TO STUDY THE ROLE OF METFORMIN ON OUTCOMES OF PREGNANCY IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

OBJECTIVES: To evaluate the effects of Metformin on outcomes of pregnancy in patients of polycystic ovarian syndrome who conceived on Metformin and then continued it till they delivered, compared to patients where use of metformin was stopped on conception.

STUDY DESIGN: This open label randomized study was conducted from October 2010 to October 2012 at the outpatients department of Maroof International Hospital, Islamabad

PLACE AND DURATION: 46 patients with polycystic ovarian syndrome who conceived on Metformin (both with and without the help of ovulation inducing agents) were included in the study. Out of these 23 patients discontinued the use (of Metformin) and remaining 23 never stopped using Metformin throughout pregnancy, both these groups were compared to each other in their outcomes.

METHODOLOGY: Forty six patients having polycystic ovarian syndrome and infertility were treated with Metformin1gm/day with or without other ovulation induction agents (Clomiphene and injections of Human Menopausal Gonadotropins). Twenty three patients were continued with Metformin 1gm/day throughout pregnancy (group A), and in the second group consisting of twenty three patients(group B) Metformin was discontinued after they conceived. The outcomes measures were first trimester abortions, preterm delivery, Live birth rate, Birth weight, gestational diabetes and fetal anamolies.

RESULTS: The incidence of first trimester abortions in group B patients of polycystic ovarian syndrome was 34.7% as compared to group A where the incidence was 4.3% (where Metformin was continued throughout pregnancy).The incidence of gestational diabetes was 8.6% in group A (when Metformin was continued) and 26 % in group B (when Metformin was not continued). There were no fetal anomalies in the women receiving Metfromin during pregnancy.

CONCLUSION: Metformin reduces the incidence of first trimester abortions gestational diabetes and impaired glucose tolerance, when the drug was continued throughout pregnancy in subjects with polycystic ovarian syndrome. In addition no adverse effects on the mother or fetus were seen.

KEY WORDS: Metformin, polycystic ovarian syndrome, early spontaneous abortions, gestational diabetes.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most commonly seen endocrinopathies among women of reproductive age[1]. This syndrome is fairly common in the western world (14%)[2]. Its incidence in Pakistan is also quite high, (20.7%) [3]. Incidence of PCOS was found to be 80.7% in women presenting with oligomenorrhoea and hirsutism.[4]

Polycystic ovarian syndrome is a complex endocrine disorder of women of unknown etiology characterized by oligomenorrhoea and clinical and biochemical hyperandrogenism, and is one of the most common causes of female infertility[5]. Most of these women have hyperinsulinaemia due to insulin resistance and obesity and there is a strong evidence to suggest that these elevated insulin levels impede ovulation[6,7]. These women with PCOS are associated with an increased risk of type 2 diabetes mellitus(DM), dyslipidemia, cardiovascular disease and endometrial carcinoma[8]. Anovulation, early pregnancy loss and late pregnancy complications have all been implicated in low fertility of women with (PCOS).[1] There is an accumulating data suggesting that hyperinsulinaemia is responsible for the hyperandrogenism (in PCOS)[9]by increasing the androgen production especially testosterone and by reducing the serum concentration of sex hormone biding globulin concentration. The raised levels of androgenic hormones affect the pituitary ovarian axis, leading to raised LH levels, anovulation, amenorrhoea, repeated pregnancy loss and infertility. [9,10]Hyperinsulinaemia is also seen to play a central role in implantation failure due to antagonist effect on glycodelin in endometrium, and results in enhanced frequency of miscarriages in women with PCOS when matched with controls[11-13]. When the woman with PCOS conceives there is an increased risk of developing impaired glucose tolerance and gestational diabetes (GD) as pregnancy increases the need for insulin secretion while at the same time increasing insulin resistance, thus increasing demands on pancreatic β cells, hence promoting gestational diabetes. These women have a significant risk of adverse perinatal outcome, the fetuses with GD have a increased risk of macrosomia (associated with increased frequency of birth injuries), asphyxia, neonatal hypoglycemia, and neonatal hypreinsulinaemia. 16.31% of obese women with PCOS have impaired glucose tolerance, 7.5%

