

GLYCEMIC CONTROL WITH CONTINUOUS SUBCUTANEOUS INSULIN INFUSION WITH USE OF U-500 INSULIN IN A PREGNANT PATIENT

Betul Hatipoglu, MD,¹ Sonia Soni, MD,² and Valerie Espinosa, MD¹

ABSTRACT

Objective: To demonstrate the benefits and to advocate the safety and efficacy of using an insulin pump with U-500 insulin in comparison with U-100 insulin for a pregnant patient with diabetes requiring massive doses of insulin.

Methods: We present a detailed case report about the use of continuous subcutaneous insulin infusion with U-500 insulin during pregnancy. Dose calculation is reviewed, and the benefits of insulin pump therapy in patients with diabetes are discussed.

Results: A 34-year-old white woman, with a history of type 2 diabetes for 7 years, was seen at 17 weeks of gestation because of episodes of hyperglycemia and hypoglycemia accompanied by a very high insulin requirement. At the time of initial assessment, the patient was hospitalized with diabetic ketoacidosis and was being treated with 400 U/day of intravenously administered insulin. She responded well to intravenous therapy, but when switched to a regimen of NPH and regular insulin, she continued to have high blood glucose levels (despite 4 to 5 insulin injections a day, with a total daily dose up to 400 to 450 U). Use of an insulin pump was instituted, which presented another challenge because of the limited reservoir capacity and the need to change sites at least once or twice a day. We decided to initiate U-500 insulin therapy with a total basal rate of 40 U/day. Her meal carbohydrate insulin ratio and correction bolus were calculated on a U-100 scale. Then each estimated dose for meal coverage, depending on her carbohydrate intake, as well as the appropriate corrections were totaled and divided by 5 to convert to U-500. Throughout the rest of her pregnancy, the patient was able to maintain tight glycemic control,

with no further hospitalizations for stabilization of hyperglycemia or hypoglycemia.

Conclusion: To our knowledge, this is the first report of successful management of difficult to control diabetes by means of an insulin pump with use of U-500 insulin in a pregnant patient who required massive doses of insulin. (*Endocr Pract.* 2006;12:542-544)

Abbreviations:

A1C = hemoglobin A1c; CSII = continuous subcutaneous insulin infusion

INTRODUCTION

The most commonly used insulin preparations for pump infusions include lispro, aspart, and regular insulin. Insulin is commercially available in concentrations of 100 U/mL (U-100) or 500 U/mL (U-500). The latter is used only in patients with severe insulin resistance and is a formulation of regular insulin (1). U-500 insulin is a 5 times concentrated form of regular insulin. Although many benefits are derived from the use of U-100 in an insulin pump, there are also drawbacks associated with its use in highly resistant patients who require massive doses of insulin. The need for frequent adjustment of the site negates the convenience factor of the pump and increases the cost because of the use of more supplies. We describe our experience with use of an insulin pump in combination with U-500 insulin in a pregnant patient with type 2 diabetes. To the best of our knowledge, the case presented is the first report in the literature of continuous subcutaneous insulin infusion (CSII) with use of U-500 insulin during pregnancy.

CASE REPORT

A 34-year-old white woman, who was at 17 weeks of gestation, had a 7-year history of type 2 diabetes with complications of retinopathy and nephropathy. Before her pregnancy, she was using 1,000 mg of metformin twice a day, 80 U of NPH insulin in conjunction with 15 U of

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From the ¹Section of Endocrinology, Diabetes, and Metabolism, University of Illinois at Chicago, and ²Department of Medicine, Mercy Hospital and Medical Center, Chicago, Illinois.

Address correspondence and reprint requests to Dr. Betul Hatipoglu, Section of Endocrinology, Diabetes, and Metabolism, University of Illinois at Chicago, 1819 West Polk, M/C 797, Chicago, IL 60612.

