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REVIEW ARTICLE

# Insulin Therapy in Diabetic Pregnancy: Clinician's Vision

Dr. Sunil Gupta

MD, FRCP (Glasgow), FACP, FICP, FIAMS, FIACM
Diabetologist, Director, Sunil's Diabetes Care n' Research Centre Pvt. Ltd, 42 Lendra Park, Ramdaspeth, Nagpur
E-mail: drsgupta_ngp@rediffmail.com

Insulin therapy is the most preferred therapy to achieve optimal glycemic control during pregnancy complicated by any form of diabetes. Inadequate glycemic control is directly or indirectly related to various fetal/neonatal complications like congenital malformations, macrosomia, premature birth, birth trauma, neonatal hypoglycemia and hyperbilirubinaemia.

Insulin therapy needs to be individualized and the success of therapy depends on various factors like, the type of insulin used i.e. regular insulin v/s insulin analogue, which regimen was used i.e. basal-bolus insulin v/s pre-mixed insulin or continuous subcutaneous insulin infusion (insulin pump). Similarly, frequent self-monitoring of blood glucose is of utmost important in pregnancy to achieve good control with least glycemic variability and less risk of severe hypoglycemia. Moreover, pre-conception counseling by health care team, family support, optimum control of diabetes before pregnancy, withdrawal of few of the medications of teratogenic potential before conception etc. play an important role to have better fetal outcome. For women with known diabetes, pregnancy should be considered as a challenging project, which needs serious commitment.[1]

## Targets of Glycemic control in pregnancy

The main goal for treatment of GDM is to prevent adverse effects on the mother and fetus by achieving glycemic goals as close as possible to those seen in normal pregnancy without undue hypoglycemia. This should be achieved throughout pregnancy, during labor and also till delivery.

High blood glucose values, specifically postprandial glucose levels, are associated with adverse pregnancy outcomes in patients with hyperglycemia in pregnancy.[2–4] Data shows that postprandial glucose levels are more closely associated with macrosomia than fasting glucose levels.[5,6] There is no randomized controlled study, which has established the optimal plasma glucose level(s) to prevent increased fetal risk. It is recommended to achieve fasting blood glucose as less than 95mg/dL, 1hr post-meal to be < 140mg/dL, 2hr postprandial blood glucose as less than 120mg/dL and target for glucose control during labor and delivery should be between 72-126 mg/dL.[7]

Neonatal hypoglycemia develops as a consequence of the fetal hyperinsulinemia secondary to high maternal glucose. After delivery, the sudden decrease in glucose supply to the newborn in the midst of high insulin levels of fetal origin results in hypoglycemia.[6,8] Observational trials have shown the correlation between glucose levels during labor and neonatal outcomes[9–15] and have agreed that maternal hyperglycemia during labor and delivery is associated with neonatal hypoglycemia, in both GDM[9] and Type2 diabetes mellitus (T2DM).[10–13]

Maternal hyperglycemia during labor is also associated with birth asphyxia and non-reassuring fetal heart rate tracings[14,15] in women with type 1diabetes (T1DM). Data says that targeting maternal glucose levels in the range of 72"126 mg/dL during labor is associated with a lower risk

of maternal hypoglycemia than lower target levels.[16] In addition, these levels during labor and delivery are helpful in reducing the incidence of neonatal hypoglycemia, birth asphyxia, and non-reassuring heart rate tracings.

## Insulin Therapy

Insulin therapy has been considered the gold standard treatment for hyperglycemia in pregnancy amongst women who are unable to achieve target glycemic control through diet and exercise. Earlier, recombinant insulin was created from animals, such as pigs and cows. However these recombinant, animal-based insulins often provoked severe immunologic responses. Insulin antibodies produced from impure bovine/porcine insulin crosses the placenta and may affect fetal outcome. The recombinant human insulin, which was created later, eliminated the problem of an antigenic response previously seen with animal-based insulin.

Insulin therapy for women with hyperglycemia in pregnancy is aimed at controlling plasma glucose levels throughout the duration of the pregnancy. Most of GDM women (who are diagnosed in 24-28weeks of gestation) presents with normal fasting with post prandial hyperglycemia. Self-monitoring of blood glucose, fasting & 2 h after each meal, preferably daily is suggested, in an attempt to control plasma glucose levels. Studies have determined that adjusting insulin therapy according to postprandial glucose levels was associated with improved glycemic control and reduced risk of neonatal hypoglycemia, macrosomia and cesarean delivery.[17]

## Rapid Acting Analogue V/s Regular Insulin

Glucose concentration reaches its post-prandial peak at ~ 1 h. In women with GDM, ACOG recommends to attain 1-h post-prandial values < 130 - 140 mg/dl.[4] Therefore, using a rapid-acting insulin analog that peaks 1 h after administration is ideal for controlling post-prandial glucose levels in women with GDM. Insulin lispro and insulin aspart are both rapid-acting insulin, which have been studied for both efficacy and safety in comparison to regular human insulin.

