Management of Diabetes in Pregnancy

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Abstract

Diabetes in pregnancy is associated with risks to the woman and to the developing fetus. Miscarriage, pre-eclampsia, preterm labour and congenital malformations in fetus are more common in women with pre-existing diabetes. Insulin requirement increases with each trimester of pregnancy in diabetic females. Treatment of gestational diabetes consists of medical nutrition therapy but insulin treatment forms the mainstay of the therapy. Monitoring glycemic control is essential in treatment of gestational diabetes. HbA1c level is helpful to differentiate between a pre-GDM and GDM. Majority of pregnant women with diabetes fail to achieve optimum glycemic control, mostly the postprandial plasma glucose with conventional insulin. In them, the best option is to administer ultra-short-acting analogs, insulin lispro or insulin aspart. These analogs improve the postprandial glucose control during pregnancy in both type 1 and type 2 diabetes and are considered safe and effective.

Pregestational Type 1 and Type 2 Diabetic Women

Congenital malformations continue to be the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes. There is an established association between elevated maternal glucose during embryogenesis, being the cause of high rate of spontaneous abortions, and major malformations in newborns. Advancement in the understanding of pregnancy metabolism and treatment has done little to address this issue.

Clinical trials have shown that preconception care and tight glycemic control during the first trimester 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 remains 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 pregnant women with elevated blood glucose during formal glucose tolerance test exhibited abnormal glucose values under continuous ambulatory glucose monitoring.1

These elevated ambulatory glucose values were correlated with increased fetal macrosomia. Thus, the fetus of pregestational diabetic women, gestational diabetic women, or women with any degree of abnormal glucose tolerance during pregnancy is at the risk of developing either congenital malformations or morbidity in the form of macrosomia.

To minimize the occurrence of lethal malformations, pregnant women with diabetes need standard care throughout pregnancy, including pregestational counseling. The goal for glycemic management in the preconception period and during the first trimester should be to obtain the lowest A1C test level possible without undue risk of hypoglycemia in expecting mothers.

The following practical self-management skills are essential for attaining good glycemic control in the 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

The same is applicable in women with gestational diabetes also.

Insulin Requirement in Pre-GDM

If appropriate prepregnancy counseling has occurred and near euglycemia had been achieved before conception and if the preconception insulin regimen incorporates 2 or more insulin injections a day, it may be suitable to achieve the near euglycemia necessary for a successful outcome of the pregnancy.

- Pre-dinner administration of NPH insulin, especially if the dose of NPH is increased in view of the next morning’s elevated fasting glucose value, has the likelihood of producing nocturnal hypoglycemia. It is due to the peak pharmacodynamic action of the intermediate acting insulin at midnight. This cannot be prevented even if the patient consumes a bedtime snack.
- Alternative strategy to address nocturnal hypoglycemia is to shift the pre dinner NPH insulin to bedtime. By this method, one can alter the time of peak action towards early morning and minimize the possibility of overnight hypoglycemia.
- Injecting NPH insulin in the morning, however, limits a patient’s flexibility with 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.
- In a few pregnant women, a split/mixed regimen (NPH and regular or insulin analogs) given in the morning and evening may achieve good glycemic control.
- Using 3 injections of regular human insulin or rapid acting insulin analogs (Humalog/NovoRapid) with each meal gives a patient more flexibility with regard to eating and exercise.
- Preprandial regular or rapid-acting insulin analogs can be particularly helpful during the first trimester, when nausea and anorexia (morning sickness) are common.
- Controlling the fasting plasma glucose concentration requires pre-dinner or bedtime NPH insulin.

Administration of short-acting human insulin should be 30 min prior to meal. This method is followed to counter the slowness at the onset of action of human insulin. On the other hand, the new rapid-acting insulin analogs administered with
meals starts to act within 10 to 15 min. Therefore, short-acting insulin analogs are effective in controlling the post-prandial peak.

Adjusting insulin doses is simpler with self-monitoring of blood glucose (SMBG) 4 times a day because each component of the insulin regimen affects only 1 SMBG value. Monitoring before meals and 2 h after a meal is recommended.

