International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 10, 2020
ISSN: 1475-7192

Pregnancy Outcome In Women With Polycystic Ovary Syndrome Who Continue Metformin During First Trimester

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Abstract

Background:*Polycystic ovary syndrome (PCOS) is a heterogenous disorder affecting 6-15% of women of reproductive age and it is considered as the most common cause of chronic anovulation and anovulatory infertility, diagnostic criteria have been proposed that generally center on the features of hyperandrogenismoligomenorrhea and polycystic ovarian morphology.The aim of this work was the effect of continue metformin in the 1st trimester in women with PCOS and its effect on pregnancy outcomes*. ***Methods:*** *This was a prospective interventional study (clinical study) that was conducted at Obstetrics and gynecologicy department of Zagazig University Hospitals in the period from March 2019 to March 2020. Included 44 pregnantPCO women, the selected patients were divided into 2 equal groups; group (I) included 22 pregnant women who continue metformin therapy during the first trimester with mean age 28.05 ± 2.44; and group (II) included 22 pregnant women with PCOs and discontinue metformin therapy during the first trimester with mean age 29.14 ± 2.09.****Results:*** *Women who continue metformin therapy during first trimester in group (I) were having significantly lower weight gain, lower incidence of gestational diabetes mellitus (GDM), Insulin therapy and spontaneous abortion and insignificantly lower incidence of pregnancy induced hypertension (PIH) in comparison with women who discontinue metformin in group (II). With p-value: 0.001, 0.004, 0.036, 0.008 and 0.549 respectively.****Conclusions:*** *Continuing of metformin therapy during 1st trimester pregnancy in women with PCOS was associated with good maternal outcomes including decrease incidence of spontaneous miscarriage, gestational DM.*

Key words:*Polycystic ovary syndrome (PCOS), Metformin, spontaneous abortion.*

I. INTRODUCTION

Polycystic ovary syndrome (PCOS), described as a syndrome of ovarian dysfunction, is considered to be one of the most common endocrine disorders affecting women of reproductive age. It may affect approximately 5–10% of women and is the most common cause of anovulatoryinfertility[1].

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There is emerging evidence that the primary pathogenesis of PCOS is associated with increased insulin resistance. Insulin sensitizers, such as metformin, may be beneficial in dealing with PCOS[2].

There are uncertainties about when metformin should be discontinued and what dose of metformin should be given. Some authorities recommended discontinuation of metformin once the pregnancy was confirmed because of concerns about harms to the fetus. However, the evidence that metformin is nonteratogenic has been obtained[3].The aim of this study is the effect of continue metformin in the 1st trimester in women with PCOS and its effect on pregnancy outcomes

II. METHODS:

This was a prospective interventional study that was conducted at Obstetrics and gynecologicy department of Zagazig University Hospitals in the period from march 2019 to march 2020. Included 44 pregnant PCO women, the selected patients were divided into 2 equal groups; group (I) included 22 pregnant women who continue metformin therapy during the first trimester with mean age 28.05 ± 2.44; and group (II) included 22 pregnant women with PCOs and discontinue metformin therapy during the first trimester with mean age 29.14 ± 2.09. Study protocol was approved by the ethics committee of Faculty of Medicine, Zagazig University. Exclusion of Age less than 18 or more than40years.Pre-gestational Diabetes Milletus.Hypertensive patient.Patients with liver or cardiac or renal or endocrinal diseases.Patients with history of coagulation disorder.BMI more than 30 kg/m2.

Full medical history were obtained from all selected women and they were subject to thorough medical and obstetrical examination. Routine Laboratory Investigations included ; Urine Analysis, Complete Blood Counting (CBC),kidney and liver function. Blood pressure measurement and urine examination for presence of protein were done for selected women for detection of pregnancy induced hypertension (PIH) including preeclampsia.

Cases in group 1 received metformin, starting in a dose of 1000 mg daily increased to 2500 mg daily according to body mass index (BMI) and response to treatment, some cases used other ovulation inducing drugs as clomiphene citrate and or gonadotrophines. When pregnancy occurred, cases continued on metformin in a dose of 1000–1500 mg daily till the end of pregnancy. Cases in group 2 got pregnant spontaneously or by use of ovulation inducing agents but did not use metformin before or after pregnancy.

