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Full Length Research Paper

Metformin Hydrochloride and Recurrent Miscarriage in Women with Polycystic Ovary Syndrome

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Abstract
Pregnant females with polycystic ovary are at higher risk for miscarriage. Thus, avoidance of early pregnancy loss in pregnant patients with polycystic ovary is crucial. To assess the efficacy of metformin treatment in reduction of early miscarriage in pregnant females with polycystic ovary.100 pregnant females with polycystic ovary were included in the study. Fifty received metformin 500mg, 3 times daily for the first 12 weeks of their pregnancy. Other 50 women received placebo. All women were assessed clinically and followed up to the end of their first trimester. The outcome of gestation at this point was documented. In addition, lab investigations especially fating insulin, oral glucose tolerance test and hormonal profile were assessed at the end of 6th, 9th and 12th week of gestation. Both study and control groups were comparable regarding patient characteristics and baseline lab investigations. Females continued their pregnancy were significantly higher in study when compared to control group (60.0% vs 28.0% respectively). In addition, inability to get pregnant was significantly higher in control group (32.0% vs 16.0% respectively), and missed abortions, spontaneous abortions were similarly higher in control group. In addition, fasting insulin was significantly reduced in females continued their pregnancy at 6, 9 and 12 weeks of gestation in aborted females at 6 week only. Metformin in pregnant females with PCOS was associated with a significant decrease in the rates of early pregnancy loss, with fewer side effects, reflecting its safety and efficacy.

Keywords: *Metformin, fasting insulin, oral glucose tolerance, recurrent miscarriage, polycystic ovary.*

Introduction

The syndrome of polycystic ovary is the commonest cause of female infertility in the United States, and it affects 5–10% of females in reproductive age. In addition to difficulty conceiving, females who had polycystic ovary are at high risk of miscarriage after either natural or assisted conception (Jalilian et al., 2015). Rates of early miscarriage, defined as miscarriage during the first trimester, are found to be between 30 and 50% in females with polycystic ovaries, which is 3-fold higher than the rate for normal women (10-15%) (Papalou et al., 2016). The true estimates of miscarriage rate in both normal females and those with PCO are underestimated as the studies calculated this incidence were retrospective trials of clinically documented pregnancies. However, 36–82% of females with recurrent early miscarriage are reported to have polycystic ovary (Baskind and Balen, 2016). Previous trials have proposed that females who had higher levels of LH, a frequent feature of the polycystic ovary syndrome, are at higher risk for miscarriage after either spontaneous or assisted conception. However, it was suggested that suppression of endogenous secretion of LH before conception, in females with high circulating LH values and a history of recurrent pregnancy loss, did not improve the live birth rate (Jalilian et al., 2015). Other proposed risk factors for early recurrent miscarriage in polycystic ovary include hyperandrogenemia and obesity. Obesity is characterized by marked insulin resistance with compensatory increased serum insulin levels and a recent trial implicates hyperinsulinemia as an independent risk factor for early recurrent miscarriage (Baskind and Balen, 2016).

Because metformin has positive effects on reduction of many risk factors for early pregnancy loss in the polycystic ovary (essentially insulin resistance with higher insulin secretion, increased androgen and obesity), we proposed that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy in females with polycystic ovary would lead to reduction of early miscarriage. Thus, the current study was designed to assess the effectiveness of metformin therapy in reducing early pregnancy loss in pregnant females with polycystic ovary syndrome (PCOS).

Methodology

This study is a prospective randomized controlled trial included 100 patients who were selected from outpatient gynaecological clinic attendants, at AI-Azhar university hospital (New Damietta), who had recurrent miscarriage with PCO in the period from May 2016, to May 2017. Patients were included if they had the following criteria: 1)

patients with PCO and complaining from recurrent miscarriage; and 2) their age is more than 20 and less than 40 years. On the other hand, patients were excluded if they had one or more of the following criteria: 1) females without PCOS, 2) Diabetic patients; and 3) patients younger than 20 or older than 40 years.

All patients subjected to detailed history taking, which includes general medical history, menstrual & obstetric history, duration of PCOS, history of gynaecologic operations, drug intake and associated symptoms. Then, a full clinical general and systemic examination was undertaken along with abdominal and vaginal examinations. Then, lab investigations were done and included oral glucose tolerance test, fasting insulin level, FSH, LH, transvaginal ultrasonography for diagnosis of PCO and follow up of pregnant woman through 1st 3months. The study protocol was explained for each patient carefully and an informed consent to continue metformin throughout the first 12 weeks of gestation was obtained. The dose of metformin was 500mg, 3 times daily, with folic acid (1 mg) daily supplementation. Patients who received metformin represented the study group and they were 50 females. The other 50 females received placebo (50 females), as a control group. All patients have been followed up every 2 weeks during the first trimester of pregnancy. Each visit oral glucose tolerance test, fasting insulin level and blood pressure had been performed.

