Ondansetron and metoclopramide as second-line antiemetics in women with nausea and vomiting in pregnancy: the EMPOWER pilot factorial RCT

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Scientific summary

The EMPOWER pilot factorial RCT

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Scientific summary

Background

Nausea and vomiting in pregnancy affects a high percentage of women, with symptoms usually starting at 6–8 weeks' gestation. Symptoms can be mild, but one-third of sufferers experience more severe symptoms. The most severe form (hyperemesis gravidarum) is characterised by vomiting, dehydration, ketonuria and weight loss. Severe nausea and vomiting in pregnancy can result in prolonged hospitalisation, multiple treatments and, where interventions fail, termination of pregnancy. It is also associated with emotional and psychological distress and has a profound impact on quality of life.

The cause of nausea and vomiting remains unclear and there is no cure. Management focuses on relieving symptoms and preventing morbidity. Women with mild symptoms are often able to self-manage the condition, but those with moderate or severe disease often require clinician-initiated interventions in the form of intravenous fluids and antiemetic drugs, primarily antihistamines (e.g. cyclizine), dopamine antagonists (e.g. metoclopramide) and 5-hydroxytryptamine 3 antagonists (e.g. ondansetron).

Nausea and vomiting in pregnancy incur substantial costs to sufferers and to the NHS. Assessment of the condition often lacks consistency, and antiemetic treatment varies across NHS trusts. To address this, in June 2016 the Royal College of Obstetricians and Gynaecologists published guidelines on the management of nausea and vomiting in pregnancy [Royal College of Obstetricians and Gynaecologists. *The Management of Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum*. 2016. URL: www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf (accessed 9 July 2020)]. An evidence synthesis suggested that some treatments were better than the dummy for mild symptoms, but there was limited evidence on the clinical effectiveness and cost-effectiveness of treatments for more severe vomiting. Although limited data suggested that metoclopramide and promethazine alleviated moderate symptoms, evidence for ondansetron was at high or unclear risk of bias. The evidence synthesis identified the need for a randomised controlled trial, including economic evaluation, to determine which second-line hospital-prescribed antiemetic therapy, in addition to intravenous rehydration, should be adopted as mainstream provision in the UK NHS.

Objectives

The EMPOWER (EMesis in Pregnancy – Ondansetron With mEtoClopRamide) trial aimed to determine which second-line hospital-prescribed therapy [metoclopramide (metoclopramide hydrochloride, Actavis UK Ltd, Barnstable, UK; IV Ratiopharm GmbH, Ulm, Germany) and ondansetron (ondansetron hydrochloride dehydrate, Wockhardt UK Ltd, Wrexham, UK; IV Hameln Pharma plus GmbH, Hameln)], in addition to intravenous rehydration, should be adopted as mainstream second–line treatment of severe nausea and vomiting in pregnancy by the NHS when first-line treatment has failed. To achieve these aims, the following objectives were set.

Primary objective

To determine whether or not, in addition to intravenous rehydration, ondansetron compared with no ondansetron and metoclopramide compared with no metoclopramide reduced the rate of treatment failure up to 10 days after initiation.

Secondary objectives

To determine whether or not, in addition to intravenous rehydration, ondansetron compared with no ondansetron and metoclopramide compared with no metoclopramide:

- improved symptom severity at 2, 5 and 10 days after intervention initiation
- improved quality of life at 10 days after intervention initiation
- had an acceptable side effect and safety profile.

In addition, we aimed to estimate the incremental cost per treatment failure avoided and the net monetary benefits from the perspective of the NHS and women and their families.

Internal pilot and qualitative trial objectives

The aim of the internal pilot phase was to assess the feasibility of recruitment and the retention of participants recruited into the trial. The aim of the qualitative component of the pilot trial was improve our understanding of why women did or did not consent to participation in the trial.

Methods

The EMPOWER trial was a multicentre, double-dummy, randomised, double-blinded, dummy-controlled 2 × 2 factorial trial with an internal pilot phase. Women attending hospital with severe nausea and vomiting in pregnancy who had experienced little or no improvement after taking first-line antiemetic medication were invited to participate. The trial was conducted in a secondary care setting (i.e. within gynaecology/early pregnancy units, maternity assessment units and/or accident and emergency departments, depending on local care pathways) in 12 NHS trusts in England.

