Faster-acting insulin aspart versus insulin aspart in the treatment of type 1 or type 2 diabetes during pregnancy and post-delivery (CopenFast): an open-label, single-centre, randomised controlled trial

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Summary

Background **Faster-acting insulin aspart (faster aspart) is considered safe for use during pregnancy and breastfeeding but has not been evaluated in this population. We aimed to evaluate the effect of faster aspart versus insulin aspart on fetal growth, in women with type 1 or type 2 diabetes during pregnancy and post-delivery.**

Methods **This open-label, single-centre, superiority trial was conducted at Rigshospitalet, Copenhagen, Denmark. Participants aged 18 years or older with type 1 or type 2 diabetes were stratified by diabetes type and insulin treatment modality (multiple daily injections or insulin pump), randomly assigned 1:1 to faster aspart or insulin aspart, from 8 weeks and 0 days (8^{+0}) of gestation to 13^{+6} weeks of gestation, and followed up until 3 months post-delivery. Primary outcome was infant birthweight SD score. Secondary outcomes included HbA_{1c} as well as maternal and fetal outcomes in all participants during the trial. This trial is registered with ClinicalTrials.gov, NCT03770767.**

Findings **Between Nov 11, 2019 and May 10, 2022, 109 participants were included in the faster aspart group and 107 in the insulin aspart group. Primary outcome data were available in 203 (94%) of 216 participants, and no participants discontinued treatment during the trial. Mean birthweight SD score was 1·0 (SD 1·4) in the faster aspart group versus 1·2 (1·3) in the insulin aspart group; estimated treatment difference –0·22 [–0·58 to 0·14]; p=0·23. At 33 weeks of gestation, mean HbA_{1c} was 42 mmol/mol (SD 6 mmol/mol; 6·0% [SD 0·9%]) versus 43 mmol/mol (SD 7 mmol/mol; 6·1% [SD 1·2%]); estimated treatment difference –1·01 (–2·86 to 0·83), p=0·28. No additional safety issues were observed with faster aspart compared with insulin aspart.**

Interpretation **Treatment with faster aspart resulted in similar fetal growth and HbA_{1c}, relative to insulin aspart, in women with type 1 or type 2 diabetes. Faster aspart can be used in women with type 1 or type 2 diabetes during pregnancy and post-delivery with no additional safety issues.**

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Introduction

Despite improvements in several maternal and pregnancy outcomes in women with type 1 or type 2 diabetes (pre-existing diabetes) over the past 20 years,[1] approximately 50% of the infants still have overweight at birth.[2] Maternal glucose is the major determinant of fetal growth, predicting fetal overgrowth and neonatal outcomes[3] and there is a strong positive independent association between HbA_{1c} and fetal growth. Appropriate insulin treatment is essential to obtain strict glycaemic control with reduced postprandial glucose excursions in order to reduce the risk of fetal overgrowth, while preventing episodes of hypoglycaemia.

The first generation rapid-acting insulin analogue aspart (insulin aspart) is safe and reduces postprandial glucose concentrations without increasing maternal hypoglycaemia during pregnancy, compared with human insulin.[4]

Faster-acting insulin aspart (faster aspart) is an improved formulation of conventional insulin aspart where vitamin B3 (niacinamide) and an amino acid (L-arginine) have been added to increase the absorption and stability.[5] Faster aspart is characterised by higher early exposure, and greater early glucose lowering effect than insulin aspart, in non-pregnant women.[5–8] Faster aspart provides a more physiological treatment response, reduces postprandial glucose excursions, and improves HbA_{1c}, without increasing hypoglycaemia, compared with insulin aspart, in children and adults with type 1 or type 2 diabetes on multiple daily injections or insulin pumps.[5–20] In non-pregnant women with type 1 diabetes using intermittently scanned continuous glucose monitoring (isCGM) faster aspart increases time in target range without increasing hypoglycaemia.[21] In Denmark, isCGM is offered during pregnancy in women with type 1 diabetes.[1,22]

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For the Danish translation of the abstract see **Online** for appendix 1

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Research in context

Evidence before this study

Approximately half of infants born to women with type 1 or type 2 (pre-existing) diabetes have overweight at birth. Maternal glucose is the major determinant of fetal growth, predicting fetal overgrowth and neonatal outcomes. During pregnancy, appropriate insulin treatment is essential to obtain strict glycaemic control, with focus on postprandial glucose excursions, to reduce the risk of fetal overgrowth, while preventing episodes of mild and severe hypoglycaemia. Faster-acting insulin aspart (faster aspart) is an improved formulation of conventional insulin aspart characterised by a more physiological profile than insulin aspart, with a higher early exposure and greater early glucose lowering effect leading to reduced postprandial glucose excursions. In people with diabetes who are not pregnant, using multiple daily injections or insulin pumps, faster aspart improves HbA_{1c} without increasing hypoglycaemia, when compared with insulin aspart. As the formulation of faster aspart only differs from that of insulin aspart by the addition of vitamin B3 and L-arginine, faster aspart is considered safe for use during pregnancy and breastfeeding but has not been evaluated in this population. Thus, it is important to compare efficacy and safety of faster aspart with insulin aspart to be able to offer women with pre-existing diabetes the best possible option for insulin treatment during pregnancy and post-delivery. We conducted a literature search in PubMed using the search terms "faster-acting insulin aspart/faster aspart/Fiasp", "pregnancy/pregnant", and "breastfeed/breastfeeding/lactation/lactating" in any language. We had no date restrictions on our search and the final search in relation to protocol finalisation was May 1, 2019. This search resulted in no studies; however, the search was updated on June 12, 2023, for this report showing a retrospective study on 60 women with gestational diabetes, but no randomised controlled trials evaluating the effect or safety of faster aspart during pregnancy or post-delivery.

Added value of this study

The results of the CopenFast trial in participants with pre-existing diabetes showed that treatment with faster aspart during pregnancy and post-delivery resulted in similar fetal growth and HbA_{1c}, relative to insulin aspart in women with pre-existing diabetes. No additional safety issues were observed with faster aspart compared with insulin aspart.

Implications of all the available evidence

Faster aspart, with its greater early glucose-lowering effect, can be used in women with pre-existing diabetes during pregnancy and post-delivery with similar fetal growth and HbA_{1c}, relative to insulin aspart. However, future studies of larger cohorts of women with pre-existing diabetes during pregnancy and post-delivery are required to provide further evidence for clinical and safety outcomes.

Post-delivery, lower insulin doses are needed than pre-pregnancy to maintain glucose values within target while avoiding hypoglycaemia.[1,23] Faster aspart is considered safe for use in pregnancy and breastfeeding with a similar safety profile as insulin aspart,[24] but has not been evaluated in pregnant or breastfeeding populations.

