Use of Oral Hyperglycemic Agents in Pregnancy Diabetes

V Balaji

The underlying principle for the use of oral hypoglycemic agents (OHAs) in pregnancy is motivated by the following factors:

Gestational Diabetes Mellitus (GDM) and Impaired Glucose Tolerance (IGT) are characterized by mild hyperglycemia due to insulin resistance. It is reasonable to assume that the treatment of GDM with OHAs would also be effective as in IGT. The use of OHAs has traditionally been contraindicated. This recommendation stems from the potential adverse effect on the developing fetus with the assumption that significant transfer occurs across the placenta. Three issues of concern include:

1. Increased rate of congenital anomalies
2. The possible induction of fetal macrosomia due to direct stimulation of the fetal pancreases resulting in hyperinsulinemia
3. The increased rate of hypoglycemia due to fetal hyperinsulinemia.

The OHA act depending upon the specific group of defects, directly upon the beta cells to increase the insulin secretion and/or to decrease hepatic glucose production and increase peripheral insulin sensitivity. But the use of OHA in pregnancy is not yet routinely recommended because of fetal abnormalities and adverse outcome like neonatal hypoglycemia and development of preeclampsia. This complication was particularly observed in pregnant women treated with first generation of Sulphonylureas (Tolbutamide and Chlorpropamide). However, in a randomized study done by Notelovitz in 1971 where he compared the use of Tolbutamide, chlorpropamide, diet, and insulin in 208 subjects, there were no significant differences among the different groups in terms of perinatal mortality and congenital anomalies when glycemic control was optimal. The author concluded that it was the poorly controlled glycemic state that was associated with the development of foetal anomalies and not the agents used to control blood sugar levels. Still physicians are resistant to use OHAs in pregnant women. An audit of members who had received OHAs in the first trimester (because their pregnant state was unknown) demonstrated an association between fetal anomalies and hyperglycemia rather than OHAs.

Ideal OHA
- Achieving and maintaining euglycemia
- Should not produce the risk of maternal as well as neonatal hypoglycemia.
- Devoid of teratogenic effect - good Neonatal outcome

Any medication must, of course, be safe for the person who takes it, or at least the benefits of its use must outweigh the risks. The second efficacy question is whether the drug’s effect on the mother will be beneficial, and not harmful, to the fetus. In keeping with the Pedersen Hypothesis, any medication that tends to normalize maternal glycemic levels should benefit the fetus as well.

SULPHONYLUREAS
Glibenclamide (Glyburide)

In a randomized, controlled trial by Langer et al., a comparison was made on the use of glibenclamide and insulin in women with GDM who were unable to achieve adequate metabolic control with diet and exercise alone. Four hundred and four women were randomly assigned to take either of the two treatments. The primary end
point was the achievement of good glycemic control and the secondary end points included maternal and neonatal complications. The results showed that 82% of glibenclamide group and 88% of the insulin group achieved good glycemic control, but there was less maternal hypoglycemia in the glibenclamide group (2%) as compared to the insulin group (20%). There were no significant differences between the 2 groups in the incidence of pre-eclampsia, macrosomia, neonatal hypoglycemia, congenital anomalies, perinatal mortality, cord serum insulin concentrations and the rate of caesarean section. Moreover, glibenclamide was not detected in the cord serum of any infant in the glibenclamide group.

Langer also studied the transfer of glyburide to fetus. He found no evidence that any drug was transferred. Elliot et al demonstrated minimal transfer of glyburide over the placenta.

Moore reviewed five retrospective reports of glyburide treatment for GDM and analyzed 504 pregnant patients who had been treated with glyburide. In summary, he reported that the failure rate for glyburide treatment was ~20%. Mean maternal fasting plasma glucose (FPG) and postprandial glucose (PPG) values were lower in glyburide-treated patients, but this was accompanied by fewer patients having asymptomatic hypoglycemia (63% in insulin-treated and 28% in glyburide-treated patients).

The authors of this article, found that Glibenclamide and insulin were equally effective in achieving good glycemic control and that perinatal outcomes were not different, which was similar to the observation of Langer et al and Towner et al.

Contradicting results regarding its trans-placental transfer, lack of adequate data regarding its safety during the first trimester and reports of increased neonatal morbidity raise concerns regarding the universal application of glyburide as an alternative to insulin therapy in diabetic pregnant women. More studies may add to the established safety and efficacy of glibenclamide in pregnancy, but the information available so far from the published data is robust enough to recommend glibenclamide to GDM women who are reluctant to accept insulin.

Given the available data, glyburide appears to be the best candidate insulin secretogogue for use during pregnancy, since it crosses the placental little or not at all and benefits the mother directly and the fetus indirectly. The two large centers in Canada and California that examine drug safety have separately demonstrated that glyburide does not cross into breast milk. Safety of glipizide, glimipride and non sulphonylurea drugs glinades has not yet been established.

BIGUANIDES
Metformin
The use of metformin in pregnancy has been quite controversial with early reports of adverse effects in those exposed to this drug. In subsequent studies, Hague et al measured plasma metformin levels in women taking metformin at a median daily dose of 2,000 mg and measured the cord blood of those 23 newborn babies. Median plasma metformin levels were 1.05 µg/ml (range 0.06 - 2.93) in maternal blood and 0.63 µg/ml (0.08 - 2.55) in cord blood samples. These data suggest that significant amounts of metformin can cross the placenta, with fetal concentrations in the range of half of maternal concentrations.

Metformin in Poly Cystic Ovary Syndrome (PCOS):
With the advent of its use in the treatment of women with PCOS, it is postulated that metformin would alleviate key pathogenetic mechanisms such as hyperinsulinaemic insulin resistance, hyperandrogenaemia, and obesity which may cause miscarriage in women with PCOS. In a retrospective study by Jakubowicz et al, a comparison was made between the pregnancy outcomes of 65 women with PCOS who became pregnant while taking metformin and remained on metformin throughout their pregnancy and the pregnancy outcomes of 31 women who also had PCOS but did not take metformin during pregnancy. The early pregnancy loss rate in the metformin group was only 8.8% as compared to 41.9% in the control group.

Metformin and Development of GDM:
Glecuk et al compared 33 non diabetic women with PCOS who were on metformin during pregnancy with 39 non diabetic women with PCOS without metformin therapy during pregnancy, GDM developed in only 3% of the women who took metformin as compared to 27% of those who did not take metformin. In addition, there were no foetal malformations nor foetal hypoglycemia noted in the metformin group.

Metformin in Gestational Diabetes (MiG) Trial:
A large prospective, randomized controlled trial called “Metformin in Gestational Diabetes (MiG)” compared the use of metformin and insulin in GDM. Of the 363 women assigned to metformin, 92.6% continued to receive metformin.
until delivery and 46.3% received supplemental insulin. The rate of the primary composite outcome was 32.0% in the group assigned to metformin and 32.2% in the insulin group (relative risk, 0.99; 95% confidence interval, 0.80 to 1.23). More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%, P<0.001). The rates of other secondary outcomes did not differ significantly between the groups. There were no serious adverse events associated with the use of metformin.

In women with GDM, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment. This trial recommends that metformin can be used as an adjunct or an alternate to insulin when there is insulin resistance and requirement of large dose of insulin.

In a recent audit of Cape Town, South Africa, data in pregnant patients with type 2 diabetes, metformin alone was not associated with increased perinatal mortality (PNM). The data on GDM at Groote Schuur Hospital have also been reviewed, and no PNM occurred in patients using metformin singly or in combination with Glibenclamide.

**Metformin and Fetal Outcomes:**
Coetzee et al reported metformin treated pregnant women had low infant morbidity/mortality rates and were not higher in metformin treated patients compared to insulin treated patients. Metformin was safe in pregnant, glucose intolerant women either as an adjunct to insulin treatment or even as a monotherapy.

**Metformin and Lactation**
A study by Hale et al, examined seven women taking metformin and their infants. The concentrations of metformin in breast milk were generally low and the mean infant exposure to the drug was only 0.28% of the weight - normalized maternal dose. As this is well below the 10% level of concern for breast feeding, and because the infants were healthy, the authors concluded that metformin use by breastfeeding mothers is safe.

No safety data is available on phenformin.

**ALPHA GLUCOSIDE INHIBITORS**
Acarbose
The use of Acarbose in pregnancy seems to be a good option because it primarily acts in the gut by delaying carbohydrate absorption and is not absorbed, thereby having no systemic effects. Acarbose is not systemically absorbed to an appreciable extent, so transplacental passage should not be an issue. It is directly beneficial to the mother and indirectly to the fetus.

In a small study by Zarate et al, 6 pregnant women with elevated FPG and PPG levels were treated with Acarbose, after which, the FPG and PPG levels were normalized.

Bertini et al compared neonatal outcome in GDM treated with insulin, Glyburide and Acarbose. They observed that, there was no statistical difference in FPG and PPG levels or in average newborn weight in the three groups.

The authors of this article were able to achieve FPG - 90 mg/ dl (5 mmol), 2 hr Plasma Glucose (PG) - 120 mg/dl (6.8 mmol) and mean PG - 105 mg/ dl (5.8 mmol) with the acarbose treatment. The mean A1c value at inclusion was 6.5% and before confinement was 5.9% (p=0.00). This good glycemic control resulted in the birth weights of newborns appropriate for gestational age. The mean birth weight of newborn infants in this study population was 2.9 kg which is within the range of average birth weight of Indian newborns 2.5- 3.5 kg.

Acarbose was found to be a safe and effective oral drug and can be considered as a potential therapeutic agent to treat GDM. Women with GDM treated with Acarbose had good glycemic control during the prenatal period. Acarbose prevented both the maternal and fetal morbidity due to hyperglycemia. This medication appears to hold promise for the treatment of GDM. More studies are required before routinely recommending Acarbose in the management of GDM.

**GLITAZONES**
Rosiglitazone
Rosiglitazone has not been recommended for use in pregnant women because it has been shown that treatment with the drug during mid to late gestation was associated with foetal death and growth retardation in animal models. It is classified as category C by the Food and Drug Authority (FDA) for use in pregnancy, which means the risk of adverse outcomes, cannot be ruled out.

A study on the placental transfer of rosiglitazone in the first trimester of pregnancy was recently reported by Chan...
et al. In this study, rosiglitazone was given to 31 pregnant women between the 8th to 12th week of gestation who were undergoing surgical termination of their pregnancy. Rosiglitazone was detected in 19 foetal samples (61.3%). This shows that there is a high risk of placental transfer and foetal exposure to the drug.

PIOGILITAZONE:
No data is available

REFERENCES