Use of Insulin Lispro Protamine Suspension in Pregnancy

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ABSTRACT

Maternal metabolism changes substantially during pregnancy, which poses numerous challenges to physicians managing pregnancy in women with diabetes. Insulin is the agent of choice for glycemic control in pregnant women with diabetes, and the insulin analogs are particularly interesting for use in pregnancy. These agents may reduce the risk of hypoglycemia and promote a more physiological glycemic profile than regular human insulin in pregnant women with type 1 (T1D), type 2 (T2D), or gestational (GDM) diabetes. However, there have been concerns regarding potential risk for crossing the placental barrier, mitogenic stimulation, teratogenicity, and embryotoxicity. Insulin lispro protamine suspension (ILPS), an intermediate- to long-acting insulin, has a stable and predictable pharmacological profile, and appears to have a favorable time–action profile and produce desirable basal and postprandial glycemic control. As the binding of insulin lispro is unaffected by the protamine molecule, ILPS is likely to have the same mitogenic and immunogenic potential as insulin lispro. Insulin lispro produces similar outcomes to regular insulin in pregnant women with T1D, T2D, or GDM, does not cross the placental barrier, and is considered a useful treatment option for pregnant women with diabetes. Clinical data support the usefulness of ILPS for basal insulin coverage in non-pregnant patients with T1D or T2D, and suggest that the optimal regimen, in terms of balance between efficacy and hypoglycemic risk, is a once-daily injection, especially in patients with T2D. Available data concerning use of ILPS in pregnant women are currently derived from retrospective analyses that...
involved, in total, >1200 pregnant women. These analyses suggest that ILPS is at least as safe and effective as neutral protamine Hagedorn insulin. Thus, available experimental and clinical data suggest that ILPS once daily is a safe and effective option for the management of diabetes in pregnant women.

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**Keywords:** Fetal outcome; Gestational diabetes; Insulin lispro protamine suspension; Maternal outcome; Pregestational diabetes; Pregnancy

**INTRODUCTION**

The prevalence of diabetes is increasing globally [1, 2], as are the incidences of pre-existing and gestational diabetes (GDM) in pregnant women [3]. Since the prevalence of diabetes (both types 1 and 2) in children and adolescents is also increasing [4], it is likely that we will continue to see increases in the incidence of pregnancy complicated by diabetes.

Women with pre-existing type 1 diabetes (T1D) or type 2 diabetes (T2D) have increased risk of several maternal and fetal adverse outcomes during pregnancy [5–13]. In this context, increased glucose levels play an important role in the pathogenesis of congenital malformations and perinatal complications, and there is an association between poor glycemic control in the periconceptional period and increased risk of maternal and fetal anomalies [5, 9, 14–16].

It is therefore recommended that glycemic targets for pregnant women with diabetes be as close as possible to the normal range [10, 17, 18], taking into account the physiological decreases in glucose and glycated hemoglobin (HbA1c) levels that occur during pregnancy in non-diabetic women [19]. Very good glycemic control should thus be achieved, while avoiding hypoglycemic episodes [20] and ensuring that fetal growth is not compromised [21–23].

This review provides an overview of the insulins available for treating pregnant women with diabetes, with an emphasis on insulin analogs in general and on insulin lispro protamine suspension (ILPS), an intermediate-to long-acting insulin, in particular. ILPS could be utilized for control of hyperglycemia during pregnancy. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

**PHYSIOLOGICAL CHANGES DURING NORMAL AND DIABETIC PREGNANCY**

Briefly, maternal metabolism changes substantially during pregnancy [24, 25]. These changes occur to allow the efficient storage of nutrients during feeding and the rapid use of stored nutrients, with minimal catabolism of maternal protein, during fasting [26].

Early gestation is characterized by an increase in maternal fat stores and small increases in insulin sensitivity, to provide stored nutrients to meet the feto-placental and maternal demands of late gestation and lactation. Late pregnancy is characterized by markedly reduced insulin sensitivity and increased beta-cell responses, which lead to increases in maternal plasma glucose and free fatty acid levels, thereby allowing for greater availability of nutrients for fetal growth [25, 27].

