ORIGINAL ARTICLE

Effect of Metformin on maternal and fetal outcomes in over weight and obese pregnant women

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ABSTRACT

Keywords:
Metformin,obesity,gestational diabetes mellitus.

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Background: Obesity in pregnant women had serious effects. So, management of obese pregnant women is important to reduce such complications. **Aim of the work:** Toassess role of Metformin on the outcome of pregnant obese and overweight women in a tertiary care center located in Upper Egypt**. Methodology:** A single blind randomized controlled trail was conducted between 2018 and 2019. It enrolled 100 pregnant women, overweight and obese, who were randomly subdivided into either received 1 gm/day Metformin (study group) or received osteocare (placebo group). Both groups were followed up till time of delivery where maternal and fetal outcomes were assessed. **Results:** Both groups had insignificant diffrences as regard baseline data. Femur length and biparietal diameter were comparable. Study group had significant decrease with the incidence of gestational diabetes mellitus (GDM), gestational hypertension, preeclampsia , excessive weight gain,premature rupture of membrane (PROM)and fetal macrosomia but both groups had insignificant diffrences as regard other fetal outcomes. **Conclusion:** Metformin had significant effects on fetal birth weight. but it had insignificant diffrences as regard other fetal outcomes. Also decrease maternal outcomes as GDM , gestational hypertension, preeclampsia , excessive weight gain and PROM in comparison to placebo but future randomized controlled trails are recommended to confirm these benefits.

INTRODUCTION

Obesity is defined when body mass index **(BMI)**(a measurement obtained by dividing the person's weight by the square of the person's height) is over 30kg/m2.while over weight is defined when BMI ranges from (25-30)kg/m2**.**

There has been a lot of interest as regard antenatal nutritional and lifestyle counseling to pregnant women who are obese or overweight as a way to reduce gestational weight gain and enhance mother and baby health. However, such prenatal therapies appear to have only a little impact(1).

Preeclampsia, prenatal hypertension, gestational diabetes, macrosomia, stillbirth, intrauterine fetal death, higher incidence of caesarian section, and higher incidence of maternal weight gain are all connected with obesity during pregnancy. These complications could be explained secondary to increase insulin resistance with obesity (2).

Metformin is the main line of therapy of patients with type 2 diabetes mellitus, particularly those who are overweight and obese.The main mechanism of action is to reduce hepatic gluconeogenesis and promote insulin sensitivity of body tissues. Gastric upset is the main drawbacks of it (3).

Previous published report found that it reduces complications during pregnancy suchwith no effect on baby's development. Also, it was found that babies born to women treated with Metformin had less visceral fat and decrease insulin resistance(3).And yet, there is paucity in studies about that issue in our locality.

AIM OF THE WORK

This work was designed to assess the effect of Metformin on both fetal and maternal outcomes in over weight and obese pregnant women.

PATIENTS& METHODS

Informed consent was obtained from all women after being informed about the aims and process of the study as well as applicable objectives. The study was performed in accordance with the Declaration of Helsinki on medical protocol and ethics. It was approved by Institutional Review Board, Faculty of Medicine of Aswan University.

Study setting& design

A single blind randomized control trial was conducted in period between

April 2018 to April 2019.

Participants

One hundred over weight (body mass index (BMI) was between 25-29.9 kg/m^2) and obese (BMI was ≥30 kg/m^2) pregnant women were recruited in the study. All women had singleton pregnancy with gestational age was between 12^{th} and 18^{th} week.

Any woman with one or more of the following was excluded; diabetes mellitus, major fetal defects detected at the scan, medical disorders with pregnancy (renal diseases, liver diseases,and hyperemesisgravidarum), sensitivity to Metformin and multiple pregnancies.