Assessment of Glycemic Status And Insulin Resistance:

Glycemic status of all selected pregnant women by measurement of fasting blood glucose “FBG” and fasting serum insulin levels, followed by calculation of HOMA IR (Homeostatic Model Assessment Of Insulin Resistance) was done at 8 weeks and repeated between 24 and 28 weeks. HOMA-IR index was calculated using this formula:

Fasting blood glucose (mg/dL) × fasting insulin level (mU/mL)/ 405.

Detection of Gestational Diabetes Mellitus (GDM) was done at 8 weeks pregnancy and repeated between 24 and 28 weeks, when negative repeated lastly at 36 weeks by using oral glucose tolerance test (OGTT), which was based on 100 gm glucose tolerance. The limiting glucose levels were 95, 180, and 155

mg/dl for fasting, 1 and 2 h, respectively, when one value was above the limit it was considered impaired glucose tolerance (IGT), and when two values were above the limit, it was considered as GDM[4].

Fetal outcomes were measured and recorded including the rate of; spontaneous miscarriage (fetal loss before 24 weeks), prematurity (delivery before completed 36 weeks), fetal macrosomia (fetal weight more than 4.5 kg)[5], intrauterine growth restriction (IUGR) (fetal abdominal circumference less than 5th percentile for GA), suspected fetal asphyxia at birth (5 min Apgar score ≤ 7) and recording of congenital malformation and neonatal mortality.

Statistical Analysis:

Student's t test , SD and Chi-Square test (X2) were used to assess the statistical significance when appropriate, two-tailed value of P<0.01 was considered statistically significant; The SPSS version 20.0 (SPSS Inc, Chicago, IL, 2001). statistical package was used to analyze data.

III. RESULTS:

There was no significant difference between the studied groups as regard maternal age, body mass index "BMI", gestational age at start of study and presence of previous infertility figure 1,2.

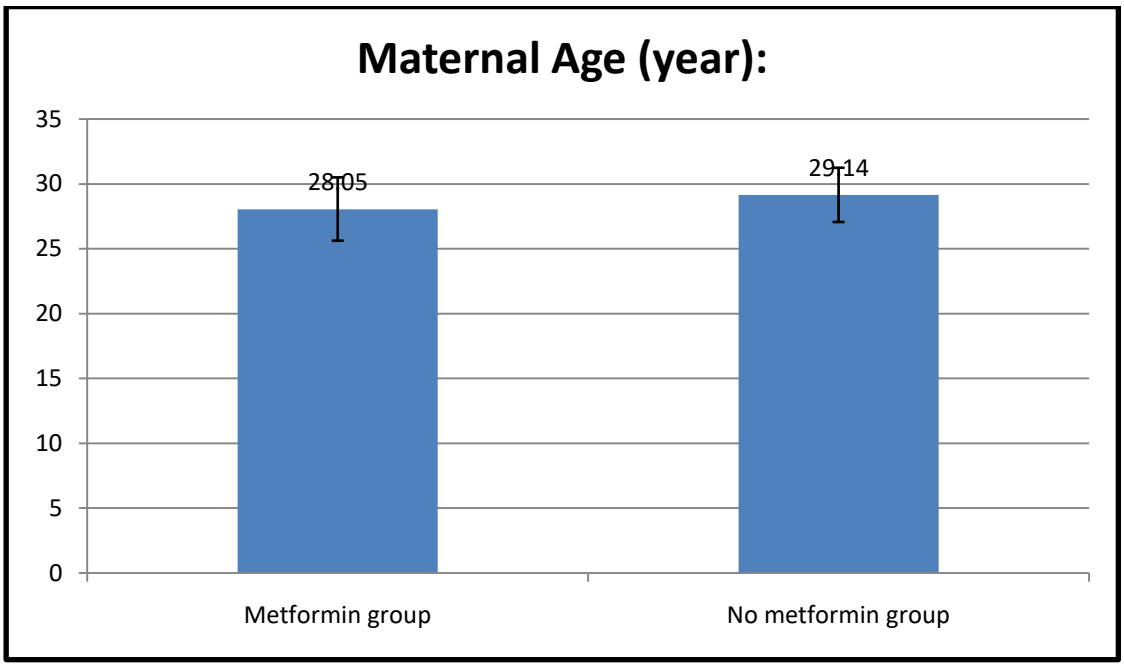

Figure (1): Age distribution among studied groups.