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regular insulin in the morning, and 90 U of NPH in conjunction with 15 U of regular insulin in the evening. The patient's pregnancy was complicated by frequent episodes of hyperglycemia, despite administration of large doses of insulin, as well as hypoglycemia. The patient had been hospitalized 5 times for hypoglycemia and once for diabetic ketoacidosis. The patient also had widely fluctuating preprandial blood glucose levels, ranging from 50 mg/dL to 293 mg/dL. Her dosage adjustments during the first trimester were made by her primary care physician, who attempted to combine NPH insulin twice a day and regular insulin 3 times a day with multiple dose changes. Besides her medical history of type 2 diabetes for 7 years, the patient had polycystic ovary syndrome, which had been diagnosed because of irregular menstrual periods and obesity without any signs of hyperandrogenism. Her family history was negative for lipodystrophy but strongly positive for diabetes in both parents. This was her first pregnancy. She did not smoke, drink alcohol, or use any illegal drugs. She was living with her husband and worked as a hemodialysis technician. Her prepregnancy glycemic control had been suboptimal, with documented hemoglobin A1c (A1C) levels of approximately 7.5% to 8%.

On the day of presentation, the patient was hospitalized for another episode of diabetic ketoacidosis and was being treated with 400 U/day of intravenous insulin drip. She responded well to intravenous therapy, but when she was switched to a combination of NPH and regular insulin, she continued to have high blood glucose levels despite 4 to 5 insulin injections or more a day, totaling up to 400 to 450 U/day. When the endocrine service saw the patient, she had an A1C of 7.3%. Her physical examination revealed a weight of 126 kg and a height of 157.5 cm. She had acanthosis nigricans in her neck and armpits. No signs of lipodystrophy or hyperandrogenism were present.

The diagnosis was uncontrolled diabetes during pregnancy in a patient requiring high doses of insulin, most likely because of insulin resistance. Our goals were to maintain her fasting and preprandial blood glucose levels between 60 and 105 mg/dL, achieve 2-hour postprandial glucose values of less than 120 mg/dL, and maintain all glucose levels above 60 mg/dL. Because of the difficulty in maintaining her blood glucose levels within the established goals with multiple daily injections, we decided to initiate insulin pump therapy. We used the MiniMed 508 pump because it had the largest capacity—300 mL. Despite this, the insulin pump presented another challenge attributable to the limited reservoir capacity in comparison with her insulin requirements and the need to change sites at least once or twice a day. We tried to solve this challenge by instituting the use of U-500 insulin in the pump.

The patient's first total basal rate was estimated to be 40 U/day of U-500 insulin (200 U/day of U-100 insulin). The initial rate of insulin infusion was ~1.7 U/h. After this, for the bolus insulin, the patient was given a guide to calculate meal coverage depending on her carbohydrate

intake, as well as a correction ratio to add if the blood glucose level was higher than desired goals. The carbohydrate insulin ratio and correction bolus ratio were calculated on a U-100 scale. Her calculated meal boluses, depending on her carbohydrate intake, as well as the calculated correction boluses were collectively totaled and then divided by 5 to convert to U-500. This approach was found to be easier and safer than giving the patient guidelines for U-500 insulin directly.

For the following 8 weeks after the CSII therapy was initiated, her insulin pump was adjusted numerous times. The patient was seen for weekly consultations and was contacted more often. After the 8-week period, her blood glucose levels stabilized with use of the following U-500 insulin rates: 2.0 U/h between 12 AM and 6 AM, 2.3 U/h between 6 AM and 6 PM, and 2.2 U/h between 6 PM and midnight (a total of 52.8 U of U-500 insulin or 264 U of U-100 insulin). Her meal bolus was 1 U of U-100 insulin per 1 g of carbohydrate, and her correction bolus was approximately 1 U for 4 mg/dL above the premeal goals. The total was then divided by 5 to convert it to the appropriate insulin concentration, as described in the foregoing material.