Insulin lispro is a rapid-acting insulin that does not cross the placenta at therapeutic dosages.[18] Lispro was found to be safe and effective alternative to regular insulin in the treatment of GDM, but this study lacks statistical power as only 42 women participated.[19] A larger clinical trial, with 213 gestational diabetic women, similarly demonstrated the safety of insulin lispro. After comparing women randomized to the regular insulin group (n = 138) to the insulin lispro group (n = 75), there was no statistically significant difference in maternal or fetal outcomes and no increase in adverse effects using insulin lispro.[20] In both the studies, Insulin lispro has shown the ability to block the post-prandial response while maintaining the same safety as regular human insulin, making it an acceptable therapy in the treatment of gestational diabetes.[21]

Trans-placental transport of lispro appears to be minimal,[22–24] and without documented teratogenic effects[19] or adverse maternal outcome.[25,26] Women receiving lispro were reported to have a significantly lower area under the curve for glucose, insulin, and C-peptide compared with women treated with regular human insulin[20, 27–29]and similar pregnancy outcomes.[30,31]

Insulin aspart is another rapid-acting insulin, one that reaches peak blood concentration ~ 40 min following administration. Pettitt et al.[32] were the first to compare the efficacy of insulin aspart with that of regular human insulin in 15 women with GDM, demonstrating improved glycemic control with insulin aspart. The Insulin Aspart Pregnancy Study Group conducted the largest evaluation to date of insulin aspart use in pregnancy. A total of 322 women with T1DM were randomized to receive either insulin aspart or regular insulin. The rates of major congenital malformations,[33] maternal and cord blood levels of insulin antibodies,[34] hypoglycemic events, and pregnancy outcomes were comparable, while glycemic control was improved in the group receiving insulin as part.[35] Based on the results of this study, the FDA changed the pregnancy use warning from category C to category B.

Cianni et al,[36] in a prospective randomized trial, compared insulin lispro, insulin aspart and regular human insulin usage in gestational diabetic women. Women with GDM, were recruited for the study at on average 27 weeks gestation. Cianni et al. found the 1-h post-prandial glucose to be significantly higher in the regular insulin group compared to the insulin lispro and insulin aspart groups. Additionally the birth weight was found to be significantly greater in the regular insulin group, whereas the percent of macrosomic births was also higher among the regular insulin group but not of statistical significance.

Although this study demonstrates the rapid-acting insulin having greater control over post-prandial glucose and to some extent improved neonatal outcomes, the study lacks significant power as only 96 women participated. The remaining studies that have analyzed insulin lispro and insulin aspart use in GDM evaluate only one rapid-acting insulin and contrast that with regular insulin.

## Intermediate Acting Insulin

Neutral protamine Hagedorn (NPH) is intermediate acting insulin that could be used in conjunction with short-acting insulin, effectively covering the immediate meal and subsequent meal.[37] Insulin detemir is a long-acting insulin analogue that was first evaluated in pregnancy involving 10 women with T1DM treated throughout pregnancy.[38] No adverse maternal or neonatal effects were documented. Several RCTs in non-pregnant women have shown that, compared with NPH insulin, detemir is associated with a lower rate of hypoglycemia and less weight gain.[39–41]

In 2014, a large RCT compared insulin detemir with human NPH insulin, and demonstrated its efficacy and safety during pregnancy in women with T1DM.[42] No specific safety issues were identified.[43] Use in GDM has not been specifically investigated but is expected to have the same efficacy and safety as demonstrated in pregnant women with T1DM.[44]

There is paucity of data on the use of insulin glargine during pregnancy. From the limited studies, however, it appears to be safe and well tolerated.[45,46] However, rapid acting analogue Glulisine& ultra long acting analogue degludeg don't have sufficient safety data and are not approved for their use in pregnancy