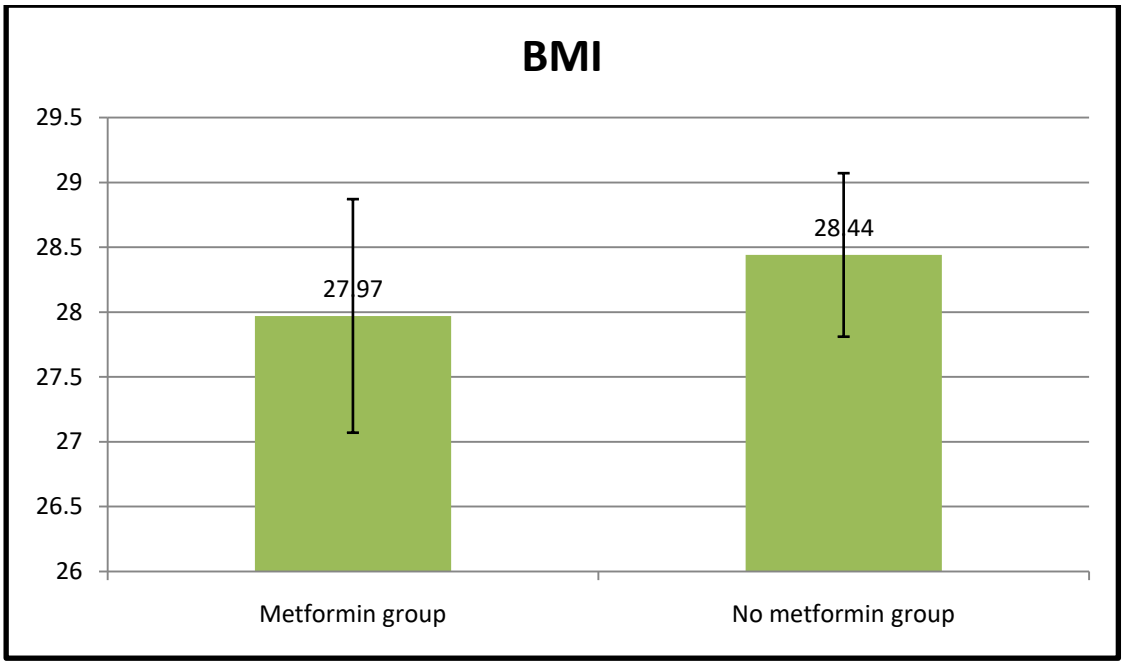

Figure (2): Mean and SD of BMI among studied groups.

Table (1): Initial clinical assessment of the studied groups:

Variable	Metformin Group N=22	No metformin Group N=22	t-value	p-value
Systolic B.P.:(mm/Hg)				
- Mean ± SD	111.82 ± 6.82	112.5 ± 7.68	0.104	0.748
- range	100 – 125	100 – 125		
Diastolic B.P.:(mm/Hg)				
- Mean ± SD	71.36 ± 6.76	72.59 ± 7.14	0.343	0.561
- range	60 – 80	60 – 85		
Proteinuria:			X^2	
- Yes	1	3	1.1	0.294
- No	21	19		

There was no statistical significant difference between studied groups as regard systolic , diastolic blood pressure and proteinuria table 1.

Table (2): Glycemic status assessment of the studied groups at 8 weeks:

Variable	Metformin Group	No metformin Group	t-value	p-value
FBG:(mg/dl)				
- Mean ± SD	100.05 ± 2.72	101.32 ± 3.06	2.117	0.153
- range	97 – 108	97 – 109		
F Insulin:(uIU/ml)				
- Mean ± SD	20.23 ± 2.14	21.5 ± 2.04	2.247	0.141
- range	14 – 25	18 – 26		
HOMA IR:				
- Mean ± SD	5.00 ± 0.58	5.38 ± 0.53	3.335	0.075
- range	3.35 – 6.13	4.44 – 6.42		

HOMA IR (**Homeostatic Model Assessment of Insulin Resistance**)

There was no statistical significant difference between both studied groups regarding fasting blood glucose, fasting serum inulin and HOMA-IR table 2.

