

CASE SERIES

# Successful Outcomes with Insulin Degludec in Pregnancy: A Case Series

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## ABSTRACT

Optimal glycaemic control pre-conception and throughout pregnancy is paramount to achieve the best outcomes and to minimise the risk of complications for the mother and baby. Current long-acting insulin analogues that have been approved by the National Institute for Health and Care Excellence in the UK for use in pregnancy include glargine and detemir. In many patients, these treatments have limitations because of their pharmacokinetic properties thus not enabling optimal glycaemic control. Efforts at rapidly achieving the recommended blood glucose targets with these analogues can be associated with recurrent and/or disabling hypoglycaemia. Degludec is a second-generation ultra-long-acting insulin analogue, which has been shown to mimic endogenous basal insulin production by the pancreas. This may offer patients better control with less hypoglycaemia

where first-generation insulins fail. There are currently no randomised controlled studies to support the use of insulin degludec in pregnancy. We report three cases of women who were on insulin degludec during pregnancy and achieved successful outcomes. Two of them were commenced on this during pregnancy because of hypoglycaemia with licenced insulin therapy. All the women showed an improvement in glycaemic control during pregnancy. There was attenuation of a wide glycaemic variability as demonstrated by a continuous glucose monitoring (CGM) system in one of the patients. They all delivered healthy babies. This case series highlights the urgent need for large randomised control trials to establish the safety and efficacy of insulin degludec in pregnancy.

**Keywords:** Insulin degludec; Pregnancy; Type 1 diabetes; Type 2 diabetes

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## INTRODUCTION

Optimal glycaemic control before and throughout pregnancy plays an important role in minimising detrimental effects on the foetus, pregnant women, and neonates. Insulin remains the gold standard of treatment for achieving blood glucose targets during pregnancy in patients with type 1 diabetes mellitus and in those with type 2 or gestational diabetes mellitus

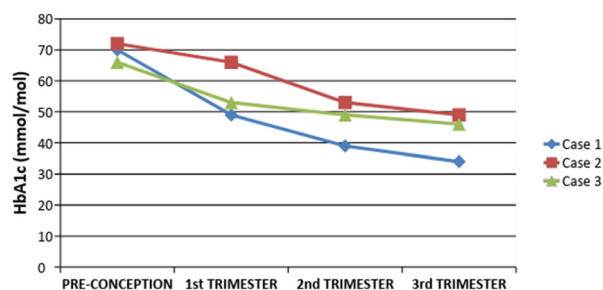
where metformin monotherapy is not tolerated or unlikely to achieve glycaemic targets [1].

Insulin analogues, such as rapid-acting lispro and aspart, and long-acting (or basal) glargine and detemir are licensed and have been approved by the National Institute for Health and Care Excellence (NICE) for use in diabetes during pregnancy in the UK [1]. The basal insulins analogues have been, in theory, designed to mimic the secretion of endogenous basal insulin. Whilst they have demonstrated good glycaemic control in pregnant women, they have limitations due to their pharmacokinetic profiles. Their activity rises to a peak/plateau gradually and then declines, thereby producing peaks and troughs that can potentially cause hypo- and hyperglycaemia. Degludec is a newer ultra-long-acting basal insulin analogue that has shown a prolonged duration of action (> 42 h) and the absence of peak in plasma concentration/activity in non-pregnant subjects [2, 3]. It reaches a steady-state concentration with 3 days of administration. A half-life of > 25 h ensures lower intra-subject variability within a 24-h dosing interval. This would provide a potential advantage for its use in pregnancy to achieve glycaemic goals without the increased risk of maternal hypoglycaemia. However, there is no evidence from controlled studies about the long-term safety and efficacy to support the use of insulin degludec in pregnancy.

We report three cases of women with pre-existing diabetes under our joint diabetes and antenatal clinic at a district general hospital who successfully conceived on therapy with degludec during pregnancy. The women had made an informed choice to be continued (case 1) or commenced (cases 2 and 3) on insulin degludec as a therapeutic trial to help them achieve their glycaemic goals in pregnancy. Informed consent was obtained from all individual participants for being included in the case series.

