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Closed Loop in Pregnancy Overnight Home Feasibility Study (CLIP-03)

Submission date
03/04/2014

Recruitment status
No longer recruiting

Registration date
03/04/2014

Overall study status
Completed

Last Edited
24/08/2016

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Controlling blood sugar levels during pregnancy is very important for the health of the mother and the baby. However, many women with type 1 diabetes find it hard to avoid high blood sugar levels without experiencing low blood sugar levels (hypoglycaemia). Hypoglycaemia is particularly concerning during the night. Closed-loop systems may help people with type 1 diabetes achieve good overnight glucose control without hypoglycaemia. Closed-loop systems consist of a continuous glucose monitor (CGM), a computer algorithm (mathematical instructions which calculate the insulin dose) and an insulin pump. During closed-loop, the CGM measures the glucose levels and relays them to the computer. The computer calculates an appropriate insulin dose according to the algorithm. It communicates with the insulin pump to give out the particular dose of insulin every 15 minutes. The closed-loop system has already been tested in women with type 1 diabetes during early, mid and late pregnancy. Our group have studied how it adapts insulin for the changing needs of pregnancy. The initial results suggest that overnight glucose control can be safely maintained in hospital settings. A large study will be needed to learn whether closed-loop will help women to achieve near-normal glucose levels throughout pregnancy. Before planning a larger closed-loop study we want to learn more about how troublesome or useful pregnant women find the study devices during short-term use. We also want to test how overnight closed-loop compares to the overnight glucose control achieved by an insulin pump and CGM without closed-loop.

Who can participate?
Pregnant women with type 1 diabetes can take part.

What does the study involve?
In this study, participants will wear an insulin pump and a CGM sensor continuously for two 4-week study phases. In one of these periods, closed-loop technology will be used overnight whereas in the other period participants will use the insulin pump and CGM without closed-loop. Participants will be randomly allocated to participate in either group. After 28 nights, they will resume their normal treatment for about two weeks, and then start on the other arm of the study for 28 nights. Participants will complete questionnaires and interviews about their

experience of the closed-loop system. They will have blood tests to find out the effect of the closed-loop system on their glucose control. After the end of the study, women will have the opportunity to continue on either of the study treatments until the end of their pregnancy.

What are the possible benefits and risks of participating?
Participating in this study may help participants to better understand what happens to their blood sugar levels during pregnancy. It will also help our research into the development of closed-loop systems. Participants may also benefit from wearing a CGM and insulin pump. Studies suggest that using CGM helps women to improve blood sugar control and reduces the risk of delivering a large baby. Outside pregnancy insulin pump use is associated with better glucose control and improved quality of life. The University of Cambridge insurance policy will include cover both for negligent and for non-negligent harm. The cover for non-negligent harm is not usually offered for clinical studies and may be considered as an additional benefit. The insulin pump and CGM sensor may produce mild pain when inserted into the skin. There is a low risk for developing a local skin infection at the site of the insulin pump or CGM insertion. Itchiness, redness, bleeding, and bruising at the pump and CGM insertion sites may occur as well as local tape allergies. The closed-loop computer may restrict mobility, and therefore will only be used overnight. Participants will be alerted by a systems alarm if the closed-loop system stops working or malfunctions in any way, for example loss of connection between the closed-loop computer and the insulin pump. If the participant does not respond to the alarm, their usual basal insulin delivery will be automatically started. During the study, participants may experience a hypo as may happen in everyday life. There will always be either a doctor or a nurse contactable by phone to help adjust to insulin doses, and advise regarding treatment.

Where is the study run from?
It will be coordinated by researchers at the University of Cambridge and Wellcome Trust-MRC Institute of Metabolic Science in Cambridge, UK.

When is the study starting and how long is it expected to run for?
April 2014 to March 2015

Who is funding the study?
Diabetes UK

Who is the main contact?
Dr Zoe Stewart
zas25@medschl.cam.ac.uk
Tel: +44 (0) 1223 769069

Contact information

Type(s)
Scientific

Contact name
Dr Zoe Stewart

ORCID ID
https://orcid.org/0000-0001-8629-3841

Contact details

Wellcome Trust-MRC Institute of Metabolic Science
Addenbrookes Hospital , Hills Road
Cambridge
United Kingdom
CB2 0QQ
-
zas25@medschl.cam.ac.uk

Additional identifiers

Protocol serial number
16426

Study information

Scientific Title
Evaluation of the feasibility, utility, safety and efficacy of overnight closed-loop insulin delivery at home in women with type 1 diabetes during pregnancy. Acronym: CLIP_03