Table (3): Glycemic status assessment of the studied groups at 24-28 weeks:

Variable	Metformin Group	No metformin Group	t-value	p-value
FBG(mg/dl):				
- Mean ± SD	115.7 ± 7.1	144.95 ± 9.65	14.6	<0.001**
- range	90 - 136	95 - 165		
F Insulin: (uIU/ml)				
- Mean ± SD	17.09 ± 2.00	20.95 ± 3.7	18.530	<0.001**
- range	14 - 20	15 - 27		
HOMA IR:				
- Mean ± SD	4.9± 0.49	7.5 ± 1.17	23.464	<0.001**

- range	3.0 - 5.0	3.3 - 7.64		

Table 3, showed that thewomen in group (I) were having significantly lower fasting blood glucose, fasting serum insulin and HOMA-IR index in comparison with those in group (II).

Table (4): Maternal outcomes of the studied groups:

Variable	Metformin Group	No metformin Group	t-value	p-value
Wt. gain:				
- Mean ± SD	9.14 ± 1.55	10.05 ± 1.53	12.022	0. 001**
- range	7.0 - 12	7.0 - 13		
Gestational age at termination (weeks)				
-Mean ± SD			6.7	0.03**
-range	38.2 ± 1.1	37.8 ± 0.8		
	36 –40	36 –39		
GDM:				
- Yes	1 (4.5%)	7(31.8%)	*FET*	0.01*
- No	21 (95.45%)	15 (68.2%)		
Insulin therapy:				
- Yes	0 (0.0%)	4 (18.2%)	*FET*	0.036*
- No	22 (100.0%)	18 (81.8%)		
Sp. abortion:				
- Yes	1 (4.6%)	6 (27.3%)	*FET*	0.04*
- No	21 (95.45%)	14 (72.7%)		
PIH:				
- Yes	1 (4.6%)	2 (9.1%)	*FET*	0.549
- No	21 (95.4%)	20 (90.9%)		

FET=Fischer exact test

This study showed that women who continue metformin therapy during first trimester were having significantly lower weight gain, lower incidence of GDM, lower need for insulin therapy and lower incidence of spontaneous abortion and insignificantly lower incidence of PIH in comparison with women who discontinue metformin table 4.

This study showed that the women who continue metformin therapy during first trimester were having insignificantly lower preterm delivery, macrosomia, IUGR, fetal asphyxia (Apgar score ≤ 7), congenital anomalies in comparison with women who discontinue metformin figure 3.

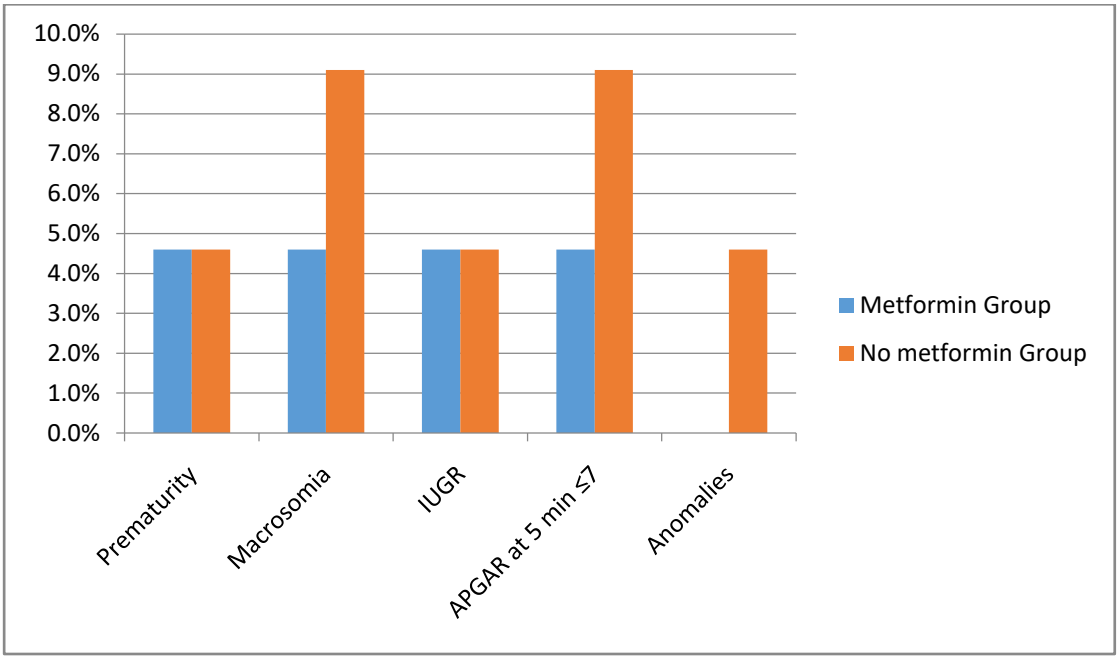

Figure (3): Neonatal outcomes among studied groups.

IV. DISCUSSION

This study showed that there was no significant data between both groups of the study as regard age, BMI, Blood pressure, CBC, fasting glucose, and fasting insulin).

This was in agreement with ***Abd El Hameed et al.***[6]who reported in their study that there was no significant difference between the studied groups at baseline visit as regard age, BMI, fasting insulin, fasting glucose, HOMA_IR index.

At 24 weeks of gestation, our results showed that the pregnant women who continue metformin therapy in group (I) were having significantly lower fasting blood level, fasting serum insulin level and HOMA-IR index in comparison with those who stopped metformin therapy in group (II) with p-value: <0.001.

These findings were in agreement with ***Abd El Hameed et al.***[6] who reported that women who continuemetformin therapy during pregnancy were having significant lower values for fasting glucose, fasting

insulin, and HOMAIR in comparison with those who conceived without taking metforminand did not take it during pregnancy.

Regarding weight gain, lesser weight gain during pregnancy was observed in women in group (I) in comparison with those in group (II) (9.14 ± 1.55 vs 10.05 ± 1.53) with p–value: 0.001.

***Syngelaki et al.*[7]**reported in their study on 400 pregnant women with PCOs divided into 202 women in the metformin group and 198 in the placebo group that the median maternal gestational weight gain was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2], P<0.001), and concluded that Metformin improves insulin sensitivity and in pregnant patients with gestational diabetes it leads to less weight gain than occurs in those who do not take metformin.

In the 4-year study done by ***Glueck et al.*[8]**they found that metformin in combination with diet was shown to safely reduce weight by 8% in women. Percentage of reductions in weight on MET-diet was significant (P < .05) and did not differ among the 3 highest BMI categories (≥40, ≥30 to <40, ≥25 to <30), but were not significant in the normal-weight category (BMI, <25).

While in disagreement with our finding was ***Abd El Hameed et al.*[6]**who reported that PCOS pregnant cases who received metformin showed insignificant lower weight gain during pregnancy in comparison with those didn't take metformin during pregnancy.

Regarding gestational diabetes mellitus (GDM), our results showed that women who didn't take metformin in group (II) were having 7-fold higher incidence of GDM in comparison with those who continue metformin therapy in group (I) (31.8%) vs 4.5%) with p-value: 0.01. there was a significant difference between both groups regarding the need for insulin therapy to achieve good control of gestational diabetes mellitus with p-value: 0.036.

This finding were in agreement with ***Ainuddin et al.*[9]**who reported that a total of 1 (4.6%) patients in metformin group developed GDM while 9 (40.9%, 0.004) developed GDM in no metformin group. Patients not receiving metformin were 4 times likely to have GDM compared to those who received it.

Against this findings was ***Syngelaki et al.*[7]**who reported that there were no significant differences between-groups in the incidence of gestational diabetes.