Based on the promising effect and safety profile of faster aspart outside of pregnancy, we hypothesised that treatment with faster aspart results in less fetal overgrowth in women with pre-existing diabetes during pregnancy than insulin aspart, with no additional safety issues.

The aim of this CopenFast trial was to evaluate the effect of faster aspart versus insulin aspart on fetal growth and glycaemic control, during pregnancy and post-delivery, in women with pre-existing diabetes.

Methods

Study design and participants

The CopenFast trial was an investigator-initiated, single-centre, open-label, randomised controlled, superiority trial in pregnant women with pre-existing diabetes at the Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark.

Participants aged 18 years or older were eligible for inclusion, if they had type 1 diabetes or maturity onset diabetes of the young for at least 1 year or type 2 diabetes (any duration), and if they were pregnant with an intrauterine singleton living fetus confirmed by ultrasound scan from 8 weeks and 0 days (8^{+0}) of gestation to 13^{+6} weeks of gestation, were willing to change to the trial drug according to randomisation, and had proficiency in Danish. Participants were excluded if they had severe mental or psychiatric barriers or concurrent disease as assessed by an investigator.[25]

The trial protocol was approved by The Danish Medicines Agency (2018-004680-31) and the Regional Ethics Committee (H-19029966) and was published before completed enrolment.[25] The trial was conducted in accordance with the Good Clinical Practice guidelines and monitored by the local Good Clinical Practice unit. Written informed consent was obtained by all participants before trial participation and by the participants' partners regarding data collection of the infant before delivery.[25]

Randomisation and masking

Participants were stratified by diabetes type and insulin treatment modality (type 1 diabetes using multiple daily injections versus type 1 diabetes using insulin pump versus type 2 diabetes requiring multiple daily injections during pregnancy). Based on clinical presentation judged by the investigators (ERM or LR), four participants with maturity onset diabetes of the young were stratified as type 1 diabetes (n=3) or type 2 diabetes (n=1). All participants were randomly assigned 1:1 to faster aspart

100 U/mL or insulin aspart 100 U/mL as mealtime insulin, both in combination with usual long-acting insulin when indicated. Randomisation was based on a computer-generated sequence (www.randomisation.com) in permuted blocks of varying sizes (2, 4, or 6) conducted by a pharmacist at the hospital pharmacy of the Capital Region, Denmark. Allocation concealment was ensured by sequentially numbered, opaque, and sealed envelopes. Participant enrolment and assignment were made by LR, SKN, ERM, and PH.

Procedures

All participants followed routine care at our centre, with consultations by a diabetes specialist approximately every 2 weeks throughout pregnancy and, for trial purposes, 1 month and 3 months post-delivery. Participants changing mealtime insulin at randomisation were given the same number of mealtime insulin units as intended with the former insulin type. Participants using continuous glucose monitoring (CGM) routinely continued their use regardless of CGM device. The remaining participants with type 1 diabetes were offered isCGM from randomisation. Women with type 2 diabetes, who had not used insulin before pregnancy, initiated insulin treatment when blood glucose monitoring profiles were over target. All oral antidiabetics (including metformin) and GLP-1 receptor analogues were discontinued at randomisation.

The mealtime insulin dose was titrated based on blood glucose monitoring or average glucose profile report provided by a CGM device. During pregnancy all participants were encouraged to adjust mealtime insulin dose at routine visits and every 3–5 days between routine visits to obtain blood glucose monitoring or CGM targets of 4·0–5·5 mmol/L pre-prandially, 4·0–7·0 mmol/L post-prandially, and 5·0–7·0 mmol/L pre-bedtime. HbA_{1c} targets were less than 48 mmol/L (6·5%) before 20 weeks of gestation and less than 38 mmol/L (5·6%) thereafter. For CGM users, treatment targets were mean sensor glucose 5·0–6·0 mmol/mol, time in range in pregnancy 3·5–7·8 mmol/mol (in isCGM users: 3·9–7·8 mmol/L as provided in the average glucose profile report where time in range in pregnancy 3·5–7·8 mmol/L was not available for routine use) more than 70%, time above range in pregnancy less than 25% and time below range in pregnancy less than 4%.[25] CGM data were recorded and uploaded (via Libre View [Abbott], Diasend/Glooko, or CareLink [Medtronic]) for insulin adjustments at each routine visit and collected at randomisation, 21 weeks of gestation, and 33 weeks of gestation for trial purposes.

Post-delivery, the blood glucose monitoring and CGM targets were 4·0–7·0 mmol/L pre-prandially and 6·0–10·0 mmol/L before bedtime and the CGM time in target range was 3·9–10·0 mmol/L.[1,25]

All participants received the same guidance on medical nutritional therapy, carbohydrate counting, and physical activity.[1,25]

Data collection and monitoring

Baseline data were noted at randomisation and included severe hypoglycaemia in the year preceding pregnancy.[25] Trial visits took place when participants attended routine obstetric visits at approximately 21 weeks, 33 weeks, and 35 weeks of gestation where the following were recorded: gestational age, weight, HbA_{1c}, blood pressure, insulin dose, urinary ketones, proteinuria, number of self-reported events of mild hypoglycaemia (events with symptoms familiar to the participant as hypoglycaemia and managed by the participant[26]) the previous week, severe hypoglycaemia (requiring third party assistance[26]), and concomitantly prescribed medication. Participants were encouraged to perform seven-point blood glucose monitoring profiles for 7 days following randomisation and 21 and 33 weeks of gestation. Based on these blood glucose monitoring profiles, mean pre-prandial, post-prandial, pre-bedtime blood glucose monitoring, and the proportion of blood glucose monitoring less than 3·0 mmol/L (level 2 hypoglycaemia) were calculated.[25] For participants with type 1 diabetes using isCGM, the following isCGM metrics for the previous 7 days were collected from the patient records at randomisation and 21 and 33 weeks of gestation: mean sensor glucose, time in range in pregnancy, time above range in pregnancy, and time below range in pregnancy.[25]

The following pregnancy outcomes were recorded: date of delivery, abortion (spontaneous or induced), perinatal death (from 22^{+0} weeks of gestation to 7 days post-delivery), pre-eclampsia (office blood pressure ≥140/90 mm Hg with proteinuria or new onset of symptoms of maternal organ dysfunction), and mode of delivery (vaginal, instrumental vaginal, or emergency or planned caesarean section).[25]

The following neonatal outcomes were recorded: infant sex, gestational age at delivery, head circumference, abdominal circumference, weight, length, duration of stay at neonatal intensive care unit, neonatal morbidity (neonatal hypoglycaemia with plasma glucose <2·2 mmol/L 2 h after birth, jaundice requiring phototherapy, respiratory distress requiring continuous positive airway pressure treatment, and stay in the neonatal intensive care unit), neonatal death (from delivery to 28 days post-delivery), and presence of congenital abnormality (classified according to the European Concerted Action on Congenital Abnormalities[27]). Data from participants who had a spontaneous or induced abortion were collected up to and including the last relevant trial visit.[25]

