



Effect of Long Protocol versus Short Protocol of Metformin Therapy in Pregnancy Outcomes in Polycystic Ovarian Syndrome – A Comparative Study

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Abstract

Background: Women with polycystic ovarian syndrome (PCOS) often have insulin resistance and hyperinsulinaemia and may therefore be at an increased risk for gestational diabetes mellitus (GDM). Metformin is widely prescribed to pregnant women with PCOS in an attempt to reduce pregnancy complications. Metformin is not approved for this indication, and evidence for this practice is lacking

Aim: the objective of this study was to compare the pregnancy outcomes if metformin was continued till delivery in pregnant PCOS patients to the outcomes if metformin was discontinued at 12 weeks.

Materials and methods: this single institution study included 81 women diagnosed with PCOS who conceived with metformin and randomised into two groups, group 1 who continues metformin till delivery and group 2 who discontinued metformin at 12 weeks. Obstetrical outcomes measured were GDM, Gestational hypertension, fetal growth restriction (FGR) and preterm delivery.

Results: Gestational hypertension was seen in 25% in group 1 and 33% in group 2. 20% patients were found to have GDM in group 1 and 33% in group 2. Preterm labour rate in group 1 and group 2 were 25% and 33% respectively. Incidence of FGR was similar in both groups, 18%.

Conclusion: Metformin appeared to reduce the incidence of GDM, especially need for insulin initiation if taken throughout pregnancy. It also appeared to reduce the incidence of hypertensive complications and preterm labour in this study. Metformin appeared to have no correlation to fetal growth restriction as evidenced by this study.

Keywords: Polycystic ovarian syndrome, Metformin, Gestational hypertension, Gestational Diabetes Mellitus, Fetal Growth Restriction, Preterm Labour.

Introduction

Polycystic ovarian syndrome is a condition associated with chronic anovulation and

hyperandrogenemia. It is considered to be the commonest cause of anovulatory infertility and affects 6-10% of women of reproductive age. Many

women with PCOS have insulin resistance with elevated insulin levels and are predisposed to developing various complications during pregnancy such as gestational diabetes, pregnancy induced hypertension and placental vascular insufficiency. Hyperinsulinemia is also believed to play a key role in implantation failure due to its antagonistic effect on glycodeclin in endometrium and results in increasing rates of miscarriage in women with PCOS compared to controls^{1,2,3,4,5}.

Metformin is a biguanide, oral hypoglycemic drug that improves tissue sensitivity to insulin while decreasing insulin levels and inhibiting hepatic glucose production. When used in patients with PCOS metformin reduces luteinizing hormone (LH), sex hormone binding globulins and ovarian androgens and also corrects hyperinsulinemia^{6,7,8,9,10}. Metformin is considered to be safe, effective and rational for the metabolic and endocrine abnormalities in PCOS. Its use as a first line agent for ovulation induction has been extensively investigated and has been found to increase the likelihood of ovulation and pregnancy rates, particularly in women who have clomiphene resistance^{11,12,13}. Metformin is a category B drug for use in pregnancy and in recent years its use in pregnancy has become increasingly popular. As there are no guidelines for its continuous use in pregnancy, the duration of treatment is therefore randomly selected by physicians based on their experience. During the last decade, several retrospective and nonrandomized studies have reported beneficial effects of metformin on pregnancy loss and pregnancy complications, in particular gestational diabetes mellitus (GDM). This study aims to evaluate pregnancy outcomes in such cases if metformin is continued till delivery.

Materials and Methods

This single institutional study was conducted in the time period NOVEMBER 2013 – APRIL 2015. PCOS diagnosed according to Rotterdam criteria. 2 out of 3 must be present. These include menstrual irregularity, hyperandrogenemia (clinical or biochemical), ultrasound morphology of polycystic

ovaries (presence of more than 12 small follicles measuring 2-9mm in subcortical region), total ovarian volume more than 10ml after exclusion of other endocrinopathies and hyperandrogenemia. The study included 81 women aged 18- 45 years with PCOS who conceived while on metformin therapy with or without other ovulation-inducing agents such as clomiphene citrate and gonadotrophins. Metformin was continued till 12 weeks. Then metformin was continued till delivery in 39 women selected randomly. Written informed consent was taken from each patient. The 39 women who continued metformin till delivery constituted group 1. The rest of 42 women who stopped metformin at 12 weeks was group 2. The exclusion criteria was Known liver disease or ALAT > 90 nmol/L, Known renal disease or creatinine > 110 micromol/L, Diabetes mellitus, Alcohol or drug abuse, Peroral steroid treatment, Cimetidine, anticoagulant or erythromycin treatment at time of inclusion. All the selected women were followed up and at every visit relevant history was taken including medical history, family history etc. the following findings are noted: General examination, Weight, Blood pressure and Obstetric examination to assess fetal growth. The following investigations are done: Baseline Hb, blood group and Rh, screening, RFT, LFT, HbA1C, FBS/PPBS, TSH, 75 GM GTT between 24-28 weeks, Serial ultrasounds to monitor fetal growth and 24 hour urine protein if required. The outcome criteria is:

