Insulin Glargine versus Neutral Protamine Hagedorn Insulin for Treatment of Diabetes in Pregnancy

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ABSTRACT

We compared maternal and neonatal outcomes in diabetic pregnancies treated with either insulin glargine or neutral protamine Hagedorn (NPH) insulin. We performed a retrospective chart review of diabetic pregnant patients using the Diabetes Care Center of Wake Forest University during the years 2000 to 2005. Outcomes of interest included maternal hemoglobin A1C, average fasting and 2-hour postprandial blood sugars, mode of delivery, birth weight, 5-minute Apgar score < 7, umbilical artery pH < 7.20, incidence of neonatal hypoglycemia, and pregnancy complications. A total of 52 diabetic pregnant patients were included in this study. Twenty-seven women used insulin glargine. A total of 13 women used insulin glargine during the first trimester. Glycemic control was similar in women who used NPH insulin and insulin glargine, as determined by hemoglobin A1C levels and mean blood sugar values. There were no differences in mode of delivery, average birth weight, or neonatal outcomes. Maternal and fetal/neonatal outcomes appear similar in pregnant diabetic women who use either NPH insulin or insulin glargine in combination with a short-acting insulin analogue to achieve adequate glycemic control during pregnancy. Insulin glargine appears to be an effective insulin analogue for use in women whose pregnancies are complicated by diabetes.

KEYWORDS: Insulin glargine, NPH, pregnancy

The incidence of diabetes in the United States has steadily risen over the past several decades. As a result, diabetes is one of the most commonly encountered medical complications of pregnancy. It is well known that uncontrolled diabetes in pregnancy can lead to serious fetal, neonatal, and maternal sequelae. Fetal complications can include congenital malformations, intrauterine growth restriction, macrosomia, and intrauterine death. Neonatal complications include hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome. Diabetes during pregnancy has also been shown to increase the risk of development of obesity, diabetes, and metabolic syndrome in offspring.[1,2] Maternal complications associated with diabetes in pregnancy include pregnancy-induced hypertension, preeclampsia, and worsening of chronic complications of diabetes including nephropathy and retinopathy. Therefore, stringent glycemic control during pregnancy

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is imperative to ensure a good maternal and fetal outcome.

Recommendations for glycemic control during pregnancy are much stricter than in nonpregnant diabetic patients: goals are less than 90 to 105 mg/dL fasting and less than 120 mg/dL 2 hours postprandial. A goal of less than 140 mg/dL should be used if assessing blood glucose levels 1 hour postprandial. Various insulin regimens and formulations have been used in an attempt to achieve tight glycemic control during pregnancy, none of which has been shown to be superior.

Insulin glargine is an insulin analogue approved for clinical use in the United States in the year 2000. Due to its chemical structure, insulin glargine is very slowly absorbed, exhibiting a peakless activity profile over a 24-hour time period. Among its attributes, insulin glargine has been shown to reduce the risk of nocturnal hypoglycemia in nonpregnant type I and type II diabetic patients.[3–5] Given the strict glycemic control that is recommended during pregnancy, nighttime hypoglycemia can be a difficult problem to address in pregnant patients, making insulin glargine an attractive choice for glycemic management in pregnancy.

Reports of insulin glargine use in pregnancy are limited.[6–14] No adverse effects in human pregnancy have been reported and animal studies have demonstrated the safety of insulin glargine during embryogenesis in animal models.[15] This retrospective study provides additional information regarding maternal and fetal/neonatal outcomes in pregnancies in which mothers used either insulin glargine or neutral protamine Hagedorn (NPH) insulin in combination with other short-acting insulin analogues for blood glucose management during their pregnancies.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we conducted a retrospective chart review of pregnant women and their infants who were treated at the Diabetes Care Center of Wake Forest University Baptist Medical Center and delivered at Forsyth Memorial Hospital. Women treated with either insulin glargine or NPH insulin during the years 2000 to 2005 were included. There were no exclusion criteria.

Maternal outcome variables included average blood glucose values, hemoglobin A1C, and mode of delivery. Fetal and neonatal outcomes included birth weight, Apgar score at 5 minutes, umbilical artery blood gas at delivery, blood glucose at delivery, nadir blood glucose level, and need for neonatal intensive care unit (NICU) observation for greater than 4 hours due to hypoglycemia.

Data were analyzed using t test, one-way analysis of variance, and χ^2 analysis. $p < 0.05$ was considered significant.

RESULTS

Maternal Outcomes

A total of eight type 1, 26 type II, and eighteen gestational diabetic patients were included in this study. The demographic data and insulin regimens used by these women are presented in Table 1. Type I diabetic patients were significantly younger and had a significantly longer duration of disease than either type II or gestational diabetic women.

