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# Treatment with the long-acting insulin analog degludec during pregnancy in women with type 1 diabetes: An observational study of 22 cases

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ABSTRACT

*Aim:* To report glycemic control and pregnancy outcome in pregnant women with type 1 diabetes on insulin degludec.

*Methods:* Twenty-two women with type 1 diabetes on degludec from conception to delivery between 2014 and 2018 were compared with 51 pregnant women with type 1 diabetes on glargine.

*Results:* Baseline characteristics were comparable, however HbA1c was higher at median 9 (range 5–19) weeks in women on degludec compared to women on glargine (6.9% (5.7–8.7); (52 (39–72) mmol/mol) versus 6.4% (5.1–10.1); (46 (32–87) mmol/mol), p = 0.04). HbA1c was similar in late pregnancy (6.3% (5.6–7.1); (45 (38–54) mmol/mol) versus 6.1% (5.2–9.0); (43 (33–75) mmol/mol), p = 0.28). The prevalence of severe hypoglycemia was 3 (14%) versus 6 (12%), p = 1.00 during pregnancy and 0 versus 1, p = 1.00 during hospital admittance after delivery. Most women on degludec used one daily injection in early (20 (91%) versus 25 (49%), p = 0.001) and late pregnancy (21 (96%) versus 19 (37%), p < 0.001). No significant differences in obstetrical and neonatal outcomes were found between the groups. Maternal hospital admittance after delivery was 2 (1–5) versus 3 (2–11) days (p = 0.004).

*Conclusions:* Glycemic control in late pregnancy, severe hypoglycemia during and immediately after pregnancy as well as pregnancy outcome were comparable in women on degludec or glargine. Degludec initiated preconceptionally may be continued in pregnancy.



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## 1. Introduction

Type 1 diabetes in pregnancy is associated with increased risk of maternal and offspring complications such as congenital malformations, preeclampsia, preterm delivery, macrosomia, perinatal morbidity and mortality [1–3]. Moreover, offspring born to women with type 1 diabetes have a long-term increased risk of obesity and type 2 diabetes [1–4]. Tight glycemic control at the time of conception and during pregnancy is mandatory to reduce the risk of adverse outcomes, though maternal severe hypoglycemia is a major barrier in achieving this goal [5].

In 2013 the long-acting insulin analog degludec entered the European market. Non-pregnant subjects with type 1 diabetes treated with degludec have lower rates of hypoglycemia and a greater reduction in fasting blood glucose levels compared with glargine or detemir [6–8].

Thus, this stable glycemic profile and lower rate of hypoglycemia documented outside pregnancy might be beneficial also in pregnancy [9]. However, so far safety and efficacy of degludec have not been studied in pregnancy. Degludec has a half-life of >25 h and a duration of action exceeding 42 h [10]. It is therefore a concern that degludec may cause severe maternal hypoglycemia within the first few days after delivery because of the abrupt drop in the insulin requirement immediately after delivery [11,12]. Nonetheless, degludec has been and is currently used off-label during pregnancy by women choosing to continue a preconceptionally instituted degludec treatment.

To our knowledge no cohort studies using insulin decludec including a control group has been published so far. Only case reports with 2–6 women with type 1 diabetes treated with degludec [13,14] have been reported where all infants were liveborn without congenital malformations. An ongoing randomized controlled multi-center study (EXPECT) in pregnant women with type 1 diabetes compares the safety and efficacy in women on degludec versus detemir, both combined with the rapid-acting insulin analog aspart [15]. Results are expected in 2021 [15]. In the meantime, clinicians and women using degludec during pregnancy urgently need information on potential benefits and risks.

Since the launch of degludec, our policy has been to let women treated with degludec continue on this drug during pregnancy. Among the women with type 1 diabetes treated with multiple dose injection regimen in our center, none were treated with degludec in 2013, 4% in 2014, 6% in 2015, 6% in 2016 and 24% in 2017. In the first half of 2018 (January-August) the figures were 57%. Thus, it is relevant to monitor degludec treatment in pregnancy closely with regards to drug safety and potential indications to discontinue treatment.

The aim of this study was to report glycemic control and pregnancy outcome in pregnant women with type 1 diabetes treated with insulin degludec from conception to early after delivery.

