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Research Article

Can metformin limit weight gain in the obese with pregnancy?

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ABSTRACT

Background: Maternal overweight and obesity is associated with many obstetric complications. Obesity is linked to insulin resistance. Improving insulin sensitivity may therefore account for weight reduction. Metformin was found to be effective in type 2 diabetes and polycystic ovarian syndrome through improving insulin sensitivity. Several studies proved its efficacy in the obese non-pregnants, but its role during pregnancy is not yet well-established. In this study, we are testing the ability of metformin to limit weight gain with pregnancy and therefore reducing complications as gestational Diabetes and hypertension.

Methods: A prospective study was conducted in Alexandria, Egypt. The study was registered in the South African Cochrane Centre under an identification number PACTR201505001142202. Two Hundreds participants with a BMI of ≥ 35 Kg/m², pregnant in the early second trimester, were equally divided into two groups; in which group 1 will receive metformin 500 mg twice a day and group 2 will receive placebo. Prior to inclusion, 75 g oral glucose tolerance test, fasting insulin, fasting blood glucose, 1 h and 2 h glucose blood and HbA1C were measured. Both groups were followed up monthly for weight and for pregnancy complications namely gestational diabetes and pre-eclampsia till 36 weeks of pregnancy.

Results: There was a significant difference in the weight gain and the one hour blood sugar measurement between the two groups, but not in the occurrence of pregnancy complications namely gestational diabetes and hypertension.

Conclusions: Metformin succeeded to limit weight gain the obese with pregnancy.

Keywords: Pregnancy, Weight gain, Metformin

INTRODUCTION

Maternal overweight and obesity are the most common high-risk obstetric conditions.¹ During pregnancy, fat is preferentially deposited in the femoral and abdominal regions.²

Regional fat distribution may differ for women already overweight or obese before pregnancy. Obese women experience more variable changes, including lower or higher gestational weight gains and lower or similar gestational fat gains, but have greater increases in central adiposity and fat deposition during the postpartum period when compared with lower BMI groups.³

Scientists have postulated that the major determinant of body fat distribution is insulin resistance. Normally, fat is deposited in subcutaneous adipose stores. It is hypothesized that as fat stores increase, so does insulin resistance, limiting further deposition in the subcutaneous stores. This leads to increased uptake of triglycerides into visceral stores and other ectopic sites such as hepatic sites and others.⁴⁻⁹

Human pregnancy is characterized by a series of metabolic changes that promote adipose tissue accretion in early gestation, followed by insulin resistance and facilitated lipolysis in late pregnancy. In early pregnancy, insulin secretion increases, while insulin sensitivity is

unchanged, decreased, or may even increase. However, in late gestation, maternal adipose tissue depots decline, while postprandial free fatty acid (FFA) levels increase and insulin-mediated glucose disposal worsens by 40–60% compared with pre pregnancy. The ability of insulin to suppress whole-body lipolysis is also reduced during late pregnancy¹⁰ and this is further reduced in GDM subjects,¹¹ contributing to greater postprandial increases in FFAs, increased hepatic glucose production and severe insulin resistance.¹²⁻¹⁶

Although various placental hormones have been suggested to reprogram maternal physiology to meet foetal needs, the cellular mechanisms for this complex transition remain obscure.¹⁶ However, it is important to note that, with the exception of tumour necrosis factor (TNF)- α , changes in placental hormones in human pregnancy do not directly correlate with changes in maternal insulin resistance. Therefore, a synergy with other obesity or pregnancy-related factors may hold the key to understanding how insulin resistance develops during pregnancy.¹⁷

Recent prospective studies have implicated adiponectin from adipocytes and secreted factors, such as TNF- α , as active candidates in mediating insulin resistance of pregnancy. Collectively, these factors, known as “adipokines,” include leptin, adiponectin, TNF- α , interleukin-6, resistin, and others. Obese humans show a positive correlation between TNF- α levels and BMI and hyperinsulinemia.¹⁸⁻²⁰

Adiponectin is a secreted globular protein synthesized exclusively in adipocytes. In humans, low plasma adiponectin concentrations correlate highly with insulin resistance in obesity, type 2 diabetes, and gestational Diabetes mellitus GDM.²¹⁻²³ Recent findings also show that adiponectin secretion and adiponectin mRNA levels in white adipose tissue decline with advancing gestation, even in lean women suggesting that there are pregnancy-associated factors that reduce adiponectin levels.²⁴