Sample size:

Based on previous studies **(**Argyro ***et al.,*** **2016)** who found that the adjusted the mean significant difference in the mean weight gain between Metformin in the obese pregnant and the non (4.3 ±3.2) non . (6.4 ± 4.3) so Calculated sample size for the current study is 100 patients using the following formula **(Charan *et al.*, 2013)**:

The sample size will be calculated using the following formula:

$$n = 2\left[\frac{(Z_{\alpha/2} + Z_{\beta}) * \sigma}{\mu_1 - \mu_2}\right]^2$$

Where:

n = sample size

$\mathbf{Z_{\alpha/2}}$ = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

$\mathbf{Z_{\beta}}$ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)

σ = the estimate of the standard deviation of the mean MCA RI = 1.27

$\mathbf{\mu_1}$ = mean in excessive weight gain in Metformin group (4.3).

$\mathbf{\mu_2}$ = mean in the excessive weight gain in control . (6.4)

So, by calculation, the sample size will be equal to 100(50in each group) patients in total.

Randomization

Simple randomization technique was performed thorough sequentially numbered opaque envelops using a random numbers table (1:1 ratio) where those patients were subdivided into two groups**(figure 1).**The enrolled women were divided into two equal groups: group 1 (study group, 50 patients) received metformin 1000 mg tablet/ after lunch starting from (12-18) weeks until delivery and group 2 (control group, 50 patients) received osteocare as single dose daily after meal starting from (12-18) weeks until delivery.

Methods

All recruited women were subjected to history taking and completeclinical evaluation. The following data were gathered; age, residence, occupation, education, duration of marriage, parity, and mode of deliveries. Also, height and weight with calculation of BMI were recorded.

Abdominal ultrasound was done for fetal biometry confirming the gestational age and detection of any fetal gross anomalies. Baseline laboratory data was ordered; complete blood count, urine analysis, random blood glucose level.

Follow up

Women were followed until delivery in the antenatal clinic of our hospital.Follow-up visits were scheduled at intervals of 4 weeks until 36 weeks then weekly till

delivery. In each visit, the following were assessed;

- Maternal weight gain and blood pressure.
- Ultrasonography to determine fetal biometry,fetal gestational age, fetal weight,amniotic fluid index, placental grade and placental site abnormalities if present.

-Laboratory investigations in form of urine analysis,random blood sugar and complete blood count.

Adherence assessment

We assessed adherence to taking Metformin or Osteocare tab by counting the tablets that were returned by the patients at each visit; if during a given visit a patient forgot to return the tablets, we relied on verbal report and on the results of previous and subsequent visits. Adherence was considered to be good if the total number of tablets consumed were at least 50% of the total number prescribed and poor if they were less than 50%**(figure 1).**

Outcomes

Maternal outcome included; maternal lweight gain, development of gestational diabetes, development of hypertension/preeclampsia, stillbirth, 2nd trimester miscarriages and need to caesarian section.

Neonatal outcomes included; neonatal hypoglycemia, prematurity, hyperbilirubinemia, respiratory distress, macrosomia, and birth trauma.

Statistical analysis

Data entry, processing and statistical analysis was carried out using MedCalc ver. 18.2.1 (MedCalc, Ostend, Belgium). Tests of significance (Kruskal-Wallis, Wilcoxon's, Chi square, logistic regression analysis, and Spearman's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

