

Effectiveness of Glycemic Control in PCO pregnancy outcome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS produces symptoms in approximately 5 to 10% of women in the age group of 12–45 years and is thought to be one of the leading causes of the female subfertility(1). According to the Rotterdam criteria(2), a diagnosis of PCOS can be made in a woman if she has 2 of the following 3 manifestations: Irregular or absent ovulation, elevated levels of androgenic hormones, and enlarged ovaries containing at least 12 follicles each. Other conditions with similar presenting signs, such as androgen-secreting tumors or Cushing's syndrome, must be ruled out before a diagnosis of PCOS is established.

During recent years, metformin, which is an effective oral biguanide insulin sensitizer, has been widely used for treating type 2 diabetes mellitus (T2DM) as an antihyperglycemic agent(3). Metformin has been increasingly regarded to be an effective and safe medicine for the metabolic and endocrine abnormalities in PCOS(4,5). Metformin is a category B drug for use in pregnancy (absence of teratogenic effects based on animal data) and its characteristics of effectiveness and safety and, as a result, its use in pregnancy have become increasingly popular worldwide, although there are no guidelines for its continuous use in pregnancy and there is debate regarding its potential adverse effects on both the mother and the fetus because of its crossing the placenta(6). A randomized, placebo-controlled, double blind study, done on 257 pregnant women with PCOS, aged 18 - 42 years, who either received metformin or placebo from first trimester to delivery, failed to demonstrate any reduction of pregnancy-related complications, such as gestational diabetes, pre-eclampsia and preterm delivery in the metformin group(7). On the contrary, a prospective study done on 98 pregnant women with PCOS who received metformin (1700 – 3000 mg/day) before conception and up to 37 weeks of pregnancy vs. 110 normal pregnant controls, showed a significant reduction of pregnancy complications, such as gestational diabetes and gestational hypertension but an insignificant decrease in pre-eclampsia incidence with comparable mean neonatal Apgar scores, weight and length between the 2 groups(8).

Metformin has been shown to have encouraging effects on several metabolic aspects of polycystic ovarian disease, such as insulin sensitivity, plasma glucose concentration, and lipid profile and since women with PCOS are more likely than healthy women to suffer from pregnancy-related problems like early pregnancy loss, gestational diabetes mellitus and hypertensive states in pregnancy, the use of metformin therapy in these patients throughout pregnancy may have beneficial effects on early pregnancy loss and development of gestational diabetes(9). In a 3-year case controlled study, conducted on 197 pregnant women with PCOS (confirmed by Rotterdam criteria), it was concluded that in comparison to the control group, the study group had a significant reduction in early pregnancy loss(10,11). Its use in pregnancy is devoid of any adverse effects on the new born as demonstrated by a case-controlled study, measuring pregnancy outcomes, conducted on 137 women with PCOS (Rotterdam criteria), in which there were 3 groups. The study found that the group, which continued metformin use throughout the entire pregnancy, had diminished incidences of fetal growth restriction, preterm labor, and increased live birth rates. There were also no congenital anomalies, intrauterine deaths or stillbirths reported in the test subjects,

suggesting metformin use is not related to teratogenicity. Besides the above, the group which continued metformin use in the entire pregnancy had reduced incidences of early pregnancy losses and gestational diabetes(12).

Metformin used throughout pregnancy in women with PCOS may reduce gestational diabetes incidence by as much as 9-fold(13). Its use during pregnancy in women with PCOS facilitates primary and secondary prevention of gestation diabetes(14). The reduction in incidence of gestational diabetes mellitus has been attributed to metformin's metabolic, endocrine, vascular, and anti-inflammatory effects. These effects of metformin were demonstrated in a prospective cohort study wherein 360 non-diabetic PCOS patients participated who conceived while on metformin by different treatment modalities. The study group comprised of 200 women who continued metformin (1000-2000 mg/ day) throughout pregnancy while the control group of 160 women discontinued metformin. The results of the study concluded in favor of the women who continued metformin use who demonstrated statistically significant prevention or reduction in the incidence of gestation diabetes mellitus(15).

