

FREQUENCY OF EFFICACY OF METFORMIN IN PREGNANT FEMALE WITH PCOS WITH REGARDS TO DEVELOPMENT OF GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a significant gynecological problem manifested by raised androgen level, menstrual irregularities, and/or one or both ovaries having small cysts. Metformin has shown to have promising effects on PCOS and its several metabolic aspects. The metformin used as therapy in these patients during pregnancy have beneficial effects regarding development of GDM.

Objective: To determine the frequency of efficacy of metformin in pregnant female with PCOS with regards to development of Gestational Diabetes Mellitus

Methods: It is descriptive cross-sectional study and conducted in Jinnah Hospital, Lahore Duration was six months from: 04-06-2018 to 04-12-2018. A total of 220 cases fulfilled the inclusion/exclusion criteria were enrolled. All cases were followed up till delivery for presence/absence of GDM. The frequency of efficacy in patients with PCOS was noted; all this information was recorded on a pre-designed proforma. Data was entered and analyzed in SPSS version for 16.0.

Results: The mean age of patients was 30.50±6.08years. About 36 (16.4%) females had parity 0, 51 (23.2%) had parity 1, 59 (26.8%) had parity 2, 42 (19.1%) had parity 3 and 32 (14.6%) had parity 4. The mean BMI of patients was 26.81±4.55kg/m². Efficacy of metformin was achieved in 190 (86.4%) cases while in 30 (13.6%) cases efficacy could not be achieved.

Conclusion: It has been inferred that metformin is effective in 86.4% cases in controlling blood sugar level among pregnant females.

Key words: Efficacy, Metformin, Pregnant, Polycystic Ovarian Syndrome, PCOS, Gestational Diabetes Mellitus

How to cite this article: Sajid A, Sajid A, Sajid A, Abid M. Frequency of efficacy of metformin in pregnant female with PCOS with regards to development of Gestational Diabetes Mellitus. *Pak Postgrad Med J* 2020;33(1): 15-19

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DOI: <https://doi.org/10.51642/ppmj.v33i01.42>

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a significant gynecological problem manifested by raised androgen level, menstrual irregularities, and/or one or both ovaries having small cysts.¹ The disorder may be morphological with presence of polycystic ovaries on

ultrasound or dominantly biochemical with elevated levels of androgen. Hyperandrogenism, one of the clinical sign of PCOS, can cause microcysts development in the ovaries resulting in suppression of follicles, menstrual changes and loss of ovulation.² About 7% of women are affected by this disorder.³ The prevalence of PCOS in Pakistan is about 21%.⁴ Abnormal glucose tolerance due to insulin resistance and hyperinsulinemia are important features in women with PCOS, especially in women with a BMI > 30, but insulin resistance may occur in lean women with normal BMI.⁵ A more latest studies showed that the frequency of Gestational Diabetes Mellitus (GDM) in 45% of the women with PCOS who are not using metformin, and

also provide evidence during pregnancy women with subfertility and known case of PCOS are at increased risk for developing GDM.⁶

In pregnant patients known to have PCOS, Metformin has been shown to be effective on various metabolic features of polycystic ovarian syndrome, such as increased insulin sensitivity and blood glucose levels & fasting lipid profile. Evidence showed that pregnant women with known cases of PCOS are at higher risk than other women to develop problems in pregnancy like miscarriages, gestational diabetes and hypertension in pregnancy, and the effective use of metformin preventive treatment in these women during whole period of pregnancy have beneficial effects on pregnancy loss and prevalence of GDM⁵

One of the studies carried out in Pakistan, Karachi, in which metformin was used throughout pregnancy showed that 90% women in metformin group remained GDM free and only 10% developed GDM.⁷ One other study carried out in Manipal, India showed 4.4% developed GDM and 96.65% did not develop. However, we are interested to determine the frequency of efficacy of metformin in pregnant females with PCOS with regards to development of GDM as most of previous literature is about efficacy of metformin in PCO / ovulation and literature about its role in prevention of GDM is limited in our setup.

Large babies are at higher risk of developing hypoglycemia and jaundice born at term. If not treated, it can also lead to stillbirth. Long term effects in children are at higher risk of increase BMI and developing type 2 diabetes.⁸ Regarding screening of low risk is recommended between 24 and 28 weeks' gestation and high risk screening at the first antenatal visit. In 90% of case GDM usually resolve after the birth of baby. However Women are at an increased risk of developing type 2 diabetes during later life.⁸

The main role of insulin is to facilitate the entry of glucose into the cells. In PCOS, insulin resistance develops and it causes inhibition of entrance of glucose in the cells properly. As a result, glucose remains high in the blood. Reactionary to overcome this resistance and about 1.5–2.5 times more insulin is produced than in a normal pregnancy.^{9 10}

Evidence is not clear that in some women are unable to adjust insulin needs and develop GDM; however some explanations have showed reasons similar to those in type 2 diabetes i.e. autoimmune, gene mutations, increases BMI, along with other mechanisms.¹¹