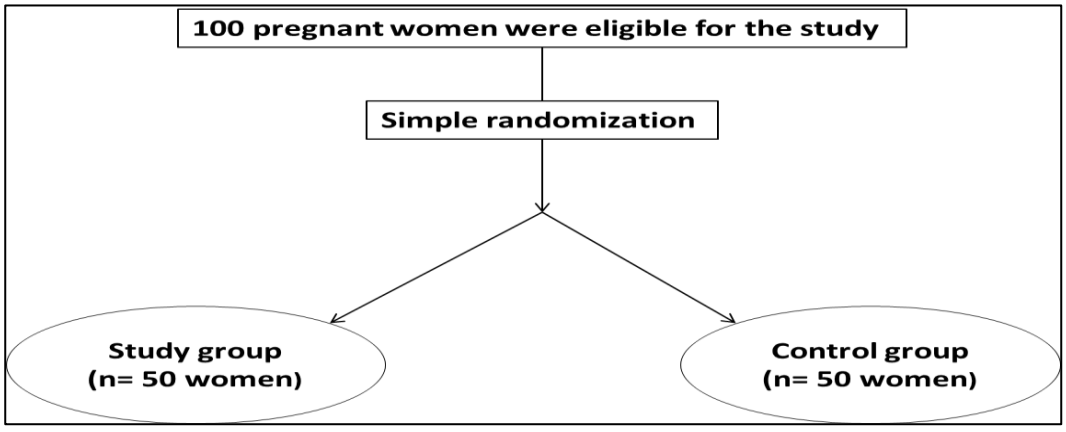

Figure (1): Flow chart of the current study

RESULTS

Table (1): Maternal demographic data and body mass index of the studied groups

Variable	Study group (n=50)		Control group (n=50)		P value
Age (Years)	31.68±5.1		32.1±4.22		0.67
Parity					0.82
Primigravida	11	22 %	10	20 %	
Multigravida	24	48 %	22	44 %	
Grandmulti	15	30%	18	36%	
Residency					0.55
Rural	23	46 %	20	40 %	
Urban	27	54 %	30	60 %	
Education					0.66
Illiteracy/primary school	35	70 %	37	74 %	
Secondary/high school	15	30 %	13	26 %	
Occupation					0.42
House wife	40	80 %	43	86 %	
Working	10	20 %	7	14 %	
Body mass index (kg/m^2)	29.68±4.3		30.8±4.93		0.23

Data expressed as frequency (percentage), mean (SD). *P* value was significant if ≤ 0.05

It was found that there are no significant differences between the studied groups as regard maternal demographic data and body mass index.

Table (2): Maternal clinical and laboratory data of the studied groups at the first visit

Variable	Study group (n=50)		Control group (n=50)		P value
SBP (mmHg)	116.56 ± 9.7		113.6 ± 10.25		0.14
DBP (mmHg)	76.96 ± 6.66		75.6 ± 7.6		0.34
RBG(mg/mmol)	68.08 ± 9.14		66.24 ± 6.83		0.26
Urine analysis Albumin	10	20 %	6	12 %	0.28
(positive)	0	0 %	0	0 %	-----
Ketones(positive)					
Hemoglobin level (g/dl)	10	20 %	6	12 %	0.28
Anemic	40	80 %	44	88 %	
Not anemic					

Data expressed as frequency (percentage), mean (SD). *P* value was significant if <0.05. SBP: systolic blood pressure; DBP: diastolic blood pressure; RBG: random blood glucose

Both studied groups had no significant differences between the studied groups as regard baseline laboratory and clinical data.

Table (3): Fetal biometry measures of the studied groups at the first visit

Variable	Study group (n=50)	Control group (n=50)	P value
Femur length(mm)	24.25 ± 3.1	23.61 ± 2.98	0.28
Biparietal diameter(mm)	38.74 ± 6.21	41.44± 3.1	0.34
Abdominal circumference(mm)	134.3 ± 4.22	146.56 ± 5.3	0.09

Data expressed as mean (SD). *P* value was significant if ≤ 0.05.

