Endocrine and Metabolic Science 1 (2020) 100064

Contents lists available at ScienceDirect

Endocrine and Metabolic Science

journal homepage: www.elsevier.com/locate/endmts

Use of insulin degludec in pregnancy: two case reports and a literature review

E. Sprio[a,*], P. Lucotti[a], C. Iadarola[a], C. Bellingeri[b], F. Beneventi[b], E. Lovati[a]

[a] First Department of Internal Medicine, IRCCS Policlinico San Matteo, University of Pavia, Italy
[b] Department of Ostetrics and Ginecology, IRCCS Policlinico San Matteo, University of Pavia, Italy

ARTICLE INFO

Keywords:
Congenital malformation
Diabetes in pregnancy
Insulin Degludec
Type 1 diabetes
Case report

ABSTRACT

As of now, insulin Degludec has no indication for use in pregnancy, because of the lack of studies that prove its safety for foetus. However it isn't infrequent that some women conceive while treating with insulin Degludec. So, before deciding to change the type of insulin therapy during pregnancy, an evaluation of the risk associated to a possible temporary worsening of glycaemic control, due to that insulin replacement, is needed. Referring to case series reported in the scientific literature could provide a support when a clinical decision need to be taken.

We report two cases of women affected by type 1 diabetes who had unplanned pregnancies during treatment with insulin Degludec. In order to avoid the risk of a possible worsening of glycaemic control due to insulin switch, we decided to continue the treatment with Degludec during their pregnancies, after obtaining the patients' written informed consent.

Daily insulin requirement gradually increased for both women pregnancy progressed, and glycated haemoglobin (HbA1c) values improved from the first observation to delivery: 55 mmol/mol (7.2%) at 9 weeks to 47 mmol/mol (6.5%) at 36 weeks, in Patient 1 (P1); 44 mmol/mol (6.2%) at 8 weeks to 33 mmol/mol (5.2%) at 36 weeks, in Patient 2 (P2).

P1 delivered at week 37 with a caesarean section due to failed induction. The newborn, a girl of 3398 g at birth, developed neonatal hypoglycaemia and respiratory distress (Apgar 6-6). Six days after birth she underwent colectomy because of necrotizing enterocolitis and was finally diagnosed with atypical cystic fibrosis.

P2 gave birth to a healthy girl (weight 2745g at birth, Apgar 7-9) at 37 weeks, undergoing a caesarean section for maternal cervical dystocia, without neonatal complications.

Our experience provides additional evidence on the safety of insulin Degludec in pregnancy without any maternal or neonatal outcome suggesting its toxicity.

Introduction

Pregnancy planning is strongly recommended in childbearing age women affected by type 1 diabetes (T1D), in order to optimize glycaemic control before conception and to adjust the treatment according to guidelines.

Congenital malformations, miscarriage, excessive foetal growth, preterm labor and adverse neonatal outcomes are the major complications linked to an unplanned pregnancy and poor glycaemic control (Alexopoulos et al., 2019). It is universally accepted that the post-prandial blood glucose values, particularly at one hour, and the daily glucose variability, offer the best prediction of adverse perinatal outcome. An appropriate therapeutic program (insulin type, timing and root of administration – MDI vs. CSII, dietary counselling and glucose monitoring) is essential to achieve a good glycaemic control during pregnancy planning and conception (Bacon and Feig, 2018).

Among basal insulin analogues available for treatment of diabetes, insulin Degludec has not yet obtained the indication for use in pregnancy because of the lack of evidence proving the safety for the foetus. However, increased embryotoxicity has not been reported in animal reproduction studies and non-clinical data reveal no safety concerns for humans based on studies of toxicity to reproduction (European Medicines Agency (EMA) 2013).

No other clinical cases reported adverse outcomes for mothers and newborns causally linked to insulin toxicity in pregnancy

Abbreviations: APGAR, American pediatric gross assessment Record; BMI, body mass index; CGM, continuous glucose monitoring; CHO, carbohydrates; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; MDI, multiple daily injection; PCT, percentile; P1, patient of the case 1; P2, patient of the case 2; RDS, respiratory distress syndrome; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

* Corresponding author: Dr. Elisa Sprio, Centre for Pregnant Women with Diabetes First Department of Internal Medicine, IRCCS Policlinico San Matteo Pavia, University of Pavia Viale Camillo Golgi 19, 27100 Pavia, Italy.

