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ORIGINAL ARTICLE

Pregnancy outcomes in women with type 1 diabetes using insulin degludec

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Abstract

Aims To evaluate pregnancy outcomes in a real-world setting of pregnant women with type 1 diabetes using the ultra-long-acting insulin analog degludec compared to other long-acting insulin analogs throughout pregnancy.

Methods This was a secondary analysis of a prospective cohort study. The prospective cohort included consecutive, singleton pregnant women with type 1 diabetes receiving long-acting insulin analogs both before and during pregnancy: 67 women using degludec compared to 95 women using other long-acting insulin analogs in a routine care setting.

Results Women using degludec had similar clinical characteristics as women using other long-acting insulin analogs including HbA1c at 9 gestational weeks [6.5 (6.2–6.9) % (48 (44–52) mmol/mol) versus 6.5 (6.0–7.0) % (47 (42–53) mmol/mol), $p=0.52$] and at 35 gestational weeks [6.0 (5.6–6.5) % (42 (38–47) mmol/mol) versus 6.1 (5.6–6.5) % (43 (38–48) mmol/mol), $p=0.68$]. Pregnancy outcomes were similar regarding preeclampsia [10% (7/67) versus 8% (8/95), $p=0.66$] and preterm delivery before 37 gestational weeks [16% (11/67) versus 23% (22/95), $p=0.29$]. There were no perinatal deaths, and neonatal outcomes as large for gestational age infants [37% (25/67) versus 39% (37/95), $p=0.83$], small for gestational age infants [4% (3/67) versus 5% (5/95), $p=1.0$] and neonatal hypoglycemia [32% (21/65) versus 41% (34/83), $p=0.28$] were similar between women using degludec and other long-acting insulin analogs.

Conclusions The use of degludec during pregnancy resulted in similar pregnancy outcomes as use of other long-acting insulin analogs in women with type 1 diabetes in a real-world setting. This suggests that degludec initiated before pregnancy can be continued throughout gestation.

Keywords Pregnancy · Type 1 diabetes · Degludec · Long-acting insulin analog · Pregnancy outcomes · Neonatal outcomes

Introduction

The choice of insulin for the management of diabetes has increased markedly over the last decade with the availability of different insulin analogs. However, during pregnancy insulin choice is largely determined by its safety profile [1].

Insulin analogs are now widely used in pregnancy [2, 3]. The safety and efficacy of insulin detemir have been evaluated in both a randomized controlled trial (RCT) [4] and a cohort study [5]. Observational data on pregnancies exposed to insulin glargine do not indicate any adverse effects on pregnancy outcomes [6–8].

Insulin degludec is a newer ultra-long-acting insulin analog on the market with a half-life of 25 h, a duration of action exceeding 42 h [9] and documented efficacy and safety outside of pregnancy with improved glycemic control and lower risk of hypoglycemia compared to insulin glargine [10–12]. Insulin degludec is now widely used in Denmark in

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the non-pregnant population of persons with type 1 diabetes (personal communication). Insulin degludec is currently used off-label during pregnancy in women with type 1 diabetes by us and others, as documented in case reports including in total 10 women who all delivered liveborn infants without congenital malformations [13–17]. However, only four of these women used insulin degludec before and throughout pregnancy [13, 16, 17].

Shifting the type of long-acting insulin in early pregnancy may lead to fluctuating glucose levels. Therefore, since the launch of insulin degludec in 2013 [18] it has been the policy at our center that women who have obtained good glycemic control and who are satisfied with using insulin degludec before conception can continue to use this insulin during pregnancy.

Previously we reported similar glycemic control and pregnancy outcomes in the first 22 women in our center using insulin degludec initiated before pregnancy compared to women using insulin glargine [19].

In this study, we aimed to evaluate pregnancy outcomes in a real-world setting of women with type 1 diabetes using insulin degludec compared to other long-acting insulin analogs throughout pregnancy.

Subjects, material and methods

This was a secondary analysis of a prospective observational cohort of pregnant women with type 1 or type 2 diabetes focusing on preeclampsia [20, 21].