At 1 month and 3 months post-delivery the following were noted: maternal weight, HbA_{1c}, insulin dose, concomitantly prescribed medication, number of mild hypoglycaemic events in the previous week when insulin-treated, number of severe hypoglycaemic events since delivery, infant weight and length, number of days with infant hospitalisation since discharge after delivery, and presence of congenital abnormality.[25]

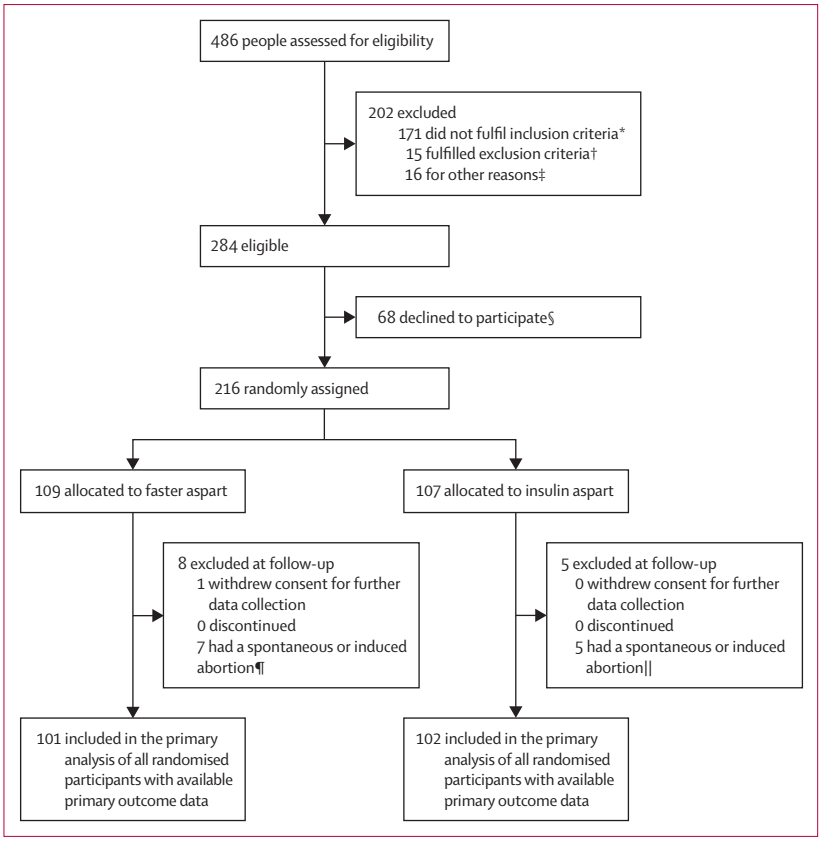

Figure 1: **Trial profile**
*Gestational age over 13 weeks and 6 days (13^{+6}; n=58), insufficient proficiency in Danish (n=48), spontaneous abortion (n=26), women using an insulin pump not compatible with trial drug (n=22), insulin treatment initiated after 13^{+6} weeks of gestation (n=11), duration of type 1 diabetes less than 12 months (n=3), twin pregnancy (n=3). †Severe concurrent disease (n=8), severe mental or psychiatric barrier (n=7). ‡Randomised in previous pregnancy (n=12), moving to another region after first antenatal visit (n=3), allergy to trial drug (n=1). §Did not give consent (n=31), treated with faster aspart and declined to change insulin (n=23), treated with insulin aspart and declined to change insulin (n=14). ¶Spontaneous abortion after randomisation (n=3), induced abortion due to congenital abnormalities (n=2), induced abortion due to severe early intrauterine growth restriction (n=1), induced abortion due to social circumstances (n=1). ||Spontaneous abortion after randomisation (n=2), induced abortion due to congenital abnormalities (n=3).

If a participant reported severe hypoglycaemia during the trial, a structured questionnaire about the event was filled in by an investigator as soon as possible.[25]

Maternal adverse events were defined as any unwanted or unintended event during the trial, related or unrelated to the trial drug. Maternal serious adverse events were defined as any experience that at any dose resulted in any of the following: death, life-threatening experience, inpatient hospitalisation for 24 h or longer or prolongation of existing hospitalisation 24 h or longer, a persistent or significant disability or incapacity or presence of a congenital abnormality, important medical events based upon appropriate medical judgement, or suspicion of transmission of infectious agents. Potential harms evaluated as adverse events and serious adverse events were recorded from randomisation until 3 months post-delivery. Serious adverse events were captured throughout the trial by SKN and LR. Data on congenital abnormalities were collected at delivery and at 1 and 3 months post-delivery and assessed by an experienced obstetrician (PD).

Participants were encouraged to complete a questionnaire at randomisation, 33 weeks of gestation, and 1 month and 3 months post-delivery. Questions included smoking status, years of education, self-estimated hypoglycaemia awareness status, number of events of mild hypoglycaemia the previous week, number of events of severe hypoglycaemia, and breastfeeding.[25]

All data were entered in a research electronic data capture database by SKN, JCS, NCD, and LR. The database was developed for this trial only and accessed with a double code. Double data entry was performed in a random sample of participants to assess data quality.[25]

Outcomes

The primary outcome was infant birthweight SD score adjusted for gestational age and infant sex based on growth curves usually used in Scandinavia.[25,28]

Prespecified secondary maternal outcomes during pregnancy were HbA_{1c} at each trial visit, blood glucose monitoring profiles including level 2 hypoglycaemia and isCGM metrics for 7 days at randomisation and 21 and 33 weeks of gestation, number of events with mild hypoglycaemia the week before each trial visit, number of events with severe hypoglycaemia in the year preceding pregnancy and during pregnancy, maternal gestational weight gain (difference between last weight measured before delivery and self-reported pre-pregnancy weight), and insulin dose at trial visits.[25]

Prespecified secondary pregnancy and neonatal outcomes were prevalence of spontaneous or induced abortion, mode of delivery, early preterm delivery (<34 completed weeks), preterm delivery (<37 completed weeks), pre-eclampsia, perinatal death, prevalence of fetal overgrowth (infant birthweight SD score ≥1·28 [equivalent to large for gestational age, ≥90th percentile]), and small for gestational age infants (infant birthweight SD score ≤–1·28, ≤10th percentile), neonatal morbidity, and neonatal death.[25]

Prespecified outcomes at 1 month and 3 months post-delivery were maternal HbA_{1c}, breastfeeding (any), gestational weight retention (>5·0 kg compared with pre-pregnancy weight), insulin dose, number of mild hypoglycaemic events the previous week, number of severe hypoglycaemic events since delivery, number of participants with at least one adverse event or serious adverse event during the trial, infant growth evaluated by weight SD score, weight, and length, as well as number of days with infant hospitalisation.[25]

Trial protocol amendments

Due to the COVID-19 pandemic, inclusion was paused from March 12, 2020, until May 1, 2020. Participants already included followed trial visits as planned in accordance with national and local guidelines. To minimise direct physical contact during the pause, participants were

not offered blinded CGM and trial visits were conducted by telephone when applicable and in case of COVID-19 symptoms. Therefore, not all clinical data were obtained.

According to the original trial protocol,[25] all participants were to be offered blinded CGM (Envision Pro Sensor, Medtronic MiniMed, Watford, UK) for 7 days following randomisation, 21 weeks of gestation, and 33 weeks of gestation.[25] However, this blinded CGM was withdrawn from the market, and was only available until Sept 17, 2020. The blinded CGM data were therefore not included in the present data analysis. As isCGM was offered to all pregnant participants with type 1 diabetes not already using CGM during the trial, their isCGM data were collected from patient records and analysed for this trial, and data from the few participants using other types of CGM were excluded. The change in procedure was planned by the sponsor (LR) and investigators, implemented before the end of the trial, and approved by the Regional Ethics Committee and aligned with the Good Clinical Practice unit.

The pre-planned inclusion period of 2 years was extended by 6 months to meet the prespecified sample size.

All trial protocol amendments are presented in appendix 2 p 3.

Sample size

Based on the assumption that in our population of women with type 1 and type 2 diabetes the mean infant birthweight SD score was 0·8 (SD 1·6)[29] and that the use of faster aspart could cause a clinically meaningful reduction in the mean infant birthweight SD score to 0·2, and a two-sided type I error of 5% and a type 2 error of 26%, assignment of 198 participants was estimated and randomisation of approximately 220 participants was planned (appendix 2 p 2).[25]

Statistical analysis

Baseline data are presented and stratified by treatment allocation. Categorical variables are presented as numbers (%) and numerical variables as medians (IQR) or means (SD) as appropriate.

The primary outcome and continuous outcomes were analysed by multiple linear regression adjusted for the stratification variables. The assumptions for linear regression were assessed by model diagnostics using quantile-quantile plots and histograms of residuals. Categorical outcomes, including adverse events and serious adverse events, were analysed using logistic regression adjusted for the stratification variables.

Number of severe hypoglycaemic events was presented as raw summarised counts and analysed as a continuous outcome using a linear model to estimate the treatment difference between the two groups.

The primary outcome analysis was done in all participants randomly assigned, except participants who withdrew consent or had a spontaneous or induced abortion after randomisation, as appropriate. Participants who had abortions were excluded from analysis at trial visits after the spontaneous or induced abortion. Safety assessment of adverse events and serious adverse events

See Online for appendix 2

	Faster-acting insulin aspart (n=101)	Insulin aspart (n=102)
Age, years	31·6 (5·2)	31·8 (5·3)
Duration of diabetes, years	12·0 (5·0–19·0)	10·5 (4·0–17·0)
Pre-pregnancy HbA_{1c}, mmol/mol	53 (10)	56 (13)
Pre-pregnancy HbA_{1c}, %	7·0 (0·9)	7·2 (1·2)
Baseline HbA_{1c}, mmol/mol	47 (8)	51 (13)
Baseline HbA_{1c}, %	6·5 (0·7)	6·8 (1·1)
Pre-pregnancy BMI, kg/m²	27·6 (6·4)	28·1 (7·3)
Diabetes type		
Type 1	73 (72%)	73 (72%)
Type 2	28 (28%)	29 (28%)
Multiple daily injection	82 (81%)	82 (80%)
Insulin pump therapy	19 (19%)	20 (20%)
Participants with severe hypoglycaemia		
The year preceding pregnancy	3 (3%)	0
In early pregnancy, prior to randomisation	2 (2%)	1 (1%)
Total insulin dose, both multiple daily injection and insulin pump therapy		
IU/day	37·0 (27·0–46·5)	37·5 (24·0–50·0)
IU/kg per day	0·5 (0·4–0·6)	0·5 (0·3–0·6)
Multiple daily injection therapy (n=164)		
Insulin dose, rapid-acting insulin		
IU/day	15·5 (12·0–21·0)	15·0 (12·0–23·0)
IU/kg per day	0·2 (0·2–0·3)	0·2 (0·2–0·3)
Insulin dose, long-acting insulin		
IU/day	19·0 (14·0–26·0)	18·0 (12·0–28·0)
IU/kg per day	0·24 (0·2–0·3)	0·24 (0·2–0·3)
Total insulin dose		
IU/day	36·0 (26·6–46·0)	34·2 (23·2–49·7)
IU/kg per day	0·4 (0·3–0·6)	0·5 (0·3–0·6)
Insulin pump therapy (n=39)		
Total daily insulin dose		
IU/day	38·1 (33·0–49·7)	38·8 (33·8–48·1)
IU/kg/day	0·5 (0·5–0·7)	0·5 (0·5–0·6)
Basal insulin, percentage of total daily dose	49·0 (43·5–55·7)	53·0 (43·5–59·0)
Routine use of continuous glucose monitoring		
Intermittently scanned*	62 (61%)	58 (57%)
Real-time†	11 (11%)	13 (13%)
None	28 (28%)	31 (30%)
Normal hypoglycaemia awareness‡	37/74 (50%)	31/78 (40%)

Data are presented as mean (SD), median (IQRs), or n (%). All clinical data were obtained from greater than 95% of the participants. Data analysis was done in all randomised participants with available data for the said outcome, based on the group to which they were initially allocated. Participants who had abortions were excluded from analysis at trial visits after the abortion. *Freestyle Libre 1 (Abbott Diabetes Care, Alameda, CA, USA) was used in 109 participants with type 1 diabetes and three participants with type 2 diabetes. Freestyle Libre 2 was used in eight participants with type 1 diabetes. †Dexcom (Dexcom, San Diego, CA, USA) was used in 18 and Medtronic (Medtronic Northridge, Los Angeles, CA, USA) in six participants with type 1 diabetes. ‡Data on hypoglycaemia awareness were obtained from a questionnaire where 152 (75%) of 203 participants responded. Hypoglycaemia awareness was derived from the participant's answer to the question: "How often do you recognise symptoms, when you have hypoglycaemia?"; participants answering "always" were classified as having normal awareness, those answering "usually" as having impaired awareness, and those answering "occasionally" or "never" as having unawareness.[26]

Table 1: **Baseline characteristics at randomisation on 203 participants with data on the primary outcome birth weight SD score**