## 2. Subjects, material and methods

### 2.1. Study designs

In the local quality assessment database Clinical Measure System (CMS) all available records of singleton pregnant women with type 1 diabetes treated with insulin degludec (degludec) from conception to delivery and followed at our center from April 2014 to July 2018 were identified. For comparison women treated with insulin glargine 100 (glargine) followed at our center from January 2016 to June 2018 served as controls. Data on all women were evaluated retrospectively. All women combined their long-acting insulin analog with the rapid-acting insulin aspart at meals. For women with more than one pregnancy during the study period only the latest pregnancy was used in the present analysis.

### 2.2. Study subjects

In total 24 unselected women on degludec and 58 women on glargine were identified. Two women on decludec and seven women on glargine were excluded from analysis due to the following reasons: One woman on degludec and two women on glargine had early miscarriages, two women on glargine had induced abortions; one at 22 weeks due to severe brain malformations; one at 8 weeks due to extremely poor glycemic control, three women on glargine were excluded as they moved during pregnancy to another region of Denmark and lastly one woman on degludec could not participate due to participation in the EXPECT study. Thus, 22 women on degludec and 51 women on glargine were eligible for the study (Fig. 1). The individual clinical data were available in 88–100% of the women.

### 2.3. Measurements

During pregnancy, the women visited the pregnancy outpatient clinic and/or their local diabetes clinic mainly at 2-week intervals. Data from first and last visit at Center for Pregnant Women with Diabetes at Rigshospitalet at median 9 (range 5–19) weeks and at 36 (33–38) weeks were assessed in the present analysis. The women were recommended to self-monitor plasma glucose (SMPG) values at least seven times daily; before and 1.5 h after main meals and pre-bedtime. They were advised to perform self-adjustment of insulin dose based on the SMPG values of the past three days aiming for pre-prandial SMPG of 4.0–6.0 mmol/l, 1.5 h post-prandial SMPG of 4.0–8.0 mmol/l and pre-bedtime SMPG of 6.0–8.0 mmol/l [16].

Severe hypoglycemia was defined as events with symptoms of hypoglycemia requiring help from another person to administer injection of glucagon, glucose or oral carbohydrate to re-establish blood glucose level [17]. Mild hypoglycemia was defined as events with symptoms familiar to the women as hypoglycemia and managed by themselves [17]. Self-estimated hypoglycemia awareness was drawn from

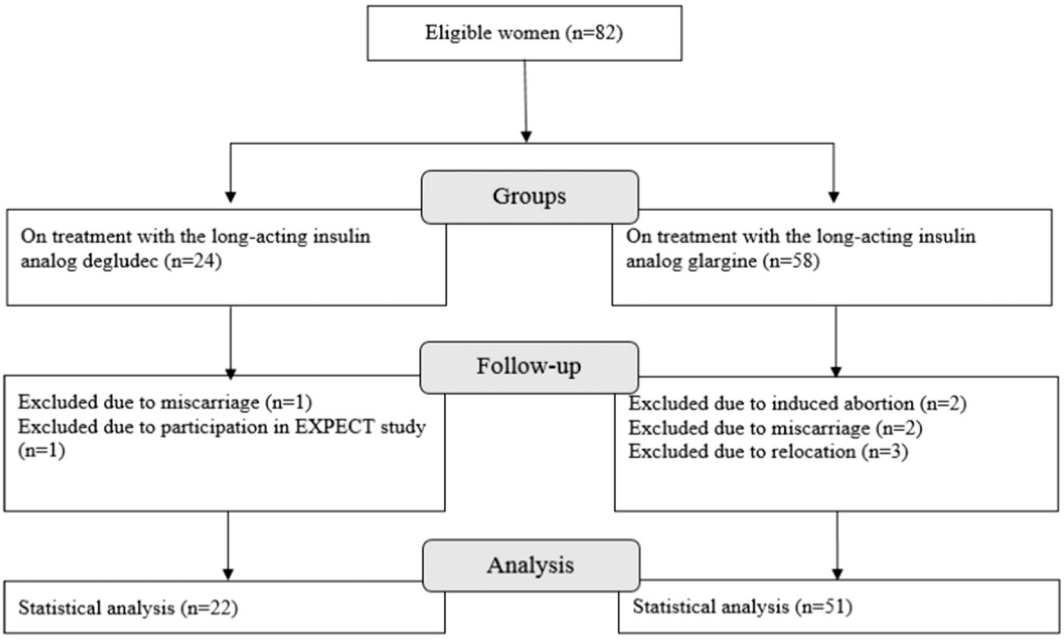


**Fig. 1 – Flowchart of women with type 1 diabetes treated with long-acting insulin analog degludec or glargine from conception to early after delivery.**

answers to the question; "Do you recognize symptoms, when you have a hypoglycemic event?" Women answering 'always' were defined as having normal awareness, 'usually' impaired awareness, and 'occasionally' or 'never' unawareness [17].

