Gestational Diabetes Mellitus: Safety and Efficacy of Regular Insulin and Metformin During Pregnancy

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Abstract
Gestational diabetes mellitus is a common metabolic disorder diagnosed during pregnancy. During pregnancy insulin resistance increases due to placental, growth and progesterone hormones. As pregnancy precedes the insulin resistance increase gradually, making hyperglycemia worse. The main task is to control hyperglycemia during pregnancy to prevent maternal and fetal complications. Initially diet and physical exercise is encouraged otherwise drug management is required. Combination of regular insulin and Metformin is an effective way to control hyperglycemia in gestational diabetes mellitus when diet and moderate exercise alone is ineffective.

Period: July 2016 to December 2016.

Objectives: The objective of this study was to determine the safety and efficacy of regular insulin and Metformin in gestational diabetes mellitus.

Study Design: A prospective descriptive study.

Place of Study: Pakistan Institute Of Medical Sciences Islamabad

Results: Among one hundred and forty seven (147) gestational diabetic women, we found that combination of regular insulin and Metformin is safe and effective to control hyperglycemia in gestational diabetes mellitus.

Conclusion: Combination of regular insulin and Metformin is an effective way to control hyperglycemia in gestational diabetes mellitus when diet and moderate exercise alone is ineffective.
Keywords: Gestational diabetes mellitus; Regular insulin; Metformin; Gestational period; Fasting blood glucose; Random blood glucose

1. Introduction
Gestational diabetes mellitus, according to the world health organization (WHO) is defined as the hyperglycemia recognized during any phase of pregnancy. Statistical data from the worldwide shows that one out of six pregnancies is associated with hyperglycemia of type 2 diabetes mellitus (T2DM). In Asia this figure count is one in four pregnancies [1-2]. This varies with age of pregnant women. For example, 16.9% lie in between 20-46 years of age. Gestational diabetes should be screened be out at 16, 24-46, and 30 weeks of pregnancy, respectively by oral glucose tolerance test (OGTT). Oral 75 G glucose after 12-14 hours overnight fasting is used. Blood glucose levels are measured after 2 hours. Gestational diabetes is better controlled by dietary restrictions. Insulin remains the first line of treatment in pregnancy. Regular insulin and NPH are commonly used while the effects of rapid insulin analog (Lispro) are being used while long acting insulin analog (Glargin) is not recommended. Insulin resistance increases progressively throughout pregnancy. Dose requirement increases 0.8-0.9/kg body weight during pregnancy. Recently, oral sulphonylurea (Glyburide) and Biguanide (Metformin) is also being used frequently. The main contributing factor in gestational hyperglycemia is insulin resistance. The likely causes of hyperglycemia are placental hormones and weight gain during pregnancy [3-4]. Sulphonylurea though bring down the blood glucose level, but it is not helpful to overcome the insulin resistance, rather it depletes pancreatic insulin store and could cause fetal hypoglycemia. Metformin is now frequently used during pregnancy. Metformin helps in maternal weight loss and prevent fatal hypoglycemia [5-7]. In our study the effects of regular insulin during the first trimester and combination of regular insulin and Metformin in second and third trimester were studied. The pregnant women were mainly treated in gynae and obs OPD and near delivery they were admitted in Mohi-Ud-Din Teaching Hospital Mirpur AJK and affiliated community hospitals from July 2016-December 2016. Total number of, one hundred and forty seven (147), pregnant women were studied.

1.1 Aims and objectives
The objective of this study was to find out the safety and effectiveness of regular insulin and Metformin in gestational diabetes mellitus.

2. Material and Methods
A study was conducted at Mohi-Ud-Din Teaching Hospital and affiliated community hospitals Mirpur AJK from July 2016 to December 2016. A total of 147 pregnant women were included in this study. All the patients were admitted through gynae and obs OPD. The patients were divided in 02 Age groups. Group A=(20-30 years)=63 Pregnant women. Group B=(31-35 years)=84 pregnant women. Fasting blood glucose (FBG) and random blood glucose (RBG) was the main screening test.
2.1 Inclusion criteria
Gestational diabetic women.

2.2 Exclusion criteria
1) Type 1 diabetes mellitus patients
2) Type 2 diabetes mellitus patients
3) Known malignancy, autoimmune and pancreatic diseases.