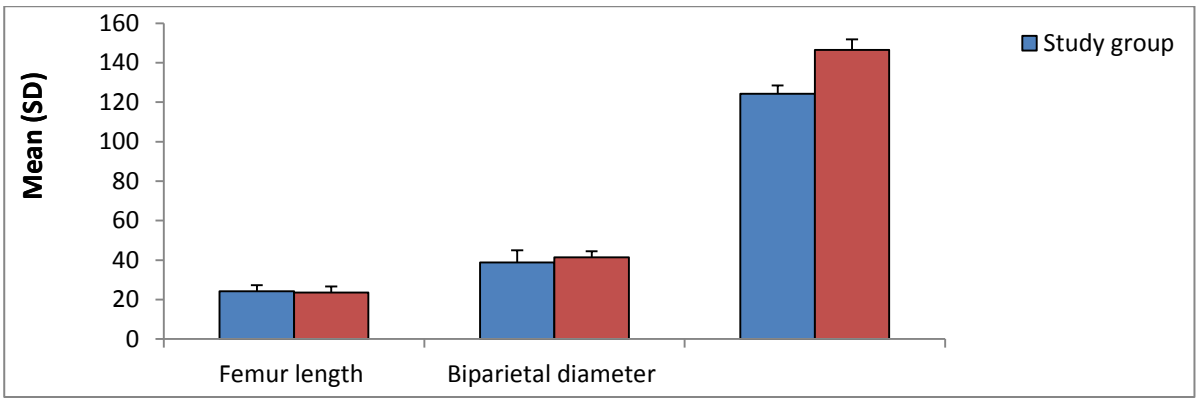

Figure (2): Fetal biometry measures of the studied groups at the first visit

It was found that there are no significant differences between the studied groups as regard abdominal circumference and no significant differences between the studied groups as regard other fetal biometric measures.

Table (4): Maternal outcomes of the studied groups

Variable	Study group (n=50)		Control group (n=50)		P value
	No.	%	No.	%	
Gestational diabetes mellitus					**0.001**
Yes	3	6 %	18	36 %	
No	47	94 %	32	64 %	
Gestational hypertension					**0.001**
Yes	4	8 %	20	40 %	
No	46	92 %	30	60 %	
Preeclampsia					**0.001**
Yes	6	12 %	22	44 %	
No	44	88 %	28	56 %	
PROM					**0.025**
Yes	2	4 %	9	18 %	
No	48	96 %	41	82 %	
Excessive weight gain					
Yes	5	10.0	15	30%	**0.030**
No	45	90.0	35	70%	
Mode of delivery					**0.010**
CS	10	20.0	19	38%	
N.V.D	40	80.0	31	62%	

Data expressed as frequency (percentage). *P* value was significant if ≤ 0.05. PROM: premature rupture of membrane; CS: cesarean section; NVD: normal vaginal delivery

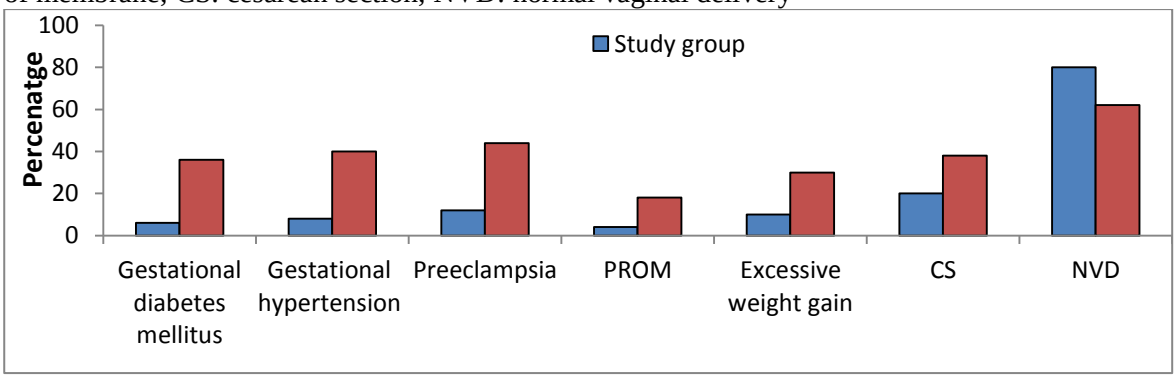

Figure (3): Maternal outcomes of the studied groups at the first visit. CS: cesarean section; PROM: premature rupture of membrane; NVD: normal vaginal delivery

It was found that there are significant differences between the studied groups as regard gestational diabetes mellitus (GDM), gestational hypertension,pre-eclampsia, premature rupture of membrane (PROM), excessive weight gain, and mode of delivery.