At every visit HbA1c, insulin dose, blood pressure and weight were recorded, and the urine screened for proteinuria by a dipstick test. If the dipstick test was positive spot urine albumin-to-creatinine ratio (UACR) measurement was performed [18].

Gestational weight gain was calculated as the difference between the last weight measured before delivery and the self-reported pre-pregnancy weight [19].

Insulin dose immediately after delivery was prescribed by an endocrinologist at a visit prior to delivery and was estimated to approximately 60% of pre-pregnancy insulin dose [11,12]. Due to the long half-life of degludec women were advised to pause the degludec treatment the first day after delivery. In practice the women delivering by planned cesarean section omitted the degludec injection on the morning of the operation and those delivering vaginally omitted the first decludec injection after delivery. With this pragmatic strategy we aimed to reduce the plasma level of degludec as fast as possible to the lower insulin level needed immediately after delivery.

HbA1c was analyzed using a Bayer DCA 2000 analyzer by a latex immunoagglutination inhibition method. HbA1c $\leq$ 40 mmol/mol (5.8%) was recommended in the second part of pregnancy. Blood pressure was measured after 5–10 min of rest. Antihypertensive treatment was initiated if blood pressure $\geq$ 135/85 mmHg and/or UACR $\geq$ 300 mg/g [18]. The women were classified as having diabetic nephropathy if UACR $\geq$ 300 mg/g [18]. Diabetic retinopathy was diagnosed by retinal photo screening [20]. Preeclampsia was defined as two measurements at least 4 h apart of either systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg, and urinary albumin excretion > 190 mg/24 h or $\geq$ 1 + on a sterile midstream urine dipstick after 20 weeks [18].

The following outcomes were collected from the CMS database. Maternal: Preeclampsia, cesarean section, gestational age at delivery, preterm delivery (<37 completed weeks). Neonatal: Birth weight, first plasma glucose value measured at 1–2 h after delivery, neonatal hypoglycemia (1–2 h plasma glucose <2.5 mmol/l), need of intravenous glucose, transient tachypnea requiring continuous positive airway pressure > 1 h, neonatal jaundice requiring photo therapy, Apgar score <7 measured 5 min after delivery and admittance to neonatal intensive care unit.

Data regarding rapid- and long-acting insulin doses, number of daily insulin injections, hypoglycemia awareness status, mild hypoglycemia events, severe hypoglycemia events and length of maternal hospital admittance after delivery were collected from local diabetes records.

Approval from the Danish Data Protection Agency was obtained. All women gave written consent. According to Danish law, the study is exempt from the requirement of approval by the Danish Research Ethics Committee.

### 2.4. *Statistical analysis*

Data were given as median (range) or number (%). Between group differences were analyzed using chi-squared test and Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables as data were not normally distributed. Standard deviation z-score was calculated to evaluate birth weight. Small (SGA) and large for gestational age (LGA) infants were defined as offspring with a birth

weight ≤10th or ≥90th percentile, respectively, adjusted for sex and gestational age [21]. Associations were considered statistically significant at a two-sided p-value <0.05. All statistical analyses were performed by SPSS statistics 24.0 (SPSS, Chicago, IL, USA).

## 3. Results

Baseline characteristics of the 22 women treated with degludec were comparable with the control group of women treated with glargine, however HbA1c was slightly higher at the first visit in women on degludec compared with women on glargine (6.9% (5.7–8.7); (52 (39–72) mmol/mol) versus 6.4% (5.1–10.1); (46 (32–87) mmol/mol), p = 0.04). HbA1c was reduced to a similar level in the two groups in late pregnancy (6.3% (5.6–7.1); (45 (38–54) mmol/mol) versus 6.1% (5.2–9.0); (43 (33–75) mmol/mol), p = 0.28) (Table 1).

