

# Insulin Therapy During Pregnancy

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The congenital malformation remains the leading cause of mortality and serious morbidity in infants of mother with type 1 or type 2 diabetes, inspite of advancement in understanding pregnancy metabolism and treatment. Studies have established association between elevated maternal glucose during embryogenesis and high rates of spontaneous abortions and major malformations in newborn. Clinical trials also have established preconception care to achieve tight glycemic control and during first trimester have resulted in striking reductions in malformations. Unfortunately unplanned pregnancy occurs in a considerable number of women with diabetes resulting in fetal mortality and morbidity.

The perinatal morbidity attributable to conditions such as macrosomia and metabolic disorders remain relatively high in women who develop glucose intolerance of any degree with onset or first recognized during pregnancy [Gestational Diabetes Mellitus (GDM)]. Yet another observation was that in pregnant women with one elevated blood glucose during formal glucose tolerance test have abnormality in glucose values under continuous ambulatory glucose monitoring.<sup>1</sup> These elevated ambulatory glucose values were significantly correlated with fetal macrosomia. Thus the foetus of pre-gestational diabetic women, gestational diabetic women or women with any degree of abnormal glucose tolerance during pregnancy is at risk of developing either congenital malformation or morbidity in the form of macrosomia.

To minimize the occurrence of lethal malformations, pre-gestational counseling is essential. The pregnant women with diabetes need standard care throughout pregnancy. The goal for glycemic management in the pre conception period and during the first trimester should be to obtain the lowest A<sub>1c</sub> test level possible without undue risk of hypoglycemia in the would be mother. Practical self management skills are essential for attaining good glycemic control in preparation for pregnancy and during pregnancy.

- 1) Use of appropriate meal plan.
- 2) Self monitoring of blood glucose
- 3) Self administration of insulin and adjustment of insulin doses.
- 4) Treatment of hypoglycemia (patient and family members)
- 5) Incorporate safe physical activity.
- 6) Development of techniques to reduce stress and cope with the denial.

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All these measures are applicable in women with gestational diabetes also.

## Insulin Requirement In Pre GDM

If appropriate pre-pregnancy counseling has occurred and near euglycemia had been achieved before conception and if the pre-pregnancy insulin regimen incorporates two or more insulin injections a day, it may be suitable to achieve the near euglycemia necessary for a successful outcome of the pregnancy. A split/mixed regimen (NPH and regular) of insulin given in the morning and evening is ideal. NPH insulin given before supper has the likelihood of producing overnight hypoglycemia if the dose is increased to control the next morning's fasting value (even though the patient eats a bedtime snack). This happens because the peak action of the intermediate-acting insulin occurs during the middle of the night. Moving the injection of the evening NPH insulin to bedtime shifts the time of peak action toward breakfast and minimizes the possibility of overnight hypoglycemia. Injecting NPH insulin in the morning, however, limits a patient's flexibility in regard to eating and exercise patterns. Unanticipated changes are more difficult to deal with because once the intermediate-acting insulin is given, it exerts its preordained effect for many hours. Using three injections of regular or rapid acting analogue insulin before each meal gives a patient more flexibility with regard to eating and exercise. Preprandial rapid acting analogue (lispro / apart) insulin will be particularly helpful during the first trimester, when nausea and anorexia (morning sickness) are common. Controlling the fasting BG concentration requires evening NPH insulin.

Regular insulin is usually given ½ hour before a meal because it does not start to work until approximately 30 minutes after injection. On the other hand, if the new rapid-acting insulin analogue, is used in place of regular insulin, delaying the meal after injecting is not an option because it starts to act within 10 to 15 minutes.

Adjusting insulin doses is simpler with self-monitoring of blood glucose (SMBG) four times a day because each component of the insulin regimen affects only one SMBG value. Monitoring before breakfast and 1 to 2 hours postprandial is recommended.