## CASE 1

A 36-year-old female with type 2 diabetes for 6 years was commenced on degludec prior to conception because of previous intolerance to insulin isophane, detemir, and glargine. Her



**Fig. 1** Glycaemic control pre-conception and during pregnancy

median daily glycaemia at the first visit was 7.9 mmol/l (5.8–8.5 mmol/l); this was reduced to 5.6 mmol/l (4.3–6.8 mmol/l) at delivery. Pre-conception body mass index was 35 kg/m<sup>2</sup>, and glycosylated haemoglobin (HbA1c) was 70 mmol/mol (8.6%). HbA1c decreased to 49 mmol/mol (6.6%), 39 mmol/mol (5.7%), and 34 mmol/mol (5.3%) during the first, second, and third trimester, respectively (Fig. 1). The degludec dose at delivery was 2.5 IU/kg/day of the double strength (U200). She had gained 15 kg during the pregnancy.

She delivered by elective caesarean section at 38 weeks of gestation. The baby was 3850 g in weight. The APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score was 9 and 9 at 1 and 5 min, respectively. There were no perinatal complications and the baby did not require neonatal intensive care unit admission (Table 1). The mother is regularly seen in the diabetes clinic and reports a healthy 3 year old achieving normal milestones.

## CASE 2

A 23-year-old female with a 16-year history of type 1 diabetes and no micro- or macro-vascular complications was changed from glargine to degludec at 8 weeks into her pregnancy due to severe hypoglycaemia with significant glycaemic variability (Fig. 2). She had previously declined insulin pump therapy. Her median daily glycaemia at the first visit was 9.8 mmol/l (2.2–12.3 mmol/l); this was reduced to 5.7 mmol/l (4.8–8.1 mmol/l) at delivery. Pre-conception body mass index was 22 kg/m<sup>2</sup>, and HbA1c was 72 mmol/mol (8.7%). HbA1c decreased to 66 mmol/mol (8.2%), 53 mmol/mol (7.0%), and

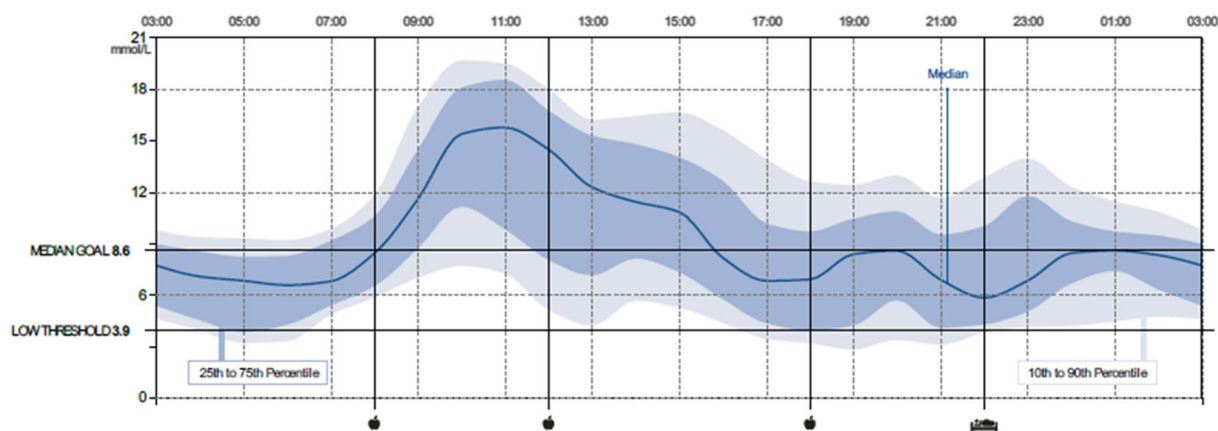
**Table 1** Demographic summary of the patients, maternal and neonatal outcomes