During pregnancy the prevalence of severe hypoglycemia was similar in women on degludec and glargine (14% versus 12%, p = 1.0) (Table 1). None of the women on degludec experienced severe hypoglycemia during maternal hospital admittance after delivery (Table 2). The length of maternal hospital admittance after delivery was one day shorter for women on degludec compared with women on glargine (p = 0.002) (Table 2).

Insulin doses in early and late pregnancy as well as after delivery were comparable between groups, except for smaller long-acting insulin doses in women on degludec in late pregnancy and after delivery compared with women on glargine (Table 3). The majority of women on degludec used one daily injection of long-acting insulin while twice daily injection was used by two women in early pregnancy. Under half of the women on glargine could be managed with once-daily dosing in early (20 (91%) versus 25 (49%), p = 0.001) and late pregnancy (21 (96%) versus 19 (37%), p < 0.001) (Table 3).

No significant differences in obstetrical or neonatal outcomes were found between the groups (Table 2).

## 4. Discussion

In this small retrospective study of 22 women with type 1 diabetes treated with degludec from conception to early after delivery glycemic control in late pregnancy, prevalence of severe hypoglycemia during and immediately after pregnancy as well as pregnancy outcome were comparable in women on degludec or glargine. No safety concerns by continuing treatment with degludec during pregnancy were observed.

HbA1c was higher at first visit in women on degludec. This difference could be due to confounding by indication as degludec could have been prescribed pre-pregnancy to women with dysregulated diabetes and/or problematic

**Table 1 – Maternal characteristics in pregnant women with type 1 diabetes treated with insulin degludec or insulin glargine.**

| | Degludec (n = 22) | Glargine (n = 51) | *p* value |
|---|---|---|---|
| Maternal age (years) | 31 (23–42) | 30 (21–47) | 0.82 |
| Duration of diabetes (years) | 14 (3–31) | 16 (1–31) | 0.90 |
| Nordic European origin | 21 (96) | 44 (90) | 0.66 |
| Gestational age at first visit (days) | 61 (47–115) | 66 (37–130) | 0.15 |
| Gestational age at last visit (days) | 258 (250–268) | 254 (233–264) | 0.01 |
| Pre-pregnancy BMI (kg/m$^2$) | 25 (19–47) | 25 (20–37) | 0.56 |
| HbA1c at first visit (mmol/mol) | 52 (39–72) | 46 (32–87) | 0.04 |
| (%) | 6.9 (5.7–8.7) | 6.4 (5.1–10.1) | 0.04 |
| HbA1c at last visit (mmol/mol) | 45 (38–54) | 43 (33–75) | 0.28 |
| (%) | 6.3 (5.6–7.1) | 6.1 (5.2–9.0) | 0.28 |
| Maternal smoking | 1 (5) | 6 (12) | 0.67 |
| Nulliparous | 10 (46) | 27 (53) | 0.62 |
| Diabetic nephropathy | 0 (0) | 2 (4) | 1.0 |
| Diabetic retinopathy | 5 (23) | 12 (24) | 1.0 |
| Gestational weight gain [§] (kg) | 15 (7–33) | 14 (6–31) | 0.56 |
| Normal awareness at first visit [*] | 16 (73) | 36 (71) | 1.0 |
| Normal awareness at last visit [*] | 15 (68) | 37 (73) | 0.78 |
| At least one episode of severe hypoglycemia the last year before pregnancy | 1 (5) | 7 (14) | 0.42 |
| At least one episode of severe hypoglycemia in pregnancy | 3 (14) | 6 (12) | 1.0 |
| Events of mild hypoglycemia per week at first visit | 3 (0–15) | 4 (0–21) | 0.86 |
| Events of mild hypoglycemia per week at last visit | 3 (0–21) | 4 (0–21) | 0.39 |
| Antihypertensive treatment | 6 (27) | 14 (28) | 1.0 |
| Treatment for thyroid dysfunction | 6 (27) | 21 (41) | 0.30 |
| Folic acid supplementation [#] | 20 (91) | 47 (96) | 0.58 |

Data are given as median (range) or n (%). The individual clinical data were obtained from 95 to 100% of the women.

