Review

CURRENT CONCEPTS IN MANAGEMENT OF DIABETES MELLITUS IN PREGNANCY: ROLE OF INSULIN PUMPS AND ANALOGUES

V. Seshiah, V. Balaji

ABSTRACT

Glucose intolerance may develop in the mother before or during pregnancy. In pre gestational diabetes, the embryo is exposed to a hostile environment from the moment of conception. Gestational diabetes (diabetes that develops during pregnancy) may cause macrosomia, childhood obesity and impaired glucose tolerance, but not congenital defects. Infants of gestational diabetic mothers are at the risk of complications related to maternal glucose concentration and presence of anti insulin antibodies. The availability of human insulin has improved fetal outcome by achieving good metabolic control and it does not produce anti insulin antibodies. Continuous subcutaneous insulin infusion (CSII) by insulin pumps can be used in those patients who cannot achieve good glycemic control with multiple injections. The experience with CSII during pregnancy is still limited. Insulin analogues are also being tried successfully.

KEY WORDS: Gestational diabetes; Neonatal complications; Insulin analogues; Insulin pumps; Continuous subcutaneous insulin infusion (CSII).

INTRODUCTION

Diabetes is a chronic disease whose phenotype ordinarily affects only the proband. A special situation occurs when the proband is gravid, for the fetus is an obligate parasite of the mother and is necessarily engulfed by the maternal metabolic milieu (1). Diabetes may develop in the mother before or during pregnancy. In uncontrolled pre gestational diabetes, the embryo is exposed to hostile environment from the moment of conception. Further growth and development of the fetus is adversely affected by maternal diabetes. If diabetes develops during pregnancy (gestational), as it usually occurs in the latter half of pregnancy, it has no effect on embryonic growth and thus is not a cause for congenital defects. Gestational diabetes (GDM) may cause macrosomia, childhood obesity and impaired glucose tolerance. In the pre insulin era, pregnancy in diabetes was rare and dangerous. Only the most mild, probably type 2 diabetics, became pregnant at that time. Yet maternal mortality was of the order of 30% and the perinatal mortality was 70 to 80 %. With the introduction of insulin, young diabetics lived long enough and well enough to conceive, and could go through pregnancy successfully. Since then, there has been a remarkable reduction in the maternal mortality and perinatal loss.

Infants of gestational diabetic mothers have an increased risk of macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia and erythremia. The rate of their complications are related to the level of maternal glucose concentration. There are reports claiming that the neonatal complications occur inspite of excellent metabolic control and this may be due to inadequate control of postprandial glucose, which has been suggested to be essential for a good fetal outcome in women with gestational diabetes (2,3). Another view is that neonatal mortality and morbidity is secondary to the presence of antibodies to insulin (4). Placental transfer of insulin complexed with immunoglobulin has been implicated for macrosomia, in spite of near normal glycemic control during gestation (5), To overcome these problems, genetically engineered, human insulins, produced by recombinant DNA technology, are being extensively used at present, with excellent fetal outcome. Yet, it is not uncommon to have neonatal morbidity. Presumably, better fetal outcome is expected using insulin Lispro, which is an ideal insulin to control the post prandial blood sugar.

INSULIN ANALOGUES

Insulin Lispro

Insulin Lispro (Humalog), is an analog of human regular insulin, and its peak insulin action is achieved within one hour after injection. This significantly improves the post prandial glucose

Consultant Diabetologists, Apollo Hospitals, Chennai.

concentration in non pregnant diabetics. Lois Jovanovic et al (6), compared the immunologic responses and metabolic effects of insulin Lispro with human regular insulin in GDM. In their study, anti insulin antibodies were similar in the two groups. Insulin Lispro was not detectable in the cord blood. During a test meal, area under the curve for glucose, insulin and C peptide, was significantly lower in the Lispro group. Mean fasting and post prandial glucose concentration and end point HbA_{1C} were similar in the two groups. The Lispro group demonstrated fewer hypoglycemic episodes (symptoms and blood glucose concentration below 55 mg/dl). No fetal or neonatal abnormalities were noted in either treatment groups. They concluded that insulin Lispro is safe and may be considered as a treatment option for women with GDM (6).

