was alleged to reduce the incidence of large for gestational age fetuses[13].

Our groups of pregnant women were matched in age, parity, BMI and gestational age at study entry. Metformin appeared to have a good patient acceptability[14] with a less weight gain during enrollment of the trial among the pregnant females with a better glycemic control. There is no difference between the 2 groups regarding incidence of fetal birth weight, developing GDM or gestational hypertension.

Our results about the effect of metformin on reducing maternal weight gain during pregnancy are consistent with María J. Picón-César, et al[15], despite their population of cohort were diabetics and ours were not.

Besides metformin was more beneficial to a better glycemic control during the second and third trimesters in a at risk groups of population, these are consistent with Carolyn Chiswick, et al[10], Hickman et al[16] and Pratap Kumar, et al[17].

However there was no difference between our two groups regarding neonatal macrosomia, nor the NICU admission, this is in agreement of María J. Picón-César, et al[15] and in contrary to Jahan Ara Hassan et al[13], who proposed that metformin prevents fetal macrosomia with lesser incidence of NICU admission and less perinatal complications; the results of their study can be attributed to the comparison with the other group of pregnant women who were on insulin therapy which can lead to more hypo or hyper glycemic events, besides this study was done on already diabetic females which carries a more potential risks for fetal macrosomia and NICU admission.

Our study showed that metformin is a safe and can be a relevant medical alternative for treating GDM. The incidence of adverse pregnancy or neonatal outcomes was not increased in women treated with metformin. Metformin was found to be especially suitable for lean and moderately overweight women with postprandial hyper-glycaemia in the latter half of pregnancy[18]. The mean birthweight of the newborns did not differ significantly between the metformin and placebo groups, which is in line with both earlier cohort studies and a prospective randomized study[14,18,19].

Because of the small study population, our study has limited power to detect differences in variables with low incidence, such as brachial plexus injuries, perinatal mortality or congenital anomalies. We will later evaluate the growth and development of the offspring born to the study groups to investigate any possible subsequent significance of the antenatal medication.

The caesarean section rate was similar to pregnancies with metformin therapy and without, it is in line with a previous Finnish study[18] but is lower than in other studies comparing metformin treatment with insulin[14,19].

Maternal hyper-glycaemia is a common adverse pregnancy event associated with an increased risk of perinatal complications.

Metformin seems to be a safe and effective adjuvant in the prophylaxis for increasing maternal weight gain during pregnancy and can be used as a treatment of GDM especially for women with mild GDM.

To our knowledge it is one of a few studies testing the effect of metformin on obese non diabetic Egyptian females.

The limitations of our study were the small sample size and the attrition of 16 cases during the study procedure.

To conclude, using metformin for obese non diabetic females, from the second trimester of pregnancy can reduce the maternal weight gain during pregnancy and provide a better glycemic control with no increase in perinatal and maternal complications.

## CONFLICT OF INTERESTS

There are conflicts of interest.

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