A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes

Hod, Moshe; Mathiesen, Elisabeth R; Jovanovi, Lois; McCance, David R; Ivanisevic, Marina; Durán-Garcia, Santiago; Brøndsted, Lise; Nazeri, Avideh; Damm, Peter

Published in:
Journal of Maternal - Fetal & Neonatal Medicine

DOI:
10.3109/14767058.2013.799650

Publication date:
2014

Document version
Publisher's PDF, also known as Version of record

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes

Moshe Hod, Elisabeth R. Mathiesen, Lois Jovanovič, David R. McCance, Marina Ivanisevic, Santiago Durán-Garcia, Lise Brøndsted, Avideh Nazeri & Peter Damm

To cite this article: Moshe Hod, Elisabeth R. Mathiesen, Lois Jovanovič, David R. McCance, Marina Ivanisevic, Santiago Durán-Garcia, Lise Brøndsted, Avideh Nazeri & Peter Damm (2014) A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes, The Journal of Maternal-Fetal & Neonatal Medicine, 27:1, 7-13, DOI: 10.3109/14767058.2013.799650

To link to this article: https://doi.org/10.3109/14767058.2013.799650

THE JOURNAL OF
MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, 2014; 27(1): 7–13
 DOI: 10.3109/14767058.2013.799650

informa healthcare

ORIGINAL ARTICLE

A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes

Moshe Hod[1], Elisabeth R. Mathiesen[2,3,4], Lois Jovanovič[5], David R. McCance[6], Marina Ivanisevic[7], Santiago Durán-Garcia[8], Lise Brøndsted[9], Avideh Nazeri[9], and Peter Damm[2,4,10]

[1]Helen Schneider Women's Hospital, Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Center for Pregnant Women with Diabetes, Rigshospitalet, [3]Department of Endocrinology, and [4]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark, [5]Sansum Diabetes Research Institute, Santa Barbara, CA, USA, [6]Metabolic Unit, Royal Victoria Hospital, Belfast, UK, [7]Department of Obstetrics and Gynecology, University Hospital of Zagreb, Zagreb, Croatia, [8]Catedra de Endocrinologia, Unidad de Diabetes y Embarazo, Hospital Universitario de Valme, Seville, Spain, [9]Novo Nordisk A/S, Søborg, Denmark, and [10]Department of Obstetrics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Objective: This randomized controlled trial aimed to compare the efficacy and safety of insulin detemir (IDet) with neutral protamine Hagedorn (NPH), both with insulin aspart, in pregnant women with type 1 diabetes. The perinatal and obstetric pregnancy outcomes are presented.
Methods: Subjects were randomized to IDet ($n = 152$) or NPH ($n = 158$) $\leq$12 months before pregnancy or at 8–12 gestational weeks.
Results: For IDet and NPH, there were 128 and 136 live births, 11 and 9 early fetal losses, and two and one perinatal deaths, respectively. Gestational age at delivery was greater for children from the IDet arm than the NPH arm (treatment difference: 0.49 weeks [95% CI 0.11;0.88], $p = 0.012$, linear regression). Sixteen children had a malformation (IDet: $n = 8/142$, 5.6%; NPH: $n = 8/145$, 5.5%). The incidence of adverse events was similar between treatments.
Conclusion: IDet is as well tolerated as NPH as regards perinatal outcomes in pregnant women with type 1 diabetes and no safety issues were identified.

Keywords

Congenital malformations, insulin detemir, perinatal outcomes, pregnancy, type 1 diabetes

History

Received 28 January 2013
Revised 3 April 2013
Accepted 19 April 2013
Published online 4 June 2013

Introduction

Pregnancy in women with type 1 diabetes is associated with an increase in adverse maternal, fetal and perinatal outcomes, such as spontaneous abortions, congenital malformations, preterm labor and macrosomia, compared with the general population [1–3]. Several studies have confirmed that poor glycemic control in women with either gestational, type 1 or type 2 diabetes during pregnancy is associated with poor pregnancy outcomes [1,4–7]. In particular, poor glycemic control prior to or at the time of conception is associated with increased rates of adverse maternal and perinatal outcomes [2,5,6].