	Case 1	Case 2	Case 3
Age (years)	36	23	34
Diabetes duration (years)	6	16	22
Pre-pregnancy BMI (kg/m <sup>2</sup> )	35	22	23
New onset or progression of pre-existing microvascular disease during pregnancy	No	No	No
Degludec treatment during pregnancy			
Indication	Intolerance to isophane, detemir, and glargine insulins	Severe hypoglycaemia; declined insulin pump therapy	Recurrent hypoglycaemia
Weeks	0–38	8–38	12–38
Dose at delivery (IU/kg/day)	2.5	0.25	0.18
Strength of formulation	U200	U100	U100
HbA1c (mmol/mol)			
Pre-conception	70	72	66
First trimester	49	66	53
Second trimester	39	53	49
Third trimester	34	49	46
Median daily glycaemia (mmol/l) <sup>a</sup>			
At first visit	7.9 (5.8–8.5)	9.8 (2.2–12.3)	7.4 (2.4–10.2)
At delivery	5.6 (4.3–6.8)	5.7 (4.8–8.1)	5.8 (4.0–8.2)
Weight gain at the end of pregnancy (kg)	15	9	8.2
Time of delivery (gestational weeks)	38	38	38
Delivery	Elective caesarean	Forceps delivery	Elective caesarean
New-born			
Birthweight (g)	3850	3680	3660
Congenital malformations	No	No	No
APGAR score (at 1 and 5 min)	9 and 9	9 and 10	9 and 9
Neonatal hypoglycaemia	No	No	No
NICU admission	No	No	No

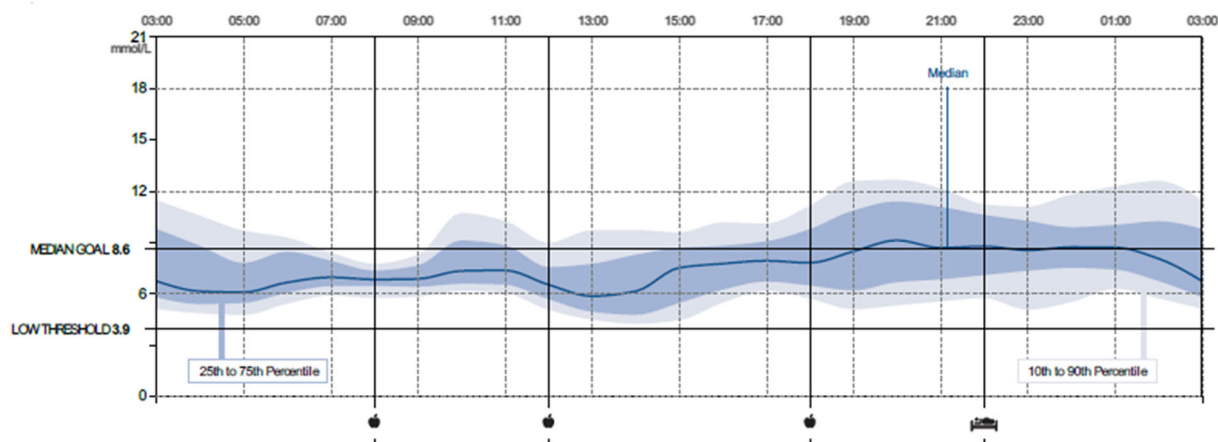
<sup>a</sup> Average of the daily median capillary glucose values, taken over 7 consecutive days prior to day of visit

49 mmol/mol (6.6%) during the first, second, and third trimester, respectively (Fig. 1). Glycaemic variability improved significantly on

degludec (Fig. 3). The degludec dose at delivery was 0.25 IU/kg/day of the standard strength (U100). Her gestational weight gain was 9 kg.



**Fig. 2** CGM profile in patient 2 obtained by FreeStyle Libre® prior to degludec treatment



**Fig. 3** CGM profile in patient 2 obtained by FreeStyle Libre® during degludec treatment

The course of pregnancy was uneventful. Labour was induced at 38 weeks of gestation with assisted delivery using forceps. The baby was 3680 g in weight. The APGAR score was 9 and 10 at 1 and 5 min, respectively (Table 1).

### CASE 3

A 34-year-old female diagnosed with type 1 diabetes since the age of 13. She had previous laser treatment for proliferative diabetic retinopathy that was quiescent for last 7 years. The patient was on novorapid and detemir until 12 weeks into her pregnancy when her basal

insulin was switched to degludec because of recurrent hypoglycaemia. Pre-conception body mass index was 21 kg/m<sup>2</sup>, and HbA1c was 66 mmol/mol (8.2%). HbA1c decreased to 53 mmol/mol (7.0%), 49 mmol/mol (6.6%), and 46 mmol/mol (6.4%) during the first, second, and third trimester, respectively (Fig. 1). The degludec dose at delivery was 0.18 IU/kg/day of the standard strength (U100). She had gained 8.2 kg during her pregnancy. She had retinopathy screening every trimester and no new microvascular event was noted.