Most high risk and precious pregnancies may require frequent monitoring of blood glucose to find out the fluctuations in levels and adjust the dose of insulin accordingly. Continuous glucose monitoring system (CGMS) and glucowatch are useful in this regard.

In a pregestational Type-1 diabetes woman, the requirement of insulin may fall during the early part of the first trimester due to increased insulin sensitivity. Insulin requirement increases during the later half of pregnancy owing to the increased concentration of circulating placental hormones. Raised level of placental hormones are known to be counteractive for insulin. Therefore, constant insulin adjustment is necessary to keep up with the increasing insulin requirement of pregnancy (Fig. 1).

The insulin dose is increased from 0.7 U/kg/day in the first trimester to 0.8 U/kg/day at week 18, 0.9 U/kg/day at week 26, and 1.0 U/kg/day at week 36 in women who maintained within 15% of ideal body weight. The insulin doses vary from person to person, but the weight is 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 2 U/kg/day at term, and 2 required 3 U/kg/day at term.

Further, type 2 DM patients require a significantly higher dose of insulin during each trimester as compared to type 1 DM patients. During the first trimester, there is no difference in insulin requirement between type 1 and type 2 subjects. However, the insulin requirement significantly increases during the second trimester (10% increase for patients with type 1 DM as compared to 33% in those with type 2 DM). In the third trimester, the insulin requirement continues to rise reaching a total increment of 40% in patients with type 2 DM (Fig - 2). This is attributed to the sudden increase in body mass and heightened insulin resistance in type 2 diabetes women during pregnancy.

In some cases of pregestational type 2 diabetes, women may require a very high dose of insulin (even up to 200 units/day). In such cases requiring very high doses, it is preferred to give insulin in divided doses. The priority should be on the glycemic control rather than the soft concerns over the high insulin requirement.

Increased insulin requirement is inevitable in pregnant women with type 2 DM. On the contrary, if the insulin requirements are not increased in spite of the advancing pregnancy in certain cases, it is a cause of concern. This could be due to poor placental growth, intrauterine growth retardation, and impending intrauterine death. Hence, in such situations, the treating physician along with the obstetrician have to be proactive in identifying the cause.

In some cases, there could be hypertrophy of fetal ß cells. Therefore, a few pregnant women may require less insulin in the last week of pregnancy, which could be due to the fetal handling of maternal glucose. At approximately 36 weeks, placental growth ceases and counter regulatory hormone production plateaus. Thus, there may be an apparent decline in the insulin requirement.

Management of GDM

A. Medical Nutrition Therapy (MNT)

All women with GDM should receive nutritional counseling. The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The aim of meal plan is to provide sufficient calories to sustain adequate nutrition for the mother and fetus. The meal should be planned in such a way that excess weight gain and postprandial hyperglycemia are avoided. Calorie requirement based on age, activity, prepregnancy weight, and stage of pregnancy should be considered while preparing a diet chart.

As a part of the medical nutrition therapy, pregnant diabetic women are advised to divide their calorie consumption, especially the breakfast. This implies splitting the usual breakfast into 2 equal halves and consuming the portions with an interval of 2 h between meals. By this method, the undue peak in plasma glucose levels after ingestion of the total quantity of breakfast at one time is avoided. For example, if 4 idlis/chapati/slices of bread (applies to all types of breakfast menu) are taken for breakfast at 8 am and peak plasma glucose at 10 am is 140 mg, the same quantity divided into 2 equal portions, i.e., 1 portion at 8 am and the remaining after 10 am, the peak postprandial plasma glucose falls by 20 to 30 mg.

This advice is relevant to address the peaking of plasma glucose which is higher with breakfast (Dawn phenomenon)
The relationship between plasma and whole blood

If a patient has elevated prelunch blood sugar, regular insulin could be as low as 4 units and intermediate-acting insulin in the morning and evening.