However, optimizing glycemic control, glycated hemoglobin [A1C] <7% [<53 mmol/mol], does not guarantee a normal outcome, as highlighted in the UK Confidential Enquiry into Maternal and Child Health (CEMACH) study, in which 25% of women whose baby had an anomaly had achieved A1C <7% [<53 mmol/mol] by 13 weeks' gestation [3,8,9]. Several studies have shown that focusing on A1C levels is insufficient to ensure that glucose concentrations are well controlled. Instead, frequent daily monitoring of capillary glucose concentrations is necessary to limit hyper- and hypoglycemic excursions, as a single day of poor glycemic control during the first trimester could negatively impact organogenesis [7].

Outside of pregnancy, short and long-acting insulin analogs have been shown to result in better glycemic control with less hypoglycemia than human insulins in subjects with diabetes [10–13]. Recently, a randomized trial showed similar benefits with short-acting analogs in pregnancy complicated by type 1 diabetes [14]. In contrast, few studies have examined the efficacy and safety of long-acting analogs in women with type 1 diabetes during pregnancy, despite their increasing use in this subject group. Consequently, basal insulin analogs have been used off-label [15]. Only one randomized controlled trial, described here, has investigated a basal analog, comparing insulin detemir (IDet) with neutral protamine Hagedorn (NPH), both in combination with insulin aspart (IAsp), in pregnant women with type 1 diabetes [16].

IDet is an insulin analog that has a consistent pharmacokinetic/pharmacodynamic profile, with lower intra-subject variability in terms of glucose-lowering effect compared with

Address for correspondence: Moshe Hod, Perinatal Division, Helen Schneider Hospital for Women, Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Petah-Tiqva 49100, Israel. Tel: +97 2528888899. Fax: +97 2099503516. E-mail: hodroyal@inter.net.il

either NPH or insulin glargine in subjects with type 1 or type 2 diabetes [17,18]. Studies have shown that IDet provides similar glycemic control, but with lower rates of hypoglycemia and less weight gain, than NPH insulin in non-pregnant subjects with type 1 or type 2 diabetes [13,19–24].

The aim of this study was to compare the efficacy and safety of IDet with NPH in pregnant women with type 1 diabetes. This manuscript presents the primary data on perinatal and obstetric pregnancy outcomes. Data on glycemic control, maternal hypoglycemia and maternal safety have been reported separately [16].

Methods

Trial design and interventions

This was a randomized, open-label, multinational, parallel-group trial comparing the safety and efficacy of IDet with NPH insulin, both used in combination with prandial IAsp in a basal–bolus regimen in pregnant women with type 1 diabetes. This trial was conducted at 79 sites in 17 countries between May 2007 and August 2010. The trial is registered as ClinicalTrials.gov number NCT00474045. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines, and was approved by respective ethics committees and health authorities according to local regulations. International review board approval was obtained prior to the start of the trial for each trial center. Written informed consent was obtained from the subjects prior to trial entry or any trial-related activities.

Women ($\geq$18 years of age) with type 1 diabetes treated with insulin (any regimen) for at least 12 months who were either planning to become pregnant (screening A1C $\leq$9.0% [$\leq$75 mmol/mol]; A1C $\leq$8.0% [$\leq$64 mmol/mol] at confirmation of pregnancy) or were already pregnant with a singleton pregnancy at gestational age (GA) 8–12 weeks (A1C $\leq$8.0% [$\leq$64 mmol/mol] at pregnancy confirmation) were eligible for inclusion. Subjects with impaired hepatic or renal function, uncontrolled hypertension (systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg), undergoing medical infertility treatment, or who had been previously randomized in this trial were excluded.