Of the women using insulin glargine, two women were using prior to conception and continued its use throughout their entire pregnancy. Eleven women initiated use of insulin glargine during the first trimester, and seven women began using insulin glargine during the second trimester. The average doses of insulin glargine at delivery were 59 ± 13.7 IU/d in type I diabetic women, 65 ± 8.2 IU/d in type II diabetic women, and 39.7 ± 7.7 IU/d in gestational diabetic women.

Although hemoglobin A1C data was limited (first trimester $n = 17$; second trimester $n = 10$; third trimester $n = 10$), glycemic control was similar between the NPH and insulin glargine–treated women (Fig. 1). There were no significant differences in hemoglobin A1C levels between treatment groups in any trimester (first trimester $p = 0.88$, second trimester $p = 0.38$, third trimester $p = 0.12$). Additionally, there was no

Table 1 Maternal Demographics

	Insulin Glargine			NPH		
	Type I (*n* = 7)	Type II (*n* = 13)	Gestational (*n* = 7)	Type I (*n* = 1)	Type II (*n* = 13)	Gestational (*n* = 11)
Age (y ± SEM)	24.4 ± 1.5	31 ± 1.3	35.0 ± 1.3	22	33.3 ± 1.1	33 ± 1.8
Years diabetic (mean ± SEM)	12.9 ± 1.9	4.5 ± 1.4	N/A	11	5.1 ± 1.1	N/A
Nulliparous (%)	57	38	14	100	43	27
Gestational age of initiation of intermediate or long-acting insulin (wk ± SEM)	11.6 ± 3.2	12.3 ± 1.2	29.9 ± 1.4	1.0	7.0 ± 2.0	30.0 ± 1.1

NPH, neutral protamine Hagedorn; SEM, standard error of the mean.
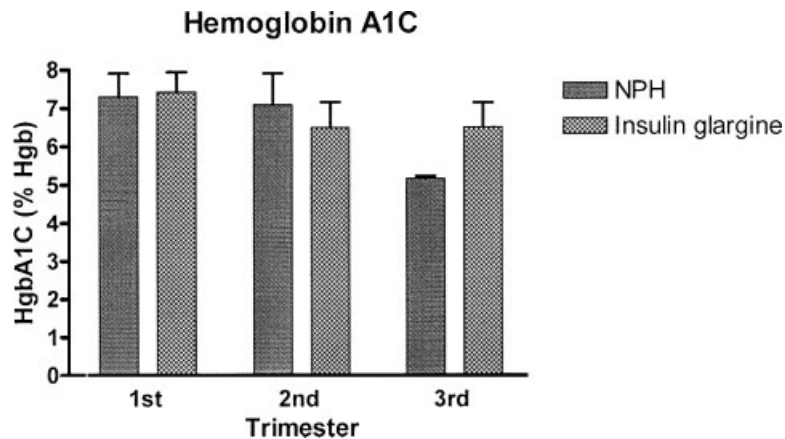
Hemoglobin A1C

Figure 1 Hemoglobin A1C values by trimester in women who used insulin glargine and neutral protamine Hagedorn (NPH) insulin. Data are expressed as mean ± standard error of the mean.

significant difference between hemoglobin A1C levels within treatment groups over the course of gestation (insulin glargine $p = 0.31$, NPH insulin $p = 0.20$).

Adequate blood sugar data were available for analysis for 21 patients who used insulin glargine and 17 patients who used NPH insulin. Fasting blood glucose levels were significantly lower than postprandial blood glucose levels in both treatment groups. There was no significant difference between fasting or postprandial blood glucose levels in women who used either insulin glargine or NPH insulin (Fig. 2).

The average gestational age at delivery was 37.0 ± 0.7 weeks gestation in women treated with NPH insulin and 36.3 ± 0.96 weeks gestation in women treated with insulin glargine ($p = 0.56$). Of women using insulin glargine, 37% delivered vaginally compared with 48% using NPH insulin (Table 2). Nine women (33.3%) using insulin glargine and seven women (28%) using NPH insulin were delivered by primary cesarean section. Indications for primary cesarean section included macrosomia ($n = 1$), failure to progress ($n = 6$), non-reassuring fetal heart tones ($n = 3$), failed induction ($n = 1$), failed forceps ($n = 1$), and breech presentation ($n = 3$). There

was no significant difference regarding mode of delivery between the women who used NPH insulin versus insulin glargine ($p = 0.6$).

