Comparing the efficacy and safety of insulin detemir versus neutral protamine hagedorn insulin in treatment of diabetes during pregnancy: a randomized, controlled study

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ABSTRACT

Objective To compare the efficacy and safety of insulin detemir (IDet) versus neutral protamine Hagedorn (NPH) insulin used in pregnant women with diabetes.

Research design and methods A randomized study was conducted in diabetic pregnant women (n=240) (including 132 with pregestational diabetes and 108 with gestational diabetes). All patients were randomly divided into two groups: IDet group (n=120) treated with IDet plus short acting insulin Novolin-R before three meals (RRR–IDet plan), and NPH group treated with NPH plus Novolin-R before three meals (RRR–NPH plan). Patients were enrolled during 12–28 gestation weeks and followed up until delivery.

Results Basal characteristics, such as age, enrollment gestational weeks, average HbA1c, fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) were similar between two groups. After 1 week of treatment, the FPG of IDet group were significantly lower than NPH group (p<0.05) and the time required to reach the targeted blood glucose level was significantly shorter (p<0.001). After 3 months of treatment, the HbA1c level in the two groups was normalized but there was no significant difference in HbA1c level. Maternal and neonatal outcomes were comparable between the two therapeutic approaches; however, the incidence of hypoglycemia in IDet group was remarkably lower than that of NPH group (p<0.05). The adverse drug reactions were rare and similar between the two groups.

Conclusions For the treatment of gestational diabetes, both RRR–IDet plan and RRR–NPH plan were reported to control blood glucose effectively. Compared with NPH, IDet could control blood glucose and reached the targets faster and more effectively, thus reducing the number of insulin injections and the incidence of hypoglycemia in pregnant women without increasing adverse birth outcomes.

INTRODUCTION

The prevalence of gestational diabetes (GDM) and prepregnant diabetes mellitus (PGDM) is increasing year by year, especially for GDM.2 In 2017, there were 21.3 million pregnant women who experienced hyperglycemia, of which 86.4% of them were diagnosed with GDM.3 In China, a total of 2.90 million pregnant women suffered from GDM in 2015.4 The maternal hyperglycemia not only increases short and long-term adverse effects on mothers, but it is also associated with a higher risk of developing neonatal complications and diseases in their later life.5 Hence, for pregnant women with diabetes whose blood glucose cannot be
controlled through the combination of diet and exercise after 1–2 weeks, insulin is strongly recommended.\textsuperscript{6} Generally, short-acting and ultra-short-acting insulin are prescribed during pregnancy and no long-acting insulin or insulin analogs are preferred clinically. The classic insulin treatment plan is an ultrashort-acting insulin injection immediately before three meals or a short-acting insulin half an hour before three meals (RRR Plan). However, insulin treatment during pregnancy should try to mimic physiology of basal insulin secretion and increased insulin secretion after meals. Therefore, a basal insulin is needed. Neutral protamine Hagedorn (NPH), as a commonly used intermediate-acting basal insulin (before bed and morning), has some issues in clinical applications, such as large absorption variation, short duration of action, significant peak effect, high risk of hypoglycemia, frequent injections, and complicated injection operations.\textsuperscript{7}

In recent years, insulin analogs have overcome the limitations of human insulin and are used widely in the management and control of diabetes.\textsuperscript{8} Insulin detemir (IDet) is a long-acting human insulin analog which is newly developed in recent years. In addition to its use in gestational diabetes, IDet improves glycemic control, and is associated with lower rates of hypoglycemia than human insulin.\textsuperscript{9,10} In 2012, the US Food and Drug Administration (FDA) and China FDA approved the insulin detemir to treat hyperglycemia during pregnancy. Compared with NPH, the effect of IDet is much closer to physiologic basal insulin secretion with a longer duration and flatter mode (no peaks) of action. However, few studies of observing the safety and efficiency of IDet in Chinese pregnant women with diabetes are reported in the literature. With an increasing incidence of gestational diabetes, the safety and efficiency of IDet during pregnancy is needed to be further studied. Therefore, this study aimed to compare the efficiency and safety between IDet combined with short-acting Novoline R and NPH in combination with Novoline R in pregnant women with diabetes.