When considering HbA1c monitoring, comparison of relevant data collected at Italian Diabetic Care Units from 445 non-diabetic pregnant women between weeks
15 and 36 of pregnancy and from 384 non-diabetic non-pregnant women showed that HbA1c reference intervals were lower during pregnancy (4.0–5.5% versus 4.8–6.2%; median, 4.8% versus 5.6%, \( P < 0.001 \)) [19]. HbA1c levels were also slightly higher during weeks 28–36 of pregnancy than during weeks 25–27 (\( P < 0.002 \)) and weeks 15–24 (\( P < 0.001 \)) [19]. However, HbA1c levels have shown poor correlation with mean, fasting, premeal, and postmeal blood glucose values, with the incidence of macrosomia and, in women with GDM, with pregnancy outcomes [28]. This suggests that the metabolic monitoring of pregnant women with diabetes should include not only HbA1c levels, but also daily glucose level monitoring, to capture glycemic peaks and glucose variability.

In addition to the changes characteristic of pregnant women without diabetes, women with GDM have an imbalance between tissue insulin requirements for glucose regulation and the ability of pancreatic beta cells to meet those requirements [24, 25]. These patients also show hepatic insulin resistance and defects in insulin signaling [24, 25]. Impaired insulin sensitivity during early pregnancy is a predictor of GDM, whereas impaired beta-cell function is only evident when GDM has developed [29].

As pregnant women with T1D have a complete absence of endogenous insulin, the proper balance of accelerated starvation and facilitated anabolism, which is characteristic of pregnancy, must be achieved by therapeutic intervention [26]. This underlies the difficulty in maintaining glucose levels in the normal range and managing the resultant large daily blood glucose excursions that occur in pregnant women with T1D. These patients are also more susceptible to developing ketoacidosis if insulin is not appropriately administered, because lipolysis and ketogenesis progress without the compensatory effect of insulin for control [26]. Importantly, lipid and lipoprotein abnormalities are observed in pregnant women with T1D and poor glycemic control (but not in those with good glycemic control) and in their newborns with fetal macrosomia [30].

In pregnant women with T2D, pre-existing insulin resistance is exacerbated by pregnancy-related decreases in insulin sensitivity, so most patients who are diet-treated at the time of conception require insulin therapy early in pregnancy [26].

**INSULINS AVAILABLE FOR USE IN PREGNANCY**

Insulin is the treatment of choice for any type of diabetes during pregnancy [10, 31]. In this context, the optimization of insulin therapy is critical to ensure (near-)normal glycemic control without the occurrence of hypoglycemia and with appropriate weight gain [31]. The physiological changes in glucose metabolism that occur in pregnant women increase demand for rapid-acting insulin postprandially and require that doses of intermediate- or long-acting insulins be adjusted throughout each trimester of pregnancy, to ensure constant and appropriate basal insulin levels [31].

Insulins available for use during pregnancy are shown in Table 1. The time–action profiles of the insulin analogs make these agents particularly interesting for use in pregnancy. These insulin preparations will therefore be the focus of this section.

In general, insulin analogs may reduce the risk of hypoglycemia and promote a more physiological glycemic profile than regular human insulin in pregnant women with T1D, T2D, or GDM [34]. However, there are a number of potential concerns associated with the use of...
these agents during pregnancy. These concerns include: the risk of anti-insulin antibody development, which allows insulin to cross the placental barrier [35]; affinity for the insulin-like growth factor-1 (IGF-1) receptor and the consequent risk of mitogenic stimulation; and the potential risk of teratogenicity and embryotoxicity (see later text).

### Rapid-Acting Insulin Analogs

The rapid-acting insulin analogs (RAIAs), insulin lispro and insulin aspart, reduce postprandial hyperglycemia more effectively than regular human insulin and both are approved for use in pregnancy by the European Medicines Agency [36, 37]. No
clinical trials involving use of insulin glulisine in pregnant patients have been published [38] and, for this reason, its use in this population is not usually advised.

Although data from randomized controlled trials (RCTs) are limited, experience with insulin lispro and insulin aspart has generally indicated that these RAIAs produce similar outcomes to regular human insulin in pregnant women with T1D, T2D, or GDM [34, 39–42]. These latter findings have led to the conclusion that there is no evidence of an adverse effect of these insulins on pregnancy or on the health of the fetus/newborn [34, 36, 37, 41, 43, 44].

**Potential Immunogenicity**

The immunogenicity of RAIAs has not been well investigated. However, insulin lispro elicited similar levels of antibody formation to regular human insulin in 42 women with GDM [45] and the potential for antibody formation with insulin aspart and regular human insulin is similar in women with T1D or T2D [46]. Insulin lispro does not cross the placental barrier [45, 47]; no published data concerning the possible placental transfer of insulin aspart or insulin glulisine have been identified.

