

## The Art and Science of Managing Diabetic Pregnancy by Insulin Injections and Insulin Pump: Evidence Based Reports from Research Trials and Meta-Analysis

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### Editorial

Managing Diabetes during pregnancy is challenging. However, proper use of Insulin regimens, insulin analogues, and insulin pump are promising. Furthermore, physicians are not much familiar with such techniques and face difficulty while managing such patients. Physicians or health care professional must know the basics of managing diabetic pregnancies.

Physiologic metabolism during pregnancy is characterized by fasting hypoglycemia (because of insulin-independent glucose uptake by the placenta), postprandial hyperglycemia, and carbohydrate intolerance (due to diabetogenic placental hormones). Type-1 pregnancy is usually associated with hypoglycemia, while type-2 pregnancy with obesity. Additionally, insulin resistance is increased after the second trimester, toward the end of the third trimester, where intensification of insulin dose and regimen is required.

Diabetes (DM) during pregnancy can be generally classified as gestational diabetes mellitus or GDM (first diagnosed during pregnancy) or pre-existing or pre-gestational diabetes (either type-1 or type-2 that become pregnant). Metabolic/glycemic targets (as recommended by Fifth International Workshop-Conference on Gestational Diabetes Mellitus, and American Diabetes Association) are as follows:

Gestational Diabetes glycemic targets:

Preprandial  $\leq 95$  mg/dL

One-hour postmeal  $\leq 140$  mg/dL

Two-hour postmeal  $\leq 120$  mg/dL

Pre-existing diabetes glycemic targets:

Premeal, bedtime, and overnight glucose 60–99 mg/dL

Peak postprandial glucose 100–129 mg/dL

A1C 6.0%

Generally, A1C should be  $< 7\%$  and as close to 6% as possible (without severe hypoglycemia); this is due to increased in red blood cell turnover during pregnancy, with resulting decrease in "A1C levels" [1-3].

Medical nutritional therapy (MNT), counseling, and diabetes self management education (DSME) are the essential aspects of diabetes management. Self-monitoring of blood glucose (SMBG) should be done frequently and at least four times per day: before the breakfast, and one hour post-meals (post prandial) [4].

Managing diabetic pregnancies by insulin is recommended one, as lacking of long-term safety data for non-insulin agents. Hence, oral anti-hyperglycemic or anti-diabetic agents should be discontinued and insulin should be initiated if diabetes is not controlled by dietary regimens.

Furthermore, newer anti-hyperglycemic agents, such as GLP-1 agonists, DPP-4 inhibitors, alpha-glucosidase inhibitors, and SGLT-2 inhibitors should also be discontinued during pregnancy as they lack safety information.

Metformin is one of the exceptions, which may be continued during the first trimester in patients with PCOS or type-2 diabetes, and anovulatory infertility. However, in these settings also, metformin is not recommended beyond first trimester, as metformin crosses the placenta and long-term safety data (randomized controlled trials, RCT) is lacking. Similarly, other oral medications also have not been studied well and lack long term safety data (RCT) [5-8].

It should be noted that all insulins are category B; insulin glargine, glulisine and degludec are category C. Regarding insulin analogs, safety data for human pregnancies is not available until date for glulisine and degludec, and their current recommendation is not to prescribe during pregnancy. Similarly, insulin glargine, a long-acting insulin analog, is associated with 5-8 fold increased IGF-1 receptor affinity with mitogenic potency (as compared to human insulin), and currently is not recommended during pregnancy [9-13].

After Diet control or MNT, initiate insulin therapy if FBS  $\geq 96$  mg/dl and RBS  $\geq 150$  mg/dl. Human regular insulin can be used (as a bolus insulin) for managing post-prandial hyperglycemia. However, if one hour post-prandial blood glucose values are above the target, documented evidence of pre-meal or nocturnal hypoglycemia, this can be replaced with insulin lispro or aspart.

NPH insulin can be used as long acting insulin, where it can be given twice a day. Detemir, a long acting insulin analog, given once daily (or best twice daily if fasting blood glucose targets not achieved), can be replaced with NPH insulin. However, detemir is non-inferior to NPH insulin in terms of safety, efficacy and outcomes [14-18].

Human regular insulin can be given before each meal, with basal insulins (NPH or detemir). Similarly, and alternatively, the rapid-acting insulin analogs (RAIs), lispro or aspart are combined and injected with basal insulins as multiple daily injections (MDI), or best as basal bolus regimens. Insulin requirement is usually 0.9–1.2 units/kg/24 h. Generally, a smaller proportion ( $< 50\%$ ) of the calculated total dose should be given as basal insulin, while a greater proportion ( $> 50\%$ ) as bolus (divided between meals); alternatively, administer 2/3<sup>rd</sup> total dose of insulin in AM and 1/3<sup>rd</sup> total dose in PM; AM ratio

of bolus to basal can be 1:2 and PM ratio is 1:1. However, these are further adjusted according to the readings of SMBG [19,20].

Although there is not clear evidence from the literature that lispro or aspart delivered as continuous subcutaneous insulin infusion (CSII) vis insulin pump is necessary for optimal treatment of type-1 diabetic pregnancies, however, this technique may be effective for GDM and type-2 diabetic pregnancies requiring large doses of insulin. Pregnancy is a state of accelerated ketosis and hence diabetic pregnancies with erratic blood glucose (hypoglycemia, hyperglycemia) or a history of diabetic ketoacidosis (DKA) usually benefit from Insulin Pump. Furthermore, intensive DSME, monitoring and surveillance of the infusion / injection site and sets is required as well. This also includes extensive calculations of insulin dosages or requirements, insulin to carbohydrate ratio / carbohydrate counting, and insulin sensitivity/correction factor. Usually pump total daily dose (TDD) can be calculated as : pre-pump TDD  $\times$  0.75. Then, 50% of that can be given as basal over 24-hours (Pump TDD  $\times$  0.5 / 24 h) and 50% as divided boluses prior to meals and then pump settings adjusted according to pre- or post-meals blood glucose levels. Generally, the infusion rates (insulin units  $\times$  weight in kg) for basal or bolus during first, second, third trimester, and term pregnancy (>38 weeks'gestation) are 0.35, 0.4, 0.45, and 0.45 respectively. Basal and bolus rates can be further adjusted by insulin pump settings during different time of the day and according to meals [21-27].

In conclusion, although management of diabetic pregnancies can be challenging, but can be managed successfully if the physician follows recent research reports or guidelines and uses the correct technique to deliver the insulin to the diabetic pregnant women.

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