2.3 Study design
Prospective descriptive study.

2.4 Data analysis
Table 1 shows that total one hundred and forty seven (147) pregnant women were included in the study.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Age in years</th>
<th>Total Number of pregnant women=147</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group=A</td>
<td>20-30</td>
<td>63</td>
</tr>
<tr>
<td>Group=B</td>
<td>31-35</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 1: Total number of pregnant women and age distribution.

These were further divided into two groups according to age range, Group-A: Contains sixty three (63) and Group-B: Eighty four (84) pregnant women. Effects and safety of Regular insulin during the first trimester and combination therapy of insulin+Metformin in second and third trimesters were studied. They were only admitted in the last trimester near delivery.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Age in years</th>
<th>Number of patients</th>
<th>Gestational age</th>
<th>FBG (mg/dl) % (avg)</th>
<th>RBG (mg/dl) % (avg)</th>
<th>Gestational FBG (mg/dl) % (avg)</th>
<th>RBG (mg/dl) % (avg)</th>
<th>Gestational RBG (mg/dl) % (avg)</th>
<th>FBG (mg/dl) % (avg)</th>
<th>RBG (mg/dl) % (avg)</th>
<th>Gestational FBG (mg/dl) % (avg)</th>
<th>RBG (mg/dl) % (avg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group=A</td>
<td>20-30</td>
<td>63</td>
<td>First trimester</td>
<td>148</td>
<td>312</td>
<td>151</td>
<td>347</td>
<td>167</td>
<td>413</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group=B</td>
<td>31-35</td>
<td>84</td>
<td>First trimester</td>
<td>157</td>
<td>416</td>
<td>164</td>
<td>458</td>
<td>195</td>
<td>517</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Fasting and random blood glucose levels, according to gestational age.
Table 2, Group-A include ages (20-30 years) and Group-B (31-35 years). Group-A: Fasting and random blood glucose levels during the first trimester was FBG (148 mg/dl), RBG (312 mg/dl). Fasting and random blood glucose levels during second trimester was FBG (151 mg/dl), RBG (347 mg/dl). Fasting and random blood glucose levels during third trimester was FBG (167 mg/dl), RBG (413 mg/dl). Group-B: Fasting and random blood glucose levels during the first trimester was FBG (157 mg/dl), RBG (416 mg/dl). Fasting and random blood glucose levels during second trimester was FBG (164 mg/dl), RBG (458 mg/dl). Fasting and random blood glucose levels during third trimester was FBG (195 mg/dl), RBG (517 mg/dl).

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Age in years</th>
<th>Number of patients</th>
<th>Gestational age</th>
<th>Regular Insulin Units (average)</th>
<th>FBG (mg/dl)% (average)</th>
<th>RBG (mg/dl)% (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group=A</td>
<td>20-30</td>
<td>63</td>
<td>First trimester</td>
<td>75 units</td>
<td>135</td>
<td>215</td>
</tr>
<tr>
<td>Group=B</td>
<td>31-35</td>
<td>84</td>
<td>First trimester</td>
<td>90 units</td>
<td>145</td>
<td>335</td>
</tr>
</tbody>
</table>

**Table 3A:** Results of glyceamic levels in first trimester after regular insulin therapy.

Table 3A shows after initiation of regular insulin therapy in first trimester. Group-A: Fasting and random blood glucose levels during the first trimester was reduced to FBG (135 mg/dl), RBG (215 mg/dl). Group-B: Fasting and random blood glucose levels during the first trimester was reduced to FBG (145 mg/dl), RBG (335 mg/dl).

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Age in years</th>
<th>Number of patients</th>
<th>Gestational age</th>
<th>Regular Insulin Units (average)+ Metformin (average)</th>
<th>FBG (mg/dl)% (average)</th>
<th>RBG (mg/dl)% (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group=A</td>
<td>20-30</td>
<td>63</td>
<td>Second trimester</td>
<td>Regular Insulin 60 Units (average)+ Metformin 500 mg BD</td>
<td>125</td>
<td>194</td>
</tr>
<tr>
<td>Group=B</td>
<td>31-35</td>
<td>84</td>
<td>Second trimester</td>
<td>Regular Insulin 85 Units (average)+ Metformin 500 mg BD</td>
<td>134</td>
<td>245</td>
</tr>
</tbody>
</table>

**Table 3B:** Results of glyceamic levels second trimester after Regular Insulin+Metformin therapy.

Table 3B shows after initiation of Regular Insulin+Metformin therapy in the second trimester. Group-A: Fasting and random blood glucose levels during second trimester was reduced to FBG (125 mg/dl), RBG (194 mg/dl). Group-B: Fasting and random blood glucose levels during second trimester was reduced to FBG (134 mg/dl), RBG (245 mg/dl).
Metformin therapy in third trimester was associated with making hyperglycemia worse. Placental Metformin and insulin physical exercise is encouraged otherwise drug management is required. It is important to diagnose and treat it at the earliest.

Gestational diabetes mellitus is a most common metabolic disorder diagnosed during pregnancy [8-10]. It is important to diagnose and treat it at the earliest stage to prevent maternal and fetal complications. Initially diet and physical exercise is encouraged otherwise drug management is required. In the new strategy, safety and efficacy of Metformin and insulin, during pregnancy is being evaluated. During pregnancy insulin resistance increases due to placental, grown and progesterone hormones. As pregnancy proceeds the insulin resistance increase gradually, making hyperglycemia worse. The risk factors include maternal age, previous history of gestational diabetes and previous history of gestational diabete.

Table 3C: Results of glycaemic levels in third trimester after Regular Insulin+Metformin therapy.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Ages in years</th>
<th>Number of patients</th>
<th>Gestational age</th>
<th>Regular Insulin Units (average)+ Metformin+ (average)</th>
<th>FBG (mg/dl)% (average)</th>
<th>RBG (mg/dl)% (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group=A</td>
<td>20-30</td>
<td>63</td>
<td>Third trimester</td>
<td>Regular Insulin 50 Units (average)+ Metformin 500 mg BD</td>
<td>115</td>
<td>156</td>
</tr>
<tr>
<td>Group=B</td>
<td>31-35</td>
<td>84</td>
<td>Third trimester</td>
<td>Regular Insulin 50 Units (average)+ Metformin 500 mg BD</td>
<td>118</td>
<td>161</td>
</tr>
</tbody>
</table>

In Table 3C, after initiation of Regular Insulin+Metformin therapy in third trimester. Group-A: Fasting and random blood glucose levels during third trimester was reduced to FBG (115 mg/dl), RBG (156 mg/dl). Group-B: Fasting and random blood glucose levels during second trimester was reduced to FBG (118 mg/dl), RBG (161 mg/dl).

3. Results

Table 1 shows the total number of pregnant women included in the study were one hundred and forty seven (147). Group-A included sixty three (63) and Group-B: Eighty four (84) pregnant women. Most of them were treated and at gynecological and obstructed OPD during the first trimester and second trimester. They were only admitted during last trimester or near labour. From Table 2, we noted that there was a rising trend of blood glucose during first, second and third trimester of gestational period despite dietary control. This appears to be due to placental hormonal and weight gain. Therapy with Regular Insulin in the first trimester and Regular Insulin+Metformin in second and third trimester were studied.

Table 3A shows that there was decreased blood glucose levels in Group-A and Group-B treatment with regular therapy. In Group-A: FBG (148 mg/dl), RBG (312 mg/dl) reduced to FBG (135 mg/dl), RBG (215 mg/dl). In Group-B: FBG (157 mg/dl), RBG (416 mg/dl) reduced to FBG (145 mg/dl), RBG (335 mg/dl). Table-3B shows that there was decreased blood glucose levels in Group-A and Group-B when treated with Regular Insulin Units+Metformin. In Group-A: FBG (151 mg/dl), RBG (347 mg/dl) reduced to FBG (125 mg/dl), RBG (194 mg/dl). In Group-B: FBG (164 mg/dl), RBG (458 mg/dl) reduced to FBG (134 mg/dl), RBG (245 mg/dl). Table-3C shows that there was decreased blood glucose levels in Group-A and Group-B when treated with Regular Insulin Units+Metformin. In Group-A: FBG (167 mg/dl), RBG (413 mg/dl) reduced to FBG (115 mg/dl), RBG (156 mg/dl). In Group-B: FBG (195 mg/dl), RBG (517 mg/dl) reduced to FBG (118 mg/dl), RBG (161 mg/dl).