PCOS is also associated with an elevated rate of early pregnancy loss. Metformin has beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to first-trimester abortion in PCOS patients. A prospective cohort study(16) was conducted to determine the beneficial effects of metformin on PCOS patients during pregnancy. Two hundred pregnant non-diabetic PCOS patients were evaluated while undergoing assisted reproduction. One hundred and twenty patients became pregnant while taking metformin and continued taking metformin at a dose of 1000–2000mg daily throughout pregnancy. Eighty women who discontinued metformin use at the time of conception or during pregnancy comprised the control group. Both groups were similar with respect to all background characteristics (age, BMI, waist/hip ratio, and levels of follicle-stimulating hormone, luteinizing hormone, estradiol, and dehydroepiandrosterone sulfate). The rate of early pregnancy loss in the metformin group was 11.6% compared with 36.3% in the control group ($P < 0.0001$; odds ratio = 0.23, 95% CI 0.11–0.42). Administration of metformin throughout pregnancy to women with PCOS was associated with a marked and significant reduction in the rate of early pregnancy loss from 30 – 50% to the rate of early pregnancy loss in normal women (10-15%). A smaller prospective pilot study(17) in 19 women with PCOS demonstrated a 63% decrease in spontaneous abortions in women treated with metformin.

The present audit was done retrospectively to understand the effect of metformin treatment among women with PCOS who have undergone infertility treatment at SAMD IVF hospital and conceived.

The increased abortion rates have become an important concern in the treatment of pregnant women with PCOS. In an aim to cope with this problem, the primary effort undoubtedly should be made in ameliorating the metabolic status of women with PCOS before they begin a pregnancy. In this context the use of the insulin-sensitizing agent metformin has been proposed to modulate insulin sensitivity through out pregnancy in women with PCOS and those women who were found to have GDM even after metformin treatment were given insulin to ensure glycemic control.

Methods

Aim: To understand the effect of glycemic control in the incidence of abortion in women with PCO

Type of study: Descriptive retrospective study.

Sampling: Census method (Conceived PCO cases from January 2012-December, 2014).

Target (Standard fixed): Previous studies shows an incidence of 30% GDM and 40% abortion among women with PCOS. Our target was to reduce GDM by 5% and abortion by 15-20%.

Criteria for diagnosing PCOS: Rotterdam criteria was used to diagnose PCOS in women. In accordance with Rotterdam Consensus Conference, PCOS was diagnosed in the presence of at least two of the following criteria: irregular menstrual cycles (or amenorrhea); clinical or biochemical evidence of hyperandrogenism; and ultrasound assessment of polycystic ovary (presence of ≥ 12 follicles in each ovary measuring 2 ± 9 mm in diameter or increased ovarian volume) after exclusion of other etiologies.

Study subjects: 252 pregnant women with PCOS with complaint of infertility attended our infertility clinic between years 2012 and 2014 were the subjects of this study .

Criteria for diagnosis of GDM: In the antenatal clinic, a pregnant woman after undergoing preliminary clinical examination, has to be given a 75 g oral glucose load, irrespective of whether she is in the fasting or non-fasting state and without regard to the time of the last meal. A venous blood sample is collected at 2 hours for estimating plasma glucose. GDM is diagnosed if 2-hour sugar is ≥ 140 mg/dL (7.8 mmol/L). A pregnant woman found to have normal glucose tolerance (NGT), in the first trimester, should be tested for GDM again around 24th–28th week and finally around 32nd–34th week. Once diagnosis is made, diet control is advised initially for 2 weeks. If this fails to achieve control, i.e. FPG ≥ 90 mg/dL and/or post-meal glucose ≥ 120 mg/dL, insulin may be initiated(18).

Treatment protocol (Criteria fixed): For PCOS women metformin was given throughout pregnancy in a dose of 500-1500mg per day. Those women in whom changes in glycemic level (FBS < 90 mg% and 2 hour PPBS < 120 mg% and at no time was the blood sugar < 60 mg%)were noticed again, were advised diet control and followed up regularly and those who were not controlled with these two treatments were given insulin to control GDM.