Inclusion criteria

- Pregnant women suffering from severe nausea and vomiting in pregnancy.
- Gestation of < 17 weeks.
- Had previously taken first-line antiemetic treatment (cyclizine, chlorpromazine, promethazine, prochlorperazine or doxylamine/pyridoxine) as prescribed, that is over a minimum of 24 hours with no sustained improvement in symptoms.
- Age ≥ 18 years.
- Able to give informed consent.
- Able to read/understand written English.

Exclusion criteria

- Allergy/hypersensitivity to any of the study drugs.
- Received either ondansetron or metoclopramide intravenously.
- Received either ondansetron or metoclopramide orally for > 72 hours (with or without intravenous rehydration).
- Pre-existing diagnosis of a medical condition: type 1 or 2 diabetes mellitus, chronic kidney disease stages 3–5, Graves' disease, significant cardiac disease (including long QT syndrome), phaeochromocytoma or epilepsy (or other seizure disorder).
- Moderate renal impairment (known chronic kidney disease grades 3b/4/5 or serum creatinine levels > 100 µmol/l in pregnancy).
- Known pre-existing diagnosis of severe liver impairment (e.g. alanine transferase or aspartate transaminase levels > 2.5 times the upper limit of normal pregnancy levels).
- Severe diarrhoea [definition: > 10 loose, watery stools in 1 day (24 hours)].
- Hypokalaemia.
- Known pre-existing diagnosis of hypomagnesaemia.

- Vomiting caused by another underlying condition/infection.
- Concomitant use of apomorphine or serotonergic drugs (e.g. selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and lithium).
- Confirmed diagnosis of severe lactose intolerance (e.g. patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose–galactose malabsorption).

Randomisation was carried out centrally using a secure web-based system. Participants were randomised on a 1 : 1 : 1 : 1 basis using a block-stratified method (stratified by site only) to receive either:

- metoclopramide (10 mg three times daily) and dummy (three times daily)
- ondansetron (4 mg three times daily) and dummy (three times daily)
- metoclopramide (10 mg three times daily) and ondansetron (4 mg three times daily)
- double dummy (three times daily).

Drugs were initially given intravenously then orally for a total of 10 days.

Measurements of outcomes

Primary outcome measure

The primary outcome measure was the number of participants experiencing treatment failure, defined as the need for further (third-line) antiemetic treatment because the participant's symptoms had not improved between 12 hours and 10 days post first dose of study drugs.

Secondary outcome measures

The secondary outcome measures were participant-reported measures of symptom severity and quality of life at 2, 5 and 10 days after intervention initiation that were assessed via completion of the following questionnaires: Pregnancy Unique Quantification of Emesis; Visual Analogue Scale for Nausea; Nausea and Vomiting during Pregnancy Quality of Life; Edinburgh Postnatal Depression Scale; six-item State–Trait Anxiety Inventory; and Maternal Social Support Scale. All questionnaires, except the visual analogue scale for nausea, were completed at baseline. The Nausea and Vomiting during Pregnancy Quality of Life, Edinburgh Postnatal Depression Scale and State–Trait Anxiety Inventory were also collected at day 10. The Pregnancy Unique Quantification of Emesis and visual analogue scale for nausea were also collected at days 2, 5 and 10.

The side effects and safety profile of the trial medication were assessed by asking participants during follow-up telephone calls that were conducted 2, 5 and 10 days after commencing trial medication whether or not they had experienced any adverse events. A grading system was used whereby patients were asked what symptoms they were experiencing at baseline (prior to commencing trial medication) and, subsequently, only new or worsening symptoms needed to be reported during the follow-up telephone calls.

Internal pilot

The main outcomes of the internal pilot phase were the recruitment and retention rates of participants in the trial to day 10. To progress from the pilot trial to the main trial, 59 participants needed to be recruited within 6 months, with $\geq$ 40 participants retained to day 10.

Sample size

As per the 2 × 2 factorial design, the trial was designed to have two main comparisons:

1. metoclopramide compared with no metoclopramide
2. ondansetron compared with no ondansetron.