**Mitogenic Potential**

In vitro findings suggest that the mitogenic potential of insulin lispro and insulin aspart is similar to that of human insulin [48, 49], but that insulin glulisine may differ in this regard, inducing significantly greater proliferation than human insulin in IGF-1 receptor-expressing cells ($P < 0.05$) [49].

**Long-Acting Insulin Analogs**

The long-acting insulin analogs (LAIAs) have potential benefits in the management of pregnancy in women with T1D because of their ability to mitigate the risk of nocturnal hypoglycemia and to provide and maintain the stringent glycemic targets needed in this population. A number of studies have shown that insulin glargine and insulin detemir are safe and promote good glycemic control during pregnancy [34, 44, 50–52], and both can be considered for use in pregnant women (Table 1) [53, 54]. There is currently no clinical experience with insulin degludec in pregnant women, although animal studies have not revealed any embryotoxicity or teratogenicity differences between insulin degludec and regular human insulin [55].

A meta-analysis of clinical studies comparing maternal and fetal outcomes in a total of 702 women with pregestational diabetes or GDM receiving either insulin glargine (N = 331) or neutral protamine Hagedorn (NPH) insulin (isophane insulin; N = 371) found no significant differences in glycemic control or safety-related outcomes between the two insulins during pregnancy [56]. However, there was considerable heterogeneity among the eight studies included in the meta-analysis. No specific malformative or feto-neonatal toxicity has been observed with insulin glargine [53].

Similarly, post-marketing data indicate no adverse effects of insulin detemir on pregnancy, nor any malformative or feto-neonatal toxicity [54]. In an RCT involving 310 pregnant women with T1D, treatment with insulin detemir resulted in lower fasting plasma glucose levels than, and non-inferior HbA1c to, NPH insulin in late pregnancy. Rates of hypoglycemia were similar with the two insulins. However, there was a non-significantly higher frequency of serious maternal adverse events with insulin detemir compared with NPH insulin (40% versus 31%), although only 8–12% of these events were considered by the investigators to be possibly or probably related to
investigational drugs [57]. Therefore, it was concluded that there were no concerns regarding the tolerability of either insulin. A subsequent analysis of this study comparing perinatal outcomes has shown that insulin detemir was as well tolerated as NPH insulin in terms of fetal and perinatal morbidity and mortality, and was without any specific safety concerns [58].

**Potential Immunogenicity**

We were unable to identify any data relating to the immunogenicity of LAIAs. However, an in vitro analysis using human placenta from uncomplicated pregnancies found that insulin glargine does not cross the placental barrier, except at concentrations higher than those that are likely to be seen clinically [59].

**Mitogenic Potential**

There are concerns regarding the affinity of LAIAs for the IGF-1 receptor and the consequent risk of mitogenic stimulation. However, the effects of insulin glargine and insulin detemir are not consistent across in vitro studies. In one study, both LAIAs had a lower affinity for the insulin receptor and a higher affinity for the IGF-1 receptor than human insulin [49]. In another study, the affinities of insulin glargine and insulin detemir for these receptors were concentration-dependent [48]. Overall, compared with human insulin, insulin glargine had similar or greater affinity for both the insulin and IGF-1 receptors [48, 60], whereas insulin detemir had similar or lower affinity for both receptors [48].

Insulin glargine has two main active metabolites, M1 and M2 [60]. The M1 metabolite is the main compound detected in plasma after administration and is responsible for the metabolic activity of insulin glargine in patients with T1D [61] and T2D [62]. In an in vitro study, the binding affinity of M1 and M2 to insulin receptors was similar to that of the parent compound, but they had lower affinity than insulin glargine for IGF-1 receptors in cells expressing these receptors [60]. The affinity of these metabolites for IGF-1 receptors was similar to that of human insulin in cells expressing these receptors, and their mitogenicity was similar to that of human insulin in human osteosarcoma Saos-2 cells [60].

Although these in vitro findings suggest an increased mitogenic potential of LAIAs as compared with human insulin and RAIAs [49], data are not conclusive, particularly with respect to insulin glargine, as its main active metabolite, M1, has low affinity for IGF-1 receptors [60]. Additionally, available clinical data do not show differences in the rate of mitogenic changes between patients with diabetes treated with insulin glargine and those receiving regular human insulin [44] and results of the ORIGIN trial (ClinicalTrials.gov identifier, NCT00069784) do not support mitogenic potential with insulin glargine [63]. In this latter trial, after a mean of 6.2 years of follow-up, patients treated with insulin glargine had a similar risk of cancer and cancer-related outcomes as patients who received standard care (not defined) [63].