Circulating levels of adiponectin have been shown to correlate with whole-body insulin sensitivity, presumably working through adiponectin receptors in skeletal muscle and liver.²⁵ Adiponectin stimulates glucose uptake in skeletal muscle and reduces hepatic glucose production through its effect on AMP-activated protein kinase. Thus, adiponectin can be viewed as an endogenous insulin-sensitizing hormone. Several studies have demonstrated that adiponectin levels are lower during late pregnancy.²⁶⁻³¹

According to these phenomena, insulin resistance of normal pregnancy is multifactorial, involving reduced ability of insulin to phosphorylate the insulin receptor, subclinical inflammation, placental hormones, reduced adiponectin secretion, and excess lipolysis.

Metformin is a biguanide that decreases hepatic glucose output by inhibiting gluconeogenesis and enhancing peripheral glucose uptake. It also decreases intestinal glucose absorption and increases insulin sensitivity.

It is a well-established anti-diabetic drug, which has been used from the late 1950s on and still first line therapy in type 2 diabetes.^{32,33}

Metformin reduces insulin resistance which is the underlying cause of both type 2 diabetes and PCOS.^{34,35,43,44} Metformin has been observed to cause weight loss in type 2 diabetes patients.^{36,37}

Obesity in non-diabetic patients is also linked to insulin resistance.³⁸⁻⁴⁰ Improving insulin sensitivity may account for weight reduction under metformin therapy, although the exact underlying patho mechanisms are unclear.^{37,41,42}

Efficacy of metformin to reduce weight in a standardized setting has been tested in few randomized trials, data on its effectiveness in the obese nondiabetic during pregnancy, and on the foetus are still lacking. If in fact less visceral and ectopic fat in the foetus may signal reduced insulin resistance, therefore there may be a long-term benefit from in utero metformin exposure which is not yet proved.⁴⁵

METHODS

A prospective study was conducted in El Shatby maternity hospital, Alexandria, Egypt after the approval of the ethics committee of Alexandria university, the study was registered in the south African Cochrane Centre under an identification number PACTR201505001142202. Two Hundreds pregnant participants with a BMI of ≥ 35 Kg/m², in the early second trimester, were offered to participate. Prior to inclusion, a 75 g oral glucose tolerance test was performed. Blood glucose, HbA1C and plasma insulin levels were measured at baseline, 1 h and 2 h after glucose ingestion.⁴⁶ All participants had normal levels irrespective of the degree of insulin sensitivity.

Participants were divided into two groups;

Group 1: Hundred participants received metformin in a dose of 500 mg twice a day.

Group 2: Hundred participants received placebo.

Both groups were followed up monthly for weight and for the development of pregnancy complications namely gestational Diabetes and pre-eclampsia till 36 weeks. Periodic ultrasonographic fetal weight estimation was also done.

The aim of the study is to evaluate if metformin in the obese pregnant will limit weight gain and thereby decreasing obesity risks with pregnancy especially pre-

eclampsia and gestational diabetes, and also to evaluate if its use will affect the fetal weight or not.

RESULTS

A total of 200 participants were included in the study. The average age was 26 years. The average dose of metformin was 1000mg daily in the metformin-treated group ranging from 500 mg to 1500 mg depending on the original body mass index.

Only 15 (15%) patients under metformin complained of gastrointestinal side effects which were well tolerated and they continued the drug. Monthly ultrasonographic evaluation of the foetal weight was done and the estimated foetal weight for all the participants matched with the percentile for foetal age.

Statistical procedure

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (ver 20). Data were entered as numerical or categorical, as appropriate. Parametric statistics (minimum and maximum, mean, standard deviation) and comparison using independent t-test was carried out. Chi-squared test (Fisher Exact) was used for analysis of association. In the present study an alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.⁷

Table 1 displays the age, BMI and basal investigations in the two studied groups.

Table 1: Age, BMI and basal investigations in the two studied groups.