B. Insulin Treatment

Insulin is essential if diet control and exercise fail to achieve euglycemia. In normal (nondiabetic) pregnancy, the fasting plasma glucose (FPG) concentration ranges between 55 and 70 mg/dl, the 1-h postprandial glucose level is <120 mg/dl. Various criteria have been proposed for the initiation of insulin therapy (Table 1). To interpret these values, one must take into account the following:

- The relationship between plasma and whole blood glucose concentrations
- The site of sampling
- Whether the value is a fasting or a postprandial 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 has not yet traversed muscles and hence glucose removal by this tissue has not occurred.

If the FPG concentration on the OGTT is >120 mg/dl, then the patient is advised insulin therapy along with a meal plan. Other GDM women are seen within 3 days and are also taught SMBG. SMBG is to be performed before breakfast and 2 h after each meal. GDM women usually have a higher post-breakfast plasma glucose level compared to post-lunch and post-dinner. A few GDM women do have high post-dinner plasma glucose level. Insulin is started within 1 to 2 weeks, if the fasting values exceed 90 mg/dl. Similarly, if the majority of postprandial values after a particular meal exceed 120 mg/dl, then insulin is started. Pen injectors are very useful and the patient’s acceptance is excellent.

The initial dose of NPH insulin could be as low as 4 units 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, as there is a lag period before the intermediate-acting insulin begins to work. The above regimen of regular and intermediate-acting insulin in the morning controls hyperglycemia

Table 1: Criteria recommended for the initiation of insulin therapy in women with gestational diabetes

<table>
<thead>
<tr>
<th>Fasting*</th>
<th>Postprandial</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>105*</td>
<td>None</td>
<td>Metzger</td>
</tr>
<tr>
<td>&gt;95</td>
<td>2 h &gt; 120</td>
<td>Langer et al.</td>
</tr>
<tr>
<td>&gt;100</td>
<td>1 h &gt; 130</td>
<td>Ramus and Kitzmiller</td>
</tr>
<tr>
<td>&gt;90</td>
<td>1 h &gt; 120</td>
<td>Jovanovic–Peterson</td>
</tr>
</tbody>
</table>

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

b – Venous plasma sample.

Table 2: Perinatal mortality to maternal blood glucose level during last weeks of pregnancy

<table>
<thead>
<tr>
<th>Mean glucose level</th>
<th>Perinatal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150 mg%</td>
<td>24%</td>
</tr>
<tr>
<td>100–150 mg%</td>
<td>15%</td>
</tr>
<tr>
<td>&lt;100 mg%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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 in the evening is known as split-mixed dosage 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-thirds should be 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 pre-dinner insulin and the dose has to be individualized.

C. Target Blood Glucose Levels:

Maintenance of mean blood glucose level <105 mg% is ideal for good fetal outcome. A study by Karlson and Kjellman from Sweden showed that perinatal mortality is proportional to maternal blood glucose level during the last weeks of pregnancy. In the uterine compartment, the maternal feto-placental blood circulation regulates the energy requirement and protects the fetus from hypoglycemia. Hesitancy to start insulin treatment may be due to the misconception that insulin administration causes hypoglycemia in the newborn. Contrary to this belief, the maintenance of mean plasma glucose around 105 mg% (fasting, 90 mg/dl and peak post-meal plasma glucose, 120 mg/dl) would protect the newborn from hypoglycemia. If glycemic control is not achieved, then the excess glucose crosses the placenta. Fetal beta cells are highly sensitive to glucose and the glucotoxicity due to uncontrolled maternal diabetes leads to fetal beta cell hypertrophy. The hypertrophied fetal beta cells respond by increased secretion of insulin. At parturition, when the fetus is expelled, the super-charged beta cells of the neonate continue to secrete high level of insulin. High insulin production without fuel supply from the maternal compartment leads to neonatal hypoglycemia. Hence, tight glycemic control in the mother reduces the incidence of neonatal hypoglycemia.

The fact that maternal hypoglycemia does not jeopardize fetal outcome, is very well brought out by a study done in Düsseldorf, Germany. Of the 77 pregnant women with type 1 DM included, 32 had 94 episodes of hypoglycemic events requiring hospital admission. There was no difference in fetal outcome between those mothers who had severe hypoglycemia and those who did not. Hence, it is confirmed that the neonatal hypoglycemia is due to poor control of diabetes in the mother, rather than the amount of insulin taken by the mother. Even though maternal hypoglycemia is not associated with adverse fetal outcomes, all efforts should
be taken to avoid hypoglycemia in the pregnant mother.