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DM, and in non obese women with PCOS 10.3% have impaired glucose tolerance and 1.5% DM.[1,7]

Effective treatment of polycystic ovarian disease remains controversial; the medical literature suggests that the endocrinopathy in lot of patients can be resolved with insulin lowering therapy, [10]. Metformin an oral insulin sensitizing agent has been shown to ameliorate the endocrinopathy associated with PCOS and facilitates resumption of normal menstruation in 50 to 90% of these women[12]. It reduces serum concentrations of insulin and androgens, reduces hirsutism and improves ovulation rates[11]. Metformin treatment for women with PCOS undergoing ovulation induction and early pregnancy improve endometrial receptivity and implantation thereby reducing the risk of future miscarriage, it also increases the levels of glycodelin which helps in preventing abortions[14]

Women with PCOS often conceive while on metformin and exposure during organogenesis is common. Metformin is classified (in general) as class B drug in pregnancy, with no evidence of animal or fetal toxicity or teratogenecity[12]. The use of this drug has become increasingly popular in the recent years during pregnancy but further prospective trials are needed to establish its safety and efficacy (in the setting of PCOS). The aim of this study is to compare two groups of patients who conceived on Metformin, one group continued it till term and the other discontinued it after conception.

METHODOLOGY

This study included forty six consecutive patients coming to the outdoor of Maroof International Hospital, Islamabad during the period of October 2010 to October 2012 having primary or secondary infertility and polycystic ovary syndrome and conceived on Metformin with or without ovulation inducing drugs like clomophene or gonadotrophins (convenient sampling). All these patients were diagnosed using the revised 2003 ESHRE/ASRMI; (the American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology consensus) having any 2 of the three Rotterdam criteria (1) oligomenorrhoea and anovulation (2) ultrasound picture of polycystic ovaries i.e. more than eight small follicles measuring less than 10mm in the subcortical region, ovarian volume $\geq$ 10ml(3) clinical or biochemical signs of hyperandrogenism[8]. In summary the inclusion criteria was a diagnosed case of polycystic ovaries aged between 18 and 35 year with a history of primary or secondary infertility.

The exclusion criteria was other endocrinonopathies like Cushing's syndrome, late onset congenital adrenal hyperplasia and hypothyroidism , previously diagnosed diabetes mellitus or fasting serum glucose higher than 126 mg/dl , and treatment with oral glucocorticoids, renal or liver disease.

The diagnosis of PCOS was based on confirmed diagnosis before the actual pregnancy.All cases were diagnosed by a consultant gynecologist they were either put on ovulation induction agents like clomiphene and human menopausal gonadotrophins or conceived on metformin only. Pregnancy was confirmed by blood /urine test and ultrasound examination, these patients were then divided into two groups group A which continued Metformin after pregnancy was confirmed and group B who discontinued Metformin 1gm twice/day throughout the pregnancy. These patients were followed in the antenatal clinics during pregnancy, their demographic data and pertinent information regarding accompanying medical conditions and family history like diabetes mellitus and hypertension was documented on data collection forms. Creatinine and alanine aminotransferase were measured to exclude kidney or liver disease before inclusion in the study. Antenatal checkups with blood pressure and weight recordings and fetal growth were regularly put on records. At twelve to thirteen weeks they had an ultrasound to assess the fetal age and nuchal translucency, then a detailed anomaly scan at twenty to twenty two weeks followed by serial ultrasounds to assess fetal well being. Pregnancy induced hypertension was defined as blood pressure > 140/90 mm Hg at a gestational age of > 20 weeks on two or more occasions 6 hours apart(in the absence of proteinuria). Obstetrical outcomes like abortions, preterm delivery and live births were also recorded. Abortion was defined as fetal loss at <24 weeks of pregnancy and premature delivery was considered as delivery between 24-36 weeks of gestation. The patients underwent blood tests on their first antenatal visit which included fasting and random blood sugar tests and were repeated every month, and between 24 and 28 weeks the patients underwent a 75 grams glucose tolerance test to diagnose gestational diabetes or impaired glucose tolerance. The criteria for diagnosing gestational diabetes was fasting blood sugar > 126mg/dl and two hour >200mg/dl and impaired glucose intolerance as fasting <126mg/dl but >105mg/dl and 2 hour blood sugar >140mg/dl. Fetal outcomes like birth weights and congenital anomalies were also documented.