	Metformin group (n=100)	Placebo group (n=100)	Significance
Age (years)			
Minimum-Maximum	18-37	17-38	t=0.950
Mean ± S.D.	26.92±5.20	26.20±5.51	p=0.343 NS
BMI (kg/m²)			
Minimum-Maximum	35.00-38.30	35.00-38.00	t=1.759
Mean ± S.D.	36.42±1.04	36.17±0.99	p=0.080 NS
Fasting blood glucose (mg/dl)			
Minimum-Maximum	57.00-87.00	57.00-89.00	t=1.176
Mean ± S.D.	72.73±8.47	71.29±8.83	p=0.241 NS
1-hour PPBG (mg/dl)			
Minimum-Maximum	89.00-142.00	90.00-138.00	t=3.621
Mean ± S.D.	107.55±13.12	114.31±13.27	p=0.000*
2-hour PPBG (mg/dl)			
Minimum-Maximum	85.00-125.00	85.00-116.00	t=1.233
Mean ± S.D.	95.86±6.73	97.09±7.36	p=0.219 NS
Fasting insulin			
Minimum-Maximum	6.90-9.00	5.90-9.00	t=1.130
Mean ± S.D.	8.10±0.59	7.99±0.75	p=0.260 NS
HbA1C (%)			
Minimum-Maximum	5.90-8.70	5.30-8.70	t=0.995
Mean ± S.D.	7.28±0.77	7.16±0.91	p=0.321

t: independent t test, p: probability of error (alpha = 0.05)

There was no difference in age between the two groups where the p was p=0.343 and no significant difference in body mass index between the two groups where the p was 0.080. Basal investigations showed no significant difference in fasting blood sugar, fasting insulin, and 2 hour postprandial blood sugar but there was a significant difference in the one hour postprandial blood sugar between the two groups where the p was = 0.000 There was no significant difference in the haemoglobin A1c (p= 0.321).

Table 2 and figure 1 displays the weight gain between the two groups, a significant reduction in weight gain in the metformin group compared to the other group where the

mean was 6.55 for the metformin group and 11.61 for the other group.

The limitation in weight gain in the metformin treated group was significant as compared to the control (p 0.000) which proved the effect of metformin in limiting weight gain.

Table 3 displays Pregnancy complications in the two studied groups.

Table 2: Weight gain in the two studied groups.

	Metformin group (n=100)	Placebo group (n=100)	Significance
Weight gain (kg)			
Minimum -	0.50-13	6-18	t=12.957
Maximum	6.55 ± 2.60	11.61 ± 2.90	p=0.000
Mean ± S.D.			

t: independent t test, p: probability of error (alpha = 0.05)

Table 3: Pregnancy complications in the two studied groups.

	Metformin group (n=100)	Placebo group (n=100)	Significance
Hypertension n (%)	2 (2%)	6 (6%)	P (FE) = 0.279 NS
Gestational diabetes n (%)	2 (2%)	6 (6%)	P (FE) = 0.279 NS

p(FE): probability of Fisher exact test

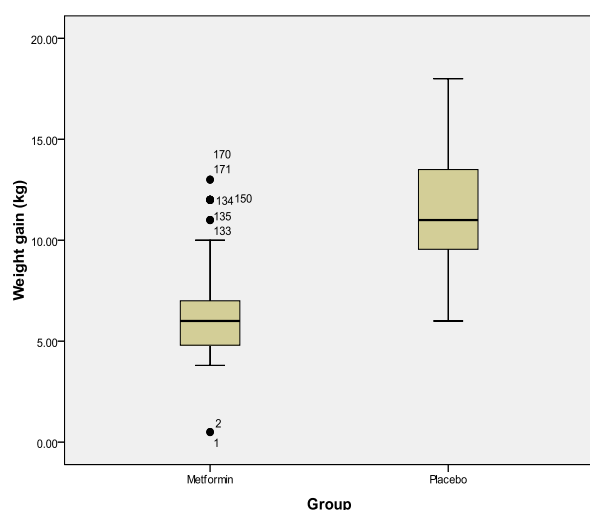


Figure 1: Box and whisker graph of weight gain (kg) in the two studied groups, the thick line in the middle of the box represents the median, the box represents the inter-quartile range (from 25th to 75th percentiles), the whiskers represents the minimum and maximum values after excluding outliers (black-filled circle) and extremes (asterisks).