	Faster-acting insulin aspart (n=101)	Insulin aspart (n=102)	Estimated treatment difference, adjusted mean difference (95% CI) or odds ratio (95% CI)	p value
Primary outcome				
Infant birthweight SD score	1·0 (1·4)	1·2 (1·3)	–0·22 (–0·58 to 0·14)	0·23
Secondary outcomes				
Abortion, spontaneous*	3 (3%)	2 (2%)	1·53 (0·25 to 9·39)	0·65
Abortion, induced*	4 (4%)	3 (3%)	1·32 (0·29 to 6·07)	0·73
Gestational weight gain, kg	13·7 (7·9)	13·4 (5·7)	0·27 (–1·79 to 2·33)	0·80
Pre-eclampsia	14 (14%)	10 (10%)	1·49 (0·63 to 3·58)	0·36
Gestational age at delivery, weeks+days	37+6 (37+1–38+3)	37+6 (37+0–38+2)	1·26 (–1·56 to 4·09)	0·38
Vaginal delivery, total	56 (55%)	49 (48%)	1·34 (0·77 to 2·36)	0·30
Instrumental, vaginal delivery	10 (10%)	3 (3%)	3·63 (0·96 to 13·49)	0·056
Planned caesarean section	24 (24%)	37 (36%)	0·54 (0·29 to 1·01)	0·054
Emergency caesarean section	21 (21%)	16 (16%)	1·42 (0·69 to 2·92)	0·34
Early preterm delivery (<34 weeks)	2 (2%)	3 (3%)	0·68 (0·11 to 4·18)	0·67
Preterm delivery (<37 weeks)	19 (19%)	22 (22%)	0·84 (0·42 to 1·70)	0·64
Birthweight, g	3475 (584)	3513 (530)	–39·99 (–190·90 to 110·91)	0·60
Length, cm	50·7 (3·2)	50·8 (3·3)	–0·14 (–1·05 to 0·77)	0·76
Head circumference, cm	35·1 (3·2)	35·0 (2·6)	0·08 (–0·74 to 0·90)	0·84
Abdominal circumference, cm	33·2 (2·3)	33·2 (2·1)	–0·02 (–0·66 to 0·62)	0·95
Large for gestational age	41 (41%)	47 (46%)	0·77 (0·43 to 1·40)	0·39
Small for gestational age	3 (3%)	2 (2%)	1·55 (0·25 to 9·58)	0·64
Neonatal hypoglycaemia, plasma glucose <2·2 mmol/L during first 2 h after birth	12 (12%)	12 (12%)	0·99 (0·42 to 2·33)	0·99
Neonatal jaundice requiring photo therapy	18 (18%)	19 (19%)	0·77 (0·35 to 1·71)	0·53
Respiratory distress requiring Continuous Positive Airway Pressure treatment	28 (28%)	19 (19%)	1·68 (0·87 to 3·27)	0·12
Neonatal morbidity (neonatal hypoglycaemia, respiratory distress, and/or jaundice requiring photo therapy)	46 (46%)	39 (38%)	1·03 (0·50 to 2·13)	0·94
Admission to neonatal intensive care unit	28 (28%)	27 (26%)	1·08 (0·58 to 2·01)	0·82
Duration of stay at neonatal intensive care unit, days	4·9 (8·0)	4·3 (5·9)	0·37 (–3·39 to 4·13)	0·85
Admission to neonatal intensive care unit >48 h	15 (15%)	13 (13%)	1·33 (0·44 to 4·08)	0·61
Perinatal death	0	0	..	..
Neonatal death	0	0	..	..

Data are presented as median (IQRs), mean (SD), or n (%). Data were available from greater than 99% of the participants during pregnancy and for infants, except for infant length (98%), head circumference (96%), and abdominal circumference (89%). Data analysis was for all 216 randomised participants excluding 12 participants with spontaneous or induced abortions and one participant who withdrew consent. *Data analysis in all 216 randomised participants.

Table 2: **Pregnancy and neonatal outcomes in 203 participants included in the primary analysis**

was performed on all participants randomly assigned while in the trial. No participants discontinued the allocated trial drug, thus a per protocol analysis was not performed.

All analyses were performed as complete-case analyses excluding patients with missing data for one or more variables when reasonable. The amount of missing data is presented in relation to tables and figures. Two-sided p values less than 0·05 were regarded as statistically significant. Adjustment for multiple testing was not pre-planned and thus not performed. R version 4.1.0 (R Core Team, 2021, R Foundation for Statistical Computing, Vienna, Austria) was used for all data analyses.

This trial is registered with ClinicalTrials.gov, NCT03770767.

Role of the funding source

The funder was not involved in initiation of the trial, the trial design or collection, analysis, or interpretation of the data.

Results

Between Nov 11, 2019, and May 10, 2022, 486 women were assessed for eligibility. 216 (76%) of 284 eligible participants were included and 109 were randomly assigned to faster aspart and 107 to insulin aspart. First participant's first visit was on November 11, 2019, last participant's first visit on May 10, 2022, and last participant's last visit on March 23, 2023.

After randomisation, seven participants in the faster aspart group and five participants in the insulin aspart

group had a spontaneous or induced abortion. One of the abortions (faster aspart group) was induced at 22 weeks of gestation due to a severe congenital anomaly and all other spontaneous or induced abortions were before 22 weeks of gestation. One participant in the faster aspart group withdrew consent with permission for the use of baseline data but no further data collection. In total, 203 (94%) of 216 participants were included in the analysis of the primary outcome (figure 1).

Baseline characteristics are presented in table 1 and appendix 2 pp 4–6. 154 (71%) of 216 participants with type 1 diabetes (113 [73%] of 154 using multiple daily injections and 41 [27%] using insulin pump) and 62 (29%) of 216 participants with type 2 diabetes all using multiple daily injections were randomly assigned. None used automated insulin delivery.

Infant birthweight SD scores were similar in the faster aspart group (mean 1·0 [SD 1·4]) and insulin aspart group (1·2 [SD 1·3]), with an estimated treatment difference of –0·22 (95% CI –0·58 to 0·14; p=0·23; table 2). Subgroup analysis of infant birthweight SD score is presented in appendix 2 p 8. At 1 month and 3 months post-delivery infant weight SD scores were similar in the faster aspart and insulin aspart groups (appendix 2 p 9).

Mean maternal HbA_{1c} declined from randomisation until 21 weeks of gestation, remained stable until 35 weeks of gestation, and increased post-delivery with no difference between the groups (figure 2A and appendix 2 p 11). At 33 weeks of gestation, mean HbA_{1c} was 42 mmol/mol (SD 6 mmol/mol; 6·0% [SD 0·9%]) versus 43 mmol/mol (SD 7 mmol/mol; 6·1% [SD 1·2%]); estimated treatment difference –1·01 (–2·86 to 0·83), p=0·28. Insulin doses were similar between the two groups during the trial (table 1 and appendix 2 p 12). The mean seven-point blood glucose monitoring profiles for 7 days showed a similar pattern at randomisation, 21 weeks of gestation and 33 weeks of gestation. The blood glucose monitoring profile at 33 weeks of gestation is shown in figure 2B and appendix 2 p 11.

The numbers of mild hypoglycaemic events in the previous week were similar during the trial except at 33 weeks of gestation where the numbers were lower in the faster aspart group (–0·90 [95% CI –1·71 to –0·09], p=0·030; figure 2C and appendix 2 p 11). Proportions of level 2 hypoglycaemia with blood glucose monitoring less than 3·0 mmol/L in the 7-day blood glucose monitoring profiles were similar between the two groups (figure 2D and appendix 2 p 11).

From randomisation to delivery, one participant in the faster aspart group (<1%) and seven (7%) in the insulin aspart group (of whom one had type 2 diabetes) reported at least one severe hypoglycaemic event (odds ratio 0·13 [95% CI 0·02 to 1·11], p=0·062). Three participants used a CGM device with hypoglycaemia alerts at the time of the events. In total, 11 severe hypoglycaemic events were reported corresponding to one (faster aspart) versus ten (insulin aspart) events (–0·08 [95% CI –0·16 to –0·01], p=0·026), from randomisation to delivery (table 3). Five (45%) of 11 events occurred during sleep, all in the insulin aspart group. The number needed to treat with faster aspart to prevent one severe hypoglycaemic event during pregnancy was 18. Post-delivery, two participants in the faster aspart group each reported one severe hypoglycaemic event versus three participants in the insulin aspart group (appendix 2 p 9). Three of these events occurred in the breastfeeding

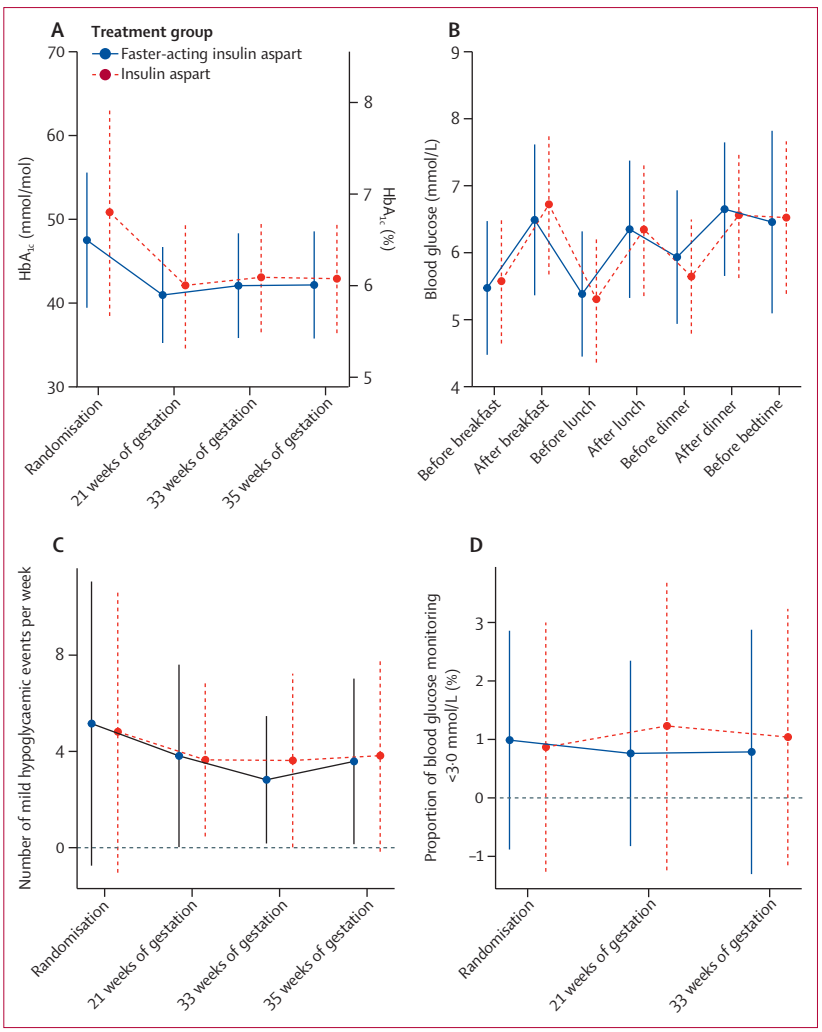

Figure 2: **Mean HbA_{1c} (A), blood glucose monitoring profiles (B), number of mild hypoglycaemic events per week (C), and proportion of blood glucose monitoring values less than 3·0 mmol/L (D)**
Estimated treatment differences are given in appendix 2 p 11. (A) Mean HbA_{1c} data shown for all participants assigned at randomisation; at 21, 33, and 35 weeks of gestation analysis, data were for all participants except those who had a spontaneous or induced abortion before the trial visit and one participant who withdrew consent. Data were available for >92% of participants. (B) Blood glucose monitoring profiles at 33 weeks of gestation, taken before, and 90 min after, each meal and before bedtime. Data were available for 64% of participants. (C) Mild hypoglycaemic events per week (mean [SD]) by treatment group in the previous week reported at randomisation, 21 weeks, 33 weeks, and 35 weeks of gestation. Data were available for >92% of participants. Mild hypoglycaemia was defined as self-reported events with symptoms familiar to the participant as hypoglycaemia and managed by the participant. (D) Proportion of blood glucose monitoring values less than 3·0 mmol/L (%, mean [SD]) per week in seven-point blood glucose profiles by treatment group at randomisation, 21 weeks, and 33 weeks of gestation. Data were available for 64% of the participants.

	Faster-acting insulin aspart (n=109)	Insulin aspart (n=107)	Estimated treatment difference, adjusted mean difference (95% CI) or odds ratio (95% CI)	p value
Participants with ≥1 adverse event during the trial	82 (75%)	85 (79%)	0·77 (0·41 to 1·49)	0·45
Participants with ≥1 severe adverse event during the trial	33 (30%)	25 (23%)	1·44 (0·78 to 2·65)	0·25
Participants with severe hypoglycaemia from randomisation to delivery	1 (<1·%)	7 (7%)	0·13 (0·02 to 1·11)	0·062
Severe hypoglycaemic events from randomisation to delivery	1*	10*	−0·08 (−0·16 to −0·01)	0·026
Participants with severe hypoglycaemia from delivery to 3 months post-delivery	2 (2%)	3 (3%)	0·65 (0·11 to 4·03)	0·65
Maternal severe hypoglycaemic events from delivery to 3 months post-delivery	2*	3*	−0·01 (−0·05 to 0·03)	0·65

Data analysis was on all randomised participants. All reported serious adverse events were hospitalisation for 24 h or more or congenital abnormalities. *Raw summarised counts presented. Severe hypoglycaemic events in pregnancy were distributed across eight participants (ie, three participants in the insulin aspart group had two events). Severe hypoglycaemic events post-delivery were distributed in five participants.

