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GLYCEMIC CONTROL WITH DIFFERENT TYPES OF INSULIN IN THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Background: Gestational diabetes mellitus is one of the most common medical complications of pregnancy. It has been demonstrated that good metabolic control maintained throughout pregnancy can reduce maternal and fetal complications in diabetes and insulin is considered as gold standard for the management of GDM. **Aim:** To compare the efficacy of regular insulin with rapid acting insulin in combination with intermediate acting insulin in the management of GDM. **Methods:** It is a retrospective review analysis of two groups of patients, in whom one group of patients was started with regular insulin and another group of patients on rapid acting insulin with one dose of isophane insulin at bed time and results were compared in terms of mean glucose values, neonatal birth weight, amniotic fluid index, period of gestation and neonatal hypoglycemia. **Results**: The mean glucose value in rapid acting insulin group was 108.2mg/dl whereas it was 116.4mg/dl with regular insulin group. The mean AFI and period of gestation in rapid acting group was 10.6 cms and 38 weeks 5 days respectively in comparison with 13 cms and 37 weeks 3 days for regular insulin group. 60% of the babies in regular insulin group had neonatal hypoglycemia and it was 30% for rapid acting group. **Conclusion:** It was found that rapid acting insulin along with isophane insulin (NPH) at bed time had better glycemic control in comparison with only regular insulin.

KEYWORDS: Gestational Diabetes, regular insulin, rapid acting insulin, isophane insulin, pregnancy.

INTRODUCTION: Diabetes mellitus is one of the most common medical complications of pregnancy; gestational diabetes mellitus (GDM) accounts for approximately 90-95% of all cases. GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. It has been demonstrated that good metabolic control maintained throughout pregnancy can reduce maternal and fetal complications in diabetes. Diet and physical activity is the mainstay of treatment in GDM, but when diet and exercise fail to maintain euglycemia, exogenous insulin is used.

OBJECTIVE: To compare the efficacy of short acting insulin with rapid acting insulin in combination with intermediate acting insulin in the management of GDM

MATERIALS AND METHODS: It is a retrospective review analysis of two groups (10 in each group) of patients, in whom medical nutritional therapy failed in achieving good glycemic control were started on insulin and these patients were followed up for about three weeks. One group of patients were started with regular insulin (short acting) whereas another group of patients were started on rapid acting insulin(lispro or aspart) with one dose of isophane insulin(intermediate acting) at bed time. One fasting sugar value and three post prandial values were checked and results were compared in terms of mean glucose values, neonatal birth weight, amniotic fluid index, period of gestation and neonatal hypoglycemia.

RESULTS: The mean glucose value in rapid acting insulin group was 108.2mg/dl whereas it was 116.4mg/dl with regular insulin group. The mean AFI and period of gestation to which the pregnancy was prolonged in rapid acting group was 10.6 cms and 38 weeks 5 days respectively in comparison with 13 cms and 37 weeks 3 days for regular insulin group. The mean birth weight of the babies in rapid acting group was 2.88 kgs and it was 3.15 kgs for regular insulin group. 60 %(6 babies) of the babies in regular insulin group had neonatal hypoglycemia in comparison with 30% (3 babies) for rapid acting group.

Table 1- Comparing the efficacy of regular & rapid acting insulin

	Rapid acting insulin + NPH	**Regular insulin**
Mean blood glucose(mg/dl)	108.2	116.4
AFI (cms)	10.6	13
Birth weight(kgs)	2.88	3.15
POG	38weeks 5 days	37 weeks 3 days
Neonatal hypoglycemia	3(30%)	6(60%)

DISCUSSION

Before the advent of insulin in 1922, <100 pregnancies were reported in diabetic women; most likely, these women had type 2 and not type 1 diabetes. Even with this assumption, these cases of diabetes with pregnancy were associated with >90% infant mortality rate and 30% maternal mortality rate. As late as 1980, physicians were still counseling diabetic women to avoid pregnancy. This philosophy was justified because of the poor obstetric history in 30–50% of diabetic women.[1]