Eligible subjects were randomized 1:1 to receive either IDet (100 U/mL; Novo Nordisk, Bagsvaerd, Denmark) or NPH (100 U/mL; Novo Nordisk, Bagsvaerd, Denmark), both in combination with prandial IAsp (100 U/mL; Novo Nordisk, Bagsvaerd, Denmark) in a basal–bolus regimen. The subjects were stratified according to pregnancy status. Subjects received the trial drug from randomization until termination/6 weeks post-delivery. An open-label trial design was chosen due to the differing appearances of the two treatments.

IDet or NPH was administered subcutaneously at the same time and with the same frequency as the basal insulin that was given prior to randomization. IAsp was administered 0–15 min before each main meal. Basal insulin doses were titrated according to fasting and pre-dinner plasma glucose (PG) values of 72–108 mg/dL (4.0–6.0 mmol/L). The bolus insulin doses were titrated according to preprandial values of 72–108 mg/dL (4.0–6.0 mmol/L) and 2-h post-prandial PG values of <126 mg/dL (<7.0 mmol/L).

Assessments and endpoints

Subjects pregnant at randomization (at 8–12 gestational weeks [GWs]) had the first trial visit at this point and subsequent visits at 14, 24 and 36 GWs, at delivery/termination, and at 6 weeks post-delivery. Subjects not pregnant at randomization had visits every 3 months until conception and then followed the same visit schedule as detailed above. Non-pregnant subjects who did not reach A1C $\leq$8.0% [$\leq$64 mmol/mol] after 9 months were withdrawn, as were subjects who did not conceive within 12 months of randomization or who had A1C >8.0% [>64 mmol/mol] at confirmation of pregnancy. Pregnancy outcome is comprised of three main categories: fetal death, termination of pregnancy and live birth.

The primary endpoint was A1C at 36 GWs as an indicator of glycemic control. Secondary perinatal and obstetric pregnancy safety endpoints included: a composite pregnancy outcome, GA at delivery, small/large (<10th or >90th percentile) for GA, birth weight, macrosomia (more than 4000 g), live births, early fetal death, perinatal mortality, neonatal mortality and induced abortions, neonatal hypoglycemia, congenital malformations, preterm delivery, pre-eclampsia and adverse events (AEs). AEs were recorded for the fetus/child until 6 weeks after birth. Maternal AEs were recorded from first trial-related activity until 6 weeks after giving birth. A serious AE included death of the fetus/neonate (miscarriage, stillbirth or neonatal death) and any congenital malformation. A severe AE was defined as an event that considerably interfered with the subject's daily activities.

The composite pregnancy outcome included at least one of the following:

- Live-born infants with a birth weight <10th or >90th percentile for GA and sex, according to local practice;
- Preterm delivery (delivery <37 completed GWs);
- Early fetal death (<22 completed GWs);
- Perinatal mortality (death of fetus/infant between $\geq$22 completed GWs and <1 completed week after delivery);
- Neonatal mortality (postpartum death after 7 completed days and before 28 completed days after delivery);
- Presence of major malformations.

Congenital malformations, defined as a morphological defect of an organ or multiple organs of the body resulting from an intrinsically abnormal developmental process, were observed at gross examination either before birth (by ultrasound) or after delivery. These malformations were classified further as either major (a life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity) or minor (relatively frequent structural anomaly not likely to cause any medical or cosmetic problems) malformations, and described using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. An appointed specialist performed a blinded (including to treatment assignment) review of all serious AEs for the identification of malformations. Due to the clinical importance of congenital malformations, the serious AE data were blinded and evaluated *post hoc* (after the primary analysis) by a second specialist. Both specialists identified malformations after a similar period of postnatal follow-up. Both classifications were subsequently reviewed and

approved by the European Medicines Agency and are included here. Congenital malformations were evaluated by randomized treatment and also by treatment during organogenesis (*post hoc*; after the primary analysis). Organogenesis was defined as the period from 3 GWs until 8 GWs.

Neonatal hypoglycemia was defined as a PG level ≤31 mg/dL (≤1.7 mmol/L) during the first 24 h after birth or a PG level ≤45 mg/dL (≤2.5 mmol/L) between 24 and 48 hours after birth.