For this study, consecutive pregnant women with type 1 diabetes referred < 20 weeks with a single living fetus to Center for Pregnant Women with Diabetes, Rigshospitalet, were included from February 2016 to February 2020 and followed in our center during pregnancy until discharge after delivery. Exclusion criteria were age < 18 years, insufficient Danish language skills, study participation in a previous pregnancy and severe concomitant diseases. Of 257 women with type 1 diabetes included in the primary study, 94 women on insulin pump treatment and one woman receiving insulin degludec as part of an RCT were excluded leaving 162 women for this study. Fifteen of the women using insulin degludec were also included in our previous publication [19].

All women followed the routine diabetes and pregnancy care program for pregnant women with diabetes as previously described [20, 21]. Briefly, the women were seen for clinical visits every second week where self-monitored blood glucose values, prevalence of mild hypoglycemia the last week (events with symptoms familiar to the women as hypoglycemia and managed by themselves [22, 23]), HbA1c, insulin doses, blood pressure (BP), proteinuria (screened with a urine dipstick) and weight were evaluated. For this study, HbA1c and hypoglycemia at median 9, 20 and 35 weeks are presented.

The type of insulin used from pregnancy onset was generally unchanged during pregnancy. The women using insulin degludec in the present study generally initiated treatment with this insulin as part of routine care prior to and unrelated to the current pregnancy and obtained improved glycemic control. Based on the individual woman's experience with insulin degludec, she was entitled to choose to continue this insulin during pregnancy, if she so wished, and when the benefits of continuing the usual insulin degludec in terms of good glycemic control were estimated to outweigh possible disadvantages. The women included in this study thus decided to continue using insulin degludec during pregnancy. However, no formal written informed consent to continue use of insulin degludec during pregnancy was obtained.

Antihypertensive treatment was initiated or intensified if office BP ≥ 135 mmHg systolic and/or ≥ 85 mmHg diastolic in combination with home BP ≥ 130 mmHg systolic and/or ≥ 80 mmHg diastolic when available, or if urinary albumin/creatinine ratio ≥ 300 mg/g [20].

Gestational weight gain was calculated from the last weight measured, often at 36 weeks, and self-reported pre-pregnancy weight [24].

Routine care changed slightly during the study period [20, 21]. Starting on February 23, 2018, aspirin 150 mg/day was recommended for all women according to new international recommendations [25], vitamin D level was measured and targets for glycemic control changed slightly: Blood glucose monitoring (BGM) targets changed from 4.0–6.0 to 4.0–5.5 mmol/l preprandially and from 4.0–8.0 to 4.0–7.0 mmol/l postprandially. HbA1c targets changed from < 6.7% (50 mmol/mol) to < 6.5% (48 mmol/l) before 20 weeks and from < 5.8% (40 mmol/mol) to < 5.6% (38 mmol/mol) thereafter.

As part of the routine diabetes care program, the dose of insulin degludec and of other long-acting insulin analogs was titrated to the early morning preprandial BGM target at each clinical visit during pregnancy, and women were instructed to adjust their dose of insulin degludec or other long-acting insulin analog, respectively, when indicated every 3–5 days between clinical visits. If indicated, the dose of other long-acting insulin analog with a shorter duration of action than degludec was given twice daily both before breakfast and before dinner to obtain BGM targets.

Before February 23, 2018, aspirin was only prescribed to women with additional risk factors for preeclampsia (previous preeclampsia, chronic hypertension, microalbuminuria/nephropathy or oocyte donation), and vitamin D level was not measured [20].

Sixteen (10%) women were pregnant during the COVID-19 pandemic with none testing positive for COVID-19.

Preeclampsia was diagnosed in the presence of BP ≥ 140/90 mmHg with coexistence of proteinuria ≥ 1 + on a urine dipstick and/or new onset of organ dysfunction [26]. Preterm preeclampsia was defined as delivery with preeclampsia < 37 weeks. Preterm delivery was defined as delivery < 37 weeks.

Birth weight z-score was calculated to adjust for gestational age and sex [27], and large and small for gestational age (LGA and SGA) were defined as birth weight > 90th percentile and < 10th percentile, respectively.