All the data was maintained in the hospital records and the antenatal records given to the patients. The cases were placed in two groups based on continuation of metformin after confirmation of pregnancy or not, the two groups were compared using SPSS version 21.Descriptive statistics, Chi-square test and Fisher Exact tests were used to calculate the P-Values.Values$\leq$ 0.05 were considered to be statistically significant.

RESULTS

The patients of both the groups were comparable regarding their age, BMI, pre pregnancy LH .The pre pregnancy mean BMI was 29.6 in group A and 29.8 in group B and the mean fasting insulin levels were 12.1 in group A and 11.9 in group B. There was no statistical difference in the family history of diabetes and hypertension, the values of pre- existing hypertension and diabetes were also comparable.

All women conceived on metformin with or without addition of clomiphene and human menopausal gonado trophins none of the patients underwent IUI.

Comparison was also made between the two groups for the prevalence of pregnancy induced hypertension, impaired glucose intolerance, gestational diabetes and intrauterine growth restriction. There was a statistically significant difference in patients who developed impaired glucose

intolerance (p 0.047) in both the groups being much less in women who continued metformin throughout pregnancy. Six patients in group B developed gestational diabetes and had to be put on insulin therapy as compared to two in the patients who continued Metformin. None of the patients who continued Metformin during the pregnancy developed hypoglycaemia. Similarly a much smaller percentage of Metformin treated patients showed pregnancy induced hypertension (30.4% Vs 13.4%).

The rate of spontaneous miscarriage in women who continued Metformin i.e. group A was significantly low as compared to group B (p 0.01), rest of the results of live birth rates, pre term deliveries, birth weights of the new born were also much improved in the metformin treated group. There were no stillbirths or any congenital anomalies in both the groups.

TABLE–I: CLINICAL FEATURES OF PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME AND INFERTILITY (n=46)

	Group A Metformin not continued (n =23)	Group B Metformin continued (n=23)
Age(years)	29.6 +3.6	29.8+4.1
BMI(kg/m3)	28.7 + 3.2	29.5+3.4
Serum LH(IU/ml)	11.37+1.8	13+5.8
Pre-pregnancy serum insulin(IU/ml)	12.1+2.4	11.9+2.4

TABLE – II: COMPLICATIONS DURING PREGNANCY

Total Number of Patients	GroupA (n=23) Continued Metformin	Group B not continued Metformin (n=23)	P-value
Pregnancy induced hypertension	7/23(17.4%)	4/23(30.4%)	0.31
GDM	2/23(8.6%)	6/23(26%)	0.417
IGT	3/23(13.0%)	11/23(47.8%)	0.047
IUGR	1/23(4.3%)	4/23(17.39%)	0.162

GDM: Gestational diabetes mellitus, IGT: Impaired glucose tolerance, IUGR: Intra-uterine growth restriction.

TABLE –III: OUTCOMES OF PREGNANCY

	Group A (on metformin)	Group B (not on metformin)	P-value
First trimester abortions.	1/23(4.3%)	8/23(34%)	0.01
preterm	1/23(4.3%)	2/23(8.69%)	0.56
Live birth rate	22/23((95.6%)	15/23(65.2%)	1.00
Birth weight(Kg0	2.6+1.5	2.5+1.4	0.81

DISCUSSION

This study agrees with earlier studies showing the beneficial effects of Metformin during gestation in patients with polycystic ovarian syndrome, it mainly concentrated on three parameters namely incidence of impaired glucose tolerance or gestational diabetes, first trimester fetal loss and tetratogenicity seen due to Metformin use in pregnancy.

