INTRODUCTION
Polycystic Ovarian Syndrome (PCOS) affects 5 - 10% of women of reproductive age group. Polycystic ovarian syndrome is defined by the presence of chronic oligomenorrhoea, or anovulation, hyperandrogenism and polycystic ovarian morphology on ultrasound examination. Women with PCOS have insulin resistance with elevated insulin levels and are predisposed to type-2 diabetes mellitus and its co-morbidities.1,2 Hyperinsulinemia is believed to play a role in the pathogenesis of PCOS. Women with PCOS are characterized by obesity, insulin resistance and hyperinsulinemia, all of which are risk factors for gestational diabetes.3,4 Women in whom gestational diabetes develops, are likely to have underlying polycystic ovaries and women with PCOS are likely to develop gestational diabetes.3

Gestational Diabetes Mellitus (GDM) is diagnosed in over 4% of pregnant women between 15 - 49 years of age.5 The prevalence is increasing as the pregnant population is becoming older and obese. Gestational diabetes is related with increasing insulin resistance during pregnancy and is associated with risk of developing type-2 diabetes mellitus later in life. The offspring of women with gestational diabetes also have increased risk of perinatal complications and long-term risks of obesity and type-2 diabetes.8,7

Metformin therapy in PCOS improves insulin resistance and reduces clinical and biochemical hyperandrogenism, facilitates ovulation and thus helps in conception.8,9 It produces its effect via IFG-1 receptors located in ovaries, which are sensitive to high insulin levels. Metformin reduces first trimester miscarriages in women with PCOS.8 Metformin is a FDA category-B medicine, safe to be used in pregnancy and is not teratogenic.3,8

Metformin therapy during pregnancy in women with PCOS appears to reduce the development of gestational diabetes and macrosomia and it also does not increase
Metformin acts by reducing insulin resistance, improving insulin sensitivity probably by activating AMP kinase and decreasing ATP concentration of hepatocytes. It improves insulin sensitivity and hyperglycemia by reducing hepatic gluconeogenesis and increasing peripheral glucose uptake and utilization. It also reduces markers of endothelial activation, which are closely associated with insulin resistance. In PCOS, metformin may protect against gestational diabetes and later development of type-2 diabetes mellitus, by reducing insulin resistance and protecting pancreatic β-cell reserves during pregnancy, when both insulin resistance and insulin secretions are increased. Metformin throughout pregnancy does not have adverse effects on infant height, weight and motor - social development during first 18 months of life. Since long PCOS with pregnancy has been associated with recurrent miscarriages, gestational diabetes and pre-eclampsia, women with PCOS are mostly nulliparous, of older age group and obese. Hyperinsulinemia is known to produce a pre-diabetic state, macrosomia, polyhydramnios and increased weight gain in pregnancy. Use of metformin throughout pregnancy in women with PCOS has been shown to reduce the risk of early pregnancy loss, preterm labor, IUGR and also has encouraging effects on several metabolic aspects of PCOS such as insulin resistance, blood sugar levels and lipid profile. The use of metformin therapy in these patients throughout pregnancy will thus have beneficial effects on early pregnancy loss and development of GDM. Since there are no recommended guidelines, regarding use of metformin in prevention of GDM in patients with PCOS and hyperinsulinemia, the study was designed in Pakistani cohort to assess this effect of metformin.

This study was conducted to assess whether metformin therapy in pregnancy reduced the development of gestational diabetes in women with PCOS.

**METHODOLOGY**

The study was conducted in the private Gynecology Clinics of Mamji Hospital, Karachi, Pakistan, after obtaining informed consent from the participants from 2008 to 2010.

It was a comparative cohort study and comprised of two groups. One group included women who had diagnosed PCOS and were on metformin treatment while they conceived, they were followed prospectively for occurrence of PCOS related complications in pregnancy. As all of the prospectively studied patients with PCOS conceived on metformin and continued it during pregnancy, an access to a second potentially informative control group was not there. The second group selected, consist of women who had diagnosed PCOS and did not take metformin at conception or took metformin but could not continue it during pregnancy, their retrospective data was analyzed for presence of PCOS related pregnancy complications.

The inclusion criteria was all diagnosed women with PCOS and hyperinsulinemia with singleton pregnancy, between 18 - 40 years of age, women who tolerated and were compliant to metformin intake in pregnancy and pregnancy continued beyond the first trimester.

The women with type-1 and type-2 diabetes mellitus, essential hypertension, women with hypothyroidism, altered liver function tests and renal function tests at beginning of study or at any time during treatment were excluded from the study.

A total of 82 women were assessed with diagnosed PCOS as per Rotterdam/ESHRE 2003 criteria (2 out of 3) (1) Oligo- and/or anovulation; (2) Clinical and/or biochemical signs of hyperandrogenism; (3) Polycystic ovaries and exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing’s syndrome), and raised serum fasting insulin levels.

All baseline parameters i.e. height, weight, BMI, blood glucose and serum fasting insulin levels were compared in the two cohorts.