Statistical analyses

The sample size was calculated as described in Mathiesen et al. [16]. The trial was powered to show non-inferiority for A1C at 36 GWs (non-inferiority margin of 0.4%) for IDet compared with NPH, and 120 subjects were planned to complete the trial in each treatment group. The trial was not powered to detect a difference between IDet and NPH in regards to the other perinatal and obstetric pregnancy safety endpoints listed above.

The safety outcomes reported here were evaluated in the safety analysis set for pregnant subjects ($SAS_{Pregnant}$) (exposed subjects who were pregnant during the trial). The $SAS_{Pregnant}$ analysis set contained data from two subgroups of pregnant women: subjects who were pregnant at randomization and subjects who became pregnant after randomization. Preterm delivery, live births, large for GA, neonatal hypoglycemia within 24 hours of delivery, macrosomia, pre-eclampsia (all *post hoc*) and the composite pregnancy outcome were analyzed using a logistic regression model with treatment and pregnancy status at randomization as factors. Birth weight and GA at delivery (both *post hoc*) were analyzed using a linear regression model with treatment, country and pregnancy status at randomization as factors. In accordance with the intention-to-treat principle, all data – and therefore all pregnancies – were used in the analyses.

Results

Baseline characteristics and subject disposition

A total of 470 subjects were randomized, of whom 313 were pregnant during the trial and 157 were not pregnant during the trial. Of the 313 pregnant subjects, 310 were exposed to the trial treatment and were pregnant during the trial ($n = 152$ IDet; $n = 158$ NPH) (Supplementary Figure 1). The majority of the 157 non-pregnant subjects were withdrawn because they met the withdrawal criteria of failure to reach A1C ≤8.0% [≤64 mmol/mol] after 9 months ($n = 14$ IDet; $n = 10$ NPH) or failure to conceive within 12 months of randomization ($n = 44$ IDet; $n = 32$ NPH). The total number of pregnancies reported for this trial was 312 ($n = 152$ IDet; $n = 160$ NPH) due to two subjects in the NPH group having miscarriages, but remaining in the trial and becoming pregnant again. In accordance with the intention-to-treat principle, all data – and therefore all pregnancies – were used in the analyses.

Baseline subject characteristics are shown in Supplementary Table 1. The baseline characteristics were similar between both treatment groups. The mode of delivery is shown in Supplementary Table 2.

Perinatal outcomes

Of the total number of pregnancies, the composite pregnancy outcome was experienced by 62.7% ($n = 89$) of IDet and 66.2% ($n = 96$) of NPH-treated pregnancies (odds ratio IDet/NPH 0.86 [95% CI 0.53;1.40], not significant) (Table 1).

Pregnancy outcomes for liveborn children are detailed in Table 1. GA at delivery was significantly greater for offspring in the IDet treatment arm compared with those in the NPH treatment arm (mean [SD] IDet: 38.2 [1.9] weeks; NPH: 37.8 [1.5] weeks; mean treatment difference IDet/NPH 0.49 weeks

Table 1. Fetal and perinatal outcomes.

	IDet		NPH		Odds ratio [95% CI]	*p* Value
	n	%	*n*	%		
Number of subjects	152	–	158	–	–	–
Number of pregnancies	152	–	160	–	–	–
Pregnancy outcome at follow-up	142		145		–	–
Live births‡	128	90.1	136*	93.8	0.61 [0.25;1.50]	$p = 0.284$
Early fetal death‡	11	7.7	9	6.2	–	–
Spontaneous abortion	10	7.0	8	5.5	–	–
Ectopic pregnancy	1	0.7	1	0.7	–	–
Induced abortion‡	1	0.7	0	0.0	–	–
Perinatal death‡	2	1.4	1	0.7	–	–
Neonatal death‡	0	0.0	0	0.0	–	–
Composite outcome: at least one issue present‡	89	62.7	96	66.2	0.86 [0.53;1.40]	$p = 0.551$
Preterm delivery (<37 weeks)¶	26	20.3	36	26.5	0.71 [0.40;1.26]	$p = 0.238$
Small† for GA (<10th percentile)¶	3	2.3	1	0.7	–	–
Large† for GA (>90th percentile)¶	59	46.1	73	53.7	0.74 [0.46;1.21]	$p = 0.228$
Macrosomia (>4000 g)¶	24	18.8	35	25.7	0.67 [0.37;1.20]	$p = 0.180$
Neonatal hypoglycemia <24 hours post-delivery¶	15	11.7	24	17.6	0.65 [0.32;1.30]	$p = 0.223$