## Doses of insulin

Doses of insulin required to achieve glycemic control depends upon different types of populations, level of obesity, demographical characteristics and level of hyperglycemia (usually 0.7 - 2 units/kg).[47] Langer et al. demonstrated a significant weekly increase in insulin dose requirement between 24 and 30 weeks of gestation whereas from 31 to 39 weeks the level of glycemic control remained constant without the necessity of altering the insulin dose. Insulin requirements are 0.8 units/kg for non-obese subjects and 0.9 units/kg for obese patients. The total insulin dose is usually 40 - 90 units.[48,49]

If fasting blood glucose concentration is high, NPH insulin is given before bedtime; starting dose is usually 0.2 unit/kg. If postprandial blood glucose concentrations are high, 1.5 units of short acting insulin is given per 10 g carbohydrate in the breakfast meal and 1 unit per 10 gcarbohydrate in the lunch and dinner meals. In cases of both fasting and postprandial hyperglycemia, a regimen of multiple injections combining intermediate-acting and short-acting insulin is utilized.[49,50] Total insulin prescription should be divided in to two-thirds in the morning (2: 1, NPH: regular) and one-third in the evening (1: 1 regular (dinner): NPH (bed- time)). This reflects the pattern of insulin release in normal pregnant women in the third trimester. Corrections in insulin dose should be made according to the self-monitoring profile and if target levels are not reached, a 10 - 20% increase per dose of insulin should be made. This could be repeated with a 10 - 15% increase in overall insulin dose.

## Method of insulin administration

In India, the most commonly used regimen is premixed insulin twice a day, but this may not be ideal regimen for pre-GDM or insulin requiring GDM women. Most of GDM women presents with typical postprandial hyperglycemia with normal fasting blood glucose. Such patients require insulin only before major meals (e.g. before breakfast, lunch & dinner) depending on size of their meal. Some women with fasting hyperglycemia require night dose of long acting insulin (either NPH or detemir insulin). Pre-GDM women need both prandial and basal insulin in basal-bolus regimen to achieve glycemic goals. Long-acting insulin analogue have a more or less stable action profile during 20–24 h and less variability.

Rarely, selected patients with brittle diabetes or subjects with hypoglycemia unawareness or patients with erratic lifestyle or those requiring very high dose of insulin therapy, may require continuous subcutaneous insulin infusion (CSII) i.e. insulin pump, to have better glucose control. Mukhopadhyay et al. published a systematic review and meta-analysis on CSII versus MDI in pregnancy.[51] The six trials were all small trials with a total number of 213 patients. No beneficial effect of CSII was shown on any maternal or foeto-neonatal outcome. However, no data are available on quality of life or manageability of the disease – aspects that patients often mention as advantages of CSII. The choice of CSII should be individualized.

## Insulin during Labor and delivery

It is recommended to keep the maternal glucose level between 80–120 mg% during labour.[52] In practice, one can give a glucose 5% solution to the woman in labour to prevent maternal hypoglycemia (e.g., 500–1000 ml every 24 h) and either add a fixed amount of short-acting (human or analogue) insulin (8 U) to 500 ml of the intravenous solution, or, alternatively, measure glucose levels every ½ hour or every one hours and adjust insulin infusion accordingly. After delivery, insulin requirement falls sharply and it is prudent to decrease the insulin dose to 25–40% of the pre-delivery dose to prevent hypoglycemia. This is more important in women after caesarean sections

who do not eat or are not allowed to eat for hours to days. Breast-feeding which should be stimulated as much as possible, does lead to even lower insulin requirements and insulin dose should be decreased further if necessary to prevent hypoglycemia. Hypoglycemia unawareness may occur in this setting. The period of acceptable lesser control may extend for a number of months. Insulin analogues can be safely used in lactation.

In our study, we evaluated the dose, distribution and factors influencing the insulin requirement in women with GDM, Decreased Gestational Glucose Tolerance (DGGT – women with 2 hour 75gm OGGT value between 120 – 140 mg%) and in Pre GDM Type 2 women. Of 348 pregnant women with varying degree of glucose intolerance 158 subjects (45.4%) required insulin to achieve euglycemia (FBG < 90 mg%, 2hr PPBG < 120 mg%). They were evaluated for insulin doses, frequency, relation with meal, age, pre pregnancy weight, BMI, weeks of diagnosis & fasting plasma glucose at diagnosis.[53] Observations were:

1. Mean Insulin Dose required: DGGT < 10 U/ days, GDM : 23 U/day, & Pre GDM : 52.5 U/day. Dose increase significantly from diagnosis till delivery by 1.5 to 2 times.
2. GDM required double the dose of DGGT, while Pre GDM required double the dose of GDM.
3. DGGT needed 0.2 U/Kg/day, GDM : 0.4 U/Kg/day while Pre GDM : 0.9 U/Kg/day of their pre pregnancy weight.
4. 27.8% of GDM, 77% of Pre GDM and 3.6% DGGT women required pre dinner NPH insulin for controlling fasting hyperglycemia.
5. Contrary to the belief, our population required lowest dose during breakfast, higher in lunch (p=0.0002) while highest dose of short acting insulin with dinner (p<0.0001). The pre dinner dose was almost double than that of pre breakfast in all three groups.
6. The insulin dose was directly proportional to FBG (p<0.0001) and pre pregnancy weight ( p<0.008), but it couldn't be correlated to Age and Pre Pregnancy BMI.

Insulin dosage regimens depend directly on the patient's weight and number of weeks of gestation. There is smooth rise in insulin requirements throughout pregnancy. The formula for determining a patient's 24-hour insulin requirement, Big I is **:**

Big I = Weight x k

where weight is in kilograms and k=0.7 units of insulin for the first trimester, 0.8 for the second trimester, 0.9 for the third trimester, and 1.0 for term[54].When using this algorithm in pregnancy, Big I is divided in half to give the daily basal insulin requirement (0.5 Big I) and daily bolus insulin requirement (0.5 Big I ).

## Insulin During Labor And Delivery[55]

Intrapartum glycemic control plays a major role in the wellbeing of the neonate. Maternal hyperglycemia is the major cause of neonatal hyperglycemia. At the onset of active labor, insulin requirements decrease to 0, and glucose requirements are relatively constant at ~2.5 mg.kg-1.min.[56] The goal is to maintain plasma glucose concentration between 70 and 90 mg/dl.

- On the evening before elective induction, the usual bedtime dose of NPH insulin may be given.
- On the morning of induction, insulin is withheld and an IV infusion of normal saline begun.
- Once active labor commences or plasma glucose level falls to <70mg/dl, normal saline should be changed to 5 % dextrose
- Glucose level should be monitored hourly, and if it is < 60 mg /dl, the infusion rate should be doubled for the subsequent hour.
- If the plasma glucose concentration rises to > 140 mg/dl, 2-4 U short- acting insulin can be given IV or subcutaneously each hour until the glucose value is within the range of 70-90 mg/dl.

## With elective cesarean delivery

- The bedtime dose of intermediate acting insulin may be given on the morning of surgery and every 8 h if surgery is delayed.
- A dextrose infusion as described above may be started if the plasma glucose falls to < 60 mg/dl
- Alternatively, glycemic control before elective cesarean delivery can be achieved with an infusion of 1-2 U/h i.v. short-acting insulin given simultaneously with 5 g/h dextrose. The insulin infusion should be discontinued immediately before surgery.
- Hourly blood glucose determinations are mandatory for individualization of these protocols.

## Postpartum Insulin Requirements[55]

After delivery, insulin requirements diminish precipitously. As a result, it is often unnecessary to administer subcutaneous insulin for 24-72 h. Insulin requirements should be recalculated, based on postpartum weight and should be started when either postprandial or fasting glucose is > 150 mg/dl.

## Breast Feeding

Several investigators have reported that patterns of glucose control may be erratic in lactating diabetic women. Episodes of hypoglycemia appear to be common. Hypoglycemia is most likely to occur within an hour after breast feeding, which can be avoided by eating a small snack before breast feeding rather than making frequent adjustments of the insulin dosage.[57] Nocturnal hypoglycemia is particularly common. Therefore, blood glucose should be periodically checked during the night, and the evening dose of intermediate insulin should be decreased if hypoglycemia is documented.

## Summary

GDM has been steadily increasing in prevalence in the last two decades. Proper diagnosis and treatment of GDM is crucial in minimizing both perinatal and maternal complications. Healthcare providers should be aware of achieving glycemic control on insulin therapy. Interventions should aim at controlling plasma glucose levels and preventing hyperglycemic or hypoglycemic events. If glycemic targets are not achieved on diet and exercise, insulin is the preferred therapy recommended by DIPSI (Diabetes In Pregnancy Study group in India), ACOG, ADA and FDA. Insulin as a mono- therapy has proved both safe and effective in controlling plasma glucose levels. Insulin dose should be individualized in relation to meal, preferably through basal-bolus regimen. SMBG plays the crucial role.

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