

Reduced Efficacy of Insulin Detemir in Controlling Hyperglycemia during Pregnancy: An Interesting Case Report

Sir,

Insulin neutral protamine Hagedorn (NPH) and detemir have been approved for use in pregnancy as basal insulin. These insulins do not have any adverse maternal or fetal effects. Studies have shown comparable results with similar insulin doses in women with type 1 diabetes but higher insulin detemir dose was required to achieve similar glycemic control among patients with type 2 diabetes. We report case of a pregnant female with diabetes, who had high fasting blood sugar (108-131mg/dL) at very high dose of insulin detemir (48 IU/day) but was controlled on relatively lesser dose of traditional insulin NPH (40 IU/day). So, clinicians should be aware of potentially increased insulin dose requirement while prescribing insulin detemir to pregnant patients with diabetes. Also, changes in basal insulin dose should be anticipated when switching from insulin detemir to insulin NPH. This case brings forward reduced efficacy of insulin detemir as an important aspect of treating diabetes with pregnancy. If fasting blood sugar is still high on a reasonable dose of insulin detemir, shifting to insulin NPH with dose adjustment may be considered.

Historically, insulin NPH, along with short-acting insulin, is used for the treatment of diabetes during pregnancy. Due to 16–18 h duration of action, it is not a true once-daily basal insulin. Night-time administration of insulin NPH increases the risk of early morning hypoglycemia. It needs to be

resuspended adequately before injection to prevent inaccurate dosing and risk of hyper- and hypo-glycemia.^[1] Its action profile does not mimic physiology and this pharmacokinetics makes aggressive glycemic control difficult, which may result poor maternofetal outcome. Insulin analogs overcome these pharmacokinetic limitations. Insulin detemir, a long-acting recombinant human insulin analog, has not shown to have adverse maternal or fetal effects. It has been approved for use in pregnancy by the United States Food and Drug Administration.^[2-4]

A head-to-head comparison between insulin detemir and NPH in pregnant women with type 1 diabetes has shown that FBS improved with insulin detemir, without an increased incidence of hypoglycemia with no difference in fetal outcome, while the mean dose was same for both insulins.^[2] However, other studies have found a higher insulin detemir dose requirement as compared to other basal insulins to achieve similar glycemic control among patients with type 2 diabetes.^[5,6] We report an interesting case of a female with pregnancy and diabetes, who had high FBS at very high dose of insulin detemir but was controlled on relatively lesser dose of traditional insulin NPH.

A 35-year-old pregnant female consulted us for better glycemic control during the first trimester of pregnancy. She was diagnosed to have diabetes a week before

presentation and was put on premix insulin (aspart and protaminated aspart 30/70) twice daily before breakfast and dinner. Her glycosylated hemoglobin (HbA1c) at presentation was 6.7%, body mass index (BMI) was 25.5 kg/m², and liver enzymes were slightly elevated (aspartate transaminase – 71 IU/L [normal levels: 10–50 IU/L] and alanine transaminase – 87 IU/L [normal levels: 10–50 IU/L]). Her lipid profile was normal. Hepatitis serology was negative. She had no other comorbid conditions. She was put on multiple subcutaneous insulin injections (MSI) regimen for better glycemic control. Insulin aspart was administered three times daily before each meal (24 IU/day) and detemir at bedtime (14 IU/day). A dietary consultation was taken, and the patient was advised to follow it strictly. Surprisingly, despite up-titration of insulin detemir dose to 0.8 IU/Kg/day (48 IU), her FBS remained high (108–131 mg/dl). The dose of insulin detemir was increased by 2–4 units every 3–4 days to control FBS [Table 1].

Even at very high total insulin dose (2 IU/kg/day), glycemic targets were not met. Insulin detemir was used for almost 3 weeks. As tight glycemic control is very important during pregnancy, she was shifted to insulin NPH at bedtime at a lesser dose than detemir (0.68 IU/kg, 40 IU) and aspart was continued. She responded well and FBS (89 mg/dl) normalized very next day. Her ultrasound abdomen and fibroscan reported fatty liver [Figure 1]. Later, her insulin doses were adjusted as per blood sugar levels. Her blood sugars were well controlled on insulin NPH and aspart till delivery. After delivery, she was put on metformin.