E-mail address: e.sprio@smatteo.pv.it (E. Sprio).

https://doi.org/10.1016/j.endmts.2020.100064
Received 15 June 2020; Received in revised form 6 September 2020; Accepted 23 October 2020

(Bonora et al., 2019, Hiranput et al., 2019, Formoso et al., 2018, Milluzzo et al., 2018, Roman-Gonzalez et al., 2019).

Degludec is an ultras long acting insulin. When compared with Glargine 100U/ml, it is associated with equivalent HbA1c control and efficacy in maintaining the Time In Range (70-180mg/dl out of pregnancy), but significantly lower nocturnal hypoglycemia rates and lower total doses of insulin (Zhang et al., 2018); however lower safety in reducing hypoglycemic events was shown when Degludec was compared with the new Glargine 300U/ml. Thus data on Degludec effect when used in pregnancy would be potentially important (Yamabe et al., 2019 Mar).

We report two cases of women who conceived during treatment with insulin Degludec and continued with this insulin throughout the whole pregnancy.

Case 1

A 34-year-old Caucasian woman, with T1D, chronic thyroiditis and epilepsy had been a patient of our division of endocrinology and diabetes since 2010.

During her regular clinical check-ups, insulin dosage was optimized and insulin Degludec was started in a basal-bolus schedule with insulin Lispro. The counting of the amount of carbohydrates at meals and a CGM were also applied. Counselling for pregnancy planning was carried out, emphasizing the usefulness of CSII and the risks of adverse outcomes associated with poor glycaemic control: HbA1c between 54 and 64 mmol/mol (7.5-8%) in the last 5 years.

Nevertheless, on October 2015, the patient came to our attention with an unplanned pregnancy at 6 weeks of gestation. She was informed about the lack of scientific studies ensuring a safe use of insulin Degludec in pregnancy. Considering the risk of a further worsening of glycaemic control due to insulin change, the treatment with insulin Degludec was continued in agreement with the patient. No micro vascular complications were present before pregnancy and has not developed after that.

The maternal weight at the beginning of pregnancy was 70 kg (BMI 24.3 kg/m2); the first tests performed at 9 weeks of gestation, showed: HbA1c 55 mmol/mol, TSH 1.65 mU/L (on daily supplementation with Levotiroxin 50 mcg), normal routine exams and negative urine albumin. Despite timely therapeutic adjustments with the increase of daily insulin units (Degludec from 23 to 28 units and Lispro as per her insulin/CHO ratio changes: breakfast 1:20 to 1:15; lunch 1:25 to 1:15; dinner 1:30 to 1:10) and a gradual decrease of HbA1c values from 55 mmol/mol (7.2%) at 9 weeks to 47 mmol/mol (6.5%) at 36weeks, an upward trend to hyperglycaemia persisted in the evening and early night, especially after meals (Fig. 1). This pregnancy experienced the effects of a poor glycaemic control.

The obstetric ultrasound at 34 weeks showed an increase in foetal growth, with abdominal circumference above 95° pct. The patient delivered by caesarean section (scheduled for polyhydramnios) due to failed induction at 37 weeks of gestation. Her body weight at the end of the pregnancy was 95.5 kg (25.5 kg more than the pre-conceptional one). The newborn (a female of 3398g at birth) developed neonatal hypoglycaemia and respiratory distress (Apgar 6-6). Six days after birth the newborn underwent colectomy for necrotizing enterocolitis and was later diagnosed with atypical cystic fibrosis.

Case 2

A 32-year-old Caucasian woman with a history of T1D since the age of 8 was admitted to our division of endocrinology and diabetes for pregnancy planning.

When admitted, she was undergoing treatment with insulin Degludec at bedtime and Aspart insulin at meals; HbA1c was 54 mmol/mol (7.1%) but glucose monitoring showed a marked glucose variability with recurrent hypoglycaemia. No recent evaluation of diabetic complications was available.