Women with gestational diabetes are unable to secrete sufficient insulin to overcome the resistance to its effect mediated by hormones and other factors during pregnancy. This is most often reflected as abnormally high one-hour glucose levels after the meal. Maternal glucose freely crosses the placenta. Maternal insulin does not cross the placenta unless it is bound to IgG antibody, which carries it through the placenta or insulin is forced through the placenta by high perfusion.[2] Diabetic fetopathy is thought to be the result of fetal hyperinsulinemia.[3]

Human pregnancy is characterized by a series of metabolic changes that promote adipose tissue accretion in early gestation, followed by insulin resistance and facilitated lipolysis in late pregnancy. In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, decreased, or may even increase. However, in late gestation, maternal adipose tissue depots decline, while postprandial free fatty acid (FFA) levels increase and insulin-mediated glucose disposal worsens by 40–60% compared with pre pregnancy. The ability of insulin to suppress whole-body lipolysis is also reduced during late pregnancy, and this is further reduced in GDM subjects, contributing to greater postprandial increases in FFAs, increased hepatic glucose production, and severe insulin resistance.[4] Although various placental hormones have been suggested to reprogram maternal physiology to meet fetal needs, the cellular mechanisms for this complex transition remain obscure.[5]

Glycemic Targets in Pregnancy

The goal of glucose management in GDM is to keep blood glucose values as near normal as possible. The Fifth International Workshop Conference (FIWC) on GDM suggests capillary whole blood glucose concentrations below 96 mg/dl before meals and either below 140 mg/dl, 1 h afterwards or below 120mg/dl, 2h afterwards. The reference plasma glucose levels suggested by the American Diabetes Association (ADA) are below 105 mg/dl before meals and either below 155mg/dl, 1 h afterwards, or below 130 mg/dl 2 h afterwards. It is worth

emphasizing, however, that these recommendations do not consider glycemic value higher than those normally recorded in pregnancy outcome.[6]

Langer et al found higher macrosomia rates with mean blood glucose levels higher than 105 mg/dl, whereas the risk of babies being small for their gestational age was high when the mean blood glucose levels dropped below 87 mg/dl; mean blood glucose values should therefore be kept between 87 mg/dl and 105 mg/dL in GDM patients to avoid these fetal complications.[7, 8]

When treatment targets are not achieved by dietary means and exercise, then insulin is required. As the level of insulin resistance varies from person to person, insulin dose also need to be individualized and there is no one particular insulin which is branded for use. Commonly prescribed regimens consisting of combined short-acting (Regular) and intermediate-acting insulins have been used to mimic endogenous insulin response.

Regular insulin, which is often used in pregnancy for the treatment of diabetes, has some drawbacks: it starts its action from 30 to 60 min after subcutaneous injection and it peaks too late (2-3 h after injection) to be very effective in postprandial control; in addition, it lasts too long (duration of 8-10 h), with an increased risk of postprandial hypoglycemia. Insulin molecules clump in hexamers that must be broken up to dimers and monomers before absorption, so delaying their effectiveness.[9] Therefore, in the last few years, insulin analogues started to be used to optimize glucose control during pregnancy.

The new rapid-acting insulin analogs lispro and aspart are more effective at controlling postprandial hyperglycemia without an increased risk of hypoglycemia. *Insulin Lispro,* the first rapidly acting analogue developed was approved for clinical use in 1996. It is obtained by inverting of the lysine at position 28 and the proline at position 29 on the ß-chain of the insulin molecule; it confers a conformational change that results in a quick dissociation of hexamers into monomers in subcutaneous tissue. Insulin lispro has a very rapid action, with a peak 1 h after subcutaneous injection, and duration of 2-4 h.[10]