Acronym
CLIP-03

Study objectives
An automated closed-loop insulin delivery system can be used reliably, safely and effectively by pregnant women with type 1 diabetes in the home setting, to improve overnight glucose control and to prevent nocturnal hypoglycaemia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/EE/0018; First MREC approval date 27/03/2013

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Diabetes; Subtopic: Type 1 ; Disease: Diabetic Control, Pregnancy

Interventions
The investigational treatment is the FlorenceD or follow-up prototypes of the automated overnight closed-loop system manufactured by the Cambridge University Hospitals NHS Foundation Trust. Component versions will be identified during regulatory submission to the MHRA. Eligible participants, who provide informed consent, complete training for the study

pump and the study CGM and are competent and compliant in the use of both devices, will be randomised using a 4-block randomisation based on computer-generated random code. The study reporting period is from the time of recruitment (obtaining informed consent) until 72 hours after the end of the pregnancy. After completing the two active study arms, participants will have follow-up HbA1c measurements at 28, 32 and 36 weeks gestation. Obstetric and neonatal outcomes will be collected at the end of pregnancy. Adverse events that continue after the subjects discontinuation or completion of the pregnancy will be followed until their medical outcome is determined or until no further change in the condition is expected.

Intervention Type
Device

Primary outcome(s)
Current primary outcome measures as of 29/04/2016:
The primary outcome is the percentage time spent with glucose levels ≥ 63mg/dl and 140mg/dl (3.5 and 7.8mmol/l), as recorded by continuous glucose monitoring (CGM) during the 28 day intervention periods.

Previous primary outcome measures:
1. The primary efficacy outcome is the overnight time spent in the target glucose range from 3.5-7.8 mmol/L, as recorded by continuous glucose monitoring (CGM) adjusted for sensor error during the 28-day intervention periods.
2. Safety evaluation will comprise number of episodes of nocturnal hypoglycaemia, the duration and outcome of those events as well as the number of subjects experiencing severe hypoglycaemia. The closed-loop intervention arm will be compared with the continuous glucose monitoring without closed-loop intervention arm. All subjects including those who withdraw will be included in the safety evaluation.
3. Utility evaluation is the frequency and duration of use of the closed-loop system as compared to the use of real-time CGM without the closed-loop system, and the users responses in terms of lifestyle change and diabetes self-management.

Key secondary outcome(s))
Current secondary outcome measures as of 29/04/2016:
1. The overnight time with glucose levels in the hypoglycaemic range, based on continuous glucose monitoring (glucose levels < 50mg/dl or 2.8mmol/L).
2. The overnight time with glucose levels in the hyperglycaemic range, based on continuous glucose monitoring (glucose levels > 140mg/dl or 7.8mmol/L).
3. The overall time (day and night) with glucose levels in the hypoglycaemic range, based on continuous glucose monitoring (glucose levels < 50mg/dl or 2.8mmol/l).
4. The overall time (day and night) with glucose levels in the hyperglycaemic range, based on continuous subcutaneous glucose monitoring, (glucose levels > 140mg/dl or 7.8mmol/L).
5. Metabolic control assessed by change in HbA1c after the use of closed-loop for 28 days, compared with that during sensor augmented pump therapy for 28 days. HbA1c will be measured before and after each intervention arm
6. CGM data collected during intervention arms will also be compared to baseline CGM readings.
7. Trends in CGM data collected within intervention arms will also be evaluated on weekly basis.
8. Percentage time spent with CGM < 63mg/dl (3.5mmol/l) to quantify borderline hypoglycaemia
9. Percentage time spent with CGM 50mg/dl (2.8mmol/l) to quantify moderate hypoglycaemia
10. Percentage time spent with CGM > 140mg/dl (7.8mmol/l) to quantify the duration of hyperglycaemia
11. Percentage time spent at CGM > 180mg/dl (10.0 mmol/l) to quantify significant