The patient also suffered from sero-negative rheumatoid arthritis, Behcet's disease and hypertension. Pharmacological therapy included ciclosporin, losartan, amitriptilin and nutritional supplements (magnesium, niacin and tryptophan). Folic acid and pidolate magnesium supplements were added as soon as the pregnancy was planned.

At the first appointment, the patient was introduced to carbohydrate counting, learned about insulin sensitivity factor and she was advised to maintain contraception until a better glycaemic control was reached.

However, she only returned to our attention eight months later, pregnant at 13 weeks. In agreement with the patient, who gave her written informed consent, we decided to carry on the treatment with insulin Degludec because of the marked glucose variability and provided a personalized diet with a standard quantity of carbohydrates.

Glycaemic control slightly worsened during the first trimester: HbA1c from 44 mmol/mol (6.2%) at 8 weeks of gestation to 48 mmol/mol (6.5%) at 16 weeks. At contrary, it progressively improved during the second and third trimester: HbA1c from 40 mmol/mol (5.8%) at 23 weeks of gestation to 33 mmol/ mol (5.2%) at 36 weeks. While the insulin Aspart doses at meals was gradually increased, no significant increase in Degludec doses was needed. The gestational weight gain was 13 kg, from 62 kg at the first visit in pregnancy (BMI 25.2 kg/m2) to 75 kg at delivery.

Data from SMBG showed 76% of blood checks in range (70-140 mg/dl), 3% lower than 70 mg/dl and 21% over 140 mg/dl, mainly in the late evening. No severe hypoglycaemic episodes occurred during pregnancy, and neither did new complications. At regular ultrasound examinations, the foetus showed normal morphology and an estimated weight adequate for gestational age.

At 37 weeks of gestation, the patient delivered a girl by caesarean section for cervical dystocia (abnormal labor due to ineffectual cervical

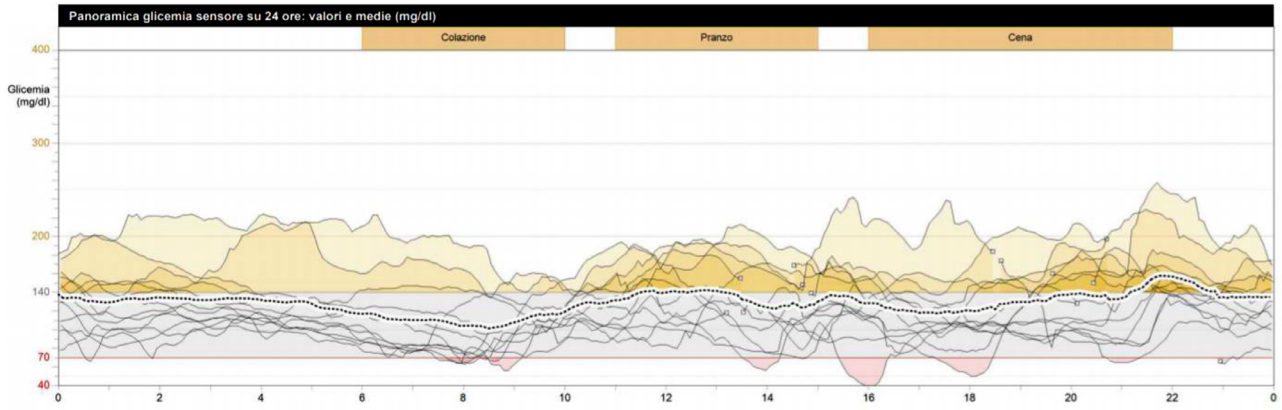

Fig. 1. Sensor 14 days data about 35-36 week of gestation (P1).

Table 1
Clinical series comparison of insulin Degludec treatment in pregnant women.
BMI: body mass index; CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; FGM: flash glucose monitoring; HbA1c: glycated hemoglobin; MDI: multiple daily injections; NA: not available; SMBG: self-monitoring blood-glucose.