Statistical methodology: Data entry and statistical analyses were performed using SPSS (statistical package of social sciences) version 21 (IBM®SPSS® Inc., Chicago, IL, USA by baron and Kenny 1086). Categorical data were expressed in number and percentage. Continuous normally distributed data were expressed in mean and standard deviation while none normally distributed data were expressed in median and range. The quantitative data were examined by Kolmogorov Smirnov test for normality of data. Student (t) test was used to compare means for continuous normally distributed data and Mann Whitney (U) test was used to compare median for non-normally distributed data. Comparing of categorical data was done using Chi square test or fisher exact test used whenever appropriate. Statistical significance was considered when probability (p) value was less than or equal to 0.05.

Results

In the present work, there was no significant difference between case and control group as regard age, parity and number of previous abortions (Table 1). Base line investigations included oral glucose tolerance test, FSH, LH and fasting insulin level, and there non-significant difference between study and control groups as regards any of basic investigations. In the present work, regarding outcome, patients that Continue to normal pregnancy is significantly higher in case group when compared to control group (60.0% vs 28.0% respectively). In addition, inability to get pregnant was significantly higher in control group (32.0% vs 16.0% respectively), and missed abortions, spontaneous abortions were similarly higher in control group (table 2).

In patients and controls who continue their pregnancy, there was significant low fasting insulin level in case group when compared with control group at 6, 9 and 12 weeks of gestation, while blood values for 2-Hour 75-gm OGTT mg/dl are insignificant between both groups at 6, 9 and 12 weeks of gestation (table 3). Similarly, in patients who were aborted, the median fasting insulin levels at 6 weeks of gestation were significantly lower in cases when compared to control (22.6 vs 26.2 respectively). Otherwise, values at 9 weeks for fasting insulin revealed non-significant difference between both cases and controls. Also, blood values for 2-Hour 75-gm OGTT mg/dl in patients with abortion at 6 and 9 weeks of pregnancy.

Table (1): Characteristics of studied females

Variable		Case (N=50)	Control (N=50)	P value
Age (mean±SD)		28.4±4.1	32.7±5.5	0.241
Parity N(%)	P0	25(50%)	23(46%)	0.822
	P1	17(34%)	18(36%)	
	P2	7(14%)	4(8%)	
	P4	1(2%)	5(10%)	
Number of abortions N (%)	Twice	1(2%)	0(0%)	0.711
	Three	37(74%)	31(62%)	
	four	12(24%)	19(38%)	

** P value >0.05 is insignificant*

Table (2): The outcome of pregnancy after follow up

Variable	Case (N=50)	Control (N=50)	P value
Continue to normal pregnancy	30 (60%)	14 (28%)	0.026*
Do not get pregnant	8 (16%)	16 (32%)	
Missed abortion	3(6%)	9(18%)	
Spontaneous abortion	5(10%)	7(14%)	
Blighted ova	2(4%)	3(6%)	
An embryonic sac	2(4%)	1(2%)	

**p<0.05 is significant*

Table (3): Follow up investigations for the patients who continue to normal pregnancy.

Variable		Case (N=30)	Control (N=14)	P value
		6 weeks		
Fasting insulin level mu/ml		19.7±3.9	24.1±4.4	***0.047****
Blood values for 2-	Fasting	78.6±5.5	91.6±2.4	0.199
Hour 75-gm	1st hour	163.6±7.8	171.9±11.2	0.601
OGTT mg/dl	2nd hour	136.6±8.9	152±4.9	0.438
		9 weeks		
Fasting insulin level mu/ml		18.3±2.8	25.2±2.9	***0.030****
Blood values for 2-	Fasting	78.7±5.2	102.1±11.2	0.059
Hour 75-gm	1st hour	160.6±8.4	182.6±6.8	0.062
OGTT mg/dl	2nd hour	135.2±7.2	151.9±12.4	0.071
		12 weeks		
Fasting insulin level mu/ml		17.7±3.1	25.9±1.8	***0.001****
Blood values for 2-	Fasting	78±6.4	91.1±7.2	0.109
Hour 75-gm	1st hour	161.1±8.7	172.9±12.3	0.341
OGTT mg/dl	2nd hour	135.4±4.4	140.4±8.1	0.602