[*] Self-estimated hypoglycemia awareness was defined as normal, when the women answered "always" to the question; "Do you recognize symptoms, when you have a hypoglycemic event?".

[§] Gestational weight gain was calculated as difference between the self-reported pre-pregnancy weight and the last weight measured before delivery.

[#] Treated with folic acid supplementation before and/or in early pregnancy.

**Table 2 – Pregnancy and neonatal outcome in women with type 1 diabetes treated with insulin degludec or insulin glargine.**

| | Degludec (n = 22) | Glargine (n = 51) | *p* value |
|---|---|---|---|
| Preeclampsia | 4 (18%) | 9 (18%) | 1.0 |
| Gestational age at delivery (days) | 264 (256–282) | 262 (247–280) | 0.96 |
| Preterm delivery (<37 weeks) | 3 (14%) | 15 (29%) | 0.24 |
| Cesarean section | 12 (55%) | 17 (33%) | 0.12 |
| Maternal hospital admittance after delivery (days) | 2 (1–5) | 3 (2–11) | 0.002 |
| Severe maternal hypoglycemia during hospital admittance after delivery | 0 (0%) | 1 (2%) | 1.0 |
| Birth weight (g) | 3,550 (2,866–4,760) | 3,408 (2,406–4,288) | 0.11 |
| Birth weight z-score | 1.27 (-0.81–4.57) | 1.00 (-1.50–4.45) | 0.20 |
| Small for gestational age (≤10th percentile) | 0 (0%) | 2 (4%) | 1.0 |
| Large for gestational age (≥90th percentile) | 10 (46%) | 18 (36%) | 0.60 |
| First plasma glucose at 1–2 h (mmol/l) | 2.4 (1.1–3.9) | 2.3 (1.1–7) | 0.75 |
| Neonatal hypoglycemia (1–2 h plasma glucose <2.5 mmol/l) | 13 (62%) | 25 (58%) | 1.0 |
| Need for intravenous glucose | 4 (18%) | 3 (6%) | 0.20 |
| Continuous positive airway pressure>1h | 3 (14%) | 5 (10%) | 0.70 |
| Neonatal jaundice (requiring photo therapy) | 2 (9%) | 10 (20%) | 0.32 |
| Apgar score <7 at 5 min | 0 (0%) | 0 (0%) | 1.0 |
| Admittance to neonatal intensive care unit | 6 (27%) | 11 (22%) | 0.77 |

Data are median (range) or n (%). The individual clinical data were obtained from 88 to 100% of the women.

**Table 3 – Metabolic parameters in pregnant women with type 1 diabetes treated with insulin degludec or insulin glargine.**

| | Degludec (n = 22) | Glargine (n = 51) | *p* value |
|---|---|---|---|
| Total insulin dose at first visit (IU/kg) | 0.54 (0.30–1.26) | 0.58 (0.12–1.34) | 0.19 |
| Total insulin dose at last visit (IU/kg) | 0.78 (0.32–1.86) | 0.81 (0.33–2.42) | 0.37 |
| Total insulin dose after delivery (IU) | 26 (13–38) | 29 (3–62) | 0.11 |
| Rapid-acting insulin dose at first visit (IU/kg) | 0.23 (0.10–0.81) | 0.26 (0.00–0.78) | 0.40 |
| Rapid-acting insulin dose at last visit (IU/kg) | 0.51 (0.13–1.33) | 0.41 (0.18–2.02) | 0.98 |
| Rapid-acting insulin dose after delivery (IU) | 12 (5–22) | 13 (0–29) | 0.68 |
| Long-acting insulin dose at first visit (IU/kg) | 0.32 (0.13–0.45) | 0.32 (0.12–0.65) | 0.36 |
| Long-acting insulin dose at last visit (IU/kg) | 0.27 (0.18–0.62) | 0.39 (0.15–0.88) | 0.01 |
| Long-acting insulin dose after delivery (IU) | 14 (7–22) | 16 (3–40) | 0.04 |
| ≥3 daily injections of rapid-acting insulin first visit | 22 (100%) | 50 (98%) | 1.0 |
| ≥3 daily injections of rapid-acting insulin last visit | 22 (100%) | 50 (98%) | 1.0 |
| One daily injection of long-acting insulin first visit | 20 (91%) | 25 (49%) | 0.001 |
| One daily injection of long-acting insulin last visit | 21 (96%) | 19 (37%) | <0.001 |