Insulin glulisine is a rapidly acting analogue with a pharmacokinetic profile that is similar to those of insulin lispro and insulin aspart. It is created by substituting lysine for asparagine at position B3 and glutamic acid for lysine at position B29 on the B chain of human insulin. Insulin glulisine mimics the pharmacokinetic and pharmacodynamic profiles of physiological

human insulin, has a rapid onset, peak effect at 1 h, and a shorter duration of action (~4 h). Its rapid-action properties are maintained across subject types.[9] Clinical trials have demonstrated comparable or greater efficacy of insulin glulisine versus insulin lispro or regular insulin, respectively. Formal clinical evaluations show that it can be administered safely and effectively pre- and post-meal. At present no reports on glulisine use in pregnancy are available.[11]

Basal insulins (*NPH, glargine, lente and ultralente*) are used to control between-meal and overnight blood glucose levels. Insulin Glargine, the first long-acting insulin analogue was approved for clinical use in patients with Type 1 and Type 2 diabetes in 2000 and it was introduced in 2001 in the USA. Insulin glargine is produced by recombinant DNA technology: it results from substitution of glycine for asparagine at position A21 of the insulin molecule and by the addition of two arginine molecules to the C terminus of the B chain, which shifts the isoelectric point from a pH of 5.4 to 6.7. It results in an insulin molecule less soluble at the injection site that precipitates in the subcutaneous tissue forming a depot from which insulin is slowly released. Its action begins approximately 90 min after subcutaneous injection and lasts approximately 24 h; it's considered 'peakless'.[9, 12] At present the use of insulin glargine in pregnancy is not approved: well-planned investigations and controlled trials are needed to achieve a final risk assessment in order to use it in pregnancy. NPH continues to be the basal insulin of choice because it has more predictability than lente or ultra lente. Thus, human NPH as part of a multiple injection regimen should be used for intermediate-acting insulin effect in GDM.[8]

The starting insulin dose can be calculated on the basis of the patient's weight [13]: for nonobese patients used doses are 0.8 U/kg and 0.9-1.0 U/kg in overweight and obese women, respectively. In a pregnant diabetic patient the rationale for insulin therapy is based on mimicking the physiology of insulin secretion. The basal insulin is supplied by the administration of NPH-lente-ultralente insulin at bedtime or both before breakfast and at bedtime. The meal-related (glucose excursion) insulin includes the use of insulin lispro or aspart before meals (0-15 min) or regular insulin before meals (30-45 min).[14] This algorithm characterized the intensified therapy (multiple injections daily) versus conventional therapy (one or two injection daily). If after 3-7 days the GDM patient does not achieve the desired level of glycemic control, the total insulin dose should increase from 10 to 20% and thereafter adjusted when needed.[15] Traditionally, insulin therapy has been considered the gold standard

for management because of its efficacy in achieving tight glucose control and the fact that it does not cross the placenta. Insulin is, however, an expensive and invasive treatment. Insulin therapy involves daily injections, and patient compliance is often suboptimal, but if the patients are well counseled and educated about the advantages and how to use insulin, patient compliance will be better with good maternal and perinatal outcome.

CONCLUSION

Insulin therapy has been considered the gold standard for management because of its efficacy in achieving tight glucose control and the fact that it does not cross the placenta. Insulin is, however, an expensive and invasive treatment. Regular insulin, which is often used in pregnancy for the treatment of GDM, has some drawbacks: it peaks too late (2-3 h after injection) to be very effective in postprandial control and in addition, it lasts too long (duration of 8-10 h), with an increased risk of postprandial hypoglycemia whereas rapidly acting insulin analogue has a very rapid action, with a peak 1 h after subcutaneous injection, and a duration of 2-4 h and human NPH was used as part of a multiple injection regimen was used for intermediate-acting insulin effect in GDM. Thus from this study it was found that rapid acting insulin along with isophane insulin(NPH) at bed time had better glycemic control in comparision with only regular insulin.

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