**RESEARCH DESIGN AND METHODS**

**Study design**

This randomized study was conducted between January 1st 2014 and December 31st 2015 in the Northwest Women and Children’s Hospital (NWCH). This study randomized 240 patients with diabetes developed during pregnancy, including GDM (n=108) and PGDM (n=132). All patients were enrolled at gestational age of 12–28 weeks and received health education regarding the fundamental knowledge of gestational diabetes, nutrition and exercise in a 1-day obstetric diabetes clinic. After 1 week of blood glucose monitoring, all patients were evaluated and those who still needed basic-prandial intensive insulin therapy were included. The inclusion criteria were as follows: (1) age ≥18 years; (2) singleton and (3) for GDM patients, the fasting plasma glucose (FPG), 30 min before meals and random blood glucose at night were >5.3 mmol/L with blood glucose of 2 hours after meals >6.7 mmol/L; for PGDM patients, the cut-offs of blood glucose were >5.6 mmol/L and >7.1 mmol/L, respectively. Patients with severe heart, liver and kidney disease or any forms of assisted reproduction were excluded. After screening, we assign subjects random numbers on the basis of patient ID, then eligible patients were randomized to either IDet (n=120) or NPH insulin groups (n=120). IDet group was treated with IDet plus short-acting insulin Novolin-R before three meals (RRR-Det plan), and NPH group was treated with NPH plus Novolin-R before three meals (RRR-NPH plan). All basal insulin doses were titrated according to FPG or prandial blood glucose values. Insulin Novolin-R doses were titrated according to prandial and postprandial blood glucose values. Insulin dose and weight gain during the pregnancy were also calculated.

**Endpoints**

The primary endpoint was FPG, prandial and postprandial blood glucose concentrations after 1 week of treatment. Secondary endpoints included HbA1c, FPG, prandial and postprandial blood glucose after 3 months of treatment. All insulin doses were adjusted, in accordance with recommendations of the Chinese Guidelines for Diagnosis and Treatment of Pregnancy with Diabetes 2014\textsuperscript{11} and were listed as follows: for GDM patients, the FPG and prandial blood glucose targets were 3.5–5.3 mmol/L, and a 2-hour postprandial blood glucose target was 4.4–6.7 mmol/L; while for PGDM patients, the FPG and prandial blood glucose targets were 3.5–5.6 mmol/L, and a 2-hour postprandial blood glucose target was 3.6–7.1 mmol/L, respectively. Hypoglycemia was diagnosed when the blood glucose was below the lower limit of target value of each level with or without symptoms of hypoglycemia. Maternal safety endpoints included gestational week, cesarean section, hypoglycemia, gestational hypertension, infection, polyhydramnios and adverse events.\textsuperscript{12} Other maternal endpoints included weight gain during the pregnancy and insulin dose. Neonatal safety endpoints included malformation, prematurity birth, hypoglycemia, hyperbilirubinemia, low birth weight and macrosomia.

**Statistics**

The sample size was calculated based on the assumption that IDet was non-inferior to NPH insulin by more than a prespecified FPG margin of 0.5%. Totally, 120 patients in each group would be needed for 80% power at the 5% level of significance. All statistical analyses were performed using SPSS V.23.0 and STATA V.12.0. Data were presented as means±SD for continuous variables and as percentages for categorical variables. Two-tail unpaired Student’s t-tests were used when applicable to compare the pairs of means or longitudinal values. \(\chi^2\) was performed to compare percentages. Otherwise, the rank sum test was used. P value<0.05 was considered significant.
RESULTS

Table 1 shows the demographics and basal glucose of patients in both the IDet and NPH groups. The main demographics at baseline, such as age, body mass index (BMI), family history of diabetes and gestational age at recruitment were similar between both groups. The blood glucose and HbA1c levels before treatment were also similar between both groups.

Efficiency

After 7 days of treatment, both the treatments decreased the blood glucose levels while the FPG (5.33±0.72 vs 5.71±0.87 mmol/L, respectively; P<0.001), 30 min preprandial blood glucose (5.26±0.70 vs 5.70±0.73 mmol/L, respectively; P<0.001) and 2-hour postprandial blood glucose (6.73±0.79 vs 7.38±0.80 mmol/L, respectively; P<0.001) were much lower in the IDet group than those in the NPH group. In addition, the declines of the three glycemic indicators mentioned above were more significant in the IDet group than in those in the NPH group. In addition, the declines of the three glycemic indicators mentioned above were more significant in the IDet group than in those in the NPH group (all P<0.05) (table 2). After 3 months of treatment, there were no significant between-group differences in the levels of HbA1c (5.66%±0.83% vs 5.80%±0.81%; P=0.191) and within-group differences between HbA1c before and after treatment in the two groups (0.77%±1.53% vs 0.68%±1.08%; P=0.740). Within this period of treatment, we also found that the days of FPG and preprandial blood glucose to reach the targeted cut-offs (4.96±3.20 vs 7.06±2.94 days; P<0.001) and days of blood glucose reaching the targeted cut-offs throughout all day (6.94±3.99 vs 10.82±2.63 days; P<0.001) in the IDet group were less than those in the NPH group (table 3).

