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ORIGINAL

The prophylactic role of metformin in obese pregnant woman

El papel profiláctico de la metformina en mujeres embarazadas obesas

Wassan R. Alkhafajy[1], Abdulqader R. Mubarak[2]

[1]University of Thi-Qar, Medical college, Dhi-Qar, Iraq.
[2]Mazaya University College, Civil Engineering Department, Dhi-Qar, Iraq.

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ABSTRACT

Introduction: obesity in pregnancy is linked to complications such as gestational diabetes, pre-eclampsia, and preterm labor. This study aimed to evaluate the prophylactic effect of metformin in reducing these complications in obese pregnant women.
Method: an interventional controlled trial was conducted at Bint-Alhuda Teaching Hospital in Iraq, involving 120 obese pregnant women (gestational age 14-16 weeks). Participants were randomly divided into two groups: one treated with metformin and the other not. Both groups were monitored monthly until delivery for outcomes including gestational diabetes, pre-eclampsia, preterm labor, congenital anomalies, mode of delivery, and postpartum hemorrhage. Statistical analysis was conducted using chi-square tests.
Results: although the metformin group showed reductions in preterm births, gestational diabetes, and gestational hypertension, these differences were not statistically significant ($p > 0,05$). However, a significant correlation was found between congenital anomalies and postpartum hemorrhage ($p = 0,001$).
Conclusion: while metformin appeared to reduce certain pregnancy complications, the results were not statistically significant. Further research with larger sample sizes and varied dosing regimens is needed. Additionally, the significant link between congenital anomalies and postpartum hemorrhage warrants further exploration.

Keywords: Metformin; Obesity; Pregnancy Complication.

RESUMEN

Introducción: la obesidad durante el embarazo se asocia con complicaciones como la diabetes gestacional, la preeclampsia y el parto prematuro. Este estudio tuvo como objetivo evaluar el efecto profiláctico de la metformina para reducir estas complicaciones en mujeres embarazadas obesas.
Método: se llevó a cabo un ensayo controlado intervencional en el Hospital de Enseñanza Bint-Alhuda en Iraq, involucrando a 120 mujeres embarazadas obesas (edad gestacional de 14 a 16 semanas). Las participantes fueron divididas aleatoriamente en dos grupos: uno tratado con metformina y el otro sin tratamiento. Ambos grupos fueron monitoreados mensualmente hasta el parto para evaluar resultados como diabetes gestacional, preeclampsia, parto prematuro, anomalías congénitas, modo de parto y hemorragia postparto. Se realizó un análisis estadístico con pruebas de chi-cuadrado.
Resultados: aunque el grupo tratado con metformina mostró reducciones en partos prematuros, diabetes gestacional e hipertensión gestacional, estas diferencias no fueron estadísticamente significativas ($p > 0,05$). Sin embargo, se encontró una correlación significativa entre anomalías congénitas y hemorragia postparto ($p = 0,001$).
Conclusiones: si bien la metformina mostró potencial para reducir algunas complicaciones del embarazo, los resultados no fueron estadísticamente significativos. Se necesitan más investigaciones con tamaños de muestra más grandes y regímenes de dosificación variados. Además, el vínculo significativo entre anomalías

congénitas y hemorragia postparto merece una mayor exploración.

Palabras clave: Metformina; Obesidad; Complicaciones del Embarazo.

INTRODUCTION

Obesity is common problem in women worldwide and its adverse effects on pregnancy are usually overlooked. Maternal obesity has short as well as long consequences for the mother and her fetus.[1]

Obesity is defined as a body mass index (BMI) of 30 kg/m or more at booking for pregnant woman. And usually classified to three classes:

Class 1: BMI 30,0 – 34,9

Class 2: BMI 35,0 – 39,9

Class or morbid obesity: BMI 40 and over [1]

The percentage of women with a body mass index above 30 of reproductive age are rising with recent estimate of over 25 % common in many countries. increasing severity of class of obesity in pregnancy is associated with greater risks of adverse perinatal outcome and other health risks.[2] fetal and maternal complications usually increase with increase BMI in a dose response manner. Obesity is associated with increase morbidity and mortality and should be considered a medical disease like any other chronic illness.[3]

Adipose tissue is an endocrine organ, synthesizing and secreting a variety of hormones and inflammatory markers, including cytokines, leptin and adiponectin. These adipocytokines can have profound effects on pregnancy.[3] Obesity in pregnancy is often associated with increased risk of:

Abortion, prematurity, gestational diabetes and hypertension, induction of labor, still birth, macrosomia postpartum hemorrhage and thromboembolism.