After 2 months of intensive treatment, the patient's A1C value was 5.9%. Weekly blood glucose recorded values ranged from 50 mg/dL to 160 mg/dL but were primarily within the desirable range. The patient was able to maintain tight glycemic control throughout the rest of her pregnancy, with no further hospitalizations needed for stabilization of hyperglycemia or hypoglycemia. A healthy baby girl was born elsewhere at 37 weeks of gestation, without known complication.

DISCUSSION

During the past 2 decades, many clinical trials have demonstrated the importance of achieving tight glycemic control to prevent chronic complications of diabetes. They have also rekindled an interest in external infusion insulin pumps for patients who are unable to achieve a euglycemic pattern with the use of conventional multiple daily dose injections of insulin. Although the insulin pump was initially devised for treating patients with type 1 diabetes, it has been used successfully for patients with type 2 diabetes who fail to achieve glycemic control with oral therapy (2).

There are several benefits to the use of CSII in patients with diabetes. The most important results are tighter glycemic control because of the ability to provide a physiologic mode of delivery by mimicking normal pancreatic function (3) and reduced frequency of hypoglycemic events (4). CSII also facilitates counteraction of the dawn phenomenon, which is experienced by 80% of patients with insulin-dependent diabetes, by increasing the delivery of insulin during the early morning hours when there is accelerated production of glucose, coupled with an increase in serum cortisol and growth hormone (2).

Pregnancy is a challenging period for patients with diabetes and their physicians. Although women without diabetes rarely demonstrate postprandial blood glucose levels above 120 mg/dL, considerable effort must be invested to maintain tight glycemic control in pregnant patients with diabetes in order to prevent both maternal complications and fetal morbidity and mortality. Therefore, pregnancy might be regarded as an indication for CSII therapy. During pregnancy, an insulin pump is advantageous in that it allows the patient to react appropriately to the changing insulin requirement (2). Studies have shown that the insulin pump is comparable to treatment with multiple daily insulin injections during pregnancy, but it has the following advantages: (1) decreases the mean amplitude of glycemic excursions, (2) significantly reduces mean levels of blood glucose, (3) decreases the frequency of hypoglycemic episodes, (4) offers greater flexibility of lifestyle, (5) responds to impaired regulation of insulin absorption, and (6) facilitates treatment of the dawn phenomenon (5,6). Moreover, it is cost-effective.

One of the challenges of insulin pump therapy is the insulin capacity; some reservoirs hold 300 mL and others hold 180 mL. Therefore, patients requiring large doses of insulin especially during pregnancy, as our patient, must fill the pump reservoir and change the delivery site more frequently—sometimes twice a day. This necessity is often inconvenient and uncomfortable, and it imposes a substantial financial burden on patients. In such cases, U-500 insulin can be considered as an alternative.

U-500 insulin is a formulation of regular insulin that is safe during pregnancy but is 5 times the concentration of U-100 insulin; thus, patients can utilize one-fifth the volume of insulin. For patients already receiving insulin pump therapy, doses can be easily converted to U-500 insulin by dividing all basal rate requirements by 5. The bolus calculation either can be converted directly to U-500 or, as in our case, can be first calculated and then divided by 5 to decrease the possibility of insulin overdose.

Because of the increased concentration of the U-500 insulin formulation, our patient's insulin supply was sufficient for up to 3 days without changing the reservoir. In a

recently published report of 4 nonpregnant patients with type 2 diabetes receiving insulin pump therapy with U-500 insulin, Knee et al (7) not only observed an A1C decline from 10.8% to 7.3% within 6 months but also estimated a potential cost savings of up to \$2,600 annually per patient, despite the increased cost of U-500 insulin per milliliter. This outcome was possible because of a dramatic reduction in pump supplies and a smaller volume of insulin used in those patients.

CONCLUSION

In light of our successful experience with the use of U-500 insulin in an insulin pump in our pregnant patient (and a few other nonpregnant patients not described in this report), we would encourage other clinicians to consider this option as well. Undoubtedly, more research is needed to explore additional strategies for the management of patients requiring massive doses of insulin.

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