Fifty women (metformin group) continued metformin throughout pregnancy at the pre-conception dose level of 1.5 gram/day in three divided doses after meals. They were followed in antenatal OPD and given routine antenatal care. Vitamin B12 and folic acid were prescribed in addition to hematinic and calcium supplements. The remaining 32 women (control group) had PCOS and conceived without taking metformin or did not continue metformin during pregnancy and their pregnancy proceeded till delivery of a live baby. It was ensured that all participants in the retrospective group had all records available.

During each antenatal visit, their blood pressure and weight was recorded and adherence to metformin therapy and its dose was reviewed.

A questionnaire was designed for evaluation of the antenatal course and pregnancy outcome.

The development of GDM was studied in both the groups. All women underwent regular routine antenatal care and were subjected to Oral Glucose Tolerance Test (OGTT) (according to WHO criteria: 75 gram oral glucose tolerance test after an 8 - 10 hours fast, FBS: ≥ 126 mg/dl, 2 hour post load: ≥ 200 mg/dl ) at 28, 32 and 36 weeks of pregnancy respectively and post-partum 6 weeks after delivery.

After delivery metformin was stopped and patients were followed till 6 weeks post-partum and OGTT repeated.

Sample size was calculated using the method of sample size calculation for comparing two cohorts on www.openepi.com with 14.3% prevalence of gestational
diabetes in pregnancies occurring in patients with polycystic ovarian syndrome taken from study done in US published in diabetes care 2006, with 5% margin of error and 95% confidence interval. Fifty samples were selected for each group. Primary outcome measure was development of gestational diabetes mellitus. Secondary outcome measures were maternal weight gain during pregnancy. Mean and standard deviations are reported for continuous variables such as age, height, weight. Comparison of continuous variables was done using student 't' test. For categorical variables, frequency and percentages are reported while, odds ratio is also estimated for GDM during pregnancy for those who were not treated with metformin compared with metformin treated group.

RESULTS

Among 82 women who were diagnosed PCOS and conceived, 50 belonged to the group who conceived on metformin and continued it during pregnancy, while 32 PCOS women did not take or stop metformin before conception. Mean age was 29.94 ± 2.87 years in metformin group and 30.13 ± 2.24 years in no metformin group. There were no significant differences in parity between two groups (p = 0.944). Similarly, pre-pregnancy weight was 76.54 ± 7.66 kg and 75.75 ± 6.24 among metformin treated and untreated groups respectively (p = 0.627). Mean height and BMI were also comparable and insignificant in both groups (p = 0.764 and 0.961 respectively, Table I). Baseline serum fasting insulin was 17.22 ± 2.3 mIU/L in metformin group and 16.93 ± 2.28 mIU/L in no metformin group (p = 0.589). Mean fasting blood sugar was 94.54 mg/dl (5.26 mmol/l) in metformin group and 99.59 mg/dl (5.53 mmol/l) in no metformin group (p < 0.001) significantly more in no metformin group (Table I). Total weight gain in pregnancy was 9.58 ± 1.32 kg in metformin group and 12.12 ± 2.14 kg in no metformin group (p < 0.001) significantly more in no metformin group. There were no significant differences in parity between two groups (p = 0.944). Similarly, pre-pregnancy weight was 76.54 ± 7.66 kg and 75.75 ± 6.24 among metformin treated and untreated groups respectively (p = 0.627). Mean height and BMI were also comparable and insignificant in both groups (p = 0.764 and 0.961 respectively, Table I). Baseline serum fasting insulin was 17.22 ± 2.3 mIU/L in metformin group and 16.93 ± 2.28 mIU/L in no metformin group (p = 0.589). Mean fasting blood sugar was 94.54 mg/dl (5.26 mmol/l) in metformin group and 99.59 mg/dl (5.53 mmol/l) in no metformin group (p < 0.001) significantly more in no metformin group (Table I). Total weight gain in pregnancy was 9.58 ± 1.32 kg in metformin group and 12.12 ± 2.14 kg in no metformin group (p < 0.001) significantly less in metformin group.