Obesity associated with increase fetal anomalies especially neural tube defect and congenital heart disease. obese patient in reproductive age group should be advice to take high dose folic acid.[4] There is increased risk of postnatal depression, maternal infection and breast-feeding failure. There is increased risk of childhood obesity and cardiac disease, this effect may be trans generational.[4]

Metformin is biguanides class of oral ant hyperglycemic agent decreased hepatic production, decrease glucose absorption from intestine and increase peripheral glucose uptake so led to increase insulin sensitivity.[5] Metformin is excreted by renal and has half-life 4 to 8,7 hour after oral administration.[6] Side effect include nausea and vomiting, diarrhea and weight loss, can also associated with vitamin B12 deficiency with prolong use. Its considered food and drug administration category B during pregnancy. its cross the placenta readily and its unbound in serum, not associated with known fetal teratogenicity.[7] Metformin cross the placenta and shows similar concentration in maternal and fetal circulation.[30]

The main objective of this study is to evaluate the prophylactic effect of the use of metformin in reducing the pregnancy-related complications, including preterm labor, gestational diabetes, and gestational hypertension, among obese pregnant women.

Further more, the study explores the correlations between these complications and other obstetric outcomes, such as congenital anomalies and postpartum hemorrhage.

METHOD

An interventional controlled trial, was conducted at Dhi Qar Governorate, south of Iraq, during the period of January 2018 to January 2024.

One hundred and twenty (120) singleton pregnant women, gestational age (14 – 16) weeks of pregnancy who were considered obese were enrolled in the study.

Obesity was diagnosed by measuring body mass index at booking visit at first trimester (around six weeks) those with BMI above 30 were considered obese and included in the study.

Patient with associated medical disease like diabetes mellitus, hypertension, thyroid disease also those with bad obstetrics history, previous abortion, history of gestational diabetes or pre-eclampsia, previous delivery by caesarian section were excluded from the study.

Clinical assessment

Detailed medical and obstetric history and thorough clinical examination were performed.

Gestational age was calculated depending on accurate last menstrual period and early obstetric ultrasound.

Body mass index was calculated for all patient.

All patient were investigated for hemoglobin concentration, glycosylated hemoglobin (HbA1C) and random blood sugar, general urine test and obstetric ultrasound.

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The participated pregnant women were divided randomly in two equal group. The first group was received Glucophage 850 mg as single daily dose from 14th to 16th weeks till delivery. Whereas the second group were not received the medication. The pregnant women in both groups were followed up and assessed every four weeks.

The outcome of the study was:

- Gestational diabetes
- Pre-eclampsia
- Prematurity
- Congenital anomalies
- Mode of delivery
- Fetal weight
- Mode of delivery

After delivery, the information records of all patient were received by the study personal. The study was started by large number of participant but those not available for fallow up were excluded from the study. The collecting data were statically analyzed and chi-square test was performed using (SPSS).

We inform all women involve in the study about the aim of research and verbal consents were taken.

RESULTS

Table 1. Age Group

		Age Group			Total
		Less than 20	20 to 30	More than 30	
Group	Control	13	39	8	60
	Treated	11	40	9	60
Total		24	79	17	120

This table show the age group of women in both groups, control and treated group, in which no significant difference was found.

Table 2. Results Summary

Chi-Square (P)	Group			
	Treated	Control		
0,297	13	18	Prim	Parity
	47	42	Multi	
1,000	56	56	Negative	PTL
	4	4	Positive	
0,171	59	56	Negative	Polyhyd
	1	4	Positive	
0,211	53	48	Negative	pE
	7	12	Positive	
0,408	54	51	Negative	GDM
	6	9	Positive	
1,000	59	59	Negative	Cong
	1	1	Positive	
0,336	42	37	VD	Delivery
	18	23	C/S	
0,752	55	54	Negative	B.wt
	5	6	Positive	
0,697	57	56	Negative	ppH
	3	4	Positive	

This table shows the frequency of occurrence of study's variable in both groups. Using Chi Squire to show the significant of use of metformin in reducing obesity related complication.

The figure 1 shows the incidence of occurrence of study's variable (preterm labor, gestational diabetes, pre-eclampsia, congenital anomalies, mode of delivery and postpartum hemorrhage) in both treated and control group.