The average needs of IDet (12.32±5.05 vs 9.10±5.93 u/day; P<0.001) and the total insulin dose (47.89±18.94 vs 42.21±17.14 u/day; P=0.016) in the IDet group were higher than those in the NPH group, but the frequency of insulin injections in the IDet group was less than that in the NPH group (3.74±0.78 vs 4.15±0.36 t/day; P<0.001).

Safety

Table 5 shows the maternal safety endpoints between IDet and NPH group. As presented, there was no difference in the incidence of pregnancy outcomes, including gestational age, cesarean section, hypertension during pregnancy, polyhydramnios and infection between both groups (P>0.05). There was also no difference in weight gain during pregnancy between both groups (12.21 kg in...
The introduction of long-acting insulin analogues, such as insulin glargine and IDet, into clinical practice, their safety and effectiveness are urgently needed to be proven. However, there is a lack of convincing evidence in this area. The largest randomized study evaluating the efficacy and safety of IDet in pregnancy versus NPH, both with prandial insulin aspart, was conducted in 310 women with Type 1 Diabetes Mellitus (T1DM) and concluded that IDet was non-inferior to NPH in type 1 diabetes pregnant women. As for Type 2 Diabetes Mellitus (T2DM), the current evidence for the use of IDet is scarce. A retrospective cohort study of 91 women with GDM who were treated with either glyburide (n=62) or IDet (29) showed that IDet had a better outcomes. Recently, a randomized trial recruited both GDM patients and pregnant women with T2DM to observe the efficacy and safety of IDet. The findings suggested that the efficacy of IDet in glycemic control was similar with NPH and hypoglycemic events were significantly lower when the short-acting insulin aspart was added. Consistently, our study showed that IDet was at least as effective as NPH in a long term of treatment when used as a basal insulin in pregnant women with diabetes. However, in the early period of treatment, IDet had a better performance than NPH in terms of controlling blood glucose. Probably, a larger sample size in our study may contribute to reveal differences of IDet and NPH in controlling blood glucose in early treatment than the study mentioned above. Although the total dose of IDet was higher than NPH because of less affinity of IDet than insulin NPH for the insulin receptor, our data revealed that IDet group had fewer injections than NPH group. This may be due to the unique hexameric form of IDet and its reversible combination with plasma albumin, which significantly prolonged the action time in patients. Moreover, IDet group also had a shorter length of stay in the hospital and reduced economic cost. Taken together, these improvements made the patients feel more satisfied and compliant when given a hypoglycemic therapy with IDet.

**Table 3** Comparison of the efficiency between the IDet and NPH groups after 3 months of treatment (means ±SD)

| Variable | IDet       | NPH        | T/Z       | P value |
|----------|------------|------------|-----------|---------|
| HbA1c (%) | 5.66±0.83  | 5.80±0.81  | 1.313     | 0.191   |
| Difference of HbA1c (%) | 0.77±1.53  | 0.68±1.08  | 0.331     | 0.740   |
| Days of FPG and prandrial blood glucose reaching the target (day) | 4.96±3.20  | 7.06±2.94  | 5.294    | <0.001  |
| Days of blood glucose reaching the target throughout all day (day) | 6.94±3.99  | 10.82±2.63 | 8.883    | <0.001  |

FPG, fasting plasma glucose; IDet, insulin detemir; NPH, neutral protamine Hagedorn.

Our study recorded the adverse drug reactions and incidence of hypoglycemia in both groups. As shown in Table 3, the incidence of hypoglycemia was significantly lower in the IDet group than that in the NPH group (P=0.017). In the IDet group, only 14 patients (11.67%) had ≥1 hypoglycemia event during the treatment period, which often occurred between 11:00 and 12:00 before lunch without nocturnal hypoglycemia; NPH group had 28 patients (23.33%) had ≥1 hypoglycemic event, among which eight events occurred between 02:00 and 03:00, seven occurred before breakfast, 13 occurred before lunch, and one patient had frequent hypoglycemia. There was no difference in the incidence of adverse drug reactions, such as local swelling and itching between both groups (P=0.652).