Due to increased rate of β -cell proliferation secretion of insulin is raised.¹² During pregnancy β -cell mass is increased due to HGF/c-MET to meet the challenge of increased requirement in this condition. Loss of this phenomenon result in faulty adaptation of β -cell.^{13,14} loss of signaling mechanism due to lack of c-MET causes increased rate of death of β -cell. It also increases cell degeneration and apoptosis.¹⁴

RAS and MAPK, are common signaling molecule which affect cell motility by downstream pathways activation and cell cycle progression. Insulin production is increased by β -cells proliferating to compensate the need. Markers for GDM are observed if neither of the processes occurs. The excess of insulin can lead to over growth and large for gestation (macrosomia). After birth, high insulin production continues and causes hypoglycemia in newborn that may be symptomatic or asymptomatic.¹⁴

Non-challenge tests of blood glucose can be done by measuring glucose levels without challenging the patient with oral glucose solutions. Blood sugar level is checked when subject is fasting then 2 hours after giving meal, or may be done randomly. Challenge tests are done by giving an oral glucose solution and then measuring thereafter sugar level in the blood. In diabetics, sugar levels usually remain high. Some women find glucose solution unpleasant because of its sweat taste; reason being artificial flavors is added at times. Nausea is a common feeling during the test and blamed to be due to high glucose concentration in the solution.¹⁵

In Uk Obstetricians usually depend on random blood glucose level and consider risk factors for doing OGTT. In the United States obstetric units perform universal screening with a challenge test.¹⁶

American Diabetes Association recommendations consider following values to be abnormal if recorded during OGTT test with 100 gm. of glucose

- Fasting blood glucose level ≥ 95 mg/dl (5.33 mmol/L)
- 1 hour blood glucose level ≥ 180 mg/dl (10 mmol/L)
 - 2-hour blood glucose level ≥ 155 mg/dl (8.6 mmol/L)
 - 3-hour blood glucose level ≥ 140 mg/dl (7.8 mmol/L)

Insulin therapy with strict control of sugar by giving more injections for better control requires more effort, but consensus is lacking that it has greater benefits.¹⁷

The metformin works as better medicine than glyburide. Combination of metformin and insulin is more effective in control of blood sugar than insulin therapy alone. Another review found Metformin as a good short-term safety drug for both baby and the mother. Patients usually prefer taking metformin orally than to injections of insulin. Treatment of PCOS with metformin significantly levels of GDM during pregnancy.¹⁸ But unclear long-term safety.¹⁹

In contrast to PCOS the diagnostic criteria of polycystic ovaries in women are at least 12 or more follicles in one ovary and the size is around 2-9 mm in diameter. Total ovarian volume more than 10 cm³ another criterion. Inappropriate gonadotropin secretion is a key feature of PCOS which is not the cause but result of this issue of ovarian dysfunction. Plasma testosterone level is raised and it is a biochemical marker and most consistent feature of PCOS.²⁰ The objective of this study was to

determine the frequency of efficacy of metformin in pregnant female with PCOS with regards to development of Gestational Diabetes Mellitus.

METHODS

The study was descriptive cross sectional and conducted in Jinnah Hospital, Lahore. Duration was six months i.e., from: 04-06-2018 to 04-12-201. Sampling Technique was non-probability consecutive sampling. Sample size of 220 cases was calculated with 95% confidence level 4% margin of error and taking expected % age of efficacy of metformin as in 90% patients with PCOS taking metformin.

Gestational diabetes mellitus: It was diagnosed as one or more value following a 75-gm. glucose load, fasting plasma glucose >7mmol/L, 2hr glucose >7.8 mmol/L during the pregnancy

Efficacy: The efficacy was considered if the patients did not develop Gestational Diabetes Mellitus @ 28, 32, 36 weeks of gestational and 6 weeks postpartum.

Inclusion criteria: All diagnosed pregnant cases of PCOS were prescribed metformin therapy and continued during pregnancy (according to operational definition), age 20-40 years, any parity, after 28-30 weeks of gestation were included.

Exclusion criteria: Already diagnosed cases of diabetes mellitus (on history and medical record), history of

GDM (in history and medical record), essential hypertension (on history and medical record), females with hypothyroidism (as it increases the risk of developing GDM), Recurrent miscarriages (>3).

A total of 220 cases fulfilled the inclusion/exclusion criteria were enrolled from Out Patients Department, Obstetrics & Gynaecology, Jinnah Hospital, Lahore. An informed consent of the patients was taken from the patients to include their data in this study. Detailed history and physical examination were done for PCOS. All cases were followed up till delivery for presence/absence of GDM. The frequency of efficacy (according to operational definition) in patients with PCOS was noted, all this information was recorded on a pre-designed proforma (annexure). The bias was controlled through exclusion criteria and data stratification.

Data was entered and analyzed in SPSS version for 16.0. Mean and standard deviation were calculated for quantitative variable like age of the patients. Frequency and percentage were calculated for qualitative variables like parity and efficacy. Stratification for age, parity and BMI was done to address the effect modifiers. Post stratification chi-square test was applied to see the significance. P-value ≤0.05 was considered as significant.

Table: Comparison of efficacy in parity strata

		Parity			Total
		Nulliparous (primigravida)	Primiparous	Multigravida	
Efficacy	Yes	32 88.9%	43 84.3%	115 86.5%	190 86.4%
	No	4 11.1%	8 15.7%	18 13.5%	30 13.6%
Total		36 100.0%	51 100.0%	133 100.0%	220 100.0%

Chi-Square Test = 0.378 P-value = 0.828 (Insignificant)

Table: Comparison of efficacy in BMI strata

		BMI			Total
		Normal	Overweight	Obese	
Efficacy	Yes	85 100.0%	66 94.3%	39 60.0%	190 86.4%
	No	0 0.0%	4 5.7%	26 40.0%	30 13.6%
Total		85 100.0%	70 100.0%	65 100.0%	220 100.0%

Chi-Square Test = 55.513 P-value = 0.000 (Significant)

DISCUSSION

Women are more prone to develop GDM with PCOS. Metformin given during pregnancy may help in prevention of gestational diabetes and it is effective in

management of pre-eclampsia especially in women suffering from PCOS.²¹

Metformin is effectively used oral hypoglycemic drug that works by increasing sensitivity of insulin and

decreases gluconeogenesis in the liver; additionally, it has shown antitumor properties. It is used during pregnancy for the treatment of glucose intolerance but also effective in infertility with PCOS. Evidence has shown its utility in spontaneous abortions and first trimester fetal losses and studies have recommended metformin in later pregnancy.²²

In our study, efficacy of metformin was achieved in 190 (86.4%) cases while in 13.6% cases efficacy could not be achieved due to development of GDM. A study by Jamilian et al., found that administration for 12 weeks of soy isoflavone to women with PCOS has significant effect on indicators of insulin resistance, biomarkers of oxidative stress, triglycerides and hormonal status.²³

In Karachi, Pakistan a local study showed that 90% remained GDM free and 10% patients in metformin group developed GDM.⁷ This is comparable with previous studies (3.44%, 7%, 3% and 0%).²⁴⁻²⁶

In a RCT, there was no significant availability of metformin on GDM with PCOS when compared with placebo (OR = 1.07, 95% CI 0.60–1.92) and there was significant availability GDM by Metformin (OR = 0.19, 95% CI 0.13–0.27) in non-RCTs. Results of our meta-analysis shows no significant effect of metformin on GDM with PCOS. More multicenter data and RCTs required to investigate the issue before final verdict.

It has been proved in clinical trials that Metformin increases the insulin sensitivity and androgen levels are raised with this treatment. This therapy helps the patients with PCOS to lose the weight in adolescent age group.²⁸⁻³¹ Another study showed promising results of nine times decrease in gestational diabetes by using metformin during pregnancy with PCOS.²⁴ Clinical trials it has shown that metformin not only reduces gestational diabetes it has also beneficial effects on pre-eclampsia.²¹

In our study, the mean age of females was 30.50±6.08years. Data was stratified for age of patients. In patient's aged 20-30years, the efficacy was achieved in 88 (85.4%) cases. In patient's aged 31-40years, the efficacy was achieved in 102 (87.2%) cases. The difference was insignificant (p>0.05).

In our study, 36 (16.4%) females had parity 0, 51 (23.2%) had parity 1, 59 (26.8%) had parity 2, 42 (19.1%) had parity 3 and 32 (14.6%) had parity 4. Data was stratified for parity of patients. In nulliparous patients, the efficacy was achieved in 32 (88.9%) cases. In primiparous patients, the efficacy was achieved in 43 (84.3%) cases. In multiparous patients, the efficacy was achieved in 115 (86.5%) cases. The difference was insignificant (p>0.05).

In our study, the mean BMI of patients was 26.81±4.55kg/m². Data was stratified for BMI of patients. In normal weight patients, the efficacy was achieved in 85 (100%) cases. In overweight patients, the efficacy was achieved in 66 (94.3%) cases. In obese

patients, the efficacy was achieved in 39 (60.0%) cases. The difference was significant (p<0.05).

CONCLUSION

It has been concluded that metformin is effective in 86.4% cases in controlling blood sugar level among pregnant females. Now in future, we will recommend metformin for resolution of PCOS among pregnant females to avoid development of GDM.

A long-term study recommended that continuous improvement in metabolic profile of women with PCOS over a 36-month treatment with Metformin, particularly improving diastolic blood pressure probably by reducing serum cholesterol level and increasing high-density lipoprotein level and ultimately reducing BMI.³² However, data are insufficient as yet to recommend metformin to all women with PCOS.

ETHICAL REVIEW BOARD APPROVAL

The study was approved from Institutional Review Board of Postgraduate Medical Institute / Ameer-ud-Din Medical College / Lahore General Hospital, Lahore

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