Insulin requirement increases during pregnancy because of the increased concentration of circulating contra insulin hormones. Constant insulin adjustment is necessary to keep up with the increasing insulin requirement of pregnancy (Fig. 1). The insulin dose is increased from 0.7U /kg/day in the first trimester to 0.8 U/kg/day at week 18, 0.9U/kg/day at week 26 and 1.0 U /kg/day at week 36 in women who maintained within 15% of ideal body weight.<sup>2</sup> The insulin dose varies from person to person though the weight is

**Table 1 : Criteria Recommended for the initiation of Insulin Therapy in women with gestational diabetes**

Fasting <sup>a</sup>	Post prandial	Reference
> 80	1 hour > 140	Jovanovic – Peterson and Peterson
105 <sup>b</sup>	None	Metzger
> 95	2 hour > 120	Langer, et al
> 100	1 hour > 130	Ramus and Kitzmiller
> 90	1 hour > 120	Jovanovic – Peterson

<sup>a</sup> – Glucose concentrations (mg/dl) measured in finger – stick whole blood samples unless designated otherwise designated otherwise.

<sup>b</sup> – Venous plasma sample.

almost the same. In a study of 11 patients who were markedly obese at the start of pregnancy, 6 required 1.2 U/kg/day at term, 3 required 2U/kg/day at term and 2 required 3U/kg/day at term. Further type 2 DM patients require significantly higher dose of insulin during each trimester compared to type 1 DM. During first trimester no difference was found between type 1 and type 2 subjects. During the second trimester, a significant increase in insulin requirement was observed. (10 percent for patients with type 1 compared with 33 percent for those with type 2 DM). In the third trimester a 40% increase was found for women with type 2 DM. This has been attributed to increased body mass and heightened insulin resistance.<sup>3</sup>

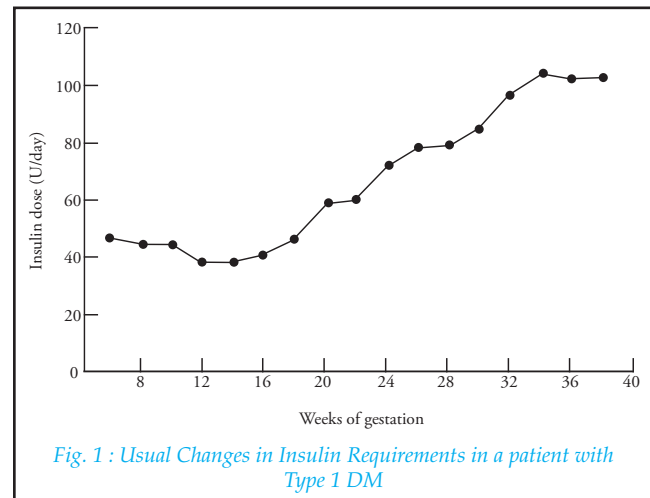
Rarely pre-gestational type 2 diabetic women may require a very high dose of insulin even up to 200 units / day given in divided dose. It is appropriate to use the dose needed to achieve near normoglycemic level without giving undue concern about giving too much insulin to the patient. The main concern should be blood glucose results rather than the dose of insulin.<sup>4</sup>

## Insulin Treatment in GDM

The treatment of GDM with insulin requires several decisions. In a normal (non-diabetic) pregnancy, the fasting plasma glucose (FPG) concentration ranges between 55 and 70 mg/dl, the 1-hour postprandial glucose level is <120 mg/dl.<sup>5</sup>

Various criteria have been proposed for the initiation of insulin therapy (Table 1 ). To interpret these values, one must take into account the relationship between plasma and whole BG concentrations, the site of sampling and whether the value is a fasting or a post prandial one. It is enough to realize that a plasma value is approximately 12% higher than a whole blood value. A finger stick yields arterialized blood, which does not influence the fasting glucose concentration because in the fasting state there is little glucose uptake by muscle tissue. After eating, however, muscle glucose utilization becomes a factor. Measurement of glucose concentrations in blood samples obtained by a finger stick yields higher values than if a venous sample had been obtained. This is because the arterialized blood in the sample has not yet traversed muscle and glucose removal by this tissue has not occurred.

The simplest way to monitor women with GDM is to measure their FPG concentration every week in the office or laboratory and not initiate insulin treatment unless their value exceeds 95 mg/dl. Measuring postprandial rather than preprandial glucose concentrations by SMBG



in women who did require insulin resulted in significant decreases in glycated hemoglobin levels, cesarean sections for cephalopelvic disproportion, macrosomia, large-for-gestational-age (LGA) babies, and neonatal hypoglycemia. However performing SMBG before breakfast and post prandially maximize the chance for a successful outcome.