**DISCUSSION**

In China, both patients and obstetricians are worried about the safety of insulin, especially the use of long-acting insulin during pregnancy. Our study investigated the efficacy and safety of IDet versus NPH in treatment of gestational diabetes in order to provide evidence for the management of diabetes with IDet during pregnancy. Compared with NPH, our study found that: (1) IDet had a more obvious hypoglycemic effect, FPG compliance and fewer injections; and (2) IDet significantly reduced the incidence of hypoglycemia without increasing the incidence of adverse pregnancy outcomes and drug reactions.

NPH is one of the most commonly used intermediate-acting insulin in the clinics. Before the safety of long-acting insulin is confirmed, NPH was often recommended as a basal insulin for pregnant women with diabetes. With the introduction of long-acting insulin analogues, such as insulin glargine and IDet into clinical practice, their safety and effectiveness are urgently needed to be proven. However, there is a lack of convincing evidence in this area. The largest randomized study evaluating the efficacy and safety of IDet in pregnancy versus NPH, both with prandial insulin aspart, was conducted in 310 women with Type 1 Diabetes Mellitus (T1DM) and concluded that IDet was non-inferior to NPH in type 1 diabetes pregnant women. As for Type 2 Diabetes Mellitus (T2DM), the current evidence for the use of IDet is scarce. A retrospective cohort study of 91 women with GDM who were treated with either glyburide (n=62) or IDet (29) showed that IDet had a better outcomes. Recently, a randomized trial recruited both GDM patients and pregnant women with T2DM to observe the efficacy and safety of IDet. The findings suggested that the efficacy of IDet in glycemic control was similar with NPH and hypoglycemic events were significantly lower when the short-acting insulin aspart was added. Consistently, our study showed that IDet was at least as effective as NPH in a long term of treatment when used as a basal insulin in pregnant women with diabetes. However, in the early period of treatment, IDet had a better performance than NPH in terms of controlling blood glucose. Probably, a larger sample size in our study may contribute to reveal differences of IDet and NPH in controlling blood glucose in early treatment than the study mentioned above. Although the total dose of IDet was higher than NPH because of less affinity of IDet than insulin NPH for the insulin receptor, our data revealed that IDet group had fewer injections than NPH group. This may be due to the unique hexameric form of IDet and its reversible combination with plasma albumin, which significantly prolonged the action time in patients. Moreover, IDet group also had a shorter length of stay in the hospital and reduced economic cost. Taken together, these improvements made the patients feel more satisfied and compliant when given a hypoglycemic therapy with IDet.

**Table 4** Comparison of insulin need in IDet and NPH group (means±SD)

| Variable | IDet       | NPH        | T/Z       | P value |
|----------|------------|------------|-----------|---------|
| Dose (u/day) | 12.32±5.05 | 9.10±5.93  | 4.523     | <0.001  |
| Novolin-R (u/day) | 35.57±16.27 | 33.11±14.23 | 1.242     | 0.216   |
| Insulin (u/day) | 47.89±18.94 | 42.21±17.14 | 2.430     | 0.016   |
| Frequency (t/day) | 3.74±0.78  | 4.15±0.36  | 5.65      | <0.001  |

IDet, insulin detemir; NPH, neutral protamine Hagedorn.
We also compared the pregnancy outcomes between both groups. In general, the incidence of adverse pregnancy outcomes for both the mothers and newborns were comparable between two groups, which suggested that IDet was as good as NPH in the aspect of safety. Our results were consistent with the findings reported by previous studies. The incidence of gestational hypertension was also lower in IDet group compared with NPH (11.67% vs 19.17%), although the between-group difference did not reach statistical significance. In addition, the drug reactions were similar in both groups except for hypoglycemia occurrence. The results showed that only 11.67% of patients in the IDet group had ≥1 hypoglycemia event during the treatment which occurred between 11:00 and 12:00 whereas the incidence of hypoglycemia was much higher in NPH group with eight nocturnal hypoglycemia and one frequent hypoglycemia. Notably, there was no nocturnal hypoglycemia in the IDet group and hypoglycemia in all patients happened before lunch, when the patients were able to treat themselves and no severe cases were reported. However, in the NPH group, hypoglycemia occurred at night and day and was irregular. Patients could not predict the occurrence of hypoglycemia, especially nocturnal hypoglycemia which threatens the safety of the fetus. This can also explain why NPH group reached the ambitious targeted blood glucose slower since more cautious procedures were needed in adjusting (ie, increasing and decreasing) insulin doses used. Meanwhile, we also assessed neonatal hypoglycemia. It is well recognized that hypoglycemia occurs more frequently during pregnancy when given the intensive insulin treatment. Hence, one of the major concerns is to reduce the rate of hypoglycemia when patients are treated with insulin or insulin analogs. Similar to other insulin preparations, insulin detemir does not cross the human placenta at therapeutic doses. Our data demonstrated that the rate of neonatal hypoglycemia was not significantly lower with IDet compared with NPH group, but it was noted that fewer newborns experienced such an event in IDet group than NPH groups (4.17% vs 8.33%, respectively). These data suggested that IDet can be safely prescribed to women with diabetes during pregnancy.