**ILPS**

**Pharmacology**

To regulate glucose metabolism appropriately in diabetic patients, low, steady basal insulin levels should ideally be maintained during fasting periods. LAIAs were developed to achieve this result, by using simple titration schedules, while avoiding the wide pharmacological variability
of traditional long-acting non-analog insulin preparations.

ILPS, an intermediate- to long-acting insulin, is a stable formulation of co-crystalized insulin lispro and protamine [64] that appears to have a favorable time–action profile and to produce desirable basal and postprandial glycemic control in patients with T1D and T2D [65]. ILPS has shown pharmacokinetic and pharmacodynamic properties similar to those of NPH insulin in healthy volunteers [66]. However, in patients with T1D, time to peak insulin concentration tended to be shorter (not significant) with ILPS than NPH insulin [67].

The duration of glucose-lowering activity of a single dose of ILPS 0.8 U/kg (>23 h) supports its use once daily and did not differ significantly from that observed with insulin glargine or insulin detemir in patients with T2D [68]. However, ILPS had significantly greater glucose-lowering activity and produced an earlier maximum pharmacodynamic response (measured by glucose infusion rate during euglycemic glucose clamp testing) compared with both insulins [68]. Similarly, in patients with T1D, ILPS produced an earlier and larger maximum pharmacodynamic response than insulin detemir (also measured by glucose infusion rate during euglycemic glucose clamp testing), with a similar duration of action of just under 24 h (22 versus 23 h, respectively) for both agents [69].

Interestingly, compared with insulin glargine given at a single equivalent dose, ILPS was associated with lower pharmacodynamic inrasubject variability, more rapid onset of action, and greater glucose-lowering activity in patients with T1D [70]. These characteristics may provide a more predictable response in these patients [70]. The pharmacological effect of ILPS in patients with T2D was dose-dependent across the dose range of 0.4–1.2 U/kg [68]. Due to an increase in the risk of hypoglycemia with twice-daily dosing, a once-daily schedule appears to provide the best balance between efficacy and hypoglycemic risk [65].

The receptor binding of insulin lispro is unaffected by the protamine molecule and ILPS therefore has the same binding profile as insulin lispro. On this basis, the mitogenic and immunogenic potentials of ILPS are expected to be the same as those of insulin lispro.

Clinical Trials

Since data from pregnant women with diabetes are limited, this section provides an overview of clinical studies conducted in non-pregnant women with pregestational diabetes or GDM.

In a prospective observational study in 64 patients with T1D or T2D whose diabetes was inadequately controlled with oral antidiabetes medications or other insulin regimens, ILPS improved glycemic control without significantly increasing hypoglycemic episodes when used as basal insulin in intensive insulin therapy [71]. Importantly, ILPS, as part of a self-prepared combination with insulin lispro, was not associated with a significant change in binding levels to antibodies cross-reactive to different insulin species (−0.1% with ILPS plus insulin lispro versus −0.3% with regular human insulin plus NPH insulin; no significant difference between treatments) in a randomized, open-label trial conducted in patients with T1D or T2D [72].

ILPS once or twice daily has been compared with other LAIAs in non-pregnant women with diabetes in randomized trials of 24 to 36 weeks duration (Table 2). Overall, ILPS achieved similar glycemic control to insulin detemir and insulin glargine, without increasing the
## Table 2 Clinical trials comparing ILPS with other basal insulin analogs in adult patients with diabetes