	Keller [12] (n=22) Median (IQR) or n (%)	*Case 1*	*Case 2*	*Bonora (case 1)[4]*	*Bonora (case 2)[4]*	*Bonora (case 3)[4]*	*Milluzzo (case 1)[7]*	*Milluzzo (case 2)[7]*	*Formoso[6]*	*Hiranput (case 1)[5]*	*Hiranput (case 2)[5]*	*Hiranput (case 3)[5]*	*Roman-Gonzalez[8]*
Maternal age, years	31 (23–42)	34	32	37	26	22	34	22	31	36	23	34	33
Nulliparous	10 (46)	YES	YES	YES	NA	NA	NO	NO	YES	NA	NA	NA	NO
Type of diabetes	T1D	T1D	T1D	T1D	T1D	T1D	T1D	T1D	T2D	T2D	T1D	T1D	T1D
Diabetes duration, years	14 (3–31)	22	24	10	19	13	8	16	3	6	16	22	17
Type of insulin therapy	MDI	MDI	MDI	MDI	MDI →CSII	MDI	MDI	MDI	MDI + Gliflozin+ Metformin	Only basal injection	MDI	MDI	MDI
Type of Glicemic Monitoring	SMBG	CGM	SMBG	SMBG	SMBG	SMBG	SMBG	SMBG	SMBG	SMBG	FGM	SMBG	NA
Reason of Degludec treatment in pregnancy	As per protocol	Unplanned pregnancy, then prosecution of therapy	Unplanned pregnancy, then prosecution of therapy	Unplanned pregnancy, then prosecution of therapy	Unplanned pregnancy, then replacement with Glargine	Unplanned pregnancy, then replacement with Glargine	Unplanned pregnancy, then replacement with Glargine	Unplanned pregnancy, then replacement with Detemir	Unplanned pregnancy, then prosecution of therapy	Intolerance to other basal insulins	Severe hypo-glycaemia and declined insulin pump	Recurrent hypo-glycaemia	Unplanned pregnancy, then prosecution of therapy
Time of Degludec use in pregnancy, weeks	38 (36-41)	37	37	29	5	7	12	8	38	38	30	26	35
Δ Degludec need [first-last prescription in pregnancy] (UI/day)	NA	+5	+3	+1	NA	NA	+22	+23	+37	NA	NA	NA	+3
HbA1c at first visit, mmol/mol [%]	52 (39–72) [6.9 (5.7-8.7)]	55 [7.2]	44 [6.2]	69 [8.5]	57 [7.4]	77 [9.2]	42 [6.0]	49 [6.6]	49 [6.6]	70 [8.6]	72 [8.7]	66 [8.2]	43 [6.1]
HbA1c at last visit, mmol/mol [%]	45 (38–54) [6.3 (5.6-7.1)]	47 [6.5]	33 [5.2]	50 [6.7]	45 [6.3]	66 [8.2]	33 [5.2]	31 [5.0]	43 [6.1]	34 [5.3]	49 [6.6]	46 [6.4]	NA
Pre-pregnancy BMI, kg/m^2	25 (19–47)	24.3	25.2	21.5	25	21.6	22.7	36.1	33.9	35	22	23	NA
Weight gain at the end of pregnancy, kg	NA	25.5	13	6	8	10	9	8	7	15	9	8	NA

Table 2
Clinical series comparison of gestational outcomes in mothers treated with insulin Degludec during pregnancy.
APGAR: American pediatric gross assessment Record; LIVB: labor induction of vaginal birth; NA: not available; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.

	Keller [12] (n=22) Median (IQR)or n (%)	*Case 1*	*Case 2*	*Bonora (case 1)[4]*	*Bonora (case 2)[4]*	*Bonora (case 3)[4]*	*Hiranput (case 1)[5]*	*Hiranput (case 2)[5]*	*Hiranput (case 3)[5]*	*Formoso[6]*	*Milluzzo (case 1)[7]*	*Milluzzo (case 2)[7]*	*Roman-Gonzalez[8]*
Cesarean section	12 (55%)	YES	YES	YES	YES	YES	YES	NO (LIVB)	YES	YES	YES	NO (LIVB)	YES
Time of delivery, weeks	38 (36-41)	37	37	29	35	37	38	38	38	38	37	37	35
Congenital malformations	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Newborns birth weight, g	3550 (2866-4760)	3398	2745	1730	2900	3930	3850	3680	3660	3280	3330	3300	2500
APGAR score ≤7 at 5 min	0 (0%)	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES
Neonatal hypoglycaemia	13 (62%) and need of glucose infusion for 4 (18%)	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES (glucose infusion for 6h)	YES (glucose infusion for 10h)	NA
Neonatal Respiratory Distress	3 (14%)	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES
Other	Bilirubin increase and photo-therapy for 2 (9%); NICU admission for 6 (27%)	Necrotizing entero-colitis	NO	Bilirubin increase and episodes of apnoea	NO	NO	NO	NO	NO	NO	NO	Bilirubin increase and photo-therapy	Non-invasive ventilation in NICU for two days

dilatation) after mechanical induction for oligohydramnios. The baby weighed 2745 g, Apgar indexes were 7, 9 and 10 at 1, 5 and 10 min, respectively and no hypoglycaemic episodes occurred for the baby.

Discussion

Insulin Degludec is an ultra-long-acting insulin analogue, approved in the EU in early 2013 as basal insulin therapy in patients with type 1 or 2 diabetes (European Medicines Agency 2013).

The prolonged action (> 42h of hypoglycaemic effect) and the flexibility of the injection time, together with a good safety profile (low hypoglycaemic risk), make it effective to improve glucose stability during the whole day (Nasrallah and Reynolds, 2012).

However, the FDA currently only approves insulins Glargine and Detemir as long-acting insulin analogues for pregnancy use. Because of the lack of clinical trials proving its safety on the foetus, insulin Degludec has not yet obtained the indication for its use in pregnancy.

Consistent findings come from a Dutch retrospective single-centre observational study by Keller et al (Keller et al., 2019). The study compared pregnant women with T1D treated with insulin Degludec (22 patients) to patients treated with insulin Glargine (51 patients). No significant differences resulted in the glycaemic control and in maternal or neonatal outcomes between the two groups, neither congenital malformations nor stillbirth in women treated with Degludec during gestation.

Others experiences on its use in pregnancy is growing as small case series are being reported in literature (Table 1).

Hiranput et al. (Hiranput et al., 2019) reported a case series of three women treated with insulin Degludec during pregnancy who achieved successful outcomes; in two of these cases insulin Degludec was started during pregnancy because of recurrent hypoglycaemia and a significant glycaemic variability with ongoing insulin therapy. Similarly, another case of insulin Degludec use during pregnancy without any maternal and foetal complication was reported by Formoso et al. (Formoso et al., 2018).

Bonora et al. (Bonora et al., 2019) reported three cases of women with T1D with unplanned pregnancies while undergoing treatment with insulin Degludec. One case of neonatal complication associated to premature birth was reported (bilirubin increase and episodes of apnoea).

Also the case report of Roman-Gonzalez et al. (Roman-Gonzalez et al., 2019) describes an unplanned gestation begun few weeks after the introduction of insulin Degludec in order to improve the glicaemic control. None important hypoglicaemic event was reported during the pregnancy, neither congenital defect of the baby.

Two cases of a switch of insulin Degludec with others basal insulins at the knowledge of the state of gestation, were reported by Milluzzo et al. (Milluzzo et al., 2018). Mother's transient worsening in the glycaemic profile occurred after discontinuing Degludec, could be the cause of the required intensive for babies.

In our experience, the choice to continue insulin Degludec treatment throughout gestation arose because of the need to achieve the best possible glycaemic control avoiding risks of a change of therapy type during the gestation. In both cases, the poor obstetric and neonatal outcomes might be related to a poor glycaemic control at conception, to the lack of an adequate pregnancy planning and to concurrent co-morbidities, rather than to the kind of insulin therapy during pregnancy. Nevertheless, no congenital malformations occurred, in line with previous observations (Table 2).

Overall, data from previous experience with insulin Degludec in pregnancy support the need to carefully balance unknown risks and favourable effects on glycaemic control.

The first multicentre randomized clinical trial (EXPECT study) designed to test the efficacy and safety of insulin Degludec in pregnant women with T1D as compared with insulin Determir (Research Study Comparing Insulin Degludec to Insulin Detemir) is currently ongoing. The study will provide further evidence for a possible use of Degludec in pregnancy. The first results are expected to be available in 2021.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures

All the authors declare to have no conflict of interest.