Follow up criteria: During pregnancy, all women underwent regular antenatal follow-up. All patients underwent screening test for gestational diabetes in the first antenatal visit and at 24 to 28 weeks. Obstetric charts were maintained for these women and they were followed till delivery. The incidence of spontaneous abortions, multiple pregnancies, gestational diabetes and congenital defects, were noted.

Data collection procedure: Case records of all pregnant PCOS women who attended the infertility clinic between years 2012 and 2014 were taken. An assessment form was prepared to transform the data from case record.

Assessment Form

OP No: -----

Year: -----

- 1) Age of mother:
- 2) Type of infertility: 1 Primary 2. Secondary
- 3) Previous obstetric history: 0. No 1.Abortion 2. GDM 3. IUD 4. NND
- 4) Family History of Diabetes: 0.No 1.Yes
- 5) PCO Diagnosis: 1.USG + Hirsuitism 2.USG+Menstrual Irregularities
3. USG+Hirsuitism+Menstrual Irregularities
- 6) Diet Restriction: 0.No 1.Yes
- 7) Insulin Given: 0.No 1.Yes
- 8) Outcome of treatment: 1.GDM 2.Abortion 3.Delivered live
4. Delivered baby dead
- 9) Birth Weight in grams: 1. < 2500 2. 2500-3500 3.> 3500

Data analysis: Data was entered and analyzed using SPSS package.

Results

Table 1. PCO diagnosis

PCO diagnosis	Number	Percentage
USG + Hirsutism	59	23.4%
USG + menstrual irregularity	143	56.7%
USG + Hirsutism + menstrual irregularity	50	19.8%
Total	252	100.0%

Table 1 shows diagnostic criteria used in the present study. Out of 252 women 56.7% had menstrual irregularity and PCO on ultrasound. 23.4% women had clinical hyperandrogenism (hirsutism) and PCO on ultrasound, while 1/5th (19.8%) of women had menstrual irregularity, clinical hyperandrogenism and PCO on pelvic ultrasound.

Table 2. Age of women

Age	Number	Percentage
<35 years	224	88.90%
>35 years	28	11.10%
Total	252	100.00%

The mean age of the PCOS women at the time of conception was 29.04 ± 4.05 years. 89% of women were in < 35 years age group and 11% were >35 years age group.

Table 3-6 shows the previous obstetric history of both group of women.

Table 3 Previous obstetric History - Abortion

History of Abortion	Number	Percentage
No	177	70.20%
Yes	75	29.80%
Total	252	100.00%

29.8% of women with PCOS were observed to have the history of abortion.

Table 4 Previous obstetric history- GDM

History of GDM	Number	Percentage
No	247	98.00%
Yes	5	2.00%
Total	252	100.00%

2% of women with PCOS had gestational diabetes in their previous pregnancies.

Table 5 Previous obstetric history-IUD

History of IUD	Number	Percentage
No	247	98.00%
Yes	5	2.00%
Total	252	100.00%

2% of women with PCOS had the history of IUD.

Table 6 Previous obstetric history - NND

History of NND	Number	Percentage
No	245	97.20%
Yes	7	2.80%
Total	252	100.00%

2.8% of women with PCOS were observed to have the history of NND.

Table 7 Family History of Diabetes

Family history of Diabetes	Number	Percentage
No	137	54.40%
Yes	115	45.60%
Total	252	100.00%

It was observed that 45.5% of the women with PCOS had family history of diabetes.

Antenatal Events

Table 8 Diet restriction

Diet restriction	Number	Percentage
No	131	52.00%
Yes	121	48.00%
Total	252	100.00%

48% of women with PCOS were advised diet restriction during antenatal period.

Outcome of treatment

Table 9. GDM

GDM	Number	Percentage
No	199	79.00%
Yes	53	21.00%
Total	252	100.00%

Gestational diabetes was observed among 21% women with PCOS.