| Trial          | Treatment (N analyzed) | Mean (SD) baseline HbA1c, % | Clinical endpoints at study end | Conclusions                                                                 |
|----------------|------------------------|-----------------------------|---------------------------------|-----------------------------------------------------------------------------|
|                |                        |                             | Mean (SD) change in HbA1c, % units | Patients with HbA1c <7.0%, % patients | Overall hypoglycemia incidence, % patients |
|                |                        |                             |                                |                                |                                          |
| **Type 1 diabetes** |                        |                             |                                |                                |                                          |
| Chacra et al. [73] | ILPS bid + IL tid × 32 weeks (192) | 8.9 (1.3) | -0.69 (0.07)<sup>a</sup> | 15 | 90.1 | Glycemic control and incidence of overall and nocturnal hypoglycemia similar with ILPS bid and ID bid |
|                 | ID bid + IL tid × 32 weeks (189) | 8.6 (1.3) | -0.59 (0.07)<sup>a</sup> | 15 | 91.5 |
| **Type 2 diabetes** |                        |                             |                                |                                |                                          |
| Arakaki et al. [74] | ILPS od + exenatide bid × 24 weeks (171) | 8.2 (0.8) | -1.16 (0.84) | 53.7 | 70.6 | Glycemic control non-inferior with ILPS od compared with IG od; incidence of overall hypoglycemia similar between treatments |
|                 | IG od + exenatide bid × 24 weeks (168) | 8.2 (0.8) | -1.40 (0.97) | 61.7 | 74.9 |
| Esposito et al. [75] | ILPS od × 36 weeks (55) | 8.8 (0.7) | -1.83 (−0.78 to −2.65)<sup>c</sup> | 62 | 74.5 | Glycemic control and incidence of overall and nocturnal hypoglycemia similar with ILPS od and IG od |
|                 | IG od × 36 weeks (55) | 8.7 (0.7) | -1.89 (−0.80 to −2.70)<sup>c</sup> | 65 | 67.3 |
| Fogelfeld et al. [76] | ILPS od-bid × 24 weeks (219) | 8.8 (0.7) | -1.47 (1.01) | 34.9 | 68.9 | Glycemic control better with ILPS od-bid than ID od-bid (P = 0.03) and with ILPS bid than ID bid (P < 0.001) but similar between ILPS od and ID od; incidence of overall hypoglycemia similar for ILPS od-bid and ID od-bid, ILPS od and ID od, and ILPS bid and ID bid; incidence of nocturnal hypoglycemia higher for ILPS od-bid than ID od-bid (P < 0.01) and ILPS bid than ID bid (P < 0.01), similar for ILPS od and ID od |
|                 | ID od-bid × 24 weeks (210) | 8.8 (0.7) | -1.24 (1.11) | 31.2 | 65.2 |
Table 2 continued

| Trial          | Treatment (N analyzed) | Mean (SD) baseline HbA1c, % | Clinical endpoints at study end | Patients with HbA1c <7.0%, % patients | Overall hypoglycemia incidence, % patients | Conclusions                                                                 
|----------------|------------------------|-----------------------------|---------------------------------|---------------------------------------|--------------------------------------------|----------------------------------------------------------------------------|
| Koivisto et al. [77] | ILPS od + IL bid-tid × 24 weeks (179) | 8.8 (0.9)                   | −1.05 (−1.05)                   | 22                                    | 56.1                                       | Glycemic control non-inferior with ILPS od compared with IG od (as bb regimens); no statistically significant or clinically relevant differences in overall or nocturnal hypoglycemia |
|                | IG od + IL bid-tid × 24 weeks (180) | 8.8 (0.9)                   | −1.20 (−1.16)                   | 29                                    | 63.6                                       |                                                                           |
| Strojek et al. [78]  | ILPS od-bid × 24 weeks (235) | 8.7 (0.7)                   | −1.46 (0.07)                    | 43.8                                  | 73.4                                       | Glycemic control and overall incidence of hypoglycemia similar for ILPS od-bid, ILPS od and ILPS bid versus IG od-bid; incidence of nocturnal hypoglycemia higher for ILPS od-bid and ILPS bid than IG od–bid (P < 0.001 for both), similar for ILPS od and IG od-bid |
|                | IG od-bid × 24 weeks (236) | 8.7 (0.7)                   | −1.41 (0.07)                    | 41.2                                  | 69.9                                       |                                                                           |

All trials were randomized, open-label, and parallel-group in design

*bb* basal–bolus, *bid* twice daily, *HbA1c* glycated hemoglobin, *ID* insulin detemir, *IG* insulin glargine, *IL* insulin lispro, *od* once daily, *ILPS* insulin lispro protamine suspension, *SD* standard deviation, *tid* three times daily

a. Least squares mean (standard error) change from baseline

b. In all patients with type 2 diabetes, insulin was added to ongoing oral antidiabetes medications

c. Mean (95% confidence interval)
risk of hypoglycemic episodes (overall or nocturnal) or weight gain when used as once-daily basal supplementation in patients with T2D receiving oral antidiabetes medications (Table 2) [74–78]. In one of these studies, ILPS was administered with prandial insulin lispro as part of a basal–bolus regimen and compared with a basal–bolus regimen of insulin glargine plus insulin lispro [77]. Glycemic control (change in HbA1c) and the risk of hypoglycemia were similar with both regimens.