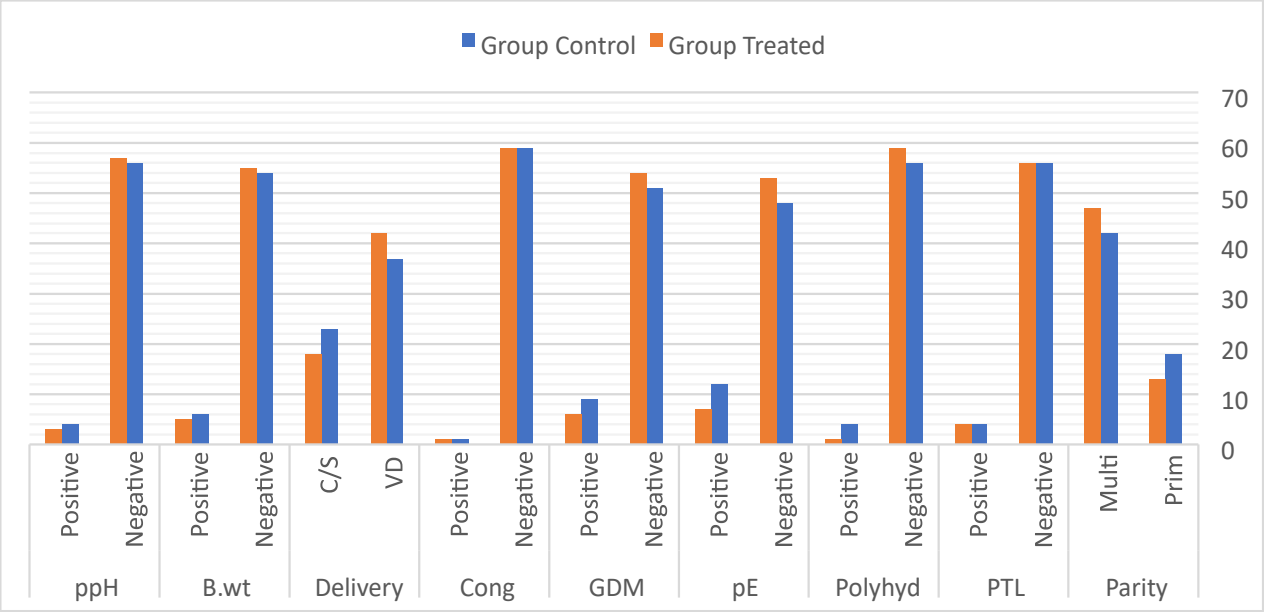

Figure 1. Results Summary

Correlation between Congenital Anomalies (Cong) and Postpartum Hemorrhage (ppH)

Table 3. Pearson Correlation

		Cong	ppH
Cong	Pearson Correlation	1	,523**
	Sig. (2-tailed)		,000
	N	120	120 1
ppH	Pearson Correlation	,523**	
	Sig. (2-tailed)	,00	
	N	120	120

**. Correlation is significant at the 0,01 level (2-tailed).

- Pearson Correlation: 0,523, p = 0,001
- Interpretation: The Pearson correlation coefficient of 0,523 indicates a moderate positive correlation between congenital anomalies and postpartum hemorrhage. The p-value of 0,001 suggests that this correlation is statistically significant, meaning that as the incidence of congenital anomalies increases, the likelihood of postpartum hemorrhage also tends to increase.

DISCUSSION

Obesity is considered as chronic disease with significant fetal and maternal complication during pregnancy and its risk is also associated with long term morbidity for child of obese mother beside long term maternal morbidity. Despite its common and serious maternal and fetal risk but usually obese patient unaware for this risk and underestimated by most of patient. interventions in pregnancy have been hindered by lack of compliance and interest and to date have failed to show any real difference.

Our aim is to use prophylactic medication to reduce obesity related pregnancy complications. We us metformin which has antioxidant effect to minimize obesity adverse effect.

Oxidative stress can be the primary or secondary cause for many health problem and obesity one of these, so a number of researches were done to evaluate the benefit of natural and synthetics anti-oxidant in controlling obesity and its related health problems.

Zienlinska-Bilizniewska et al. reviewed the possible use of phytotherapy in treated obesity related health problem.[7] A number of studies to confirm antioxidant activity of metformin through its effect at cellular level on oxidative system on of these carried by Hasanpour Dehkordi A. all evidence suggest the antioxidant effect of metformin, and its role in treated many condition which oxidative stress play a role in its pathogenesis.[8]

The safety of the use of metformin in pregnancy was confirmed by a number of studies. In European work-sharing procedure, approval of variation for label extension based on the results of Mercks cohort safety study, assessing the follow up children from 4000 pregnancies with metformin for up 11 year which confirmed no fetal

or neonatal risk from metformin exposure from conception and throughout pregnancy.[9]

There are significant number of papers discuss the role of metformin in pregnant with polycystic ovarian syndrome or pregnant with diabetes.

Metformin although its safe but usually associated with significant GI side effect which is more serious in early pregnancy because of morning sickness. So we start the medication after first trimester to reduce side effect and improve compliance. But this lead to exclude first trimester pregnancy complication from our study like abortion and congenital anomalies.