High blood sugar can increase the risk of fetal malformations. Serious adverse outcomes (perinatal death and/or congenital malformations) were associated with higher HbA1c levels before and during pregnancy. Furthermore, even small elevations in HbA1c in pregnant women with diabetes have been associated with significantly increased rates of congenital malformations. In this study, although there was no increased risk of malformations in both groups, it was worth noting that a total of six congenital malformations occurred in the newborns of both groups of patients and the total incidence of congenital malformations was 250 per 10 000, which was remarkable higher than that in 2011 (153.23 per 10 000). Some studies suggested that if the embryo is subjected to the effects of the hyperglycemia environment before and after embryo implantation, the cell’s own apoptotic program is prone to start, leading to multiple organ deformities. Therefore, even if

| Table 5 | Maternal and neonatal pregnancy outcomes in the two groups |
|---------|---------------------------------------------------------|
|         | IDet          | NPH          | T/χ² | P value |
| Maternal pregnancy outcomes | | | | |
| Gestational age at delivery (weeks | 38.64±2.19 | 38.15±3.05 | 1.418 | 0.157 |
| Cesarean section, n (%) | 78 (65.00) | 74 (61.67) | 0.287 | 0.592 |
| Gestational weight gain (kg | 12.21±3.84 | 11.99±4.11 | 0.618 | 0.662 |
| Hypertension during pregnancy, n (%) | 14 (11.67) | 23 (19.17) | 2.588 | 0.107 |
| Polyhydramnios, n (%) | 10 (8.33) | 8 (6.67) | 0.240 | 0.624 |
| Infection, n (%) | 15 (12.50) | 18 (15.00) | 0.316 | 0.574 |
| Hypoglycemia in pregnant women, n (%) | 14 (11.67) | 28 (23.33) | 5.657 | 0.017 |
| Adverse drug reactions, n (%) | 3 (2.5) | 2 (1.67) | 0.203 | 0.652 |
| Neonatal pregnancy outcomes | | | | |
| Congenital anomaly, n (%) | 3 (2.50) | 3 (2.50) | 0.000 | 1.000 |
| Preterm delivery, n (%) | 15 (12.50) | 18 (15.00) | 0.316 | 0.574 |
| Birth weight (g) | 3257.67±496.60 | 3179.75±671.81 | 1.022 | 0.308 |
| Low birth weight, n (%) | 5 (4.17) | 8 (6.67) | 0.732 | 0.392 |
| Macrosomia, n (%) | 10 (8.33) | 10 (8.33) | 0.000 | 1.000 |
| Hyperbilirubinemia, n (%) | 51 (42.50) | 56 (46.67) | 0.422 | 0.516 |
| NRDS, n (%) | 3 (2.50) | 3 (2.50) | 0.000 | 1.000 |
| Neonatal hypoglycemia, n (%) | 5 (4.17) | 10 (8.33) | 1.778 | 0.182 |
| NICU admission, n (%) | 35 (29.17) | 38 (31.67) | 0.177 | 0.674 |

IDet, insulin detemir; NICU, Neonatal intensive care unit; NPH, neutral protamine Hagedorn; NRDS, Neonatal respiratory distress syndrome.
the blood glucose reaches the targets, the rate of congenital malformations may not be significantly reduced. This suggested that the management of blood glucose before pregnancy or at early pregnancy may be more worthy of attention. Pregnant women who are at high risk of developing diabetes need to monitor blood sugar as early as possible in order to reduce the incidence of congenital malformations.

In conclusion, the use of both long-acting insulin IDet combined with short-acting insulin and NPH combined with short-acting insulin was shown to effectively control blood glucose levels in pregnancy with diabetes. IDet was much faster and more effective in controlling blood glucose with fewer injections. Furthermore, considering a lower risk of hypoglycemia and no increase in adverse pregnancy outcomes, insulin detemir is worthy of clinical promotion as an ideal basal insulin in pregnancy with diabetes. But considering the numbers of the adverse effects were small, more researches with larger sample size are needed to state that there is no difference in safety between the two treatments.

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Patient consent for publication Not required.

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