Data are median (range) or n (%). The individual clinical data were obtained from 95 to 100% of the women.

hypoglycemia with the aim to achieve better glycemic control and lower hypoglycemia risk. However, HbA1c levels were reduced to the same level in women on degludec and glargine in late pregnancy. Most women on degludec were treated with long-acting insulin once daily, while the majority of women on glargine needed two or more injections in late pregnancy as previously described in our center [22]. This difference in numbers of required injections of long-acting insulin analog could probably be ascribed to the long duration of action of degludec [10].

The prevalence of severe hypoglycemia during pregnancy was 14% in women on degludec and 12% in women on glargine. This is remarkably lower than the prevalence of 23–45% documented prospectively in previous studies from our center [17,23] and other centers [24–26], but the retrospective data collection in the current study is a limitation. Future prospective larger studies should elucidate whether lower prevalence of severe hypoglycemia during pregnancy can be obtained with degludec compared with other long-acting insulin analogs.

Due to the long duration of action of degludec [6,7], severe hypoglycemia within the first few days after delivery is of clinical concern when using this insulin. Therefore, it is reassuring that none of the women on degludec experienced severe hypoglycemia during maternal hospital admittance after delivery using the current strategy of pausing the degludec treatment on the first day after delivery. Factors leading to increased length of hospital stay after delivery include preterm delivery and neonatal morbidity. The prevalence of both preterm delivery and neonatal morbidity was low in both groups and similar to previously published data from our center [27].

A major concern regarding the use of new insulin analogs in pregnancy is congenital malformations and perinatal

death [1,28]. Our study was not designed or powered to discuss the prevalence of severe congenital malformations, miscarriage or perinatal death.

However, it is reassuring that neither severe congenital malformation nor perinatal death were identified among women on degludec. The safety and efficacy of the long-acting insulin analog detemir has been evaluated in a randomized controlled trial [29]. An ongoing international cohort study on approximately 2500 pregnant women with diabetes treated with detemir or other basal insulins aims to evaluate safety with the primary outcome measures; major congenital malformations, perinatal death and neonatal death and will probably include larger dataset on women treated with degludec [30].

No randomized controlled trial has been undertaken on the use of insulin glargine in pregnancy. However, insulin glargine is widely used in pregnancy and observational data on exposed pregnancies do not indicate any adverse effect on pregnancy or on the health of the infant [31]. For this study we compared women treated with insulin degludec and insulin glargine in order to obtain more clinical data on the use of these two insulin types in pregnancy.

The strength of our study is that it is the first observation of a clinically relevant number of consecutive women treated with degludec from conception to early after delivery and a comparable control group treated with glargine carefully reporting both glycemic control and pregnancy outcome in a real-world setting. As a control group, women on glargine was chosen, because it is widely used in pregnancy. Although the scientific evaluation of this insulin analog has been limited, clinical data on a large number of exposed pregnancies exist and do not indicate any adverse effect on pregnancy or on the health of the infant [32]. Nevertheless, further information on the use of glargine in pregnancy is still needed [33]. It is a limitation to our study that it was retrospective and with a limited number of women on degludec, which makes strong statements concerning efficacy and safety impossible. In the evaluation of the risk of severe hypoglycemia during maternal hospital admittance after delivery it is a potential limitation that women on decludec were discharged from hospital a day earlier than women on glargine leaving one day less for observation and registration of severe hypoglycemia.

A high proportion of women with diabetes become pregnant without planning their pregnancy with their diabetes care givers [34]. The increasing use of degludec therefore leads to an increasing number of women becoming pregnant on degludec. When counseling a woman with diabetes on degludec in early pregnancy the options are either to (i) change degludec to a long-acting insulin that is generally accepted for use during pregnancy and accept turbulence in the glycemic control at least the following week or two or (ii) continue treatment with degludec once daily. The data from this study may be helpful for this decision.

In summary, while waiting for the results of the ongoing large scale randomized controlled trial and larger observational studies on safety and efficacy of degludec, this cohort reports similar pregnancy outcome with decludec and glargine suggesting that degludec initiated preconceptionally may be continued in pregnancy.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.004.

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