The use of metformin is associated with significant gastro intestinal side effect more than in non-pregnant women. A variety of mechanism may responsible on these symptoms including gut serotonine excretion, malabsorption of bile salt and alteration in incretin and glucose metabolism.[23] The symptoms more difficult to tolerate due to concomitant pregnancy associated nausea and vomiting.[23,24]

Obesity associated with increased risk of preterm labor either iatrogenic because of pregnancy complication associated with obesity or spontaneous preterm labor. Obesity associated with inflammation and infection which is more associated with extreme prematurity than moderately premature.[10]

Metformin usage can reduce concentration of inflammatory protein and interleukine6, also its anti-inflammatory properties may improve the blastocyst implantation and lead to reduce risk of preterm labor It can even associate with better neonatal outcome by reducing NICU admission rate.

Study carried by Catherine A Cuver et al conclude that use of metformin can prolong gestation in pregnant with preterm pre-eclampsia.[12] Farzaneh Boroumand, Rasoul Gharaaghaji they found prophylactic use of metformin associated with reduced maternal weighting and birth weight without any effect on DM and insulin need in pregnant women.[14]

The use of metformin result in less maternal weight gain, lower risk of pregnancy induced hypertension, lower risk of neonatal hypoglycemia and reduce incidence of macrosomia. these finding by Gagan Priya,Md and Sanjay Kalra, MD.[15]

Metformin can prevent pre-eclampsia through reduction of anti angiogenic factors, and through the improvement of endothelial function via the actions on mitochondria or through the mammalian target of rapamycin pathway by alteration of energy deposition and cellular hemostasis,[25] and this explain why metformin effect limited to pre-eclampsia with multi organ involvement rather than gestational hypertension which involve blood pressure only.[26,27]

Wanget al. confirm that the use of metformin was significantly reduced the risk of pregnancy induced hypertension and no effect on pre-eclampsia incidence [16] also there is inconsistent evidence reached by several studies support reduced risk of hypertensive disorder with metformin use.[17,18,19,20,21] Ainuddin et al compared three group: metformin and insulin, metformin alone and insulin alone. pregnancy induced hypertension was significantly lower in those group who received metformin than group of insulin only.[17] On the contrary the MiTy trial found no difference in incidence or severity of gestational hypertension in two group of diabetic pregnant one with metformin and the other without.[22]

Pratap Kumar and Kashif Khan study the metformin in pregnant with polycystic ovarian syndrome,they found it can reduce pregnancy complication such as early pregnancy loss, prevent fetal growth retardation and preterm delivery.[28]

Metformin has positive effect on several metabolic aspect in patient with polycystic ovarian syndrome such as improve insulin sensitivity and plasma lipid and glucose profile. its use in pregnancy can reduce the gestational diabetes and gestational hypertension.[28]

Hui Yu et al investigate the prophylactic effect of metformin in reducing gestational diabetes in high risk pregnancy.five cohort studies and fifteen randomized control trial were involved and concluded there was role of metformin in prophylaxis.[31] Willian Barbosa Sales lacks high quality evidence to offer significant benefit of metformin use since a group without intervention was not used.[32]

When we analyze all the variable including preterm labor, polyhydromnia, preeclampsia, gestational diabetes, birth weight, mode of delivery and postpartum hemorrhage. there is noticeable difference but no statistically significant differences were observed between the treated and control group. And this may be explained: insufficient sample size to be able to detect small effect sizes, or the variability within both groups might dilute any potential effect of the drug. also, the dosage, timing and duration of administration might be not optimal for influence particular prophylactic effect.

Strictly while we analyze our result, there is statically significant relation between pregnancy complicated by congenital anomalies and development of postpartum hemorrhage. the mechanism behind this correlation might be multifactorial: the presence of congenital anomalies might reflect more complicated pregnancy with risk of polyhydromnia and postpartum hemorrhage, or may be the same physiological, anatomical and pathological factors contribute to occurrence of both congenital anomalies and postpartum hemorrhage. Further researches needed to explore these association.

CONCLUSIONS

Although there is noticeable reduction of the incidence of occurrence of studies variable in treated group but still statically non-significant. There is statically significant correlation between congenital anomalies and occurrence of postpartum hemorrhage that need further attention and study. And the obstetrician should remain vigilant in dealing with pregnancy complicated by congenital anomalies.

The study recommends:

- Reduction in population levels of obesity so women start their pregnancies with accepted BMI.
- Further study using lager sample size.
- Study with different dose regimen and long duration i.e start the treatment from first trimester.
- Study using the effect of different antioxidant like natural one.

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CONFLICT OF INTEREST

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AUTHORSHIP CONTRIBUTION

Conceptualization: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Data curation: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Formal Analysis: Wassan R. Alkhafajy, Abdulqader R. Mubarak.

Research: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Methodology: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Project Management: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Resources: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Software: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Supervision: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Validation: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Diplay: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Drafting – original draft: Wassan R. Alkhafajy, Abdulqader R. Mubarak.
Writing-proofreading and editing: Wassan R. Alkhafajy, Abdulqader R. Mubarak.