Table 3: **Safety outcomes in all 216 randomised participants**

period (one in the faster aspart group and two in the insulin aspart group).

Prespecified secondary pregnancy, neonatal, and post-delivery outcomes were similar in both groups (table 2 and appendix 2 p 9). Clinical characteristics and neonatal outcomes including infant birthweight SD score were similar in participants with type 1 and type 2 diabetes (appendix 2 p 16).

150 (97%) of 154 participants with type 1 diabetes used a CGM device during pregnancy. At randomisation, 125 participants used isCGM (appendix 2 p 4), of whom 122 had type 1 diabetes and three had type 2 diabetes (appendix 2 p 4). Two participants with type 1 diabetes and one participant with type 2 diabetes initiated isCGM later, giving a total of 128 isCGM users at some point during the trial, of whom 124 had type 1 diabetes. The isCGM data from participants with type 2 diabetes were not analysed due to low numbers. isCGM metrics in the 124 participants with type 1 diabetes were similar at randomisation, whereas mean sensor glucose decreased numerically until 33 weeks of gestation in both groups and was lower in the faster aspart group than the insulin aspart group at 21 weeks of gestation (6·6 [SD 0·9] *vs* 7·0 [SD 1·0] mmol/L, estimated treatment difference −0·37 [−0·73 to −0·00], p=0·048). Numerically, time in range in pregnancy increased, time above range in pregnancy decreased, and time below range in pregnancy remained stable from randomisation until 33 weeks of gestation with no differences between the groups (table 4).

None of the participants developed diabetic ketoacidosis during the trial. There were no maternal deaths. There were similar numbers of participants with adverse events, serious adverse events, or both during the trial (table 3). All reported serious adverse events were hospitalisation for 24 h or longer or congenital abnormalities. None of the serious adverse events were unexpected or related to the trial drug. None of the fetuses with congenital abnormalities were exposed to faster aspart during organogenesis before 8 completed weeks (appendix 2 p 18).

Discussion

This open-label, randomised controlled trial in participants with pre-existing diabetes showed that the use of faster aspart during pregnancy and post-delivery resulted in similar fetal growth and HbA_{1c}, relative to insulin aspart. Treatment with faster aspart was well tolerated and no participants discontinued the trial drug. There were no observed issues regarding adverse events in both groups.

Fetal overgrowth remains a common complication to pregnancy in women with pre-existing diabetes.[1] Based on the promising effects of faster aspart on reducing postprandial glucose excursions in non-pregnant populations of people with type 1 and type 2 diabetes,[5–20] we hypothesised that treatment with faster aspart resulted in less fetal overgrowth in women with pre-existing diabetes during pregnancy, with no additional safety issues, than insulin aspart. As there was no literature to guide the estimation of effect size, 0·60 SD was chosen. Infant birthweight SD score was numerically lower, but not statistically significant, in the faster aspart group than the insulin aspart group, and the 95% CI ranged from −0·58 to 0·14, thus close to the estimated reduction of 0·60 in infant birthweight SD score. A sample size of approximately 220 was planned and obtained.

Participants had similar HbA_{1c}, and both treatment with faster aspart and insulin aspart resulted in HbA_{1c} declining from randomisation until 21 weeks of gestation and remaining stable around 42 mmol/mol (6·0%) until 35 weeks of gestation. With these near-normal HbA_{1c} values, HbA_{1c} might not be sensitive at detecting differences in glycaemia, and the CGM metric might be

	Faster-acting insulin aspart		Insulin aspart		Estimated treatment difference, adjusted mean difference (95% CI) or odds ratio (95% CI)	p value
	Participants	Data	Participants	Data		
Randomisation (faster-acting insulin aspart n=62; insulin aspart n=60)						
Mean sensor glucose, mmol/L	58	7·0 (1·2)	54	7·0 (1·5)		..
Percentage time below range (< 3·9 mmol/L)	57	7·0 (2·0–14·0)	53	8·0 (5·0–13·0)		..
Percentage time in range (3·9–7·8 mmol/L)	43	60·3 (15·8)	40	59·1 (18·2)		..
Percentage time above range (>7·8 mmol/L)	43	30·0 (20·5–40·0)	40	27·5 (20·5–42·2)		..
21 weeks of gestation (faster-acting insulin aspart n=61; insulin aspart n=56)						
Mean sensor glucose, mmol/L	58	6·6 (0·9)	55	7·0 (1·0)	–0·37 (–0·73 to –0·00)	0·048
Percentage time below range (<3·9 mmol/L)	58	7·0 (5·0–11·0)	55	9·0 (4·0–14·0)	–0·03 (–2·50 to 2·44)	0·98
Percentage time in range in (3·9–7·8 mmol/L)	44	64·8 (12·7)	42	60·0 (16·3)	4·71 (–1·58 to 10·99)	0·14
Percentage time above range (>7·8 mmol/L)	44	24·5 (17·8–36·0)	42	29·5 (19·2–42·2)	–5·59 (–12·36 to 1·18)	0·11
33 weeks of gestation (faster-acting insulin aspart n=61; insulin aspart n=53)						
Mean sensor glucose, mmol/L	58	6·3 (1·0)	53	6·5 (0·8)	–0·11 (–0·45 to 0·23)	0·52
Percentage time below range (<3·9 mmol/L)	58	6·0 (3·0–11·0)	53	9·0 (4·0–12·0)	–0·75 (–2·96 to 1·45)	0·50
Percentage time in range (3·9–7·8 mmol/L)	52	73·0 (13·9)	46	69·9 (11·5)	2·94 (–2·25 to 8·13)	0·26
Percentage time above range (>7·8 mmol/L)	52	16·0 (10·5–27·2)	46	22·0 (11·2–27·0)	–2·73 (–7·82 to 2·36)	0·29

Data are presented as n (%), mean (SD), or median (IQR). Data analysis was done in all randomised participants with available data for the said outcome, based on the group to which they were initially allocated. Participants who had abortions were excluded from analysis at trial visits after the abortion. After randomisation, prior to 21 weeks: four women using intermittently scanned continuous glucose monitoring (isCGM) at baseline had an abortion, one woman discontinued use of isCGM, and two women contemporarily discontinued isCGM use at 21 weeks. At 21 weeks: two women who did not use isCGM at randomisation used isCGM from 13 and 21 weeks, respectively. After 21 weeks, before 33 weeks: one woman had an abortion, one woman gave birth, two women discontinued isCGM use, two women resumed isCGM use after discontinuation at 21 weeks, one woman changed to real time continuous glucose monitoring.