Pregnancy complications in the women using insulin glargine included preeclampsia ($n = 2$), preterm premature rupture of membranes (PPROM; $n = 1$), and intrauterine fetal demise ($n = 1$). The intrauterine fetal demise occurred at $20^4/_7$ weeks gestation in a patient with a history of venous sinus thrombosis who was being treated with heparin and baby aspirin. Pregnancy complications in the women using NPH insulin were similar and included preeclampsia ($n = 5$) and PPROM ($n = 2$).

Neonatal Outcomes

Average birth weights were not significantly different between patients treated with insulin glargine and those treated with NPH insulin (3294 ± 189 g and 3274 ± 137 g, respectively; $p = 0.93$). Additionally, there were no significant differences in the distribution of birth weights between the NPH insulin and insulin glargine groups (Table 3). There was only one 5-minute Apgar score < 7. Although data were limited (insulin glargine $n = 10$,
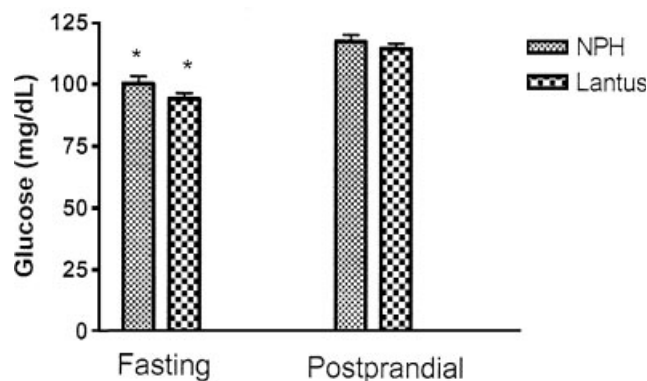
Figure 2 Fasting and postprandial blood glucose values in women who used insulin glargine and neutral protamine Hagedorn (NPH) insulin. Data are expressed as mean ± standard error of the mean. *$p < 0.05$ compared with postprandial blood glucose levels.

Table 2 Mode of Delivery

	NPH Insulin (n = 25)	Insulin glargine (n = 27)
Vaginal delivery	12 (48%)	10 (37%)
SVD	12	7
FAVD	0	2
VBAC	0	1
Cesarean delivery	13 (52%)	17 (62.9%)
Primary	7	9
Repeat	6	8

NPH, neutral protamine Hagedorn; SVD, spontaneous vaginal delivery; FAVD, forceps assisted delivery; VBAC, vaginal birth after cesarean.

NPH insulin $n = 2$), there was no significant difference between umbilical artery cord gas values ($p = 0.55$).

Neonatal blood sugars on admission to the NICU were 66.3 ± 3.2 mg/dL in infants of women treated with NPH insulin ($n = 20$) and 58.9 ± 3.8 mg/dL in infants of women treated with insulin glargine ($n = 23$; $p = 0.16$). Nadir neonatal blood sugars were not significantly different between groups (50.3 ± 2.8 mg/dL insulin glargine versus 51.4 ± 2.9 mg/dL NPH insulin, $p = 0.79$; see Table 3). Thirteen neonates were observed in the NICU for more than 4 hours after delivery, six from the NPH-treated group and seven from the glargine-treated group. Of these infants, three were observed for only 5 hours. None of the remaining infants were observed for blood glucose management alone.

Maternal and neonatal outcomes were also determined for the subgroup of patients for whom adequate blood sugar data were available, and there were no significant differences from the data presented above.

DISCUSSION

A pregnancy category class C drug, insulin glargine is an insulin analogue that was approved for clinical use in 2000. Compared with NPH insulin, insulin glargine use in nonpregnant diabetic patients is associated with lower fasting plasma glucose levels, lower hemoglobin A1C levels, and greater patient satisfaction.[5,16] Although insulin glargine appears superior to NPH insulin in nonpregnant patients, use of this insulin analogue during pregnancy has been limited.[6–14] These reports have suggested that insulin glargine use during pregnancy is effective in achieving adequate glycemic control. Although randomized, controlled trials have not been completed, there have been no adverse pregnancy outcomes reported to suggest than insulin glargine use during pregnancy is not safe.

This retrospective review comparing maternal and neonatal outcomes in pregnant women who used either insulin glargine or NPH insulin as the long-acting insulin analogue in their insulin regimen adds additional information to the growing literature regarding insulin glargine use in pregnancy. Although limited in numbers, prior animal and human studies have failed to demonstrate any adverse effects of insulin glargine use during the first trimester of pregnancy.[6,8–10,15] In this retrospective review, we report maternal and neonatal outcomes of an additional 13 women who were exposed to insulin glargine during the first trimester of pregnancy. Our study lacks sufficient power to definitively report that insulin glargine does not *cause* any adverse outcomes when used during pregnancy. However, we did not demonstrate any significant differences in either maternal or fetal/neonatal outcomes between women who were exposed to either insulin glargine or NPH insulin during their pregnancy. There were no congenital anomalies observed in the women who were exposed to insulin glargine during the first trimester.