	IDet		NPH		Treatment difference [95% CI]	*p* Value
	Mean	SD	Mean	SD		
Birth weight (g)§	3504	645	3571	601	−41.8 [−191.0;107.1]	$p = 0.581$
GA at delivery (weeks)§	38.2	1.9	37.8	1.5	0.49 [0.11;0.88]	$p = 0.012$

*There is 1 less live child at follow-up compared with live births as 1 liveborn child died shortly after birth (classified as a perinatal death); †Refers to body weight; ‡Percentage of pregnancy outcomes at follow-up; ¶Percentage of live births; §Analyses based on live births.
GA, gestational age; g, grams; IDet, insulin detemir; NPH, neutral protamine Hagedorn.

Table 2. Congenital malformations as diagnosed by two independent experts.

Group	MedDRA preferred term	Basal insulin at organogenesis	Expert 1 classification	Expert 2 (blinded *post hoc*) classification
Pregnant at randomization				
	Hip dysplasia	IDet	Major (reclassified to minor due to FU information)	Not a congenital malformation (developmental disorder that disappears)
	Cleft lip	NPH	Major	Major
IDet ($n=79$)	Meningomyelocele	NPH	Major	Major
	Atrial septal defect Hemangioma congenital	NPH	Both minor	Both major
	Hemangioma congenital (diagnosed after the EOT)	NPH	Minor	Not a congenital malformation
	Dandy–Walker syndrome Pulmonary hypoplasia	NPH	Both major	Both major
	Polydactyly	Insulin glargine	Minor	Minor
NPH ($n=83$)	Cardiac hypertrophy Patent ductus arteriosus	NPH	Both minor	Not congenital malformations (FU: patent ductus arteriosus was minor and did not require surgery)
	Atrial septal defect	NPH	Minor	Not a congenital malformation (FU: atrial septal defect spontaneously closed)
Pregnant after randomization				
	Congenital hydronephrosis Pelviureteric obstruction Pyelocaliectasis	IDet	All major	All major
IDet ($n=73$)	Hydronephrosis	IDet	Major	Major
	Heart disease congenital	IDet	Minor	Not a congenital malformation. Transient minor anomaly
NPH ($n=75$)	Heart disease congenital	NPH	Minor	Not a congenital malformation. Transient minor anomaly
	Congenital laryngeal stridor	NPH	Minor	Not a congenital malformation
	Atrial septal defect	NPH	Minor	Major
	Ventricular septal defect	NPH	Minor	Major
	Pelvic kidney* (diagnosed after mother was withdrawn while pregnant due to A1C >8% [>64 mmol/mol] at confirmation of pregnancy	NPH	Major	Major

*This malformation from a woman withdrawn from the study is not included in the trial database or further calculations.
Follow-up was from birth until 6 weeks after birth.
A1C, glycated hemoglobin; EOT, end of trial; FU, follow-up; IDet, insulin detemir; MedDRA, Medical Dictionary for Regulatory Activities; NPH, neutral protamine Hagedorn.

[95% CI 0.11;0.88], $p=0.012$). There were no other statistically significant differences between the two treatment groups.

Fetal and perinatal mortality were similar between treatment groups (Table 1). The only induced abortion reported was in the IDet treatment group, and was due to social circumstances.

Congenital malformations were classified by two specialists as detailed in Table 2 and evaluated by randomized treatment (Table 3). Furthermore, as congenital malformations develop during early pregnancy, their frequency by insulin treatment during organogenesis is also presented (*post hoc* analysis) (Table 3). Both of these approaches showed a similar frequency of malformations for both treatments. In the first classification by randomized treatment among women who gave birth or terminated their pregnancy during the trial, a total of 16 children were recorded as having one or more malformations (IDet: $n=8/142$, 5.6%; NPH: $n=8/145$, 5.5%). Of these, 10 children had minor malformations (IDet: $n=3/142$, 2.1%; NPH: $n=7/145$, 4.8%) and 6 children had major malformations (IDet: $n=5/142$, 3.5%; NPH: $n=1/145$, 0.7%). Among the women who were pregnant at withdrawal, we are aware of only one child with a malformation, classified as a major malformation. Major malformations were related to the renal system, the central nervous system, a hip dysplasia and a cleft lip. Only minor discrepancies between the two specialists' classifications were seen, the key differences being the classification of atrial

Table 3. Summary of congenital malformations by randomized treatment and treatment during organogenesis for children delivered during the trial.

Group	Expert 1 classification				Expert 2 (blinded *post hoc*) classification			
Randomized treatment	IDet ($n = 142$)		NPH ($n = 145$)		IDet ($n = 142$)		NPH ($n = 145$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	8	5.6	8*	5.5	5	3.5	4*	2.8
Minor	3	2.1	7	4.8	0	0.0	1	0.7
Major	5	3.5	1	0.7	5	3.5	3	2.1
Treatment during organogenesis†	IDet ($n = 84$)		NPH ($n = 154$)		IDet ($n = 84$)		NPH ($n = 154$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	4	4.8	11	7.1	2	2.4	6	3.9
Minor	1	1.2	8	5.2	0	0.0	0	0.0
Major	3	3.6	3	1.9	2	2.4	6	3.9

*There was one additional malformation (preferred term: pelvic kidney; treatment during organogenesis: NPH; randomized treatment: NPH; classification: major), that was diagnosed after the mother was withdrawn from the trial (detail in Table 2). As this table is based only on those women who gave birth during the trial, this malformation is not included.

†Those subjects treated with a basal insulin other than IDet or NPH ($n = 35$) or who were unclassifiable ($n = 14$; i.e. used more than one basal insulin or had missing information about their basal insulin) were not included in the treatment during organogenesis calculations. The woman treated with insulin glargine during organogenesis (detail in Table 2) is not included.

IDet, insulin detemir; NPH, neutral protamine Hagedorn.

septal defect and ventricular septal defect in the NPH (pregnant after randomization) group and hip dysplasia in the IDet (pregnant at randomization) group.

Adverse events

Adverse events in children were recorded during the entire trial period and covered both fetuses and newborn children up to the age of 6 weeks (Supplementary Tables 3 and 4). There was no difference in the incidence of AEs in the offspring between the treatment groups (IDet: 37%; NPH: 35%) or in the number of AEs per child (IDet: 2.2; NPH: 2.7) (Supplementary Table 3). There was no difference between the treatment groups in the incidence of severe AEs. Only one AE (fetal distress syndrome), which was in the IDet group, was considered by the investigator to be possibly or probably related to both the basal and bolus insulins (Supplementary Table 3). Serious AEs occurred in slightly more children in the IDet group (23.7%) than in the NPH group (20.3%). Pregnancy, puerperium and perinatal AE profiles for pregnant women were similar between the two groups, and did not exceed that expected in pregnancy complicated by diabetes; for example, 16 (10.5%) women in the IDet group and 11 (7.0%) women in the NPH group experienced preeclampsia (not statistically significant).

Discussion

This is the first randomized controlled trial of a basal insulin analog in pregnant women with type 1 diabetes. This study demonstrates that IDet is as well tolerated as NPH with respect to perinatal morbidity and mortality, and no specific safety issues were identified. The overall numbers of AEs in the offspring were similar for both treatment groups, although a numerically higher frequency of serious AEs in the offspring was seen for IDet compared with NPH. In addition, the frequency of malformations was similar for IDet compared with NPH, regardless of whether the malformations were evaluated by randomized treatment or treatment during organogenesis.

The maternal outcomes of this trial have been reported in detail separately, but the overall findings indicated that treatment with IDet resulted in significantly lower fasting PG, and comparable A1C levels and hypoglycemia incidence compared with NPH [16]. Previous studies were small and retrospective, and focused on treatment with either insulin glargine or NPH [15]. The present trial included a large number of subjects in a challenging population. The trial was powered to show non-inferiority for IDet compared with NPH with regards to efficacy late in pregnancy. It is of note, however, that to power a trial to detect uncommon perinatal outcomes would always require a much larger sample size. In light of this, long-term observational databases would be the most appropriate method to complement the safety data from randomized controlled trials, and collection of such data is currently in progress.

There are no direct data with which to compare our trial [15]. One other randomized controlled trial compared IAsp with soluble human insulin, both used in combination with NPH, in pregnant women with type 1 diabetes [14,25]. Compared with this trial, perinatal outcomes, including live births and fetal losses, were similar to the results presented here. In addition, the number of serious AEs in children was numerically lower in our trial compared with the IAsp trial [25]. The incidence of perinatal deaths in our trial (IDet: 14 per 1000 births; NPH: 7 per 1000 births) was lower than previously reported incidences for pregnancies complicated by diabetes (23–28 per 1000 births) [26,27].

The frequency of malformations with either IDet or NPH in this trial was similar regardless of randomization, treatment during organogenesis or assessment by two independent specialists. While there were certain differences between the two specialists' classifications, these differences reflect the complexities and subtleties that exist in diagnosing congenital malformations, and some degree of variation between the specialists is to be expected [28]. In addition, the results from

both specialists may provide further insights into the classification of congenital malformations.

While a strict A1C inclusion criteria (<8% at confirmation of pregnancy) was used in the present trial, IDet has been shown in previous studies to have a consistent glucose-lowering effect and one that was similar in magnitude to that seen with NPH insulin in non-pregnant subjects with type 1 or type 2 diabetes [13,19–24]. Therefore, based on the evidence provided by these previously published studies, we would not expect there to be any differences between IDet and NPH insulin in women with a high A1C with respect to perinatal outcomes.

Both in the rapid-acting analog IAsp study [25] and the present long-acting analog IDet study, the use of analogs was associated with a tendency towards pregnancy reaching closer to term. One could speculate whether a slightly more appropriate growth of the fetus, although not significantly, contributed to this.

At the time of the initial IAsp trial, pretrial use of insulin analogs was approximately 48% [25]. By the recruitment stage for the current trial, the use of bolus and basal insulin analogs in pregnancy had increased to approximately 90% and 47%, respectively [15]. This trend may reflect an improved perception of insulin analog safety in pregnancy, particularly following the change in the US Food and Drug Administration (FDA) categorization of IAsp from category C to category B. Therefore, our trial, the first randomized controlled trial of a basal insulin analog in pregnant women, could, in a similar manner, alter prescribing habits, especially following the update to the US and European labeling for the use of IDet in pregnant women, with IDet now also being classified as category B by the FDA following this trial [29,30].

In conclusion, this randomized controlled trial has shown that IDet is well tolerated without any specific safety concerns in pregnant women with type 1 diabetes. These data should help reassure clinicians in their choice of basal insulin during pregnancy. Further reassurance will be provided with the collection of long-term observational data from a large cohort of mothers and their infants treated with different glucose-lowering drugs during intra-uterine life.

Acknowledgements

The authors would like to thank Francesca Hemingway, Liz Southey and Helen Marshall, of Watermeadow Medical, Witney, UK, for their writing and editorial assistance in this process, funded by Novo Nordisk A/S. Prof Moshe Hod is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interest

M.H., S.D.G. and M.I. have no conflicts of interest. E.R.M. is a member of an international scientific advisory board and has received fees for giving talks for Novo Nordisk. D.R.M. is a member of an international scientific advisory board, contributed to advisory committees and has received honoraria from Novo Nordisk in the past for giving lectures. P.D. and L.J. are members of an international scientific advisory board for Novo Nordisk. L.B. is an employee of Novo Nordisk and owns stocks in the company. A.N. is an employee of Novo Nordisk. Presented at meetings of the 6th International Symposium on Diabetes and Pregnancy, Salzburg, Austria, 23–26 March 2011; the 71st Scientific Sessions of the American Diabetes Association, San Diego, CA, USA, 24–28 June 2011; the 47th European Association for the Study of Diabetes Annual Meeting, Lisbon, Portugal, 12–16 September 2011. The maternal outcome results of this trial have been published [16]. This study was funded by Novo Nordisk. Editorial assistance for this manuscript was also funded by Novo Nordisk. ClinicalTrials.gov number NCT00474045. A list of trial sites are included in Supplement S5.

References

1. MacIntosh MCM, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales and Northern Ireland: population based study. BMJ 2006;333:177–80.
2. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetes pregnancies. Diabetes Care 2004;27:2819–23.
3. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004;328:915–19.
4. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. Diabetologia 2000;43:79–82.
5. Nielsen GL, Sorensen HT, Nielsen PH, et al. Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1diabetic pregnancies. Acta Diabetol 1997;34:217–22.
6. DCCT Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. Am J Obstet Gynecol 1996;174: 1343–53.
7. Murphy HR, Rayman G, Duffield K, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care 2007;30:278–91.
8. Confidential Enquiry into Maternal and Child Health (CEMACH). Pregnancy in women with type 1 and type 2 diabetes in 2002–2003, England, Wales and Northern Ireland. London: CEMACH; 2005.
9. Casson IF. Pregnancy in women with diabetes—after the CEMACH report, what now? Diabet Med 2006;23:481–4.
10. Home PD, Lindholm A, Riis A, European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000;17:762–70.
11. Rosenstock J, Schwartz SL, Clark Jr CM, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001;24:631–6.
12. Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004;47: 622–9.
13. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–9.
14. Mathiesen ER, Kinsley B, Amiel SA, et al; Insulin Aspart Pregnancy Study Group. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care 2007;30:771–6.
15. Mathiesen ER, Damm P, Jovanovic L, et al. Basal insulin analogues in diabetic pregnancy: a literature review and baseline results of a randomised, controlled trial in type 1 diabetes. Diabetes Metab Res Rev 2011;27:543–51.
16. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal efficacy and safety outcomes in a randomized controlled trial comparing insulin

detemir with NPH insulin in 310 pregnant women with type 1 diabetes mellitus. Diabetes Care 2012;35:2012–17.
17. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53: 1614–20.
18. Klein O, Lynge J, Endahl L, et al. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes Metab 2007;9:290–9.
19. Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004;26:724–36.
20. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005; 7:73–82.
21. Kølendorf K, Ross GP, Pavlic-Renar I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabet Med 2006;23:729–35.
22. Hermansen K, Davies M, Derezinski T, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29:1269–74.
23. Philis-Tsimikas A, Charpentier G, Clauson P, et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006;28:1569–81.
24. Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients: the PREDICTIVE BMI clinical trial. Diabet Med 2008;25:916–23.
25. Hod M, Damm P, Kaaja R, et al; Insulin Aspart Pregnancy Study Group. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. Am J Obstet Gynecol 2008;198:186.e1–7.
26. Penney GC, Mair G, Pearson DW, Scottish Diabetes in Pregnancy Group. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. BJOG 2003;110: 315–18.
27. Bell R, Bailey K, Cresswell T, et al; Northern Diabetic Pregnancy Survey Steering Group. Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes. BJOG 2008;115:445–52.
28. Lisi A, Botto LD, Robert-Gnansia E, et al. Surveillance of adverse fetal effects of medications (SAFE-Med): findings from the International Clearinghouse of Birth Defects Surveillance and Research. Reprod Toxicol 2010;29:433–42.
29. Novo Nordisk. Levemir prescribing information. 2012. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021536s037lbl.pdf [last accessed 1 Oct 2012].
30. Novo Nordisk. Levemir summary of product characteristics. 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000528/WC500036662.pdf [last accessed 1 Oct 2012].