- Gestational diabetes based on 75gm glucose tolerance test between 24-28 weeks. The cut off value is taken as FBS < 92, 1HR < 180 and 2HR < 153. Any one abnormal value is diagnosed as GDM
- Gestational hypertension by BP more than 140/90 with or without proteinuria (> 0.3 gm in 24 hours) after 20 weeks on two separate occasions at least 6 hours apart.
- Preterm labour- between 24 -36 weeks
- Fetal growth restriction- abdominal circumference less than 5th centile for that gestation on ultrasound.

Statistical Methods; Descriptive and inferential statistical analysis has been carried out in the present study. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

Results

There were 39 patients in group 1 and 42 in group 2. They were followed up till delivery and relevant findings were recorded.

The study variables are shown in table 1. Majority of the patients were in the age group 20-30. 95% in group 2 and 84% in group 1 belonged to this age. 60% patients were primis. Both groups were similar in this aspect. Most of the patients (50%) were of normal BMI. 45% were overweight.

Table 1: comparison of study variables

	Group I	Group II	P-value
Age in years	26.36±3.96	25.45±3.67	0.288
Period of infertility in years	3.88±3.79	2.69±1.52	0.063
Pre pregnancy BMI in kg/m ²	27.56±2.69	24.60±2.95	0.001
FBS in mg/dl	96.69±7.33	101.26±15.32	0.095
PPBS in mg/dl	121.00±11.61	124.67±19.07	0.304
SBP in mmHg	133.33±15.62	137.45±17.99	0.276
DBP in mmHg	84.87±10.23	86.45±12.51	0.537
Birth weight in kg	2.74±0.58	2.71±0.70	0.830

Most of the patients (around 73%) conceived with just metformin and weight reduction. 27 % required CC in addition

The incidence of pre-eclampsia was 7% in group 1 and 12% in group 2 (table 2)

Table 2: Pre Eclampsia in two groups of patients studied

Pre Eclampsia	Group I	Group II	Total
No	36(92.3%)	37(88.1%)	73(90.1%)
Yes	3(7.7%)	5(11.9%)	8(9.9%)
Total	39(100%)	42(100%)	81(100%)

P=0.714, Not significant, Chi-Square test

The prevalence of FGR was similar in both groups, 17% in group 1 and 19% in group 2 (table 3)

Table 3: Incidence of FGR in two groups of patients studied

FGR	Group I	Group II	Total
No	32(82.1%)	34(81%)	66(81.5%)
Yes	7(17.9%)	8(19%)	15(18.5%)
Total	39(100%)	42(100%)	81(100%)

P=0.899, Not Significant, Chi-Square test

20% patients were found to have GDM in group 1 whereas 33% had GDM in group 2. Of these in group 1 10% required insulin and 20% in group 2 required insulin (table 4)

Table 4: Incidence of GDM in two groups of patients studied

GDM	Group I (n=39)	Group II (n=42)	Total (n=81)	P value
GDM ON DIET AND METFORMIN	4(10.3%)	5(11.9%)	9(11.1%)	0.814
GDM On Insulin	4(10.3%)	9(21.4%)	13(16%)	0.171

Macrosomia was there in around 6% of the population, majority of which was in group 2

Gestational hypertension was seen in 25% in group 1 and 33 % in group 2. Severity of gestational hypertension was found to be similar (table 5)

Table 5: Incidence of Hypertension in two groups of patients studied

Hypertension	Group I (n=39)	Group II (n=42)	Total (n=81)	P value
Hypertension on 1 drug	7(17.9%)	9(21.4%)	16(19.8%)	0.694
Hypertension on more than 1 Drug	3(7.7%)	5(11.9%)	8(9.9%)	0.525

Preterm labour rates in group 1 and group 2 were 25% and 33% respectively (table 6)

Table 6: Occurance of Pre-term labour in two groups of patients studied

Occurance of Pre-term labour	Group I	Group II	Total
No	29(74.4%)	28(66.7%)	57(70.4%)
28-32 weeks	7(17.9%)	12(28.6%)	19(23.5%)
32-36 weeks	3(7.7%)	2(4.8%)	5(6.2%)
Total	39(100%)	42(100%)	81(100%)

P=0.589, Not significant, Fisher Exact test

67% were full term deliveries. Preterm delivery incidence was similar in both groups. Vaginal delivery was the predominant mode of delivery (60%). It was similar in both groups. The mean birth weight was similar around 2.7kg.

Discussion

The use of metformin in reproductive medicine has exploded since clinical trials showed that a metabolic medication improved reproductive abnormalities in women with polycystic ovary syndrome. Metformin soon became an essential element for restoring ovulation, curing infertility, preventing pregnancy loss, and reducing pregnancy complications such as gestational diabetes mellitus (GDM), preeclampsia, and preterm labor, all of which were linked to insulin resistance and systemic inflammation in PCOS. As for the safety profile, studies have reported that the use of metformin in the treatment of GDM had no increased risk of perinatal complications, which settled a previous controversy regarding metformin safety in pregnancy.

This study focused on mainly four outcomes

- Development of gestational diabetes mellitus
- Development of gestational hypertension
- Occurrence of preterm labour
- Development of fetal growth restriction

This study shows a slightly decreased prevalence of hypertension in PCOS patients who continued metformin till their delivery. The severity of hypertension does not seem dependent on metformin. Development of pre-eclampsia was comparable in both groups.

PCOS appears to increase the risk of gestational hypertension and pre eclampsia by insulin resistance. Metformin can reduce these complications by reducing IR. However studies are yet to prove the role of metformin in reducing hypertensive disorders in pregnancy^{14,15}.

More than a decade ago it was demonstrated that GDM in women with PCOS is 8% compared to 3% in controls. Subsequent studies from the Asian subcontinent have shown a higher rate of GDM (20–25%) than in controls (9%). This is probably because of the high prevalence of insulin resistance in Asian women. Insulin resistance is three-fold increase in pregnancy, and also plays a crucial role in development of hypertension in pregnancy and subsequent fetal growth-related problems secondary to placental vascular insufficiency.^{16,17,18}

It is well known that hyperinsulinemia, insulin resistance and obesity are common in women with PCOS. It has been well appreciated that continuation of metformin imparts a more therapeutic effect on GDM requiring insulin treatment compared to preventive effects. Current study results are comparable to those of Norman et al., Hague et al., Legro and Glucek et al. who have shown a significant reduction of GDM and better control with continued metformin treatment^{[19],[20],[21]}. In general, the number of studies reporting on the use of metformin in women with type 2 diabetes or GDM is still small. One retrospective study reported increased rates of pre-eclampsia and perinatal loss in a cohort of women with GDM or type 2 diabetes treated with metformin compared with a reference group treated

with insulin, but the groups were not well matched for age or body mass index. In the study of PCOS patients treated with metformin, the rate of pre-eclampsia did not differ compared with healthy control women even though women with PCOS were older and more obese. There are two randomized studies comparing insulin and metformin in the treatment of GDM. One study with a small number of patients suggests that metformin is an effective alternative to insulin.^{19,20}

This study shows a higher incidence of preterm labour in those who discontinued metformin after 12 weeks. Previous studies have not shown any effect of metformin in preterm labour. Several studies have assessed the association of metformin and preterm labour in women with PCOS, of which few showed that metformin statistically reduced preterm labour rates. One RCT showed no difference in preterm labour rates with use of metformin throughout pregnancy compared to eight weeks, and one retrospective study showed higher preterm rates compared to normal populations^{13,14}.

Incidence of FGR was 17% in group 1 and 19% in group 2. Based on this study there is no effect of continuing metformin to reduce FGR. Previously study by FauziaHaq Nawaz, Roha Khalid, TahiraNaru and Javed Rizvi showed reduced incidence of FGR in women on metformin[22].

Conclusion

The conclusions drawn from this study are the following

1. Metformin appeared to reduce the incidence of GDM, even though statistically not significant, if continued throughout pregnancy.
2. Also metformin appeared to reduce the need for insulin initiation in patients with GDM. Still statistically found to be non significant.
3. Metformin also appeared to reduce the incidence of hypertensive complications in this study, if given till delivery, but not statistically significant.

4. Metformin also appears to reduce the incidence of preterm labour, again not statistically significant.

5. Metformin appeared to have no role in reducing the incidence of fetal growth restriction as evidenced by this study.

The prevalence of pregnancy complications in our study was lower than in previous reports on PCOS. This can probably be explained by differences in baseline characteristics of the study populations and also by the low sample size.

Previous studies have shown conflicting results, some advocating for the use of metformin due to its beneficial effects and some against its use due to no additional benefits. Despite these favorable effects of metformin use with scarce serious side effects, no definite guidelines recommending metformin use in pregnant women with PCOS exists. According to the findings in this study metformin definitely helps lower the incidence of GDM, and insulin requiring GDM and to some extent, hypertensive complications and preterm labour, and can be safely continued till delivery, however further research on the topic is necessary before setting any guidelines.

Acknowledgements

I would like to acknowledge my HOD Dr. Sareena Gilvaz, my consultants, Dr Neetha George, Dr Aswath Kumar, Dr Annie Thadicaren, Dr Lola R. And Dr Saley Daniel for helping me with my cases. I would also like to acknowledge the principal and director of this institution. I would also like to thank Dr K. P. Suresh and Dr Sunanda for helping me with the statistical calculations.

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