hyperglycaemia
12. Percentage time spent at CGM > 63mg/dl to 180mg/dl (3.5 to 10.0mmol/l) to quantify near optimal target range
13. Area under the curve (AUC) for glucose levels:
13.1. > 140mg/dl (7.8mmol/l)
13.2. > 120mg/dl (6.7mmol/l)
13.3. < 63mg/dl (3.5mmol/l)
13.4. <50mg/dl (2.8mmol/l)
14. Percentage time CGM worn to quantify compliance
15. Low blood glucose index (LBGI) to quantify the risk of hypoglycaemia
16. Standard deviation (SD) of the rate of change of CGM to quantify glucose variability
17. Insulin delivered (basal, bolus, and total) to assess insulin needs
18. HbA1c and mean CGM glucose to quantify glucose control
19. Episodes of severe hypoglycaemia requiring assistance (to assess safety)
20. Mild-moderate episodes of hypoglycaemia <63mg/dl or <3.5mmol/l (mild) and <50mg/dl or <2.8mmol/l (moderate) from CGM data defined as AUC<63mg/dl or AUC ≤50mg/dl for ≥ 20 minutes duration (to assess safety)
21. Nocturnal hypoglycaemia (NH): CGM glucose <63mg/dl or <3.5mmol/l (mild) and <50mg/dl or <2.8mmol/l (moderate) for ≥ 20 minutes duration between 23:00 and 07:00 hours (to assess safety)
22. The frequency and duration of use of closed-loop system as compared to sensor augmented pump therapy (to assess feasibility)

Previous secondary outcome measures:
1. The overnight time with glucose levels in the hypoglycaemic range, based on continuous glucose monitoring (glucose levels < 2.8 mmol/L).
2. The overnight time with glucose levels in the hyperglycaemic range, based on continuous glucose monitoring (glucose levels > 7.8 mmol/L).
3. The overall time (day and night) with glucose levels in the hypoglycaemic range, based on continuous glucose monitoring (glucose levels < 2.8 mmol/l).
4. The overall time (day and night) with glucose levels in the hyperglycaemic range, based on continuous subcutaneous glucose monitoring, (glucose levels > 7.8 mmol/L).
5. Metabolic control assessed by change in HbA1c after the use of closed-loop system for 28 days, compared with that during continuous glucose monitoring without the closed-loop system for 28 days. HbA1c will be measured before and after each intervention arm.
6. CGM data collected during intervention arms will also be compared to baseline CGM readings.
7. Trends in CGM data collected within intervention arms will also be evaluated on weekly basis (i.e. week 1 versus week 2 versus week 3 versus week 4).

Completion date
31/03/2015

Eligibility

Key inclusion criteria
1. Signed informed consent obtained before study-related activities. Study-related activities are any procedure that would not have been performed during standard medical care
2. The participant is between 18 and 45 years of age (inclusive)
3. The participant has type 1 diabetes (T1D), as defined by WHO for at least 12 months and has had a viable singleton pregnancy confirmed by ultrasound at gestational age ≥ 8 and ≤ 24 weeks
4. The participant is using intensive insulin therapy (at least three or more daily injections or

insulin pump therapy) and compliant with diabetes self-management i.e. doing ≥4 SMBG tests per day
5. The participant is able and willing to use the study devices and has completed the CGM run-in assessment
6. The participant is able to speak and understand English
7. The participant has access to email

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
45 years

Sex
Female

Key exclusion criteria
1. Non-type 1 diabetes mellitus including those secondary to chronic disease
2. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results such as coeliac disease or untreated hypothyroidism
3. Current treatment with drugs known to interfere with glucose metabolism such as systemic corticosteroids, non-selective beta-blockers and MAO inhibitor
4. Known or suspected allergy against insulin
5. Women with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator
6. Documented gastroparesis
7. Very good or very poor glycaemic control i.e. HbA1c ≤6.5% at booking (48 mmol/mol) or baseline HbA1c ≥10% (86 mmol/mol)
8. Significant obesity i.e. Body Mass Index (BMI) at booking > 35 kg/m2
9. Total daily insulin dose >/= 1.5 IU/kg at booking
10. Women who have conceived with IVF or assisted reproductive techniques

Date of first enrolment
08/04/2014

Date of final enrolment
31/03/2015

Locations

Countries of recruitment

United Kingdom

England

Study participating centre
Cambridge University Hospital NHS Foundation Trust
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Norwich
United Kingdom
NR4 7UY

Study participating centre
Ipswich Hospital NHS Trust
Ipswich
United Kingdom
IP4 5PD

Study participating centre
King's College Hospital NHS Foundation Trust
London
United Kingdom
SE5 9RS

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust (UK)

Organisation
University of Cambridge (UK)

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Charity

Funder Name
Diabetes UK (UK); Grant Codes: BDA07/0003551

Alternative Name(s)
The British Diabetic Association, DIABETES UK LIMITED, British Diabetic Association

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	18/08/2016		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes