Chapter

44

OHA and Pregnancy: Current Scenario

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Pregnancy with diabetes mellitus by definition is a high-risk pregnancy. Approximately 0.3% pregnancies occur with pre-existing diabetes mellitus (PGDM) whereas 2– 3% more are complicated by gestational diabetes mellitus (GDM). The later thus constitutes 90% of all cases of DM complicating pregnancy which is responsible for much perinatal morbidity and mortality in the mother and offspring. The incidence of DM in India is rising at alarming rate due to faulty lifestyle, obesity and genetic predisposition. Prevalence of GDM has been cited as 16.55%. Clinical recognition and good control of DM can lessen perinatal morbidities. Successful treatment also prevents or delays the development of DM both in the mother and child later on. So far, cornerstone of diabetic management had been diet, permissible exercise and insulin, if required. The use of insulin is associated with the disadvantages of injection site pain, phobia of injection and problems of administration and storage. It is in this context that the use of alternative medicines like OHAs have been explored and needs scientific analysis.

Maternal and Fetal Complications in Diabetic Pregnancy

Pregnancy is associated with increased insulin requirement and resistance. The pregnant diabetics are more susceptible to develop hypertension during pregnancy, hydramnios, pre-eclampsia and increased incidence of cesarean delivery. The incidence of fetal congenital anomalies in non-diabetic women is 2–3%, in pregnant diabetics 7–9% and still higher in uncontrolled diabetics[1,2]. Glucose, having teratogenic potential by itself, crosses the placenta whereas insulin does not. This leads to fetal hyperglycemia resulting into fetal hyperinsulinemia. This causes macrosomia because of anabolic and growth effecs of insulin. The other congenital anomalies are cardiac, neural tube and skeletal defects and caudal regression syndrome[3]. The control of maternal hyperglycemia is therefore of paramount importance.

Management of Pre-gestational and Gestational Diabetes Mellitus

Women should first be advised medical nutrition therapy (MNT) and permissible exercise. If they fail to control hyperglycemic status, insulin is the drug of choice as it does not cross the placental barrier and thus prevents the fetal hypoglycemia. But the problem of storage, affordability and administration, especially in remote villages in our country and elsewhere is an important constraint. On the other hand, OHAs have been contraindicated in the management of pregnant diabetic women. This traditional recommendation needs a second look.

OHAs in Pregnant Diabetic Women

The most important issue with the use of OHAs in pregnant diabetic women is their placental transfer and resultant teratogenicity, congenital anomalies, Sulfonylureas(SU)- induced fetal hyperinsulinism and resulting macrosomia and neonatal hypoglycemia. In spite of these shortcomings following issues are worth consideration:

- Most of the pregnancies, particularly in India, are unplanned. By the time a diabetic woman is aware of her pregnancy and consults a physician she is already well into first trimester of gestation. All this time, the woman is using OHAs as prescribed earlier. Organogenesis in a fetus mainly occurs during this initial 4–8 weeks of gestation.

- The advice against the use of OHA in these women is often based more on studies done with older drugs and individual expert advice.
- Though insulin by itself does not cross placental barrier but some workers have shown that insulin antibody complexes can readily cross placenta[4] whereas another study established the correlation between insulin antibody complex and fetal macrosomia[5]. These observations should prompt us to look anew into the safety of insulin in pregnant diabetic women.
- Beside the possible teratogenic effects of OHAs, fetal hyperglycemia is also feto-toxic. The individual effects of these two factors should be analyzed by well-controlled studies.
- But while contemplating the use of OHAs in pregnant diabetics, one should give consideration to the following:
  - Can euglycemia be achieved with OHAs?
  - In the postprandial phase can the drug reduce the time lag between plasma glucose rise and insulin secretion?
  - Are drug-drug interactions, if any, are acceptable?
  - Does a particular OHA cross the placenta and, if yes, to what extent?
  - Will OHA produce fetal hyperinsulinism and secondary hypoglycemia?
  - Is the OHA itself teratogenic?

Firm recommendations for the use of oral agents in pregnancy are limited by the paucity of level 1 evidence. Some authors do not believe that OHAs can achieve adequate glycemic control[6]. Furthermore as beta-cell damage increases, oral agents lose their ability to achieve euglycemia.

Towner, et al[7] in 1995 concluded that major neonatal malformations were associated with high maternal glycosylated hemoglobin level at initial presentation for care and maternal age at onset of DM. The malformations were unrelated to type of antidiabetic therapy used.