If the FPG concentration on the OGTT is  $\geq 120$ mg/dl, the patient is started on insulin immediately. Others are seen within 3 days and are also taught SMBG to be performed before breakfast and 2 hours after each meal. Insulin is started within 1 to 2 weeks if the majority (i.e., at least four of seven per week) of fasting BG values exceed 95 mg/dl. Similarly, if the majority of post prandial values after a particular meal exceed 120 mg/dl, insulin is started. Pen injectors are very useful and the patient acceptance is excellent. The initial dose of NPH insulin could be as low as 4 units and adjusting the dose of insulin on follow up. A few GDM patients may require combination of short acting insulin and intermediate acting insulin in the morning and evening. If a patient has elevated prelunch blood sugar, regular insulin is usually necessary in the morning to handle the post breakfast hyperglycemia, because of the lag period before the intermediate-acting insulin begins to work. The above regimen of regular and intermediate-acting insulin in the morning controls hyperglycemia in most cases.

If the post dinner blood sugar is high a small dose of regular insulin is necessary before dinner in addition to the regular and intermediate acting insulin given in the morning. Combination of regular and intermediate acting insulin before dinner may be necessary if fasting blood sugar is high. This combination of short and intermediate acting insulin in the morning and as well as in the evening is known as mixed and split dose of insulin regimen. In this regimen two-thirds of the total daily dose of insulin is given in the morning and one-third in the evening. For each combination one-third dose should be regular insulin and two-third intermediate acting insulin. With this regimen if the patient continues to have fasting hyperglycemia, the intermediate acting insulin has to be given at bedtime instead of before dinner. It is ideal to use highly purified porcine or human insulin which are least immunogenic. Though insulin does not cross the placenta, the anti-insulin antibodies due to bovine insulin can cross the placenta, and stress the fetal beta cell, increase insulin production and induce macrosomia. The goals of

Table 2

Blood Glucose	Insulin / IV Fluids
60-90 mg/dl	5% GNS - 100 ml/hr
90-120 mg/dl	NS or RL - 100 ml/hr
120-140 mg/dl	NS or RL-100 ml/hr plus 4 units of Reg. insulin added with IV fluid
140-180 mg/dl	NS or RL - 100 ml/hr plus 6 units of Reg. insulin added with IV fluid
>180 mg/dl	NS or RL - 100 ml/hr plus 8 units of Reg. insulin added with IV fluid

therapy are to keep the glucose concentration below the levels used to initiate insulin therapy (FPS < 95mg and 2 hr PPBS < 120mg).

### INSULIN TREATMENT DURING DELIVERY

Metabolic studies of non-diabetic pregnant women during labor revealed that glucose turnover increased fourfold with little change in insulin levels. This strongly suggests that muscle contractions (probably both uterine and skeletal) independent of insulin are the predominant determinant of glucose utilization during labor. During active labor, the insulin requirement was zero while glucose requirements were relatively constant at 2.6 mg/kg/min or approximately 10 g/h in a 60-kg woman.<sup>6</sup>

The following approach is suggested for treating an insulin-requiring woman with pre gestational diabetes as she progresses through labor and delivery. If labor is to be induced, the usual evening NPH insulin should be taken the night before, but no subcutaneous insulin is given the following morning when induction begins. A similar approach is followed in GDM women also. The goal is to maintain the glucose concentration between 70 and 100 mg/dl. Most labor and delivery units have the ability to measure

finger-stick glucose concentrations, and this should be done every hour. If labor is to be induced, intravenous saline is infused until active labor begins. If the initial glucose concentration is <70 mg/dl, 5% dextrose is infused at 100 ml/h until the glucose level is in the appropriate range.

The IV fluids, insulin dose to be given on monitoring the blood glucose level is given in table 2.

When active labor begins, the same insulin infusion rate described earlier is used, depending on the glucose concentration at this time as well. In contrast, a woman with GDM does not require insulin once labor begins.

In a gestational diabetic the requirement of insulin will fall precipitously and no insulin may be required immediately after expulsion of placenta. In a known diabetic the dose of insulin has to be adjusted by monitoring blood glucose.

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