Notably, the glycemic control achieved with ILPS was often maintained with lower total daily insulin doses than those required with insulin detemir or insulin glargine in patients with T1D [73] or T2D [74, 75]. In some studies, when administered twice daily, ILPS appeared to be associated with increased risk of nocturnal hypoglycemia (Table 2) [73, 76, 78].

These data were confirmed in a meta-analysis [79] and support the usefulness of ILPS as an insulin analog for basal coverage in non-pregnant patients with T1D or T2D. Furthermore, the findings suggest that the optimal regimen, in terms of balance between efficacy and hypoglycemic risk, is a once-daily injection [79], especially in patients with T2D [65].

**ILPS in Pregnancy**

Insulin lispro does not cross the placental barrier and is considered a useful treatment option for pregnant women with diabetes [34]. As discussed in the Pharmacology section, ILPS has the same binding properties as insulin lispro, and also has a stable and predictable pharmacological profile. Available data concerning use of ILPS in pregnant women are currently derived from retrospective analyses conducted in Italian centers.

A retrospective cohort study of 89 pregnant women with T2D or GDM showed that basal therapy with either ILPS (N = 53) or NPH insulin (N = 36), in addition to RAIAs (insulin aspart or insulin lispro) in most patients, resulted in similar maternal and pregnancy outcomes, including glycemic control, hypertension rates, and number of hypoglycemic events. However, NPH insulin resulted in a greater prevalence of high-ponderal-index infants (three versus zero infants with index >2.85 g/cm³; all three were also receiving a RAIA) and in higher total insulin doses than ILPS. Both insulins appeared safe in this population [80].

A larger retrospective study evaluated data from 612 pregnant women with T1D, T2D, or GDM treated with ILPS insulin and data from a control group of 793 similar women treated with NPH insulin [81]. HbA1c improved during pregnancy in both prepregnancy diabetes groups (Table 3). Although no statistical results were presented, there were fewer severe hypoglycemic events and ketoacidosis events reported in ILPS-treated women with T1D than NPH insulin-treated women with T1D. In women with T1D or T2D, the frequency of cesarean section was lower with ILPS than with NPH insulin (Table 3) [81]. In patients with GDM, maternal and fetal outcomes were not different in the two treatment groups (mean maternal HbA1c values were not reported). Thus, these data also suggest that ILPS is safe and effective for use in pregnancy.

A separate and more recent Italian multicenter observational retrospective study evaluated pregnancy outcomes in another 119 women with T1D and 814 women with GDM treated during pregnancy with ILPS or NPH insulin [82]. Among patients with T1D, HbA1c did not differ significantly between the two treatment groups either before the pregnancy or
Table 3 Relevant outcomes in pregnant women with diabetes receiving ILPS or NPH insulin in a multicenter retrospective cohort study [81]

| Patients | Insulin (N) | Age (years) | Mean BMIa, kg/m² | Mean maternal HbA1c (trimester), % | Maternal outcomes, % patients | Pregnancy/fetal outcomes, % pregnancies | Mean fetal birth weight, g |
|----------|-------------|-------------|------------------|----------------------------------|--------------------------------|----------------------------------------|--------------------------|
|          |             |             |                  | 0b 1st 2nd 3rd                  | Severe HG                      | DKA                                    |                                         |
|          |             |             |                  |                                   | HTNc                          |                                        |                                         |
|          |             |             |                  |                                   | Cesarean section               | Congenital malformation               | Macrosomia               |
| GDM      | ILPS (508)  | 36.3        | 27.2             | NA NA NA NA                    | 0 6.9 0                         | 48.7 0                                  | 5.3 3295                  |
| T1D      | NPH (125)   | 24.9        | 26.0             | NA NA NA NA                    | 0 6.9 0                         | 48.8 0                                  | 6.9 3423                  |
| T1D      | ILPS (37)   | 35.5        | 24.0             | 7.5 7.1 6.5 6.4                 | 5.4 8.1 0                       | 45.9 0                                  | 21.6 3550                 |
| T1D      | NPH (504)   | 29.9        | 23.3             | 7.5 7.2 7.2 6.4                 | 15.1 12.8 5.4                   | 73.0 5.9                                | 13.3 3300                 |
| T2D      | ILPS (67)   | 33.2        | 28.7             | 6.7 6.4 5.8 6.2                 | 1.5 8.9 0                       | 46.5 0                                  | 8.9 3235                  |
| T2D      | NPH (164)   | 33.2        | 28.1             | 6.6 6.1 6.4 5.7                 | 1.3 9.4 0                       | 69.3 1.9                                | 11.9 3200                 |