**p<0.05 is significant*

Discussion

This present trial was done to investigate the role of metformin treatment on gestation outcome by comparing the rate of recurrent abortion between two groups of patients who received or did not receive it during their first trimester. This study included fifty women received metformin throughout 1st 12weeks of pregnancy and fifty women didn't receive it. All females were submitted to full history taking, detailed clinical examination, ultrasound examination and laboratory investigations with special interest for serum FSH, serum LH, serum fasting glucose level and serum fasting insulin level. In the present work, there is insignificant difference between both groups regarding age, number of parity and abortion. These results are comparable to those reported by Roy et al. (2009) who reported that, there was statistically non-significant difference between both groups. Shahine and Lathi (2015) evaluated the role of metformin therapy on gestational outcome by comparing the rate of early miscarriage between two groups of patients received or did not receive it throughout the pregnancy. In the treated group, the mean gestational age was 8.6 ± 0.2 weeks and 50% of females (28/56) become pregnant with therapy by clomiphene citrates or human chorionic gonadotropin for induction of ovulation. Four patients (7.1%) get pregnant after in vitro fertilization. None of the females in both groups had diabetes before gestation and all females had normal blood glucose level at a range of 5.6 ± 0.6 mmol/L in the study group and 5.2 ± 0.4 mmol/L in control group.

In our study, there is insignificant difference between study and control groups regarding FHS, LH, fasting insulin, serum FSH, LH level and pregnancy outcome. Morin-Papunen et al. (2003) proved that metformin therapy was followed by a statistically significant decrease in basal levels of LH, this was explained on the base of the possibility that spontaneous or induced ovulation or a decrease in androgens may lead to a secondary reduction in LH. Nardo et al. (2008) found positive correlation of ovarian volume and LH levels. The results of fasting insulin, fasting blood sugar reported in this study are agreed with these reported by Ng (2005). Shahine and Lathi (2015) demonstrated that there were no significant differences as regards to maternal age, BMI, fasting glucose concentration, and serum-free testosterone values between the study and control groups. In our study, patients that continue to normal pregnancy is significantly higher in case group when compared to control group. But missed abortion was significantly associated with control group. Nausea and mild gastrointestinal symptoms are the side effects most frequently encountered in metformin treatment. It is expected that treatment by metformin might be associated with exaggeration of morning sickness with pregnancy. However, it was well tolerated in all patients, with no serious complications Hall and Nicholson (2009). Shahine and Lathi (2015) stated that metformin was well tolerated in all patients. None of the patients required cessation or reduction in the treatment dose. No unwanted effects or severe complications were observed.

Our study showed that there is a significant low fasting insulin level in case group when compared with control, while Blood values for 2-Hour 75-gm OGTT mg/dl Do not present any significant difference between both group. Glueck (2004) proposed that reducing insulin resistance by metformin in females with PCOS leading to reduction of early miscarriage rate. Motta (2010) stated that the valuable effect of metformin is independent of its hypoglycemic action but happens through the action on lipid, inflammation, hemostasis, endothelial cells, and platelet function. In addition to these, there are several mechanisms for the action of this drug in females with PCOS. One important action is exerted by reduction of the hyper-androgenization of the fetus. In addition to the action of immunoglobulin G-binding protein, which looks to simplify the adhesions at the endometrium? Shahine and Lathi (2015) evaluated the incidence of early miscarriage. Among the 56 females who treated by metformin throughout their gestation, there were five females (8.9%) of early miscarriage, whereas there were 18 women (36%) in the control group. The difference was statistically significant. The results of the previous gestational outcome in the females studied revealed that among the 56 females in the metformin group, there were 25 females with a positive history of early miscarriage in previous gestations and 31 had a negative history. Females with a negative history of early miscarriage were either primigravidas or cases with preceding successful pregnancies. None of the females had received metformin in the preceding gestations. In addition, among the

25 females in the metformin therapy group with a history of prior gestations, there were 50 gestations (15 live births and 35 miscarriages), with a miscarriage rate of 45%. In the control group, 20 (40%) of the 50 women had a history of prior pregnancy loss, whereas 30 cases were primigravidas. Among the 20 women with prior pregnancy loss, there were 25 gestations, which resulted in 16 live births and nine miscarriages, yielding a miscarriage rate of 36%. For the patients in the metformin group with a previous history of early pregnancy loss, there was a decrease in the rate of miscarriage from 45% in the prior gestations to 8.9% in the current gestations. In the control group, however, there were no significant variations between the rates in the prior and current pregnancies (40% vs. 35%), respectively. Shahine and Lathi (2015) concluded that metformin therapy in pregnant females with PCOS was linked with a significant decrease in the rate of early pregnancy loss.

In short, results of the present study demonstrated that, the metformin therapy in pregnant females with polycystic ovary during gestation was linked with a significant reduction in the rates of early miscarriage. It was well tolerated with a minimum of side effects. In addition, metformin therapy have been accompanied by improvement of clinical manifestations of PCO, ovulation, return of menses, pregnancy in some females and decrease in hirstuism .

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