We assumed an antiemetic failure rate of 10% based on prior ondansetron studies and our external pilot trial of midwife-led outpatient care. With 266 participants in each comparison (i.e. 133 in each of the four treatment combinations; 532 in total) and assuming no interaction between the two active treatments, it was estimated that we would have 90% power to detect an increase in failure rate from 10% in either antiemetic group to 20% in either dummy group (based on a two-sided test at the 5% level). Given that the primary outcome was treatment failure, we anticipated obtaining outcome data from ≥ 90% of participants. To account for a 10% drop-out rate, we planned to recruit 600 patients (150 in each randomised group).

Statistical methods

Given that the trial did not progress past the internal pilot phase, none of the planned statistical analyses was performed. Outcome data have been summarised descriptively by randomised treatment group. Had the trial progressed to the main stage, analyses would have been based on a comparison of:

- active metoclopramide (with either active or dummy ondansetron) and dummy metoclopramide (with either active or dummy ondansetron)
- active ondansetron (with either active or dummy metoclopramide) and dummy ondansetron (with either active or dummy metoclopramide).

Health economic analysis

To estimate the incremental cost per treatment failure avoided and the net monetary benefits from the perspective of the NHS and women, health utilisation and contingent valuation questionnaires were completed by participants at day 10. Information was collected on accident and emergency attendance, receipt of primary care and other NHS/Personal Social Services care services, medication and the purchase of private health care or personal care. Participants were also asked to express their willingness to pay to improve symptom severity for a 10-week period.

Qualitative study

The sample comprised women who accepted or declined trial participation and research staff. Interviews were completed by e-mail or telephone using a structured topic guide. All transcripts were checked for accuracy, anonymised and entered on NVivo 12 (QSR International, Warrington, UK) for indexing and retrieval. Data were analysed using a generative thematic approach.

Results

Between April 2018 and August 2019, 592 patients were screened, with 122 considered eligible. Thirty-three patients were recruited, with 29 retained to day 10. The main reason for ineligibility was prior treatment with trial medication(s) in the current pregnancy ($n = 320$; 68%). This remained the case, despite broadening the eligibility criteria to allow patients who had received only suboptimal treatment to be included (orally for < 72 hours). Owing to slower than anticipated recruitment, the trial did not progress from the internal pilot stage. Overall, 30 participants were evaluable for the primary outcome of treatment failure (metoclopramide and dummy, $n = 7$; ondansetron and dummy, $n = 8$; metoclopramide and ondansetron, $n = 8$; double dummy $n = 7$). Of those evaluable, 15 participants (50%) reported treatment failure [metoclopramide and dummy, $n = 4$ (57%); ondansetron and dummy, $n = 2$ (25%); metoclopramide and ondansetron, $n = 4$ (50%); double dummy, $n = 5$ (71%)].

Health economics results

Overall, 48% of participants did not complete any part of the Healthcare Utilisation and Contingent Valuation questionnaires. Thirteen participants (39%) provided the maximum amount that they would be willing to pay to improve symptom severity for a 10-week period, with a mean value across all groups of £674 (minimum £20.00, maximum £2000).

Qualitative results

Twenty-one women and 22 research staff were interviewed. Altogether, 72 codes were generated, of which 36 nodes related to patient interviews and 36 to research staff. The hurdles to and enablers of recruitment mapped to three themes: (1) requirements of the EMPOWER trial in the context of the Royal College of Obstetricians and Gynaecologists guidelines, (2) the presentation of women to maternity services and (3) research staff roles.

Conclusions

Owing to the small sample size, it was not possible to draw meaningful conclusions from the main trial outcomes or the health economic outcomes. Overall, the treatment failure rate observed (50%) was higher than predicted in the sample size calculation at the design stage (10–20%). A higher proportion of women than anticipated were ineligible for the trial; the main reason was prior prescription of trial medication(s). This reflected a change in prescribing practice, often inconsistent with national antiemetic guidelines, with greater use of second-line drugs, particularly ondansetron. The qualitative study identified that the hurdles to and enablers of recruitment were both trial specific and site specific.

Recommendations for future research

Further research is needed on the clinical effectiveness and cost-effectiveness of treatment strategies in women with nausea and vomiting in pregnancy who fail to achieve symptom improvement with first-line antiemetic drugs. Further research is also required to understand the barriers to recruitment of complex randomised controlled trials involving pregnant women.

Trial registration

This trial is registered as ISRCTN16924692 and EudraCT 2017-001651-31.

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This report

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