The following neonatal outcomes were recorded: perinatal mortality (death between 22 weeks and one week after delivery), major congenital malformations (leading to death, causing significant future handicap or requiring surgery), neonatal hypoglycemia (plasma glucose < 2.2 mmol/l within 4 h after birth), transient tachypnea (requiring continuous positive airway pressure for > 60 min), jaundice (requiring phototherapy) and admission to neonatal intensive care unit [21].

Statistical Analysis

Categorical data were given as number (%) and compared using Chi-square test or Fisher's exact test. Continuous data were given as mean (SD) or median (interquartile range) and compared using unpaired t-test or Mann–Whitney U test depending on distribution. A statistical power analysis was not performed a priori for this secondary analysis. Associations were considered statistically significant at a two-sided p-value < 0.05. All statistical analyses were performed by SPSS 25 (IBM Corp., Armonk, NY, USA).

Results

Sixty-seven (41%) women used insulin degludec and 95 used other long-acting insulin analogs: insulin glargine 100 ($n = 58$ (61%)), insulin detemir ($n = 24$ (25%)), insulin glargine 300 ($n = 9$ (10%)), biosimilar insulin glargine 100 ($n = 2$ (2%)) and NPH insulin ($n = 2$ (2%)). At our center, the proportion of women becoming pregnant while using insulin degludec increased over the years being 9% in 2016, 30% in 2017, 57% in 2018, 66% in 2019 and 88% in 2020. Forty-nine (73%) women using insulin degludec and 29 (31%) ($p < 0.0001$) women using other long-acting insulin analogs were included after implementation of the updated guidelines on February 23, 2018.

Mealtime insulin was insulin aspart, except in eight (12%) women using faster-acting insulin aspart (fiasp) with insulin degludec, while two (2%) used insulin fiasp and two (2%) used insulin lispro with other long-acting insulin analogs.

Clinical characteristics of the women using insulin degludec were comparable to the remaining women (Table 1). Vitamin D insufficiency (serum 25-hydroxy-vitamin D < 50 nmol/l) was diagnosed in 10 out of 46 (22%) versus 6 out of 29 (21%), $p = 0.91$.

All maternal pregnancy outcomes including preeclampsia (10% versus 8%, $p = 0.68$) and preterm delivery (18% versus 23%, $p = 0.39$) were similar between women using insulin degludec and other long-acting insulin analogs. There were no perinatal deaths, and all other neonatal outcomes including birth weight z score, SGA and LGA infants were similar between the groups (Table 2). Labor dystocia was the main contributing factor for emergency cesarean section in 53% (8 out of 15) of women using insulin degludec and in 48% (13 out of 27) of women using other long-acting insulin analogs, $p = 0.75$.

Discussion

In this secondary analysis of prospectively collected data in women with type 1 diabetes using insulin degludec before and during pregnancy, similar pregnancy outcomes compared to women using other long-acting insulin analogs were seen. No clinical concerns by continuing insulin degludec during pregnancy were observed in this cohort.

This study supports the findings from our previous study of 22 women using insulin degludec from preconception until after delivery, where use of insulin degludec seemed safe [19].

We cannot rule out confounding by indication to a certain degree, as insulin degludec probably was prescribed pre-pregnancy to women who had dysregulated diabetes with hyperglycemia and/or problematic hypoglycemia with the aim of achieving better glycemic control. So much the more is it reassuring that glycemic control and pregnancy outcomes in women using insulin degludec were similar to those in women using other long-acting insulin analogs. The use of insulin degludec increased over time and the majority of women using insulin degludec were included after February 23, 2018, where slightly tighter glycemic targets and a new practice for aspirin prescription and measurement of vitamin D level were implemented [20] resulting in a higher prevalence of women prescribed aspirin in the insulin degludec group of the present study. However, the prevalence of preeclampsia, preterm delivery and LGA did not differ between women included before and after this date in the original cohort [20], and HbA1c, total insulin doses and prevalence of vitamin D insufficiency were similar between women using insulin degludec and other long-acting insulin analogs.