Gestational diabetes and hypertension were less in the metformin group compared to the other group, only two cases came with gestational diabetes among metformin users compared to six cases among the non- users, the same with hypertension, but this difference was not statistically significant where the p was 0.279 for hypertension and p was 0.279 for diabetes.

DISCUSSION

In our study we found an average weight gain of 6.55kg under treatment with metformin for 6 months started at twelve weeks gestation and ended at thirty six weeks gestation in overweight and obese pregnant participants , mostly insulin-resistant compared to an average weight gain of 11.61 kg without metformin which was statistically significant.

Although metformin is clinically recognized as a weight reducing agent, there is little evidence in the literature supporting this knowledge.^{47,48}

Some researchers used metformin for a short duration ranging from 15 days to 3 months in 6 out of 9 studies, the Body mass index of the participants was limited to overweight (BMI 25-29.9 kg/m²) or grade I obesity (BMI 30-34.9 kg/m²), therefore severe insulin resistance in these patients was unlikely and these studies were conducted on non- pregnant subjects. No decrease in weight was noticed with metformin.⁴⁹

Other studies investigated metformin in women suffering from PCOS with base line weight of 97.0 kg (Gamberini et al) reported an insignificant weight reducing effect of metformin.⁵⁰⁻⁵³

In this study, patients were on a hypocaloric diet before metformin was started. The only possible explanation for the insignificant effect of metformin is the diminished insulin resistance produced by the hypocaloric diet.⁵⁴ Also the dosage of metformin was only 850 mg daily.

In our study, we increased the dose of metformin depending on the weight of the patient up to 1500 mg per day with an average dose 1000 mg per day and the participants were not on diet.

On the contrary, other studies proved a role for metformin in reducing weight where a weight loss of 6 kg was described in severely obese patients with mostly elevated fasting insulin levels (base line weight 117.3 kg).⁵⁵

Another study observed in obese type 2 diabetes patients -insulin resistant a weight loss of 8 kg after metformin treatment used for 24 weeks.⁵⁶

In a study by Mogul et al, 25 out of 26 hyperinsulinemic, severely obese women lost weight of at least 5% within 6 months of metformin therapy. Hyperinsulinemia of these patients indicates insulin resistance making them more sensitive to effects of metformin on body weight.⁵⁷

These data suggests that the efficacy of metformin to reduce weight depends on the degree of insulin resistance explained by the fact that insulin-receptor binding, the tyrosine kinase activity of insulin receptor and glucose

transport are altered in the same way in type 2 diabetes patients and comparably obese individuals without diabetes, supporting the efficacy of metformin in both conditions matching with our results when metformin was given to the obese with pregnancy.⁵⁸

Carbohydrate and lipid metabolism change during pregnancy to ensure a continuous supply of nutrients to the fetus.⁵⁹ In early pregnancy, glucose tolerance is normal or improved slightly, and peripheral sensitivity to insulin and hepatic basal glucose production are normal or increase by 15%.⁶⁰⁻⁶² As pregnancy advances, nutrient-stimulated insulin responses increase progressively despite only minor deterioration in glucose tolerance, which is consistent with progressive insulin resistance.⁶³ In late pregnancy, insulin action is 50-60 percent lower than in non-pregnant state.^{64,65} By the third trimester, basal and 24-hour mean insulin concentrations may double.⁶⁶ The first and second phases of insulin release increase threefold by late pregnancy.⁶⁰ These alterations in maternal insulin sensitivity affect both glucose and lipid metabolism resulting in a decreased ability of insulin to suppress lipolysis.⁶⁷

Metformin improves blood glucose control by insulin-stimulated glucose disposal in skeletal muscle, decreases hepatic glucose output inhibits gluconeogenesis and decreases intestinal glucose absorption from the gastrointestinal tract providing less glucose for energy storage in adipose tissue.

Metformin also decreases appetite^{37,68} and certain authors stated that metformin contains a primary anorectic factor.⁶⁹ One other reason may be a decrease of leptin levels suggesting an underlying improvement of leptin resistance.^{70,71}

CONCLUSIONS

Metformin in high enough doses is a beneficial and cost effective drug to limit weight gain in the obese during pregnancy.

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