The role of Metformin in pregnant patients with polycystic ovarian syndrome has been a subject of studies for the last many years.[11,13,15,16,] and since the mid-nineties the beneficial metabolic effects of Metformin in polycystic ovarian syndrome have been shown[6,7,12,17,19]. At the same time a better definition of the syndrome itself has also helped in defining and refining the validity of the results achieved in these studies.[8,5]

More than a decade ago it was established that GDM in women with PCOS is 8% and only 3% in controls.[8]Later studies from the Asian subcontinent have shown a much higher frequency of GDM(20 to 25%) than in controls (9%). Since the early 2000 a number of studies were done on patients with polycystic ovarian disease with pregnancy[15,18,20]. These studies demonstrated a statistically significant beneficial effect of Metformin on gestational diabetes, in these studies an average of 2-3gm of metformin daily was used and demonstration of the lack of teratogenicity for this drug was simultaneously achieved.In the last two years a number of studies have compared Metformin and Insulin in patients with gestational diabetes with PCOS, with Metformin showing comparable results to Insulin.[21-26] Continued metformin therapy throughout pregnancy significantly reduced the incidence of impaired glucose intolerance in our study, there were 47.8% cases in group B where Metformin was not continued and 13% in group A where Metformin was continued till term.

It has to be admitted that there have been relatively few studies which had accounted all the factors which result in poor gestational outcomes in pregnant patients with polycystic

ovarian syndrome namely: gestational diabetes, hypertension /preeclampsia, miscarriage, preterm labor. In Pakistan one such study done at Agha khan hospital Karachi[27]reported that a favorable reduction in all measured outcomes of relevance (the above mentioned ones).

Two international studies done by Glueck CJ done in 2004 and 2008 tested Metformin and Metformin plus diet respectively again reported a favorable tendency in all the measured outcomes mentioned above.[19,20].

The association between PCOS and recurrent pregnancy loss is still not clear, it can be due to the raised LH levels or raised insulin levels, the risk of these abortions is increased by obesity, but Metformin does help to decrease these risk factors and lowers the rate of miscarriages as shown in our study. Another retrospective study done by Jakubowicz DJ et al in 2002 also showed a statistically significant reduction (41.9(control) and 8.8% (intervention group) respectively) in first trimester fetal loss in the subjects administered Metformin during pregnancy.[9]

Not all studies however show this favorable trend in all outcomes measured. A fair sized study done in 2010Vankyet al.[29] which randomly assigned 274 singleton pregnancies (in 257 women) to receive Metformin or placebo, from first trimester to delivery showed no statistically significant beneficial effects on the main Outcome Measures recorded i.e. the frequency of preeclampsia, gestational diabetes mellitus, preterm delivery. Hellmuth reported that perinatal mortality was increased in women who were treated with Metformin. (Though here it may be relevant to mention that later on these results were made subject of criticism because the groups were not well matched)[30].

In our study there were 4 cases of intrauterine growth impairment in group A and only one in group B where metformin was continued throughout pregnancy, the reason for this might be prevention or a better control of gestational diabetes with metformin which prevented placental vascular insufficiency. Overall birth rate was 65.6 % for group A and 95.6% in group B which is statistically significant and there were no congenital anomalies in the newborns.

Reviewing the studies done on this topic in our region an Iranian study done in 2009 on 75 patients receiving a dose of 1500 mg od of Metformin in the first trimester of pregnancy showed a beneficial effect the rate of miscarriage in this group.[26]

Our study used a slightly smaller dose of Metformin compared to most of the international studies but the results were quite similar to what the bulk in the investigational literature written on this subject agrees upon.

CONCLUSION

Our study favors the use of Metformin during pregnancy in patients with polycystic ovaries provided there is no contraindications as it reduces the rates of abortions in the first trimester and definitely decreases the incidence of gestational diabetes or impaired glucose intolerance without any adverse effects on the mother or the fetus.

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