BMI body mass index, DKA diabetic ketoacidosis, GDM gestational diabetes, HbA1c glycated hemoglobin, HG hypoglycemia, HTN hypertension, ILSP insulin lispro protamine suspension, NA not available, NPH neutral protamine Hagedorn, T1D type 1 diabetes, T2D type 2 diabetes

a Prepregnancy maternal BMI
b Preconception period
c During pregnancy
**Table 4** Pregnancy outcome and fetal parameters relating to women with T1D and GDM treated with ILPS or NPH insulin in a multicenter observational retrospective study (reproduced with permission from [82])

| Outcome                                      | T1D                      | GDM                      |
|------------------------------------------------|--------------------------|--------------------------|
| **ILPS (N = 58)**                             | **NPH (N = 61)**         | **P value**              |
| Weight gain during pregnancy, kg              | 11.9 (4.6)               | 13.2 (9.4)               | ns                        | 10.2 (6.1) | 9.7 (4.6) | ns            |
| HbA1c preconception<sup>a</sup>/at diagnosis<sup>b</sup>, mmol/mol | 61.7 (11.9) | 57.4 (13) | ns | 36.6 (4.2) | 35.5 (3.1) | 0.04 |
| HbA1c first trimester, mmol/mol                | 56.3 (11.9)              | 56.3 (11.9)              | ns                        | –          | –          | –             |
| HbA1c second trimester, mmol/mol               | 48.6 (7.5)               | 47.5 (7.5)               | ns                        | –          | –          | –             |
| HbA1c third trimester, mmol/mol                | 49.7 (6.4)               | 47.5 (8.6)               | ns                        | 36.3 (6.4) | 35.6 (4.2) | ns            |
| Fasting glucose third trimester, mmol/l        | 6.0 (1.4)                | 7.7 (2.2)                | 0.001                     | 4.9 (0.7)  | 6.3 (1.5)  | <0.001        |
| Severe hypoglycemic episodes, %                | 5.2                      | 13.1                     | ns                        | 0.3        | 2.1        | ns            |
| Ketoacidosis episodes, %                       | 0                        | 0                        | –                         | 0          | 0.4        | ns            |
| Basal insulin need at term of pregnancy, U/kg  | 0.40 (0.20)              | 0.33 (0.14)              | ns                        | 0.12 (0.09)| 0.11 (0.07)| ns            |
| Delivery, gestational week                     | 37.4 (2.4)               | 36.9 (2.2)               | ns                        | 38.4 (1.9) | 37.8 (1.7) | 0.001         |
| Cesarean section, %                            | 48.2                     | 63.9                     | 0.001                     | 31.2       | 46.2       | 0.01          |
| Preterm delivery (<37 gestational weeks), %    | 15.5                     | 32.8                     | 0.05                      | 8.6        | 14.9       | 0.01          |
| Stillbirths, %                                 | 3.4                      | 1.6                      | ns                        | 0.5        | 0.4        | ns            |
| Birth weight, g                                | 3372 (788)               | 3304 (745)               | ns                        | 3304 (505) | 3286 (567) | ns            |
| Ponderal index, g/cm³                          | 2.75 (0.4)               | 2.87 (0.5)               | ns                        | 2.72 (0.3) | 2.78 (0.6) | ns            |
| Ponderal index ≥2.85 g/cm³, %                  | 29.3                     | 42.6                     | ns                        | 18.2       | 26.4       | 0.01          |
| Macrosomia (>4000 g), %                        | 18.9                     | 16.3                     | ns                        | 6.1        | 5.3        | 0.01          |
| Small for gestational age, %                   | 5.2                      | 0                        | ns                        | 3.1        | 5.4        | ns            |
| Large for gestational age, %                   | 43.1                     | 37.7                     | ns                        | 16.6       | 19.4       | ns            |
| Congenital malformations, %                    | 6.9                      | 6.5                      | ns                        | 0.5        | 1.6        | ns            |
| Neonatal hypoglycemia, %                       | 8.6                      | 4.9                      | ns                        | 2.3        | 4.1        | 0.01          |