Interestingly, almost half of the gestational diabetics described in this study were able to use a single daily injection of insulin glargine alone to control their diabetes. Therefore, a once-daily dosing regimen using insulin glargine may be appropriate for a large percentage of patients with gestational diabetes. This simplified insulin administration regimen may improve patient compliance and therefore decrease the incidence of complications associated with uncontrolled or poorly

Table 3 Neonatal Outcomes

	NPH (n = 25)	Insulin glargine (n = 27)
Gestational age at delivery (wk ± SEM)	37.0 ± 0.7	36.3 ± 1.0
Birth weight (g)		
< 2500	4	2
2500–4000	18	16
4000–4500	3	5
> 4500	0	1
5-min Apgar score < 7	0	1
Uterine artery pH < 7.20	3 ($n = 10$)	0 ($n = 3$)
Infants staying in NICU for > 4 h (n)	6	7
Neonatal blood sugar on admission (mg/dL)	66.3 ± 3.2	58.9 ± 3.8
Nadir neonatal blood sugar (mg/dL)	51.4 ± 2.9	50.3 ± 2.8

NPH, neutral protamine Hagedorn; SEM, standard error of the mean; NICU, neonatal intensive care unit.

controlled gestational diabetes during the third trimester of pregnancy.

Based on existing literature, two major concerns exist regarding insulin glargine use during pregnancy. The first is the concern that insulin glargine may exhibit mitogenic properties. This concern is based on in vitro receptor binding studies that demonstrated that insulin glargine exhibited an increased binding affinity for the insulin-like growth factor (IGF)-1 receptor compared with human insulin.[17] In addition, initial in vitro studies also demonstrated that insulin glargine exhibited an eightfold increased potency for stimulating DNA synthesis in human osteosarcoma cells.[17] Further studies in human diabetic muscle and several cell lines overexpressing the IGF-1 receptor have failed to demonstrate an increase in the mitogenicity of insulin glargine.[18–20] In addition, in vivo studies in rats and mice receiving between 2 and 12.5 IU/kg of insulin glargine failed to show an increase in tumor formation after prolonged exposure.[21] Perhaps most importantly, despite widespread use in the adult diabetic population, there have been no reports of adverse effects in non-pregnant humans.

Given the increased affinity for the IGF-1 receptor, another concern regarding insulin glargine use during pregnancy is the reported association between elevated serum IGF-1 levels and progression of diabetic retinopathy in pregnant patients.[22] However, a recent study by Loukovaara et al[23] failed to confirm these findings. In fact, they reported that there was no correlation between progression of diabetic retinopathy and systemic levels of IGF-1 and IGF binding proteins. Similar concerns regarding progression of retinopathy were raised after the introduction of insulin lispro use during pregnancy.[24] Although an adequately powered prospective randomized controlled study has not been performed to definitively address this concern, subsequent reports have failed to demonstrate an increased risk of retinopathy with insulin lispro use in pregnancy.[25–27] The incidence or progression of retinopathy was not specifically addressed in this retrospective review. Prospective, randomized controlled trials are necessary to further address the incidence and progression of diabetic retinopathy as well as incidence of macrosomia in association with various insulin analogues during pregnancy. To achieve adequate power, these studies will need between 100 to 300 patients per treatment arm.[25]

Although this study presents important information regarding insulin glargine use during pregnancy, it is limited by its retrospective nature. Blood sugar records and hemoglobin A1C data were limited. Unfortunately, blood sugar records were too limited to comment on the incidence of nighttime hypoglycemia in patients treated with insulin glargine versus NPH insulin. As this is one benefit of insulin glargine in nonpregnant patients, future studies need to be performed to investigate whether insulin glargine use also decreases the frequency of nighttime hypoglycemia in pregnant patients as this can be an especially difficult problem during pregnancy given the stringent recommendations for glycemic control. Devlin et al have published a case report detailing the use of insulin glargine specifically for a patient who had been plagued by nighttime hypoglycemia with excellent blood glucose control and resolution of hypoglycemia.[11]

From this study, one can conclude that the level of glycemic control achieved during pregnancy with insulin glargine is comparable to that achieved with NPH insulin. In addition, maternal and fetal/neonatal outcomes appear to be similar whether a pregnant diabetic patient uses NPH insulin or insulin glargine as the long-acting insulin analogue in their regimen. A single daily dose of insulin glargine may be effective for management of gestational diabetes. Large prospective, randomized studies are needed to confirm the safety and efficacy of insulin glargine during pregnancies complicated by both pregestational and gestational diabetes.

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