Table 10. Outcome of treatment

Outcome	Number	Percentage
Abortion	6	2.40%
Delivered live baby	246	97.60%
Total	252	100.00%

Spontaneous abortion occurred in 2.4% women with PCOS.

Table 11. Birth weight of baby

Birth weight	Number	Percentage
<2500 gm	52	21.10%
2500-3500 gm	183	74.40%
>3500 gm	11	4.50%
Total	246	100.00%

Only 4.5% of the neonates were observed to have macrosomia and 21.1% were low birth weight babies.

DISCUSSION

Polycystic ovarian syndrome is the most common causes of anovulation and female infertility. Not only are these women infertile but they are also more likely to have pregnancy complications, like spontaneous abortions and gestational diabetes, compared to the general population. Recent understanding of polycystic ovarian syndrome has revolutionized the treatment options available for these women. Glycemic control in PCOS pregnancy is a very important measure to be followed up till delivery. Metformin, an insulin sensitizing agent, is known to restore regular ovulatory menstrual cycle in majority of these oligomenorrhic PCOS women many of whom thereafter conceive naturally(19). Besides helping in conception, it is also shown to improve the pregnancy outcomes in these women by reducing the incidence of spontaneous abortions, gestational diabetes and macrosomia.

In a study, 23 (5.7%) out of 400 cases, were diagnosed as having GDM using the DIPSI method in a rural population(20).

In an another study, among 819 pregnant women, 86 (10.5%) were diagnosed as having GDM(21).

In a study conducted by Vollenhoven, et al, there was no difference in the prevalence of GDM between the PCOS (22%) and control group (17%)(22).

In another study conducted by Mikola M, et al, GDM developed in 20% of the PCOS patients and in 8.9% of the controls ($P < 0.001$)(23).

In the index study, the incidence of gestational diabetes was 21%, when metformin was continued throughout pregnancy. In a study conducted by Jill Stein, gestational diabetes developed in 17 (32%) of 53 pregnancies in the cohort of 35 women with PCOS who conceived without metformin versus 3 percent in 33 women with PCOS who conceived on

metformin(24). The incidence of GDM with metformin treatment was slightly more than expected. However, along with metformin we adopted appropriate measures to control GDM and this brought out some fantastic results. Simultaneously, we could reduce the abortion rate to 2.4% and incidence of macrosomia was 4.5%. No congenital anomaly, intrauterine death or stillbirth was reported in this study. In a case control study conducted by Nawaz et al, it was observed that continuous use of metformin during pregnancy significantly reduces the rate of miscarriage, gestational diabetes requiring insulin treatment and fetal growth restriction. More over no congenital anomaly, intrauterine death or stillbirth were reported(25). In another study conducted by Zolghadri et al, it was found that the abortion rate was significantly reduced after metformin therapy in women with history of recurrent abortions in comparison to the placebo group (15% vs 55%).

Conclusion

The prevalence of GDM among PCOS women with metformin treatment through out pregnancy was 21% and this was higher than expected. We expected that we could reduce the incidence of GDM to 10% with metformin treatment alone among pregnant women with PCOS. However, along with metformin, with other appropriate measures adopted like diet control and insulin treatment, we could achieve our target reduction in abortion level to a much lower level than (2.4%) expected. We were able to reduce the incidence of macrosomia also to a greater extent (4.5%). No congenital anomaly, intrauterine death or stillbirth was reported in this study. These findings suggested that metformin treatment through out pregnancy along with proper monitoring of glycemic level and additional interventions if needed will reduce the complications associated PCOS pregnancy.

Future Aim

Our aim is to maintain the following results

1. very low early pregnancy loss achieved in women with PCOS
2. to prevent macrosomia
3. to prevent IUGR
4. to prevent intrauterine deaths, still births and neonatal deaths due to hyperglycemia.
5. to reduce the incidence of gestational diabetes to 10% by following a uniform pattern of metformin dosage, and strict diet control in women with PCOS.

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