Table (5): Fetal outcomes of the studied groups

Variable	Study group (n=50)		Control group (n=50)		P value
Birth weight (kg)	3.7±0.44		3.9±0.384		0.05
Birth outcomes					
Miscarriage	0	0 %	2	4 %	0.24
Stillbirth	1	2 %	3	6 %	
Neonatal death	0	0 %	1	2 %	
Live birth	44	88 %	36	72 %	
Delivery at <37 weeks	5	10 %	8	16 %	
NICU admission					0.576
Yes	4	8 %	9	18 %	
No	46	92 %	41	82 %	
Respiratory distress syndrome					0.356
Yes	3	8 %	6	16 %	
No	47	92 %	44	84 %	
Hyperbilirubinemia					0.766
Yes	6	12 %	7	14 %	
No	44	88 %	43	86 %	
Hypoglycaemia					0.538
Yes	5	10 %	7	14 %	
No	45	90 %	43	86 %	
Birth trauma					0.99
Yes	2	4 %	5	2 %	
No	48	96 %	45	98 %	
APGAR score at 5 minute	9.88±1.3		9.7±1.5		0.522

Data expressed as frequency (percentage), mean (SD). *P* value was significant if ≤ 0.05. NICU: neonatal intensive care

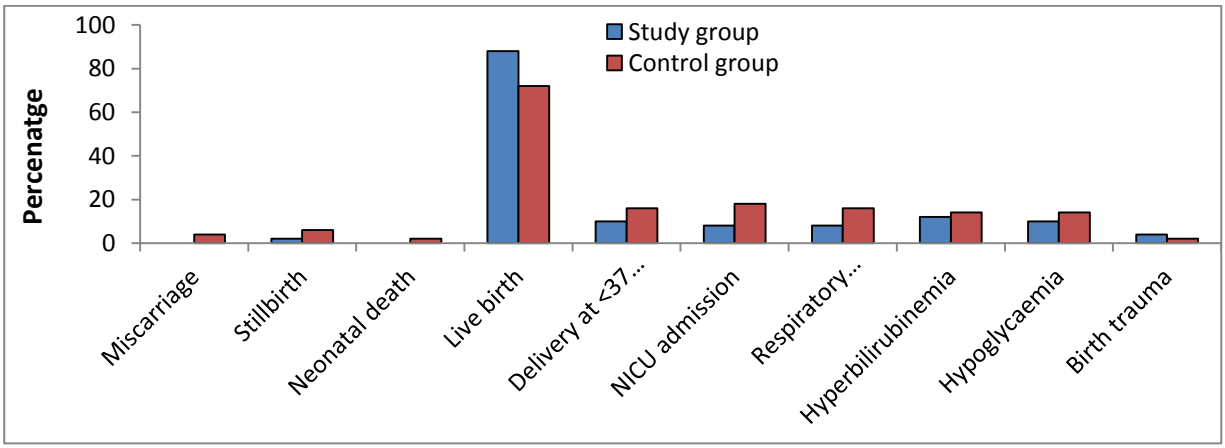

Figure (4): Fetal outcomes of the studied groups. NICU: neonatal intensive care unit

It was found that there are significant differences between the two studied groups as regard fetal weight. And there are no significant differences as regard other fetal outcomes.

DISCUSSION

Metformin has been used extensively in the treatment of gestational diabetes mellitus, and there has been no evidence of an increase in the incidence of birth defects associated with its use (4). Studies involving women with gestational diabetes mellitus have shown that Metformin reduces gestational weight gain (3,5).

We conducted this study to evaluate maternal and fetal outcomes in overweight and obese pregnant women with the use of Metformin. The current study revealed no significant diffrences between both studied groups as regard baseline data.In consistent with these results, **Syngelaki *et al.* (2016)** found no significant differences between the two groups in the characteristics at baseline (6).