***Nawaz et al.*[10]** explainedlower incidence of GDM in women who continue metformin therapy by that metformin and diet reduce BMI, insulin secretion and insulin resistance resulting in reduced demands on the beta cells of pancreas and this effect is maintained during pregnancy in women that continue metformin Also, continuous metformin had significant therapeutic effect and better control compared to its preventive effect on GDM requiring insulin therapy .

Regarding spontaneous miscarriage, our results showed that women in group (I) were having significantly lower incidence of spontaneous miscarriage in comparison with those in group (II) with p-value: 0.04.

Glueck et al.[11]explained that metformin alters plasminogen activator inhibitors thus improving implantation also, ***Jakubowicz et al.*[12]** explained that metformin increases blood flow to the uterus and ***Thatcher and Jackson,* [13]**explained that the reduction in early pregnancy loss is mostly due to improvement in

egg quality and reported that immediate discontinuation and continuation during the first trimester showed no difference in early abortion rate.

This study showed that women in group (I) were having insignificantly lower incidence of pregnancy induced hypertension in comparison with group (II) p-value: 0.549.

This finding was in agreement with ***Abd El Hameed et al.***[6]as they reported that PIH was less common in the metformin group in comparison with the non-metformin group but this was of no statistical significance. Also,***Syngelaki et al.***[7] reported the incidence of preeclampsia was lower in the metformin group than in the placebo group (3.0% vs. 11.3%; odds ratio, 0.24; 95% confidence interval, 0.10 to 0.61; P=0.001).

Regarding fetal outcomes, our results showed that there was no significant difference between the two studied groups as regarding incidence of preterm delivery, macrosomia, IUGR, APAGR score at 5 min, with p-value 1.0, 0.549, 1.0, 0.549, 0.314 respectively.

These findings were in agreement with ***Abd El Hameed et al.***[6]and ***Begum et al.***[14]the incidence of preterm birth, fetal macrosomia, IUGR, suspected fetal asphyxia at birth were lowered in group 1 but it was of no statistical significance, but in disagreement with ***Nawaz et al.*** [10]who showed significant reduction of IUGR and preterm birth in the metformin treated group and this may be due to the small number of cases in this study compared with those of ***Nawaz et al.*** [10]whom carried their study on 137 cases.

There is accumulated evidence about the safety of use of metformin throughout pregnancy, but evidence of increased risk of congenital abnormalities has ever been reported [8]. Explored the effect of metformin in pregnant women and concluded that metformin did not lead to higher incidence of major congenital abnormalities. A retrospective study done by ***Diamanti-Kandarakis et al.***[15]had examined the perinatal outcomes in metformin-treated and control pregnancies, and found that the rates of neonatal growth deficits, congenital defects, and neonatal unit admission were either comparable in both groups or less common in the metformin-treated group. ***Gilbert et al.*** **[16]**also believed there was no evidence of an increased risk of major malformations when metformin was taken during the first trimester.

Study done by **Zenget al.**[3]to evaluate the effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome (PCOS) Concluded that, metformin treatment in pregnant women with PCOS throughout pregnancy could reduce the risk of EPL, preterm delivery, and increase the chance of term delivery sharply. As to pregnancy complications, continual use of metformin resulted in sharp reduction in the rates of GDM and PIH without increasing serious side effects **.**

Metformin started before pregnancy and continued until term in women with PCOS has benefits both for the mother (reducing GDM, gestational hypertension, preterm labour) and the developing foetus (reducing early pregnancy loss, foetal growth retardation).The largely unanswered question is the long term impact of intrauterine metformin exposure on childhood development. The MiG TOFU results at 9 years could be interpreted as showing a neutral effect as body fat, visceral adipose tissue, and liver fat were similar in metformin and insulin groups. Conversely the unexpected finding of increased body mass index in the metformin offspring might indicate an increased risk of childhood obesity. The low follow-up rate, however, makes the results difficult to interpret. On-going long term follow-up studies including from the offspring of mothers in the obesity trials will help answer this current uncertainty**[17].**

V. CONCLUSIONS

Continuing of metformin therapy during 1st trimester pregnancy in women with PCOS was associated with good maternal outcomes including decrease incidence of spontaneous miscarriage, gestational DM, Also it was associated with slight but insignificantly improvement in fetal outcome.

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