She delivered a healthy baby at 38 weeks of gestation by an elective caesarean section. The

baby was 3660 g in weight and the new-born assessment was unremarkable (Table 1).

## DISCUSSION

Poor glycaemic control causes significant risk to the mother in addition to increased foetal morbidity and mortality due to increased rates of miscarriage, preterm labour, congenital malformations, macrosomia, and neonatal hypoglycaemia. These complications could be prevented by promoting tight glycaemic control. This is however difficult to achieve without the associated risk of hypoglycaemia.

The safety and efficacy of the insulin analogue in pregnant women were first reported in 1999 with lispro [4]. This has led to larger-scale clinical trials that confirmed its beneficial effects in rapidly lowering the postprandial glucose levels during pregnancy without causing additional harm to the foetus [5, 6]. Long-acting insulin analogues are required along with short-acting insulin analogues to manage glycaemia through the day. Long-acting insulin analogues currently approved by Food and Drug Administration (FDA) for use in pregnancy are glargine and detemir. Insulin glargine is associated with within-subject variability and high affinity for insulin-like growth factor 1 (IGF-1) receptor, leading to unexpected hypoglycaemia and concerns regarding mitogenic potential, respectively [7, 8]. Insulin detemir, although it demonstrates low variability, is dose-dependent and appears to have a shorter duration of action at lower doses and may require twice daily dosage in those with higher basal insulin requirement [8].

Although insulins glargine and detemir are proven to be safe in pregnancy and non-inferior in their efficacy compared with human insulin, they do not meet the criterion of an ideal basal insulin that would, in theory, have a duration of action long enough to reduce intra-patient and inter-dose variations in insulin concentration in the steady state. Degludec is the new-generation long-acting insulin analogue that comes close to addressing this criterion. It is manufactured through modification of human insulin whereby the threonine at position B30 is

deleted and a 16-carbon fatty diacid is added to lysine at position B29 via a glutamic acid spacer [8]. These structural changes allow soluble multi-hexamers to form upon subcutaneous injection and for continuous slow release of degludec monomers, without variation in the concentration once a steady state has been reached. With a once daily injection, degludec provides a uniform glucose-lowering effect with the duration of action that extends beyond 24 h. This unique pharmacokinetic property lowers the risk of nocturnal hypoglycaemia that has been supported by many studies [9–11]. Furthermore, it demonstrates low IGF-1 receptor binding affinity and low mitogenic potential [8].

Published reports on two cases of females with type 1 diabetes who were on degludec prior to conception have described no long-term adverse effects after it was promptly discontinued in the first trimester upon confirmation of pregnancies [12]. A more recent case report described a successful pregnant outcome in a woman with type 2 diabetes who was on degludec pre-conception and had continued the treatment throughout pregnancy [13]. To date, there are no results of randomised clinical trials of degludec use during pregnancy, given the ethical concern of potential harm to the foetus, although animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity [14].

The fear of foetopathy and adverse pregnancy outcomes per se elicits positive maternal behaviour and attitudinal changes in most pregnancies leading to modest-to-significant improvement in glycaemic control. Healthcare-enabled factors such as use of CGM [15], regular specialist contacts, easier access to specialist advice, and capillary blood glucose (CBG) monitoring equipment contribute to the improvement [16]. But the single most important contributor that dictates the hard-end point of a successful pregnancy outcome is the patient's glycaemic journey within the clinically defined euglycemic parameters, which can be facilitated by the pharmacological treatment provided.



In these three patients who failed or did not tolerate treatment with the insulins glargine or detemir, insulin degludec demonstrated a marked improvement in glycaemic control as demonstrated by the trends in HbA1c (Fig. 1) and lower glycaemic variability, without causing any diabetes-related or foetal/maternal complications. The pregnant state did not appear to affect the pharmacodynamics or pharmacokinetics of insulin degludec. Cases 1 and 3 elected to have a caesarean section. Case 2 was delivered by forceps for the obstetric indication of prolonged labour in a nulliparous woman. There were no adverse neonatal outcomes.

Our cases highlight insulin degludec as a potential alternative to existing basal insulin analogues licensed for use during pregnancy. This is especially pertinent to those patients who have recurrent or severe hypoglycaemia despite intensive management with currently licensed analogues who would otherwise progress to insulin pump therapy. Larger controlled clinical trials are warranted to establish the safety and efficacy profile of degludec in pregnancy.

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**Data Availability.** Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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