Table I: Demographic findings, BMI and biochemical tests.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Metformin group (n=50)</th>
<th>No metformin group (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.94 ± 2.874</td>
<td>30.13 ± 2.24</td>
<td>0.758</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>0.92 ± 0.966</td>
<td>0.91 ± 0.68</td>
<td>0.944</td>
</tr>
<tr>
<td>Pre-pregnancy weight (kg)</td>
<td>76.54 ± 7.66</td>
<td>75.75 ± 6.24</td>
<td>0.627</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.86 ± 3.89</td>
<td>156.60 ± 3.22</td>
<td>0.764</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.97 ± 3.34</td>
<td>30.93 ± 3.05</td>
<td>0.961</td>
</tr>
<tr>
<td>S. Fasting insulin mIU/L</td>
<td>17.22 ± 2.3</td>
<td>16.93 ± 2.28</td>
<td>0.569</td>
</tr>
<tr>
<td>Fasting blood sugar mg/dl (mmol/l)</td>
<td>94.54 ± 5.35 (5.25)</td>
<td>99.59 ± 6.65 (5.53)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>OGTT at study entry</td>
<td>Negative</td>
<td>Negative</td>
<td>-</td>
</tr>
<tr>
<td>Body weight at delivery (kg)</td>
<td>86.12 ± 7.6</td>
<td>87.93 ± 7.01</td>
<td>0.280</td>
</tr>
<tr>
<td>BMI at delivery (kg/m²)</td>
<td>34.93 ± 3.5</td>
<td>35.90 ± 3.4</td>
<td>0.225</td>
</tr>
<tr>
<td>Total weight gain in pregnancy (kg)</td>
<td>9.58 ± 1.32</td>
<td>12.12 ± 2.14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Five (10%) patients in metformin group developed gestational diabetes, of them only one developed GDM at 28 weeks of pregnancy, 3 at 32 weeks of pregnancy and 1 at 36 weeks of pregnancy. In no metformin group 11 patients (34.37%) developed GDM with 8 at 28 weeks of pregnancy, 2 at 32 weeks of pregnancy and 1 at 36 weeks of pregnancy. One patient (3.12%) in no metformin group continued to have positive OGTT after delivery (Table II). The odds ratio for the development of GDM in no metformin versus metformin group was 4.174 at a CI of 95%. Patients not receiving metformin were 4.7 times likely to have GDM (OR: 4.714) compared to those who received it (Table III).

DISCUSSION

The study was prospective and partly retrospective. The occurrence of GDM in PCOS pregnancies was compared in two groups of patients with polycystic ovarian syndrome who had insulin resistance and a successful pregnancy. One group, received metformin throughout pregnancy and the other did not. Mean age, parity and pre-pregnancy weight and BMI were same in both the groups, similar to other previously conducted studies.17,18 All the patients in both groups had normal blood glucose levels at study entry. However, they had raised fasting insulin levels, mean 17.22 mIU/L in metformin group and 16.93 mIU/L in no metformin group. All the patients were obese in both groups with mean BMI of 30.97 kg/m² in metformin group and 30.93 kg/m² in no metformin group. PCOS is associated with obesity, insulin resistance and hyperinsulinemia, all of which are risk factors for development of gestational diabetes.19 Obesity is thus a contributing factor for the increased risk of gestational diabetes in PCOS pregnancies and it is estimated to affect 5 - 40% of pregnant women with PCOS.20 It was observed that obesity with BMI > 30 was seen in 49% of women.

Women with PCOS enter pregnancy with a higher insulin resistance as compared to normal women and...
46% develop gestational diabetes.\textsuperscript{7,18,21} This is because the pancreatic cells cannot overcome the physiological insulin resistance of pregnancy when it is superimposed on their own high insulin resistance due to PCOS. Metformin has been used in pregnancy in patients with GDM and PCOS and is known to decrease the complication rate associated with insulin resistance.\textsuperscript{22} The prevalence of GDM in pregnancies in women not taking metformin was found to be 34.37% comparable to other previous studies (30%, 30%, 31%).\textsuperscript{17-19} Similarly in the group taking metformin throughout pregnancy it was found that only 10% developed GDM as compared to other studies (3.44%, 7%, 3% and 0%).\textsuperscript{17,18,20,23}

Thus the study showed a 3-fold reduction in development of GDM (34.37% vs. 10%) in PCOS women taking metformin treatment throughout pregnancy. The odds ratio for GDM was 4.715 (95% CI) in women taking metformin versus those not taking metformin (p=0.01).

The development of GDM was found more in women who were obese with BMI > 30 and who had high pre-pregnancy insulin levels. GDM developed early in PCOS women not taking metformin. Eight developed GDM at 28 weeks and 2 at 32 weeks of gestation while only one woman in metformin group developed GDM at 28 weeks of pregnancy while the rest had altered OGTT after 32 weeks of pregnancy indicating protective effect of metformin in maintaining glucose homeostasis.

Exhaustion of β-cell reserves during pregnancy complicated with GDM is associated with a 50% chance of developing type-2 diabetes in next 10 years after gestational diabetes.\textsuperscript{24,25} It was observed that only one patient persisted to have impaired glucose tolerance after delivery and was the one who did not receive metformin treatment during pregnancy.

It is thus recommended that it would be beneficial to use metformin as a primary protection against pancreatic β cell exhaustion in GDM pregnancies thus giving protection against future development of type-2 diabetes in this high risk group of obese PCOS patients of South-Asian origin.

Similarly, it is recommended that metformin be continued in all women with PCOS and hyperinsulinemia throughout pregnancy thus reducing the chances of developing gestational diabetes and its associated morbidities, at the same time providing protection against pancreatic β-cell exhaustion.

The limitation of the study is the relatively small sample size and the two groups were not statistically comparable.

**CONCLUSION**

Continuation of metformin therapy throughout pregnancy in PCOS resulted in significant reduction in development of gestational diabetes.

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