Insulin therapy in pregnancy

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Abstract

Insulin is the mainstay of pharmacotherapy in pregnancy complicated by diabetes. This review covers the various insulin regimes and preparations, explaining how to use them, and decide appropriate doses in pregnancy. It approaches insulin treatment from a patient - centred, as well as physician and obstetrician friendly viewpoint, providing pragmatic guidance for management of diabetes in pregnancy.

Keywords: Aspart, Lispro, Insulin, Pregnancy, Detemir, Glargine, GDM, Type 1 diabetes, Type 2 diabetes.

Introduction

Insulin is the mainstay of diabetes management during pregnancy. The importance of this pharmaco therapeutic area has increased manifold over the past few years. An increase in the prevalence of gestational diabetes mellitus (GDM); earlier onset of type 2 diabetes (T2DM); trends towards later marriage and conception in women; and increased prevalence, better control and higher conception rates in women with type 1 diabetes (T1DM) are some of the factors that contribute to this.[1] In parallel, development and introduction of newer insulin preparations, combinations and delivery systems has increased the complexity of this field.[2] The decision of the United States Food and Drug Administration (USFDA) to abolish the letter-based classification of drug approval for use in pregnancy has increased the responsibility of prescribers. Diabetes care professionals are now expected to read and understand a molecule's label in its entirety before prescribing it to antenatal or lactating women.[3]

It is a challenge to manage these pregnant women with diabetes, as their blood glucose levels have to be maintained at a level as close to that of non-diabetic pregnant women, while avoiding hypoglycaemia. This is necessary to prevent adverse foetal and maternal outcomes of pregnancy.

Keeping these factors in mind, it is necessary to review insulin use in pregnancy, in a simple, clinically oriented manner which will be useful to diabetolgists and obstetricians alike. This review will focus on subcutaneous insulin regimes and preparations that can be used safely in pregnancy.

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Classification of Insulin Regimes and Preparations

Insulin regimes and preparations can be classified as in Table. Usage of insulin in pregnancy can be studied according to the type of diabetes and pre-conception treatment; or according to the glucotype. While crafting an insulin prescription, it must be remembered that one should first decide the regimen, then the preparation, and finally the total dose and dose distribution.

Table: Classification of insulin in pregnancy.

Regime	Preparation	Use in pregnancy
Basal	NPH	Safe
	Glargine	To weigh risk benefit ratio
	Detemir	Safe
	Degludec	To weigh risk benefit ratio
Premixed	Biphasic human insulin	To weigh risk benefit ratio
	Biphasic aspart	To weigh risk benefit ratio
	Biphasic lispro	To weigh risk benefit ratio
Prandial	Regular insulin	Safe
	Aspart	Safe
	Lispro	Safe
	Glulisine	Not studied in pregnancy
Basal bolus	Human analogue	Safe
Coformulation	Degludec aspart	Not studied
	Degludec liraglutide	Not studied
	Lixisenatide glargine	Not studied

Indications for Insulin in Pregnancy

Good glycaemic control is essential not only during pregnancy, but also prior to conception. It is an established fact that risk to the foetus increases with rising levels of maternal glycaemia. Hyperglycaemia in the early phase of pregnancy can cause neural tube defects, skeletal and cardiac malformations in the foetus. Carbohydrate intolerance is closely related to adverse perinatal outcome also. Treatment should aim at optimal glycaemic control to achieve a good perinatal result.[4]

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[5] also showed significant risks of adverse outcomes with maternal glucose intolerance, though these were less severe than those seen in overt

diabetes mellitus. Insulin is therefore necessary in women with Type 1, Type 2 and Gestational Diabetes Mellitus.

Prophylactic Insulin in GDM has been used by some researchers, who have used risk assessment of foetal growth to inform insulin therapy. The easy availability of obstetrical ultrasound allows assessment of foetal growth by measurement of foetal abdominal circumference. Ute Schaefer-Graf et. al[6] report the results of their study on women with GDM, divided in two groups. Group 1 required insulin for hyperglycaemia and Group 2 was started on insulin when the 75th percentile of the abdominal circumference was exceeded before 36 weeks of gestation irrespective of the glycaemic levels remaining in the acceptable levels. The target blood glucose levels were <80 mg/dl (fasting) and <110 mg/dl (2 hour post-prandial). No infant was born Small for Gestational Age or Large for Gestational Age or was transferred to NICU in Group 2. The study concluded that management with insulin based on foetal growth had the same perinatal outcome as that of the group with good glycaemic control. There was no episode of severe hypoglycaemia in this group.

Glucotype or Glucose Mapping

Insulin regimen choice is based upon what we term the 'glucotype,' 'glucogram' or 'glucose map'. Glucose mapping describes not only the overall severity of hyperglycemia [as judged by HbA1c], but also the relative contribution of fasting and postprandial glycaemia, at different times of the day. Numerical parameters to help bring objectivity to this subjective process have been described earlier.[7] The glucotype, or the pattern of glycaemia, informs the choice of insulin regimes. The glucotype includes the level of fasting glycaemia, postprandial glycaemia, and overall glucose control (HbA1c), and glycemic variability.

Women with a relatively high fasting glucose, and low postprandial excursion, may be managed with a single dose of basal insulin. Such a situation may be found in some women with T2DM, but is rare in GDM. Women with high postprandial values and normal or near normal fasting glucose will require bolus coverage using human regular insulin, aspart or lispro. Such a glucotype is frequently encountered in GDM, which is characterized by impaired glucose tolerance, but not impaired fasting glucose. Those with both fasting and postprandial hyperglycaemia will benefit from intensive or basal-bolus coverage. In select cases, premixed insulin may be used to provide comprehensive glycemic control in a convenient, less intrusive manner.

Human vs Analogue Insulin

Insulin preparations available can be classified as human or analogue insulin.[8] Insulin analogues are frequently being used in pregnancy now, instead of human insulin. Rapid acting insulin analogues are preferred over regular human insulin in pregnancy. The analogues are superior to human insulin in terms of hypoglycaemia risk, while being equally effective. Analogues are rapidly absorbed from the injection site, attain a faster peak, higher concentration, and have shorter duration of action.

Insulins lispro, aspart and detemir are safe in pregnant women with type 1 diabetes. Correspondingly, they were reclassified for the treatment of pregnant women with diabetes from category C to category B. For insulin glargine use in pregnancy, most studies are small and retrospective. Yet, no major safety concerns are reported. Insulin glulisine and degludec have not been studied in pregnancy.[9] More data, specifically for their use in pregnancies complicated by gestational diabetes or type 2 diabetes, is needed.

An extensive analysis of 29 studies included data on 1286 foetuses exposed to short-acting insulin analogues (compared to 1089 exposed to human insulin), and 768 foetuses exposed to long-acting insulin analogues (compared to 685 exposed to Neutral Protamine Hagedorn insulin). The congenital anomaly rate was 4.84% and 4.29% among the foetuses of mothers using lispro and aspart. For glargine and detemir, the congenital anomaly rate was 2.86% and 3.47%, respectively. No statistically significant difference in the congenital anomaly rate among foetuses exposed to insulin analogues (lispro, aspart, glargine or detemir) was found as compared with those exposed to human insulin.[10]

Dose Distribution

The total daily dose, and distribution among various doses, is done based upon individual glucose mapping. In general, person with type1 diabetes and type 2 diabetes will experience an increase in insulin requirements during pregnancy, especially in the 2nd and early 3rd trimester. Requirements may fall in the 1st trimester, because of reduced intake. Administration of antenatal corticosteroid therapy (ACS) will necessitate a spike in insulin requirement.[11] Though this is highly variable, an increase of 30% in dose for 5 days can be anticipated after ACS.

One should start low and go slow while initiating insulin in GDM. A safe method of calculating initial dose would be to begin 0.1-0.2 U/kg body weight. If basal insulin is used (which is not so frequent), the entire dose will be given as one dose, or divided into two equal doses. A premixed human insulin regime will be prescribed as two thirds dose before breakfast and one thirds before dinner. Premixed insulin analogues, of used, are initiated in a 50:50 or 60:40 dose distribution. At times, a heteromix regime (e.g., BI Asp 50 or lispro 50:50 with breakfast, and BI ASP 30 or lispro 25:75 with dinner) can be used. Here too, the distribution is 50: 50 or 60:40. If a basal - bolus regime is initiated, a pragmatic dose distribution would be 20:20:20 (bolus) and 40 (basal).

In all cases, frequent glucose monitoring is mandatory for appropriate adjustment of dose and dose distribution.

Type of Diabetes

Type 1 diabetes

Women of child bearing age with type 1 diabetes, who are planning conception, should ideally be on basal bolus therapy.[12] The bolus component may be regular insulin, aspart or lispro: all are studied in subjects with pregnancy. Glulisine has not been studied in pregnancy. The basal component should ideally be NPH insulin or detemir. While no randomized controlled trials have been done on glargine in pregnancy, there are ample case reports of its safety during this period. Degludec has not been studied in women with pregnancy. It may be prescribed, after shared and informed decision making, to women who are unable to achieve fasting glycemic control with any other basal insulin preparation.

Women with type 1 diabetes who happen to be on premixed insulin based regimes should be switched to intensive regimes as part of preconception management. This interchange should be accompanied by an explanation of the physiological need for this.

Type 2 Diabetes

Women with type 2 diabetes should be initiated on basal bolus insulin regime in the preconception period, using preparations that are approved for use in pregnancy. There may be some women who wish to avoid frequent injections: such patients may be given an option of premixed insulin, while counseling them in detail about the risk; benefit ratio.[13]

Women with T2DM who present after having conceived on oral drugs, should preferably be switched to insulin therapy, using appropriate preparations, described above.

Gestational Diabetes Mellitus (GDM)

GDM, by definition, is diagnosed or identified during pregnancy. While the initial management consists of lifestyle modification, including medical nutrition therapy (MNT), insulin will be required in a significant proportion of patients, and is safer than other options such as glyburide.[14] The majority if patients who are initially prescribed metformin will also need insulin therapy at some time during pregnancy.[15]

Insulin should be initiated immediately in women with severe hyperglycemia, symptoms of hyperglycemia, ketosis or ketoacidosis, evidence of foeto-maternal compromise, (e.g., hydramnios, intrauterine growth retardation, significantly large-for-gestational age foetus).[16]

In women with relatively mild hyperglycemia, a trial of MNT may be given for a few days. The choice of insulin remains the same as in T1DM or T2DM. Women with GDM require relatively lower doses of insulin, especially for fasting control.

Summary

Basic understanding of the pathophysiology of diabetes in pregnancy, and pharmacology of insulin preparations, allows one to craft appropriate insulin therapy. A pragmatic prescription is one which matches pathophysiology requirement with pharmacological effect, to achieve maximal efficacy and safety.

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