Since shifting the type of long-acting insulin in early pregnancy may lead to fluctuating glucose values, it was the policy at our center to let women who had obtained good glycemic control and who were satisfied with using insulin

Table 1 Clinical characteristics in 162 women with type 1 diabetes using insulin degludec or other long-acting insulin analogs before and during pregnancy

	Insulin degludec ($n=67$)	Other long-acting insulin analogs ($n=95$)	p-value
Maternal age (years)	31 ± 5	31 ± 6	0.94
Duration of diabetes (years)	14 (8–21)	14 (5–21)	0.62
Gestational age at inclusion (days)	66 (59–75)	63 (57–79)	0.54
Nulliparous	47 (70)	54 (57)	0.09
Pre-pregnancy BMI (kg/m^2)	24.4 (21.5–28.6)	24.4 (22.0–29.1)	0.77
Smoking	8 (12)	8 (9)	0.49
Northern European origin	60 (91)	83 (87)	0.48
HbA1c before pregnancy			
%	7.0 (6.6–7.9)	7.0 (6.6–7.9)	0.93
Mmol/mol	53 (49–63)	53 (49–63)	
HbA1c at 9 weeks			
%	6.5 (6.2–6.9)	6.5 (6.0–7.0)	0.52
Mmol/mol	48 (44–52)	47 (42–53)	
HbA1c at 20 weeks			
%	6.1 (5.7–6.5)	6.1 (5.5–6.4)	0.39
Mmol/mol	43 (39–48)	43 (37–46)	
HbA1c at 35 weeks			
%	6.0 (5.6–6.5)	6.1 (5.6–6.5)	0.68
Mmol/mol	42 (38–47)	43 (38–48)	
Total insulin dose at 9 weeks (IU/kg)	0.52 (0.40–0.66)	0.57 (0.47–0.72)	0.06
Total insulin dose at 20 weeks (IU/kg)*	0.50 (0.44–0.70)	0.57 (0.47–0.75)	0.47
Total insulin dose at 35 weeks (IU/kg)**	0.93 (0.65–1.19)	0.82 (0.60–1.21)	0.41
Events with mild hypoglycemia per week at 9 weeks	7 (3–10)	5 (3–9)	0.48
Events with mild hypoglycemia per week at 20 weeks***	3 (2–5)	3 (1–5)	0.89
Events with mild hypoglycemia per week at 35 weeks****	3 (2–5)	3 (2–7)	0.56
Systolic office blood pressure (mmHg) at 9 weeks	116 ± 10	118 ± 11	0.24
Diastolic office blood pressure (mmHg) at 9 weeks	74 ± 7	75 ± 7	0.19
Kidney involvement	6 (9)	8 (8)	0.30
Microalbuminuria	3 (4.5)	7 (7)	
Diabetic nephropathy	3 (4.5)	1 (1)	
Diabetic retinopathy	24 (37)	38 (46)	0.28
Aspirin prescribed in early pregnancy	53 (79)	41 (43)	< 0.0001
Antihypertensive treatment during pregnancy	21 (31)	25 (26)	0.49
Gestational weight gain (kg)	12.3 (9.3–14.8)	12.2 (8.5–14.3)	0.58

Using insulin degludec or other long-acting insulin analogs before and during pregnancy

Data are given as number (%), mean (SD) or median (interquartile range)

Microalbuminuria was defined as urinary albumin/creatinine ratio 30–299 mg/g

Diabetic nephropathy was defined as urinary albumin/creatinine ratio ≥ 300 mg/g

The individual clinical data were obtained from 94 to 100% of the women unless otherwise stated: *$n=106$; **$n=94$; ***$n=114$; ****$n=101$

degludec before conception continue to use this insulin during pregnancy. This is in line with how the insulin analogs lispro [28, 29] and insulin glargine [6, 30] were introduced to pregnant women with diabetes.

This is the largest study on pregnancy outcomes in women with type 1 diabetes using insulin degludec both before and throughout pregnancy. The data were collected prospectively under routine conditions in a real-world setting [21], and the development of preeclampsia was carefully assessed. The original study focused on hypertension in pregnancy [20, 21], but other pregnancy and neonatal outcomes were also reported. We considered the present cohort as a unique opportunity to evaluate data on the use of insulin degludec during pregnancy under real-world conditions.