D. Insulins

Human insulin is being extensively used during pregnancy, but due to the pharmacokinetic action of this insulin a considerable segment of pregnant women with diabetes fail to achieve optimum glycemic control, mostly the postprandial plasma glucose. In them, the best option is to administer ultra-short-acting analogs, insulin lispro (Humalog) or insulin aspart (NovoRapid). These analogs improve the postprandial glucose in pregnant women with both type 1 and type 2 DM and are safe and effective.8,9

Newer Insulin Analogs in Pregnancy

The rapid-acting analog insulins are useful in pregnancy complicated by diabetes, since they are more able to reduce postprandial hyperglycemia with respect to regular insulin. It should also be emphasized that postprandial hyperglycemia must be reduced, as several studies have shown that this state is more predictive of adverse neonatal outcomes than fasting glycaemia.10,11

All the 3 rapid-acting insulin analogs available in the market are more effective for early postprandial glucose control, reducing the risk of later postprandial hypoglycemia. Therefore, studies in pregnancy are limited to lispro and aspart, both demonstrating clinical effectiveness, no evidence of teratogenesis, low antigenicity, and placental transport of autotibodies similar to human regular insulin. Lispro and aspart are assigned in the pregnancy category “B” rating, indicating that adequate clinical studies in pregnancy have not revealed increased risk to the fetus. Data currently available on glargine in pregnancy, although not resulting from randomized controlled trials and limited to about 350 observations, show similar fetal outcomes compared with human insulins in terms of congenital malformations. The apparent safety of glargine in pregnancy justifies the need for a large randomized controlled trial to confirm its safety and efficacy in pregnancy; up to now, glargine has been assigned a pregnancy category “C”.12

There are no published data concerning the use of detemir in pregnancy but the results of a prospective study are expected in 2011.

Monitoring Glycemic Control

The success of the treatment during GDM depends on the glycemic control maintained with a meal plan or pharmacological intervention. To know the effectiveness of treatment, monitoring of glycemic control is essential.

• Women with type 1 or type 2 diabetes need pre-pregnancy counseling to maintain blood glucose levels (FPG, 80 to 90 mg/dl and 2-h PPG, 110–120 mg/dl) and A1c level at an acceptable level (A1C <7%, ideal <6%) to conceive.

For women with type 1 and type 2 diabetes who are already on treatment, intensive monitoring is required from the day 1 of conception. They will have to do self-monitoring of blood glucose or get the levels checked at a laboratory at least once a week to adjust the dosage of insulin.

• Once target blood glucose is achieved, women with GDM till the 28th week of gestation require monitoring of both fasting and 2-h post-breakfast once a month and at other time of the day as the clinician decides.

• After the 28th week of gestation, the monitoring should be more frequent, at least once in 2 weeks, if need be more frequently.

• After 32 weeks of gestation, monitoring should be done once a week till delivery.

• In high-risk pregnancies, the frequency of monitoring may be intensified with SMBG.

Continuous glucose monitoring devices are available but these equipment need special training, and furthermore are expensive. These devices may be useful in high-risk pregnancies to know the glycemic fluctuations and to plan proper insulin dosage.

Measuring Other Parameters

It is rewarding if blood pressure is monitored during every visit along with examination of the fundus and estimation of microalbuminuria, every trimester.

HbA1C Levels

If glucose intolerance is detected in early pregnancy, HbA1c level will be helpful to differentiate between a pre-GDM and GDM. If the HbA1c level is more than 6%, she is likely to be a pre-GDM. HbA1C is useful in monitoring the glucose control during pregnancy, but not for the day-to-day management. HbA1C level may serve as a prognostic value. If HbA1c level is used to monitor glucose control in pregnancy, the target level to be maintained is 5.3%, which corresponds to a fasting blood sugar level of 90 mg/dl and 2-h post-meal level of 120 mg/dl.

Estimation of fructosamine during pregnancy is less frequently used.

References