Insulin detemir is produced by a process including expression of recombinant DNA in *Saccharomyces cerevisiae*. It differs from human insulin by the deletion of the amino acid threonine in position 30 of the B chain, plus the addition of a C14 fatty acid chain (myristic acid) at position 29 of the B-chain. This allows insulin detemir to reversibly bind to serum albumin and characterizes it as hepatoselective insulin.^[7] It has a peakless action for 18–20 h. The benefits of insulin detemir such as improved glycemic control, lower glycemic variability, reduced nocturnal hypoglycemia, and no weight gain have been demonstrated in patients with type 1 diabetes.^[8] A comparative study between insulin detemir and NPH during pregnancy in patients with type 1 diabetes has demonstrated no different fetal outcome between treatments.^[9]

The insulin detemir has a lower affinity (18%) for the human insulin receptors than other insulins as the myristic acid interferes with receptor binding.^[10] To overcome this reduced potency, detemir is formulated at a higher molar concentration, 2400 nmol/ml versus 600 nmol/ml for all other insulin preparations. This ratio was based on type 1 diabetes trials showing comparable glycemic control with detemir and NPH, provided that four times the molar dose was used.^[11,12]

Table 1: Changes in fasting blood sugar and insulin detemir dose

Day	FBS (mg/dl)	Insulin detemir (U/day)
1	123	14
4	130	16
6	118	20
9	116	24
11	128	28
15	131	34
17	101	36
18	122	40
20	116	44
21	108	48

FBS: Fasting blood sugar

Three heterogeneous randomized trials have shown that the unit dose equivalence observation does not apply to patients with type 2 diabetes.^[5,6,13]

It is possible that the reduced receptor-binding affinity of insulin detemir and/or its longer residence at the site of injection allows a greater fraction of detemir than of other insulins to undergo nonreceptor-mediated clearance.^[10] Alternatively, as more than 98% of insulin detemir is bound to albumin and only free detemir is physiologically active, increased protein binding in type 2 diabetes may be another theoretical explanation.

Whyte *et al.*^[14] reported relative lack of efficacy of insulin detemir in two patients with hypertriglyceridemia and nonalcoholic fatty liver disease (NAFLD). The possible explanation given was that insulin detemir molecule, a hepatoselective insulin, is able to pass freely through hepatic sinusoids. Hence, its effect may be reduced in NAFLD by less hepatic exposure to insulin due to increased insulin clearance or portosystemic shunting or direct hepatic parenchymal cell damage. This is contrary to human insulin clearance of which is reduced in patients with chronic liver disease like cirrhosis.^[15] The insulin clamp studies with human insulin have also shown decreased clearance in patients with fat infiltration of the liver.^[16] It is a known fact that higher the BMI, higher is the risk of NAFLD. Porcellati *et al.*^[17] assessed the role of adiposity on the pharmacodynamics of basal insulins NPH, detemir, and glargine in patients with type 2 diabetes, using glucose infusion rate and endogenous glucose production rate in the euglycemic clamp. They concluded that adiposity blunts the pharmacodynamics of all basal insulins in type 2 diabetes mellitus. However, as adiposity increases, the effect of detemir is lower versus NPH and glargine.

The inability to control FBS in our patient on very high dose of insulin detemir may be due to NAFLD as shown in ultrasound and fibroscan. Another possible cause may be due to diagnosis of “undiagnosed type 2 diabetes” during the first

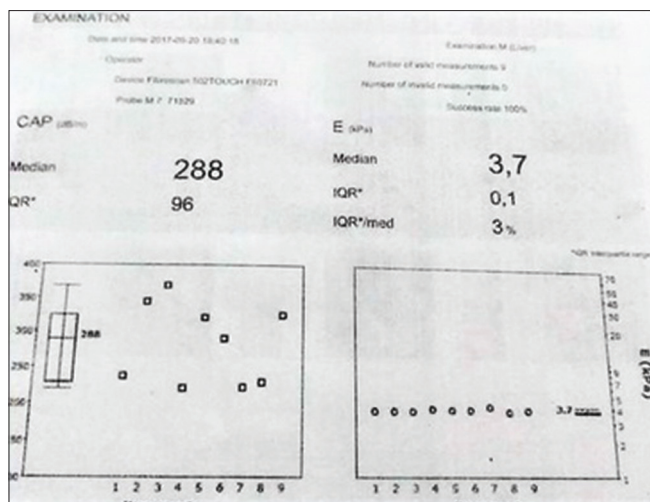


Figure 1: Fibroscan of the liver

trimester where higher dose of insulin detemir is required. Both these conditions reduce the efficacy of insulin detemir. This is probably the first case reporting reduced efficacy of insulin detemir during pregnancy.

This case highlights that clinicians should be aware of potentially increased insulin dose requirement while prescribing insulin detemir in pregnancy with type 2 diabetes. Furthermore, changes in basal insulin dose should be anticipated when switching from insulin detemir to insulin glargine or NPH insulin and vice versa to avoid hypoglycemia or deterioration in glycemic control.

Insulin detemir is one of the two basal insulins approved for diabetes control during pregnancy and is frequently used in pregnancy. The reduced efficacy of detemir is an important aspect of treatment in diabetes with pregnancy. If FBS is still high on a reasonable dose of insulin detemir, shifting to insulin NPH may be considered.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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