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Does Ondansetron vs placebo Ondansetron and Metoclopramide vs placebo Metoclopramide (in addition to IV rehydration) reduce the rate of treatment failure in women suffering from nausea and vomiting in pregnancy

Submission date 04/12/2017	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data [_] Record updated in last year
Registration date 08/01/2018	**Overall study status** Stopped	
Last Edited 15/07/2022	**Condition category** Pregnancy and Childbirth	

Plain English summary of protocol

Background and study aims
Around 30% of women suffer from moderate to severe nausea and vomiting in pregnant (NVP), causing physical and emotional distress and reducing quality of life (QOL). The most severe form, hyperemesis gravidarum (HG), affects up to 3% of women, leading to dehydration, weight loss and nutrient deficiency. Moderate or severe NVP requires medical treatment, but care varies in different hospitals as some women have reported feeling unsupported, dissatisfied, anxious and depressed. The aim of this study is to compare the effectiveness of two drugs (metoclopramide and ondansetron) for treating women with severe symptoms of nausea and vomiting in pregnancy (NVP) who have already tried using one anti-sickness drug but without improvement in their symptoms.

Who can participate?
Women attending hospital with severe NVP, 16+6 weeks pregnant or less, who have had little or no improvement whilst taking initial (first line) anti-sickness treatment.

What does the study involve?
Participants are randomly allocated to one of groups. Those in the first group receive metoclopramide with a placebo (dummy medication). Those in the second group receive ondansetron with a placebo. Those in the third group receive metoclopramide and ondansetron. Those in the last group receive a double placebo. The medications are initially given into a vein three times a day for up to four days. Once women are able drink without vomiting, the same drugs are given by tablet for up to ten days. Participants are monitored and if at any point after 12 hours of treatment starting symptoms have not improved, the study drugs are deemed to have failed and the medical staff prescribes a third line antiemetic treatment. Patients are also offered the opportunity to take part in an interview. Both women who take part and those that decline are offered the opportunity to take part. These interviews are being carried out to help

us understand the patient's reason for participating or not participating in a complex trial of medication in pregnancy.

What are the possible benefits and risks of participating?
The study may not directly benefit participants but the study treatment in combination with IV rehydration may help alleviate their NVP symptoms. The information we gain from this study may help other patients in the future. Participants will also be more closely monitored and have follow up phone calls to check how they are doing, which would not normally happen. Participants may become sick again at the end of the 10 days when the study drugs are stopped. If this happens the participant can contact the doctors or midwives at the hospital or one of the research team members for advice. The research team and the participants will not know which of the study drugs the participant has received so if the participant felt better while taking part in the study, they will not be able to necessarily give them what they received while in the study. Participants will therefore be given whatever drug is normally given as part of standard care. This will probably be ondansetron or metoclopramide. Both drugs might cause side effects such as: drowsiness, restlessness, constipation, diarrhoea, headache, dizziness, visual disturbance (e.g., blurred vision), light headedness, irregular heart rhythm, (fast or slow), rash, itching, sensation of flushing. Metoclopramide very occasionally causes muscle spasms. In rare cases ondansetron and metoclopramide may react with some other prescription medication, such as antidepressants, sedatives, morphine, medication for epilepsy and some antibiotics. During the research study we will collect information about any reactions or side effects. Metoclopramide and ondansetron are licensed for use but not in pregnancy. However there is enough evidence for doctors to believe they are safe and both drugs are routinely used to treat pregnant women.

Where is the study run from?
This study is being run by the Newcastle University (UK) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?
September 2017 to January 2022

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Dr Nicola Goudie (Scientific)
nicola.goudie@ncl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Nicola Goudie

Contact details
Trial Manager
Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle upon Tyne

Newcastle upon Tyne
United Kingdom
NE2 4AE
+44 191 2087187
nicola.goudie@ncl.ac.uk

Additional identifiers

EudraCT/CTIS number
2017-001651-31

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
36233

Study information

Scientific Title
EMPOWER: EMesis in Pregnancy - Ondansetron With mEtoclopRamide

Acronym
EMPOWER

Study objectives
The aim of this trial is to compare the effectiveness of two drugs (metoclopramide and ondansetron) for treating women with severe symptoms of nausea and vomiting in pregnancy (NVP) who have already tried using one anti-sickness drug but without improvement in their symptoms.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Newcastle & North Tyneside 1 REC, 30/11/2017, ref: 17/NE/0325

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Reproductive Health and Childbirth

Interventions
Participants initially receive the study drug via IV, they receive IV treatment 3 times per day, once they are able to tolerate liquids they are converted to oral treatment which they take three times daily. Participant can be allocated to one of four treatment groups – these are outlined below with details of the dosage they are given:
1. Metoclopramide (10 mg three times daily via IV and then tablets) + placebo (via IV and then tablets)
2. Ondansetron (4 mg three times daily via IV and then tablets) + placebo (via IV and then tablets)
3. Metoclopramide (10 mg three times daily (via IV and then tablets) + ondansetron (4 mg three times daily via IV and then tablets)
4. Double placebo three times daily (via IV and then tablets)

The study drug is initially given intravenously for up to four days. Once the women are able to tolerate fluids, the same drugs are given by tablet for up to ten days. Treatment lasts a maximum of ten days in total.

Follow up takes place at 48 hours post first dose of IMP, then at 5 days and the final follow up questionnaires at 10 days. Participants are then be followed up post birth via a review of their medical records.

Intervention Type
Other

Phase
Phase III

Primary outcome measure
Treatment failure is defined as the need for further treatment as a participant's symptoms have worsened between 12 hours and 10 days post treatment initiation.

Secondary outcome measures
1. Participant reported symptom severity is measured using PUQE at 48 hours, 5 days and 10 days post treatment commencing.
2. Participant reported severity of nausea is measured using VAS for nausea at 48 hours, 5 days and 10 days post treatment commencing.
3. Quality of life is measured using NVPQOL (Health-Related Quality of Life for Nausea and Vomiting during Pregnancy) at baseline and 10 days post treatment commencing
4. Anxiety, depression and social support will be measured using Edinburgh post-natal depression scale (EPDS) and State Trait Anxiety Inventory [STAI] at baseline and 10 days
5. Anxiety, depression and social support will also be measured using the Maternity Social Support scale at baseline.

6. Clinical indicators of anti-emetic effectiveness is measured via:
6.1. Number of participants experiencing a treatment failure at 48 hours
6.2. Relapse rate at 5 and 10 days (defined as a PUQE score of ≤ 6 at 48 hours followed by an increase to > 12 at 5 / 10
days)
6.3. Remission rate at 10 days (defined as a PUQE score of ≤ 6 at 48 hours with return to persistent symptoms [PUQE
score of 7 or above] at 10 days)
6.4. Readmission rates (the number of participants readmitted with NVP within 10 days of recruitment and between 10
days of recruitment and 20 weeks of pregnancy)
6.5. Total in-patient days related to NVP between recruitment and 20 weeks of pregnancy and between 20 weeks of
pregnancy and delivery
6.6. Additional antiemetic use
7. Side effects and adverse events is measured by asking participants about the occurrence of side effects and adverse events at 48 hours, 5 days and 10 days
8. Pregnancy and neonatal outcomes will be gathered via a chart review at 20 weeks gestation and birth

Overall study start date
01/09/2017

Completion date
31/01/2022

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/05/2020:
1. Pregnant women suffering from severe NVP
2. Gestation ≤166/7 weeks
3. Taken first line antiemetic treatment (cyclizine, chlorpromazine, promethazine, prochlorperazine (as recommended by the RCOG [10]) or doxlamine/pyridoxine (a new licensed antihistamine), as prescribed i.e. over a minimum of 24 hours with no sustained improvement in symptoms
4. Age ≥18 years
5. Able to give informed consent
6. Able to read/understand written English

Previous inclusion criteria:
1. Pregnant women suffering from severe NVP (nausea and vomiting in pregnancy)
2. Gestation ≤166/7 weeks
3. Taken first line antiemetic treatment (cyclize, chlorpromazine, promethazine or prochlorperazine as recommended by the RCOG), as prescribed i.e. full course taken by participant in the current pregnancy with no sustained improvement in symptoms (over a minimum of 24 hours use)
4. Age ≥18 years