Satish K Garg et al (7) compared maternal and fetal outcomes between regular insulin and Humalog insulin in type 1 diabetic pregnancies. The material included age matched pregnant women with type 1 diabetes. The work up included metabolic profile, maternal complications like albumin excretion rate (AER), progression of retinopathy, development of toxemia and fetal outcome. They concluded that the treatment with Humalog was safe, with better glycemic control, without any increase in the adverse effects of retinopathy, nephropathy and fetal outcome, when compared with human regular insulin during pregnancy (7).

There are contradictory reports regarding the worsening of diabetic retinopathy with insulin Lispro during pregnancy (8,9). The common grounds for the progression of retinopathy appears to be higher HbA_{1C} at entry, duration of diabetes more than six years and correction of blood sugars in the first 6 to 14 weeks of entry (10,11). The safe course would be to check the fundus at the time of conception and at frequent intervals during the gestational period.

Insulin Aspart

Another fast acting insulin analog, insulin Aspart, has been found to have excellent post prandial glycemic control as compared to human insulin. Aspart is similar to Humalog in its action.

Insulin Glargine

The most recent addition to the growing family of insulin analogues, is insulin Glargine. It is produced by recombinant DNA technology. This biosynthetic insulin analog, has a prolonged duration of action as compared with NPH insulin. Data on the use of this insulin in pregnancy is not yet available. Robert Ratner et al (12) have documented that lower fasting plasma glucose levels with fewer episodes of hypoglycemia were achieved with insulin Glargine, as compared with once or twice daily NPH insulin, as part of the basal - bolus regimen, in patients with type 1 diabetes.

IMPLANTED INSULIN PUMPS

Continuous intraperitoneal insulin infusion (CIPII), with programmable implanted pumps, have been proven to achieve safety and efficacy in patients with type 1 diabetes. This mode of treatment is not recommended for women planning to become pregnant. Pauline Belicar et al (13) have reported the outcome of pregnancy in five women who were on CIPII. Actually, in these women pregnancy was not recommended because of investigational policy and for the fear that they may run the risk of adverse events, as they had unstable and complicated diabetes. However, implanted insulin pumps allowed these patients to achieve good metabolic control and glycemic stability with resultant successful outcome of the pregnancies. From this unexpected experience, there is a feasibility of pregnancy management with CIPII.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII)

CSII with insulin pump devices is to date, the best therapeutic option to achieve near normal blood glucose control. CSII is ideal for patients with low insulin requirement, motivated patients, those who have frequent episodes of hypoglycemia and patients with jobs that require a high level of flexibility with regard to meal planning and timing. However, even with CSII, flexibility is limited, because of the pharmacokinetic properties of subcutaneously injected regular human insulin. Insulin Lispro molecule dissociates directly after subcutaneous injection and action starts rapidly. Peak activity is achieved in 45 to 50 minutes after injection and the duration of action is 3 to 5 hours. As such insulin Lispro fits better with the metabolic requirements during and after a meal, than regular human insulin. Insulin Lispro is a very convenient, efficient and safe insulin to be used in CSII, leading to improvement in post prandial and long term blood glucose control, without increasing the number of hypoglycemic events (14).

INTENSIFIED INJECTION THERAPY

Pen injections are very useful devices for metabolic control during non pregnant and pregnant states. Use of "Novopen" for administering insulin during pregnancy was well accepted by the pregnant diabetics, as they found the pen convenient for self administration of insulin and painless, or they felt less pain (15). Coustan et al (16), observed no difference in mode of delivery, birth weight, congential anomalies and occurrence of neonatal hypoglycemia in women who were on intensified therapy with multiple injections or CSII.

CONCLUSION

The availability of human insulins has improved the fetal outcome. These insulins, besides achieving good metabolic control, do not produce anti insulin antibodies. Insulin analog, Lispro, has further improved the fetal outcome, because of its unique action profile of controlling post prandial hyperglycemia. Various regimes of intensified conventional insulin therapy have been introduced. The most popular regimen is to give a combination of short acting and intermediate acting insulin before breakfast and dinner. A few prefer to use short acting and intermediate acting insulin before dinner and intermediate acting insulin at bed time, while continuing mixture of short and intermediate acting insulin before breakfast. Multiple pre prandial, fast acting insulin and bed time, intermediate acting insulin, may be required in a few instances. The multiple pre prandial injections of fast acting insulin has a physiological advantage. This regimen has increasing acceptance among patients, following the introduction of pen injectors. Another regimen which may be considered, is continuous subcutaneous insulin infusion (CSII) by insulin pumps, for those few patients, who cannot adequately be controlled on multiple injections. The experience with CSII during pregnancy is still limited.

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