The most debatable issue with the use of OHAs in pregnant diabetes is its placental transfer and resultant secondary complications as outlined above. The effects and problems associated with various OHAs, therefore, are being considered below:

Scientific Evidence for the use of OHAs in Diabetic Pregnancy

1. **Sulfonylureas**–Early experience with first generation SU (tolbutamide and chlorpropamide) induced severe hyperinsulinemic hypoglycemia among neonates of mothers who took these drugs during pregnancy. These drugs therefore were contraindicated in this setting.

   One study showed negligible placental transfer of glyburide (glibenclamide). The fetal concentration of drug was 26 ng / ml as compared to 1000 ng / ml in mothers[8]. Elliot, et al[9] in their study showed that the levels of glipizide and glibenclamide in fetal blood was insignificant. Coetze, et al[10] showed that SU was well tolerated during pregnancy provided excellent control of blood glucose was obtained. In contrast, another study showed that 16 women who received SU during embryogenesis had 50% of the infants having congenital malformations compared to 15% with infants of mothers who did not receive SU[11].

   Langer, et al[12] in a randomized-controlled trial compared glyburide during 11 to 33 weeks of pregnancy with traditional insulin therapy in 404 women. There was no difference in cord serum insulin concentration or in the incidence of macrosomia, cesarean delivery or neonatal hypoglycemia. The study, however, had no sufficient statistical power to examine fetal or perinatal mortality. By design, all women began therapy after 11 weeks of gestation and the study thus did not address the issue of congenital malformations or neonatal hypoglycemia.

   A retrospective study on 584 women by Jacobson GF[13] in 2005 comparing glyburide with insulin in 316 and 268 patients respectively, observed no significant difference in birth weight, macrosomia and cesarean delivery. However, neonates born to mothers on glyburide had prolonged hyperbilirubinemia and longer NICU stay.

   In India, Repaglinide was used in GDM and pregestational DM[14] There was no difference in outcome in 29 women receiving the drug and insulin. The authors asserted that this drug is safer in GDM.

2. **Metformin**- It crosses the placenta only partially in humans[15] and does not alter placental metabolism of glucose in mice[16]. MF has been used in pregnant diabetics during the first trimester of pregnancy with favourable outcome[9,10] but these studies had small sample size and were not well controlled .

   MF has widespread use for treatment of insulin resistance associated with infertility and polycystic ovarian syndrome (PCOS). When MF was used in first trimester of pregnancy to prevent miscarriage in PCOS, no increase in fetal malformation was

reported[17]. Though promising, more controlled randomized clinical trials are required to recommend MF in pregnant diabetics.

3. **Alpha glucosidase inhibitors**- It is an oral drug which delays the digestion of ingested carbohydrates. Less than 2% of the drug is absorbed in its active form. But its use in pregnant diabetic women has produced conflicting results in safety. One study used Acarbose in 6 women with uneventful pregnancy and normal newborns[15]. In another study, Acarbose, when given in 5 women during first trimester of pregnancy resulted, in 2 spontaneous abortions[18]. In view of this, large scale studies are needed to assess the risk profile for the use of Acarbose and other newer molecules available now.
4. **Thiozolidinediones**- These are used as insulin sensitizers. Their low molecular weight may lead to cross–placental transfer but data are not available. Though no human studies have been done but experimental studies in pregnant rats and rabbits have shown fetal deaths and growth retardation[13]. These drugs therefore cannot be recommended at present in pregnant diabetic women.

According to clinical practice recommendations of ADA (2006), Metformin and Acarbose have been classified as category 'B' and all other OHAs as category 'C' drugs. Potential risks and benefits of OHAs in the preconception period must be carefully weighed, recognizing that sufficient data are not available to establish the safety of these agents in pregnancy. They should generally be discontinued in pregnancy unless expert consensus or clinical experience is available[19].

CONCLUSION

To what extent the foregoing data be extrapolated to clinical practice? Have the physicians been too cautious in avoiding OHAs as opposed to insulin therapy in pregnant diabetic women. The long term effects of OHAs specially on the insulin secretion in mother and child are still to be studied.

As of now, OHAs cannot be recommended for use in pregnant diabetic women except metformin in patients with PCOS. For the use of OHAs in diabetic pregnancy we will have to wait for well controlled, head-to–head, large scale studies. It is worth remembering that pregnancy is an important phase during the life of a woman and any abnormality of glucose tolerance and drug side effects puts two generations at risk.

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