Our study showed that there were no significant differences between the studied groups in maternal clinical and laboratory data.We found a significant difference between the studied groups as regard fetal abdominal circumference at the first visit with no significant difference between the studied groups as regard to fetal femur length& biparietal diameter. On the contrary **De Leo *et al*.(2011)**showed a comparable mean fetal weight and femur length between the study and control groups (8).

In this study, there was a significant difference between the studied groups as regard GDM, gestational hypertension, preeclampsia, and PROM. Also, there were significant differences between the studied groups as regard weight gain in Metformin and placebo group and mode of delivery as larger number of cases with excessive weight gain and C.S delivery were among placebo group.

In agreement with us **Fougner *et al.* (2008)**stated that Metformin was associated with a significantly lower rate of preeclampsia than those who received placebo (9).In contrast**Vanky *et al*.(2010)** found that both group of women either on placebo or on Metforminshowed no significant diffrences as regardGDM, pre-eclampsia and pre-term delivery (11). Also, in contrast to the current study **Chiswick*et al.* (2015)**found no significant difference between both groups as regard maternal weight gain (7).

This study shows that, there was a significant difference between the two studied groups as regard fetal weight, NICU admission, respiratory distress syndrome, hyperbilirubinemia, hypoglycemia, birth trauma, and Apgar score. This was consistent with **Chiswick *et al.* (2015)** who stated that both groups had insignificant diffrences as regard fetal outcome (7).

In contrast, **Balani *et al*.(2009)**showed that women who were treated with Metformin alone had lesser incidence of prematurity, neonatal jaundice and admission to neonatal unit with an overall improvement in neonatal

morbidity as compared to the women treated with insulin (5).

Interestingly **Ijäs *et al*. (2011)**found that Metformin was better suited than insulin for prevention of fetal macrosomia, especially in lean or in moderately overweight women developing GDM in late gestation, and insulin was preferred therapy for women with considerable obesity, high fasting blood glucose levels and an early need for pharmacological treatment (12).

However, a larger study by**Vanky *et al*. (2010)**the same group, which randomized women with PCOS to either Metformin or placebo throughout pregnancy, showed no difference in birth weights of the babies in the two groups. However, the mean BMI of the participants in these studies was less than 30 kg/m^2(11).

On the agree with our finding, a prospective **De Leo *et al*.(2011)**study done on pregnant women with PCOS who received Metformin before conception and up to 37 weeks of pregnancy *vs.* normal pregnant controls, showed a comparable mean neonatal Apgar scores between the 2 groups (8).Also,**Silva *et al* (2017)** found compared the use of Metformin and insulin in the management of GDM. There was no increased chance of low Apgar score, both at the first and the fifth minutes, according to the therapy used (13).

The study has certain limitations as; 1) it was not adequately powered for the secondary outcomes, 2) lack of cooperation of some women who refused to participate, and 3) long time was needed to convince women to participate in this study. On the other hand, there is much strength among the current study as; 1) our trial included women, who had moderate obesity and were selected from a screened population of women receiving routine pregnancy care, and 2) in addition, a high percentage of eligible women agreed to participate, and they also had a high rate of adherence to the study regimen.

Another point of strength among the current study is the design of the study that was a single blind randomized control trial, making the study robust and generalizable, eliminate any bias and that, despite women's natural reluctance to take medication during pregnancy, we were able to recruit to our target sample size, generating adequate power to address our hypothesis

Finally, Metformin is recommended as line of treatment of overweight and obese pregnant women. A large Randomized control trials on a large number of pregnant women are needed to support our conclusion.

Conclusion: Metformin supplementation during pregnancy for obese and overweight women was found to be beneficial in reducing excess birth weight, preeclampsia, gestational diabetes mellitus, and excessive weight gain.

AUTHORS' CONTRIBUTIONS

AbdouSaeedAit-Allah (study design and revising manuscript critically for important intellectual content)

NahlawaerAlsayed Shady (interpretation of data, and revising manuscript)

Elham Mohammed Ahmed (acquisition of data, analysis and interpretation of data, and drafting the manuscript)

All authors have approved the final article for submission

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