Table 4: **Mean sensor glucose, time below range, time in range, and time above range in pregnancy 7 days before randomisation, 21 weeks, and 33 weeks of gestation in 124 participants with type 1 diabetes using isCGM**

better. In participants with type 1 diabetes, isCGM at 21 weeks of gestation showed significantly lower mean glucose in the faster aspart group than the insulin aspart group. The use of CGM data collected during the entire pregnancy might have enabled detection of more differences in isCGM metrics, but this was not part of the protocol.[25]

The numbers of severe hypoglycaemic events were low, and the number needed to treat with faster aspart to prevent one event with severe hypoglycaemia was 18. We speculate that enhanced clinical focus on reducing severe hypoglycaemia with increased use of CGM with hypoglycaemia alerts and insulin analogues contributed to the low numbers of severe hypoglycaemic events in this trial, especially in the faster aspart group. In support of less hypoglycaemia in the faster aspart group we find it clinically meaningful that the prevalence of mild hypoglycaemia, level 2 hypoglycaemia, and in participants with type 1 diabetes using isCGM, time below range in pregnancy were similar or lower in the faster aspart group than the insulin aspart group during the trial. This trial thus emphasises the need for continued focus on reducing the prevalence of hypoglycaemia during pregnancy and post-delivery.

With the rapid development of insulin analogues, studies evaluating their efficacy in pregnant and breastfeeding populations are important. To our knowledge, no study has assessed the physiological properties of faster aspart in pregnancy or breastfeeding. In pregnant women with type 1 diabetes, absorption of insulin aspart is delayed with advancing gestation.[30] It remains speculative whether this also applies regarding faster aspart.

More than 40% of infants were born large for gestational age. This warrants further investigation of prediction and prevention of fetal overgrowth with focus on clinically relevant CGM metrics, glucose fluctuations, HbA_{1c}, and gestational weight gain. Likewise, the effect of automated insulin delivery systems for reducing severe hypoglycaemia during pregnancy and breastfeeding and for improving pregnancy outcomes are warranted.

Strengths of this trial are the randomised design with previous publication of the trial protocol and the large number of participants including 76% of eligible women and 94% of participants completing the trial. Participants were included and randomly assigned in early pregnancy, none discontinued treatment allocation, and the amount of missing data was overall low, with complete data on the primary outcome and with most data obtained from over 95% in pregnancy and approximately 80% at 1 month post-delivery and 70% 3 months post-delivery. Blood glucose monitoring profiles were available in 64% thus limiting the

possibility for conclusions regarding level 2 hypoglycaemia. Bias related to missing data is considered low regarding the primary outcome and the majority of secondary outcomes, however it is a limitation that the prespecified secondary outcomes of blood glucose monitoring, time in range in pregnancy, and time above range in pregnancy had a higher amount of missing data, thus the results of these outcomes analysed as complete case analysis should be interpreted cautiously. Adjustment for multiple testing was not performed; we acknowledge this as a limitation with potential risk of chance findings and type I error in the analyses of secondary outcomes. All participants were treated according to the same treatment recommendations and CGM metrics were available in the majority of participants with type 1 diabetes. Glycaemic control was both evaluated by HbA_{1c}, 7-day blood glucose monitoring profiles, and isCGM metrics. Evaluation of hypoglycaemia included mild, severe, and level 2 hypoglycaemia, as well as time in range in pregnancy. The unselected cohort and few exclusion criteria might benefit the generalisability, and the objective primary outcome was less prone to bias. However, the single-centre trial design could contribute to less external validity. The open-label trial design was potentially subject to bias but might also have contributed to the high participation rate, as participants might be reluctant to participate in a blinded study, especially during pregnancy. A relatively large number of women declined participation out of concern for changing mealtime insulin during pregnancy or due to previous experience with the trial drug. This emphasises the importance of discussing insulin type during pregnancy planning so women can make informed choices regarding insulin treatment.

The trial protocol was amended when the blinded CGM device was withdrawn from the market. Instead, data from all participants with type 1 diabetes using isCGM were collected and analysed, as they were offered isCGM during pregnancy. The decision to include isCGM data and exclude the relatively few other CGM device types was to align the type of CGM data collected, as originally planned with the blinded CGM, and increase the homogeneity and generalisability of the data.

In conclusion, faster aspart with its greater early glucose lowering effect could be used in women with pre-existing diabetes during pregnancy and post-delivery with similar fetal growth and HbA_{1c}, relative to insulin aspart, with no additional safety issues. Future studies of larger cohorts of women with pre-existing diabetes during pregnancy and post-delivery are required to provide further evidence for clinical and safety outcomes.

Contributors

SKN and LR wrote the first draft of the manuscript and had full access to the raw data and verified the data. The trial was initiated by the principal investigator LR in collaboration with senior investigators ERM and PD and coordinating investigator SKN. SKN, ERM, KN, TDC, PD, and LR contributed to the concept of the trial. SKN, JCS, ERM, PH, NCD, and LR collected the data. JCS, ERM, KN, TDC, PH, NCD, and PD critically read and revised the manuscript. All authors have approved the manuscript and consented to publication of the manuscript before submission.

Declaration of interests

The trial was funded by Novo Nordisk, grant number U1111-1209-6358. The grant covered full-time salaries for SKN and JCS, part-time salaries for NCD, ERM, and LR and the costs of trial products. The trial products were purchased at the cost negotiated with Hospital Pharmacy of the Capital Region, Denmark. ERM has contracts with Novo Nordisk for the investigation of the Expect trial and the Evolve trial that are investigating newer insulin analogues and pump treatment in pregnant women with diabetes, has received honoraria from Novo Nordisk for lectures, received support from Novo Nordisk for traveling to one international scientific meeting in the field of diabetes, and is participating on an advisory board for Novo Nordisk. PD has participated in clinical studies on the use of insulin in pregnant women with pre-existing diabetes in collaboration with Novo Nordisk. Papers from these studies are still being produced. No personal honorarium was involved. KN has received funding from Novo Nordisk for an investigator-initiated trial (grant number U1111-1209-6358), for another investigator-initiated trial with faster aspart in insulin pump treated adults with type 1 diabetes, is an advisory board member, for which an honorarium was given to her institution Steno Diabetes Center Copenhagen. KN owns stocks in Novo Nordisk. TD and PH declare no competing interests.

Data sharing

The dataset generated during or analysed during the current trial are available from the corresponding author on reasonable request.

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