Data are presented as mean (standard deviation), unless stated otherwise

**GDM** gestational diabetes, **HbA1c** glycated hemoglobin, **ILPS** insulin lispro protamine suspension, **NPH** neutral protamine Hagedorn, **ns** not significant, **T1D** type 1 diabetes

<sup>a</sup> In patients with T1D
<sup>b</sup> In patients with GDM

during each trimester; however, third trimester mean fasting blood glucose levels were significantly lower in ILPS-treated women (Table 4). Rates of severe hypoglycemic episodes during pregnancy and insulin requirements at the end of pregnancy were
similar between treatment groups and no patient had a ketoacidosis episode. As regards pregnancy outcomes, rates of cesarean section and preterm delivery were significantly lower in women treated with ILPS than in those treated with NPH insulin, although the mean duration of pregnancy did not differ between treatment groups. Fetal outcomes, including rates of congenital malformation, were also similar in the ILPS and NPH groups, with the exception that a slightly higher proportion of newborns in the NPH group had a ponderal index ≥2.85 g/cm³ (not significant; Table 4).

Among women with GDM, third trimester HbA1c did not differ significantly between treatment groups, but fasting blood glucose was lower in ILPS-treated women (Table 4). There were no significant between-treatment differences in the rates of severe hypoglycemic or ketoacidotic episodes, or in insulin requirements at the end of the pregnancy. Pregnancy outcomes were generally better in ILPS- than NPH-treated women, with the duration of the pregnancy being significantly longer, and the cesarean section and preterm delivery rates lower in the ILPS-treated group. When fetal outcomes were considered, ILPS was associated with a significantly higher incidence of macrosomia, and significantly fewer episodes of neonatal hypoglycemia and newborns with ponderal index ≥2.85 g/cm³ (Table 4). This higher rate of macrosomia in the ILPS group was possibly a result of the longer duration of pregnancy, because the incidence of neonates with a high ponderal index was lower in this group than the NPH group, ruling out dysmorphic growth as an etiological factor.

Bivariate logistic regression analysis of birth weight and neonatal complications, including congenital malformations and events associated with perinatal complications, revealed no statistically significant differences between ILPS and NPH treatment. This large study therefore confirms that use of ILPS in conjunction with rapid-acting analogs in pregnant patients with T1D or GDM is safe in terms of maternal and fetal outcomes, and this regimen achieves good metabolic control while limiting fetal overgrowth [82].

CONCLUSION

Maternal metabolism changes during pregnancy, posing numerous challenges in the management of women with diabetes. As insulin is the agent of choice for glycemic control in these patients, selecting the most appropriate insulin formulation is important. Although a number of insulins are available for use during pregnancy, insulin analogs are particularly interesting for this use, as they appear to reduce the risk of hypoglycemia and promote a more physiological glycemic profile than regular human insulin in pregnant women with T1D, T2D, or GDM. The RAIAs, insulin lispro and insulin aspart, and LAIAs, insulin glargine and insulin detemir, can all be used in pregnancy and are considered safe in terms of maternal and fetal health. ILPS, an intermediate- to long-acting insulin, is a stable formulation of co-crystallized insulin lispro and protamine that is expected to have the same mitogenic and immunogenic potentials as insulin lispro. Clinical data support the usefulness of ILPS as a basal insulin in non-pregnant patients with T1D or T2D, and suggest the optimal regimen, in terms of balance between efficacy and hypoglycemic risk, is a once-daily injection, especially in patients with T2D.

Most information regarding the use of insulins in pregnant women with diabetes is based on the results of observational studies; the sample sizes of all RCTs comparing different
insulin formulations in pregnant women have not been adequate to allow sufficient power to detect differences in neonatal outcomes. Data concerning use of ILPS during pregnancy are no exception to this, although findings from more than 1200 pregnant women with T1D, T2D, or GDM receiving this insulin are available and have been compared with outcomes in pregnant women receiving NPH insulin [81, 82]. Results of these retrospective studies suggest that ILPS is at least as safe and effective as NPH insulin in pregnant women. Therefore, until adequate RCTs are performed to provide more definitive findings, available experimental and clinical information indicates that ILPS has a stable and predictable pharmacological profile and appears to be a safe and effective option for pregnant women with diabetes.

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**Compliance with ethics guidelines.** This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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