Compliance with ethics guidelines

Informed consent was obtained from all individual participants for being included in the case series, according to local committee requirement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

Funding

No funding or sponsorship was received for this publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.endmts.2020.100064.

References

Alexopoulos, AS, Blair, R, Peters, AL, 2019. Management of Preexisting Diabetes in Pregnancy: A Review. JAMA 321 (18), 1811–1819. doi:10.1001/jama.2019.4981.

Bacon, S, Feig, DS., 2018. Glucose Targets and Insulin Choice in Pregnancy: What Has Changed in the Last Decade? Curr Diab Rep 18 (10), 77. doi:10.1007/s11892-018-1054-9.

European Medicines Agency (EMA). London: Committee for Medicinal Products for Human Use, 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002498/WC500138940.pdf Accessed March 30, 2017.

Bonora, BM, Avogaro, A, Fadini, GP, 2019. Exposure to insulin degludec during pregnancy: report of a small series and review of the literature. J Endocrinol Invest 42 (3), 345–349. doi:10.1007/s40618-018-0926-9.

Hiranput, S, Ahmed, SH, Macaulay, D, Shazli, A, 2019. Successful Outcomes with Insulin Degludec in Pregnancy: A Case Series. Diabetes Ther 10, 283–289. doi:10.1007/s13300-018-0532-z.

Formoso, G, Ginestra, F, Di Dalmazi, G, Consoli, A, 2018. Empagliflozin, metformin and insulin degludec, during pregnancy: a case report. Acta Diabetol 55 (7), 759–761. doi:10.1007/s00592-018-1134-y.

Milluzzo, A, Tumminia, A, Scalisi, NM, Frittitta, L, Vigneri, R, Sciacca, L, 2018. Insulin degludec in the first trimester of pregnancy: Report of two cases. J Diabetes Investig 9, 629–631. doi:10.1111/jdi.12721.

Roman-Gonzalez, A, Builes-Barrera C, A, Aristizabal Baron, A, 2019. Exposure to Degludec During Pregnancy: A Case Report. Cureus 11 (7), e5158. doi:10.7759/cureus.5158.

Zhang, Xiao-Wen, Zhang, Xin-Lin, Xu, Biao, Kang, Li-Na, 2018. Comparative Safety and Efficacy of Insulin Degludec With Insulin Glargine in Type 2 and Type 1 Diabetes: A Meta-Analysis of Randomized Controlled Trials. Acta Diabetol 55 (5), 429–441. doi:10.1007/s00592-018-1107-1.

Yamabe, Mizuho, Kuroda, Mami, Hirosawa, Yasuyo, Kamino, Hiromi, Ohno, Haruya, Yoneda, Masayasu, 2019 Mar. Comparison of Insulin Glargine 300 U/mL and Insulin Degludec Using Flash Glucose Monitoring: A Randomized Cross-Over Study. J Diabetes Investig 10 (2), 352–357. doi:10.1111/jdi.12894.

European Medicines Agency. Tresiba (insulin degludec): EU summary of product characteristics. 2013. http://www.emea.europa.eu/ema/. Accessed 1 Feb 2013

Nasrallah, SN, Reynolds, LR, 2012. Insulin degludec, the new generation basal insulin or just another basal insulin? Clin Med Insights Endocrinol Diabetes 5, 31–37. doi:10.4137/CMED.S9494.

Keller, MF, Vestgaard, M, Damm, P, Reinhardt Mathiesen, E, Ringholm, L, 2019 May 15. Treatment with the Long-acting Insulin Analog Degludec During Pregnancy in Women with Type 1 Diabetes: An Observational Study of 22 Cases. Diabetes Res Clin Pract doi:10.1016/j.diabres.2019.05.004.

Research Study Comparing Insulin Degludec to Insulin Detemir, Together With Insulin Aspart, in Pregnant Women With Type 1 Diabetes (EXPECT). https://www.clinicaltrials.gov/ct2/show/results/NCT03377699.