5. Able to give informed consent
6. Able to read/understand written English

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 600; UK Sample Size: 600

Total final enrolment
33

Key exclusion criteria
Current exclusion criteria as of 20/05/2020:
1. Allergy/hypersensitivity to any of the study drugs
2. Received either ondansetron or metoclopramide intravenously
3. Received either ondansetron or metoclopramide orally for more than 72 hours (with or without IV rehydration)
4. Pre-existing diagnosis of medical condition: type 1 and 2 diabetes, Chronic kidney disease (CKD) stage 3-5, Graves' disease, significant cardiac disease (including long QT syndrome), phaeochromocytoma, epilepsy (or other seizure disorder).
5. Moderate renal impairment (known CKD 3b/4/5 or serum creatinine > 100 micromoles/l in pregnancy)
6. Known pre-existing diagnosis of severe liver impairment (for example: ALT or AST of > 2.5 x upper limit of pregnancy normal)
7. Severe diarrhoea (definition >10 loose, watery stools in a day (24 hours))
8. Hypokalaemia
9. Known pre-existing diagnosis of hypomagnesaemia
10. Vomiting caused by another underlying condition/infection
11. Concomitant use of apomorphine, serotonergic drugs (e.g. selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium)
12. Confirmed diagnosis of severe lactose intolerance (for example: Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption)

Previous exclusion criteria:
1. Allergy/hypersensitivity to any of the study drugs
2. Prior treatment with the study drugs in this pregnancy
3. Pre-existing diagnosis of medical condition: type 1 and 2 diabetes, Chronic kidney disease (CKD) stage 3-5, Graves' disease, significant cardiac disease (including long QT syndrome), phaeochromocytoma, epilepsy (or other seizure disorder).
4. Moderate renal impairment (known CKD 3b/4/5 or Cr > 100 in pregnancy)

5. Severe liver impairment (ALT / AST > 150)
6. Severe diarrhoea (definition > 10 loose, watery stools in a day (24 hours))*
7. Hypokalaemia**
8. Vomiting caused by another underlying condition/infection
9. Concomitant use of apomorphine, serotonergic drugs (e.g. selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium)

*If a woman who has severe diarrhoea (as defined above) meets other inclusion criteria and is subsequently found to have a serum potassium > 3 mmol/L and has not yet been prescribed an antiemetic it would be reasonable to offer participation in EMPOWER.
**all women with severe NVP will have routine assessment of 'Urea & Electrolytes' - in the absence of severe diarrhoea women can be approached, consented and given study treatments before results are available. If the serum potassium is subsequently found to be low (< 3 mmol /L) they should not be withdrawn from the trial but the hypokalaemia corrected quickly with intravenous supplementation.

Date of first enrolment
01/02/2018

Date of final enrolment
12/08/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre

The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
St George's Hospital (London)
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Birmingham Women's Hospital
Mindlesohn Road
Birmingham
United Kingdom
B15 2TG

Study participating centre
St James University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Queen's Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Salford Royal Infirmary
The Pennine Acute Hospitals NHS Trust
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Royal Stoke University Hospital
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Cosham
Portsmouth
United Kingdom
PO6 3LY

Sponsor information

Organisation
The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road

High Heaton
Newcastle-Upon-Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The Chief Investigator will co-ordinate dissemination of data from this trial. This will be achieved by publication in academic peer reviewed journals and dissemination through social media and the patient network, thereby reaching large numbers of women and health professionals. Findings will also be presented at national and international conferences (both academic and charity/voluntary sector based).

It is anticipated that there will be several outputs from EMPOWER. In addition to submitting the full study protocol for publication the aim is to submit the primary research paper, detailing the main results of EMPOWER, to a high impact academic peer reviewed journal as well as the HTA open access journal.

By publishing all components of the EMPOWER study in relevant journals and ensuring the results are included in relevant guidelines the aim is to maximise awareness (and impact) of the trial results to both academic and NHS clinical communities.

Intention to publish date
31/01/2023

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	internal pilot results	01/11/2021	17/11/2021	Yes	No
Results article	qualitative study on trial recruitment failure	14/07/2022	15/07/2022	Yes	No
HRA research summary			28/06/2023	No	No