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Effects of Metformin on Early Pregnancy Loss in Patients with Polycystic Ovary Syndrome (PCOS)

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Author`s Contribution

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A B S T R A C T

Objective: To determine the outcome of metformin therapy in early pregnancy loss in women with polycystic ovary syndrome (PCOS) at Tertiary Care Hospital, Karachi.

Methodology: This descriptive cross-sectional study was conducted at Department of Gynecology and Obstetrics, Civil Hospital, Karachi, from February 2021 till August 2022. Newly diagnosed pregnant women, aged age of 18-40 years, gestational age ≤ 4 weeks with polycystic ovary syndrome before pregnancy and started on metformin therapy were enrolled. Patients were started on metformin therapy (1000 mg/day) and were followed by the researcher to evaluate the occurrence of early pregnancy loss. All the relevant data of the study were entered and statistically analyzed by the IBM SPSS Statistics, Version 23. Moreover the frequency of early pregnancy loss was computed and post stratified based on effect modifiers by applying chi-square test taking p-value (<0.05) as statistically significant.

Results: Mean age and duration of PCOS in our study was 32.58±4.51 years and 5.72±2.89 years. Out of 125 patients, 32 (25.6%) patients were observed with early pregnancy loss. Moreover, the incidence of early pregnancy loss was statistically insignificant according to maternal age, parity, residential status and SES (p>0.05)

Conclusion: Metformin observed to be a protective management therapy to significantly reduces the early pregnancy loss among women with PCOS, possibly by correcting IR, hyperinsulinemia, and androgen excess the key metabolic drivers of miscarriage.

Keywords: PCI, metformin, insulin resistance and early pregnancy loss.

Introduction

Polycystic Ovary Syndrome (PCOS) remains a most commonly diagnosed multifactorial disorder among women of reproductive age. Its diagnostic criteria based global prevalence reaching up to 20%.[1] The symptoms typically include acne, disproportionately high hair growth, abnormal menstrual cycles, and elevated insulin levels. These symptoms commonly develop during 18-39 years of age. However the condition mostly remains underdiagnosed with delayed treatment.[2] PCOS is associated with metabolic issues (including obesity and insulin resistance) in around 60%-80% of women and fertility issues (including infertility and miscarriage) among nearly 20% women, leading to adverse mental outcomes and poor quality of life. [2-4]

Although exact etiology of PCOS has yet not been fully understood, several interrelated factors including age, ethnicity, lifestyle, family history, lifestyle, environmental exposure, and genetics factors have been proposed to play their role in its development and progression.[5] Insulin resistance leads to alopecia, acne, and hirsutism through hyper-androgenism, while ovarian malfunction caused by hyper-insulinemia results in anovulation and inability to conceive. Women struggling with PCOS are more prone to diabetes mellitus type 2, cardiovascular disorder, and dyslipidemia. Obesity further worsens these risks though hormonal imbalance and inflammation.[6] additionally, reduced libido, hypertension, fatigue, ovarian cysts, ovarian cancer, and breast cancer have also been noted in these women. 5 The prevalence of PCOS has significantly risen during past 30 years, accounting for around 89% additional cases, with more than 65 million PCOS cases documented only in 2021.[7] The life-threatening complications of PCOS and significant rise in global

prevalence over past decades have raised significant concern, necessitating the targeted screening interventions and prompt treatment strategies.[7,8] Although lifestyle management remains the first-line therapy for PCOS, the characteristic endocrine and metabolic disorders of PCOS often require pharmacological support for its optimal management.[9]

Metformin, an oral biguanide commonly prescribed in diabetes mellitus type 2, has emerged as a promising pharmacological intervention for PCOS. It has shown enhanced insulin sensitivity, reduced hepatic glucose production, improved peripheral glucose uptake, decreased circulating androgen levels, and improved ovulatory cycles and endometrial function in PCOS cases.[10] Metformin, a synthetic biguanide, is widely used to manage the type-II diabetes, and is commonly prescribed in polycystic ovary syndrome (PCOS) to address insulin resistance and associated metabolic and reproductive disturbances. [10] However, the role of metformin in reducing early pregnancy loss among women remains a subject of ongoing investigation. In this context, some studies proposed promising effects of metformin in reducing miscarriage risk during early pregnancy, while others remained either inconclusive or reported conflicting findings. [11] Therefore this study has been conducted, to evaluate the effectiveness of metformin therapy in early pregnancy loss in women with PCOs, at Tertiary Care Hospital, Karachi.

Methodology

This descriptive cross-sectional designed study was conducted at the Gynaecology and Obstetrics departments of Civil Hospital, Karachi. The data were collected over a period of six months following approval of the synopsis by the institutional Ethical Review Committee, from 21 February 2021 to 21 August 2022. A sample size of 125 patients was calculated based on the reported prevalence of early pregnancy loss around (8.9%) among pregnant women with PCOS on metformin therapy, with the margin of error of 5% and a confidence interval of 95%, by the World Health Organization (WHO) sample size estimation software.[11]

Non-probability consecutive sampling was employed. All the newly diagnosed pregnant women, with the pre-existing diagnosis of PCOs based on prior to pregnancy and documented in medical records, aged 18 to 40 years and gestational age of four weeks or less at the time of enrolment and had been started metformin therapy were enrolled. However, the patients with history of anti-phospholipid syndrome, connective tissue disorders, hyperthyroidism or hypothyroidism, metabolic syndrome; type II diabetes mellitus and patients with known allergy to metformin were excluded. Women, who fulfill the defined inclusion and exclusion criteria, were consecutively enrolled from the outpatient department (OPD) of Gynaecology and Obstetrics, Civil Hospital, Karachi. Complete medical history was obtained from each patient, including demographic information such as age, parity, and educational status, as well as the duration of the PCOs. The informed consent was obtained from all women willing to participate on a voluntary basis, after explanation the objective of the study, along with potential risks and anticipated benefits, in a language they could understand. Subsequently all enrolled women were taking on metformin 1,000 mg per day. Patients were prospectively followed by the principal investigator throughout the first trimester to monitor for the occurrence of early pregnancy loss. The early pregnancy loss was defined as spontaneous loss of pregnancy occurring at or before 12 completed weeks of the gestation, with the absence of fetal viability as per findings of ultrasonography. All the study variables were recorded by the pre-designed structured proforma. All the relevant data of the study were entered and statistically analyzed by the IBM SPSS Statistics, Version 23. The frequencies and percentages were reported for categorical variables, while means and standard deviations were calculated for continuous variables. Moreover the frequency of early pregnancy loss was computed and post stratified based on effect modifiers by applying chi-square test taking p-value ($\leq$0.05) as statistically significant.

Results

According to the demographic profile of the 125 enrolled women, the mean age was 32.58 ± 4.51 years and a mean PCOS duration was 5.72 ± 2.89 years. Most of the enrolled women presented with more than two weeks of gestational age (76.0%), resided in urban areas (75.2%), and belonged to poor to middle socioeconomic status (64.8%). Majority of the women were unemployed (62.4%), half the cohort had only higher education level (50.4%), followed by secondary (25.6%), primary (19.2%), and illiterate around women were (4.8%), highlighting that the study population was predominantly educated, urban-dwelling, and with poor middle income status. Table I.

Out of a total of 125 pregnant women with polycystic ovary syndrome (PCOS) receiving metformin therapy (1,000 mg/day), early pregnancy loss was recorded in 32 patients, yielding a frequency of 25.6%. The remaining 93 patients (74.4%) did not experience early pregnancy loss and continued their pregnancies beyond 12 weeks of gestation. Figure 1.

According to the stratified analysis, the socioeconomic status was the only significantly related to early pregnancy loss (p = 0.02), while it was statistically insignificant according to maternal age, gestational

age at, residential status and duration of PCOS, p>0.05. Table II

Table I: Descriptive statistics of demographic variables. (n=125)		
Variables	Statistics	
Age (years)	32.58±4.51	
Duration of PCOS (years)	5.72±2.89	
Gestational Age Distribution		
≤ 2 weeks	30	24.00%
> 2 weeks	95	76.00%
Residence		
Urban	94	75.20%
Rural	31	24.80%
Socioeconomic status		
Poor	44	35.20%
Middle to upper	81	64.80%
Occupational Status		
Employed	47	37.60%
Unemployed	78	62.40
Educational status		
Illiterate	6	4.80%
Primary	24	19.20%
Secondary	32	25.60%
Higher	63	50.40%

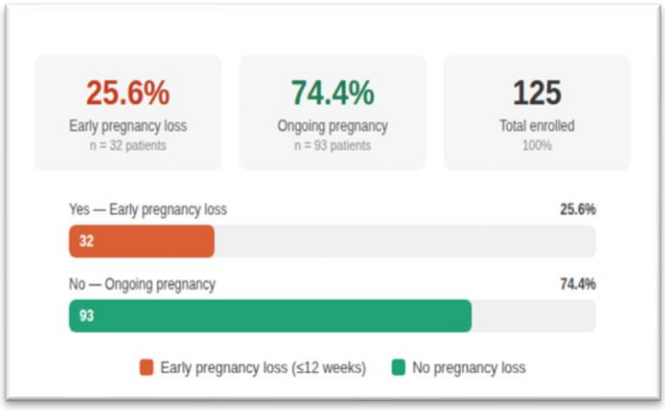

Figure 1. Frequency of early pregnancy loss. (n=125)

Table II: Distribution of study variables according to early pregnancy loss .(n=125)			
Variables	Early Pregnancy Loss		P-value
	Yes	No	
Maternal age (years)			
18-30	19 (26%)	54 (74%)	0.89
31-40	13 (25%)	39 (75%)	
Gestational Age			
≤ 2 Weeks	09 (30%)	21 (70%)	0.52
> 2 Weeks	23 (24.2%)	72 (75.8%)	
Residence status			
Rural	11 (35.5%)	20 (64.5%)	0.58
Urban	21 (22.3%)	73 (77.7%)	
Duration of PCOS			
≤ 2 YEARS	13 (26.5%)	36 (73.5%)	0.84
> 2 YEARS	19 (25%)	57 (75%)	
SES			
Poor	06 (13.6%)	38 (86.4%)	0.02
Middle-upper	26 (32.1%)	55 (67.9%)	

Discussion

The PCOs, is one of the most common endocrine disorders affecting women of reproductive age and is well recognized as a significant risk factor for the loss of early pregnancy. The Metformin therapy (an insulin-sensitizing agent) is widely used in the PCOs management and has been proposed to reduce this risk by improving hormonal and metabolic parameters; however, the precise effect of it on early pregnancy outcomes remains a subject of ongoing clinical exploration. In this study 125 PCOS patients were evaluated for the efficacy of metformin on early pregnancy loss with majority of participants were young adults falling in age range of 18-30 years (58.4%), with overall mean age of patients was 32.58±4.51 years, and mean duration of PCOS around 5.72±2.89 years. Comparably in the study of Talpur DN et al[12] reported that the majority of women (57.95%) were in age range of 18–25 years, with mean age of 26.39 ± 3.33 years, and mean duration of infertility was 4.49 ± 2.21 years, suggesting delayed diagnosis or prolonged untreated disease duration.

In this study, most of participants represented gestational age > 2 weeks (76%), urban residence (75.2%), low monthly family income (64.8%), unemployed (62.4%), secondary and higher (25.6% and 50.4% respectively), and duration of PCOS > 3 years (76%). Comparable baseline demographic statistics were documented in the study of Naz S et al[13], where a higher proportion of individuals had received secondary and higher education, with most reporting moderate socioeconomic status (86.5%). Similarly, in the study of Hassan MM et al[14] most of the participants had educational status up to secondary and higher education (42.7% and 8.4% respectively), only 37.2% of participants were employed, majority belonged to low socioeconomic status (70%), and rural residence (62.8%) were more common.

In our study, prevalence of early pregnancy loss was 25.6%. Aligning with this finding, in the study conducted by Al-Biate MA et al[15] prevalence of early pregnancy loss was 8.9% in metformin group and 36% in those without metformin. Similarly, in the study of Nawaz FH et al[16] the pregnancy loss rate in metformin group (12.5%) was lower than in controls (49.4%). In aligns to this series Afridi H et al[17] reported the effectiveness around (86.7%) in the metformin group compared to only 43.3% in the control group, whereas failure of treatment was recorded in (13.3%) cases of metformin group compared to (56.7%) in the control group, indicating the superior protective role of metformin among women with PCOS. The greater rate of early

pregnancy loss in this study compared to other relevant studies may because of the tertiary care setting with a high-risk cases referral base, and specific demographic of population and metabolic characteristics.

In present study, early pregnancy loss after metformin administration was comparable between patients in age group 18-30 years (26%) and those in 31-40 years (25%), with statistically no significant difference (p=0.89). Aligning with these findings, in the study of Ibrahem BS et al[18] early pregnancy loss was not associated with maternal age (p>0.05). Contrary to these findings, study carried out by Haripriya S et al[19] found significant association between maternal age and early pregnancy loss (p=0.004). Another study conducted by Zhao D et al[20] also reported significant association between maternal age and early pregnancy loss. Moreover, we found no significant difference was noted in early pregnancy loss after metformin administration between patients with gestational age ≤ 2 weeks and those with gestational age > 2 weeks (p=0.52). Contrasting to these findings, in the study of Ibrahem BS et al[18] pregnancy loss was significantly associated with gestational age (p=0.004). Another study conducted by Cai H et al[21] also reported contrary findings with significant association between early pregnancy loss and gestational age (p=0.046)

In our study cohort, duration of PCOS (≤ 3 years and > 3 years) showed no significant effect on early pregnancy loss (p=0.84). In agreement with this finding, in the study of Cai H et al[21] early pregnancy loss was not associated with PCOS after adjustment for confounding variables (adjusted OR 0.91). Comparable findings were documented in the study Hudecova M et al[22] reporting no association of early pregnancy loss with the duration of PCOS itself. Additionally, in this series, SES was significantly associated with early pregnancy loss (p=0.02). Consistent findings were documented by Lim GY et al[23] who reported significant association between early pregnancy loss and socioeconomic status (p<0.001). Consistently, the study carried out by Norsker FN et al[24] reported inverse association between income status and pregnancy loss. This study carries several limitations like relatively limited sample size, patients were not stratified or analyzed based on the severity of disease and high risk cases, and other important confounding factors like dietary habits, obesity, metabolic syndrome, insulin resistance, thyroid function, and other co-existing metabolic and hormonal variables were not analyzed for, which may have independently influenced the risk of early pregnancy loss and may cause the difference in frequency of early pregnancy loss. However further large-scale, multicenter studies with adequate sample sizes and rigorous control of these confounders are strongly recommended to more precisely and comprehensively evaluate the effectiveness of metformin according to varying disease severity and related factors.

Conclusion

Metformin therapy plays a clinically meaningful role in the management of early pregnancy in women with polycystic ovary syndrome. Effective rate of metformin observed around 74.4%, indicating a protective potential role in reducing adverse early pregnancy outcomes in this high-risk population. However, the true magnitude of metformin should be more precisely determined by the future large-scale, multicenter studies based on disease severity, obesity, insulin resistance, dietary patterns, and other metabolic cofactors that were beyond the scope of the present investigation, to guide the clinicians in optimizing metformin-based therapeutic strategies to improve early pregnancy outcomes among women with PCOs.

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