4. Discussion

Gestational diabetes mellitus is a most common metabolic disorder diagnosed during pregnancy [8-10]. It is important to diagnose and treat it at the earliest stage to prevent maternal and fetal complications. Initially diet and physical exercise is encouraged otherwise drug management is required. In the new strategy, safety and efficacy of Metformin and insulin, during pregnancy is being evaluated. During pregnancy insulin resistance increases due to placental, growth and progesterone hormones. As pregnancy proceeds the insulin resistance increase gradually, making hyperglycemia worse. The risk factors include maternal age, previous history of gestational diabetes and previous history of gestational diabetes.
family history of diabetes. It is necessary to screen out women before conception, during pregnancy and after delivery for risk of development of diabetes [11-15]. Screening for diabetes is important, during pregnancy to avoid the maternal and fetal complications. A pregnant woman having blood fasting glucose higher than 126 mg/dl and random blood sugar more than 200 mg/dl is confirmed case of gestational diabetes. Glycated hemoglobin >6.5% shows pre-existing diabetes. After delivery, when hyperglycemic effects of placental hormones are removed so majority of women return to normal glycemic state. The subsequent outcome after birth of a child is; 2/3 will have gestational diabetes in the next pregnancy; 20% have impaired glucose tolerance in the postpartum and 50% will have type 2 diabetes mellitus [16-24]. The most common fetal complications are macrosomia, spontaneous abortion; congenital malformation and intrauterine death. The most common maternal complications are risk of recurrence of diabetes in future pregnancies, polyhydranmosis, toxemia of pregnancy, urinary tract infections, higher incidence of premature birth and cesarean section.

The purpose of treatment is to avoid adverse effects of hyperglycemia during pregnancy. Dietary control includes intake of dietary fibers and fruits and chicken, fish, fruits and vegetables [25-27]. Vitamin-D deficiency is common in Pakistan and India, mainly because of dietary deficiencies. Insulin remains the main first line of therapy. As insulin does not cross the placental barrier, therefore it does cause the fetal hypoglycemia. The type of insulin used depends on glycemic level. In case fasting or pre-prandial hyperglycemia, long acting insulin is used while short acting insulin is used in postprandial hyperglycemia. The pregnant women whose hyperglycemic is not by insulin, the category –B drugs like Glibinclamide and Metformin is added. Glibinclamide causes fetal hypoglycemia [28-29]. Metformin, now commonly used alone or in combination with insulin. Metformin inhibits hepatic gluconeogenis, Decreases peripheral insulin resistance, therefore decreases insulin dose. It also causes weight reduction in pregnancy. No teratogenic effects of Metformin have been reported. The ideal glycemic control values are, preprandial blood glucose <90 mg/dl. One hour after the start of a meal <140 mg/dl. Two hours after the start of a meal <120 mg/dl. The diabetes mellitus should be screened at prenatal period consultation. If fasting blood glucose is >126 mg/dl, random blood glucose >200 mg/dl, and Glycated hemoglobin >6.5%, the women should be labeled as diabetic. A single test of fasting blood glucose higher than 90 mg/dl and less than 126 mg/dl during any gestational age is diagnosed as gestational diabetes. The women who do not meet the diagnosed criteria, should be screened at 24th and 28th gestational periods by oral glucose tolerance test (OGTT) [30]. A 75-g oral glucose tolerance test (OGTT) after 1 hour, higher than 180 mg/dl and 75-g oral glucose tolerance test (OGTT) after 2 hours, higher than 150 mg/dl confirm the diagnosis of gestational diabetes. The purpose of treatment is to maintain glycemic level at normal range. The preprandial blood glucose level should be less than 90 mg/dl. One hour after meal less than 140 mg/dl and two hours after meal less than <120 mg/dl. The women diagnosed as gestational diabetes mellitus must be followed at 02-03 months and screened annually for risk of type 2 diabetes [30-31].

5. Conclusion

Diagnosis of gestational diabetes mellitus should be according to standard criteria and its treatment during the gestational periods prevents maternal and fetal complications. Prenatal screening is important for the pre diabetic
and established type 2 diabetes mellitus. Postnatal follow up and screening is equally important as gestational has a 50% chance to be a type 2 diabetic. Hyperglycemia during pregnancies likely due to increase insulin resistance because of placental hormones as the pregnancy proceeds. Insulin is the mainstay of treatment. Addition of Metformin will further improve glyceamic control if insulin is insufficient alone. Till now Metformin has been found safe both for maternal and fetal well being.

References


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