Table 2 Maternal pregnancy outcomes and neonatal outcomes in 162 pregnancies of women with type 1 diabetes using insulin degludec or other long-acting insulin analogs before and during pregnancy

	Insulin degludec ($n=67$)	Other long-acting insulin analogs ($n=95$)	p-value
Maternal pregnancy outcomes:			
Preeclampsia	7 (10)	8 (8)	0.66
Delivery with preeclampsia before 37 weeks	2 (3)	6 (6)	0.47
Mode of delivery:			0.37
Vaginal	35 (52)	52 (55)	
Elective cesarean section	17 (25)	16 (17)	
Emergency cesarean section*	15 (23)	27 (28)	
Neonatal outcomes:			
Gestational age at delivery (days)	265 (261–268)	262 (259–267)	0.27
Preterm delivery (< 37 weeks)	11 (16)	22 (23)	0.29
Birth weight (g)	3510 (3118–3885)	3514 (3125–3796)	0.91
Birth weight z score	0.95 ± 1.4	0.99 ± 1.3	0.85
Small for gestational age infants	3 (4)	5 (5)	1.0
Large for gestational age infants	25 (37)	37 (39)	0.83
Perinatal mortality	0	0	–
Admission to neonatal intensive care unit	16 (24)	22 (23)	0.87
Neonatal hypoglycemia (< 2.2 mmol/l)	21 (32)	34 (41)	0.28
Transient tachypnea of the newborn	9 (14)	10 (11)	0.56
Neonatal jaundice	16 (24)	18 (19)	0.44
Apgar score < 7 at 5 min	0	0	–
Major congenital malformation	1 (1)	1 (1)	1.0

Data are given as number (%), mean (SD) or median (interquartile range)

*Cesarean section < 8 h from decision making

The individual clinical data were obtained from ≥ 99% of the women or infants, except neonatal hypoglycemia where data were obtained from 148 (91%) of the infants

However, data on basal insulin doses were not collected in the original study [20, 21] and were therefore not available in this secondary analysis. We acknowledge this as a limitation in this study. Continuous glucose monitoring (CGM) was only used in selected women in this cohort. Therefore, data on use of CGM are not available in this study. Likewise, despite being the largest cohort so far of women using insulin degludec during pregnancy, we also acknowledge that the observational study design and the relatively small sample size limit our possibility to elucidate the safety in details. Larger studies in pregnant women with diabetes, preferably as RCTs, are warranted to evaluate the efficacy and safety in detail. Likewise, cohort studies or registry studies are needed to evaluate rare neonatal complications as congenital malformations and perinatal mortality.

The lack of data on severe hypoglycemia (requiring third-party assistance [31]) is also a limitation of this study. However, in our previous publication on 22 women with type 1 diabetes using insulin degludec from conception until after delivery, the prevalence of severe hypoglycemia was low [19]. Likewise, in previous case reports no women using insulin degludec during pregnancy reported severe hypoglycemia [13–17].

Data on number of women planning their pregnancies were not available in this study, but generally a high proportion of pregnancies in women with type 1 diabetes are unplanned [32]. The increasing use of insulin degludec therefore leads to more women becoming pregnant while using this insulin [13, 15–17]. When considering whether to continue insulin degludec or to change to another long-acting insulin analog and risk temporary worsening of glycemic control due to insulin change [17, 19], data from this study may be helpful for this decision.

To conclude, we found similar pregnancy outcomes with insulin degludec and other long-acting insulin analogs in women with type 1 diabetes, suggesting that insulin degludec initiated before pregnancy may be continued throughout gestation.

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Declarations

Conflict of interest ERM have received fees for giving talks for Novo Nordisk A/S. ERM, PD and LR are participating in multicenter and

multinational clinical studies on the use of insulin in pregnant women with preexisting diabetes in collaboration with Novo Nordisk; no personal honorarium is involved. NCD is funded by Novo Nordisk Foundation.

Ethical standard statement This study was in accordance with the Helsinki declaration. In addition, the study was approved by The National Committee on Health Research Ethics (H-15019186 and H-15009413) and The Danish Data Protection Agency (2012-58-0004, RH-2015-289, I-Suite: 04305).

Informed consent disclosure All participants gave written informed consent before the data collection.

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