Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment

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Scientific summary

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Scientific summary

Background

Nausea and vomiting in pregnancy (NVP) is one of the commonest symptoms of pregnancy affecting 50–85% of women during the first half of pregnancy. Symptoms usually start between 6 and 8 weeks, and most resolve by 20 weeks. Most women (65–70%) self-manage, but for the remainder symptoms are more severe. The most severe form – hyperemesis gravidarum (HG) – affects 0.3–1.0% of pregnant women and is characterised by intractable vomiting, dehydration, electrolyte imbalance, nutritional deficiencies and weight loss. There is no widely accepted point at which NVP becomes HG. A number of different treatments are available grouped as (1) first-line interventions, usually initiated by women before seeking medical care and tend to be used in less severe NVP; (2) second-line interventions, typically prescribed when a women presents to medical care [initially this may be a general practitioner (GP) but it may involve referral of women with more severe symptoms to hospital care]; and (3) third-line interventions, reserved for women in hospital with intractable symptoms, despite second-line therapies.

Aims

This study aimed to:

- review systematically the clinical effectiveness and cost-effectiveness of each treatment for NVP/HG
- determine which therapies are most likely to be cost-effective for implementation into the NHS
- identify and prioritise future research needs.

Methods

Clinical effectiveness review

We conducted a systematic review of the clinical effectiveness of randomised controlled trials (RCTs) and non-randomised comparative studies. Population-based case series were also reviewed for evidence of estimates of rare adverse events and fetal outcomes.

We searched MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, PsycINFO, Commonwealth Agricultural Bureaux (CAB) Abstracts, Latin American and Caribbean Health Sciences Literature, Allied and Complementary Medicine Database, British Nursing Index, Science Citation Index, Social Sciences Citation Index, Scopus, Conference Proceedings Index, NHS Economic Evaluation Database, Health Economic Evaluations Database, China National Knowledge Infrastructure, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects from inception up to September 2014. References from included studies and literature reviews were also examined. *Obstetric Medicine* was hand-searched, alongside websites of relevant organisations. The search strategy was based around nausea, vomiting and HG, and pregnancy terms. Costs were obtained from NHS sources.

All pharmacological and non-pharmacological interventions including novel treatments relevant to the NHS were considered. These included dietary/lifestyle interventions; vitamins such as vitamins B6 and B12; ginger; acupressure/acupuncture; hypnosis; antiemetic drugs (such as antihistamines; dopamine antagonists; 5-hydroxytryptamine receptor antagonists); corticosteroids; intravenous (i.v.) fluids; enteral feeding; and total parenteral nutrition.

Primary outcomes were severity of symptoms [such as Pregnancy-Unique Quantification of Emesis and Nausea (PUQE)]. Secondary outcomes included duration of symptoms; study-specific measures of NVP; quality of life; health-care utilisation; patient satisfaction; maternal weight; fetal outcomes [fetal or neonatal death, congenital abnormalities, low birthweight (< 2.5 kg), preterm birth (before 37 weeks' gestation) or small for gestational age (birthweight < 10th centile)]; adverse events, for example pregnancy complications (as reported in the study); costs; and cost-effectiveness. Both fixed- or random-effect model meta-analysis and a Bayesian mixed-treatment comparison were planned but were not performed due to heterogeneity in interventions, trial populations, reporting and definitions of outcome measures and methods. Thus, data on effectiveness, fetal outcomes and adverse events were tabulated and narratively reviewed.

Cost-effectiveness

The cost-effectiveness of the different treatments was planned to be assessed in an economic model but, due to the limited evidence, a simpler analysis considered the intervention costs, the difference in effectiveness implied if a more costly intervention was used. The perspective for cost was a health services perspective and all costs were reported in Great British Pounds (prices correct in 2014).

Results

Clinical effectiveness

Seventy-five papers from 73 studies met the inclusion criteria. For RCTs, 33 studies had a low risk of bias and 11 had a high risk of bias, with the remainder ($n = 20$) unclear. The non-randomised studies ($n = 9$) were judged low quality. There were 33 separate comparators. The most common comparisons were acupressure versus placebo ($n = 12$); steroid versus usual treatment ($n = 7$); ginger versus placebo ($n = 6$); ginger versus vitamin B6 ($n = 6$) and vitamin B6 versus placebo ($n = 4$). A common finding was that symptoms in all arms (including placebo) improved from baseline.

Ginger

Use of ginger was explored in 16 RCTs. The evidence available was at high or unclear risk of bias, in all but three trials. Six studies comparing ginger preparations with placebo generally reported evidence of ginger as improving a range of symptoms. Considering low risk of bias studies only, ginger still looked promising in reducing symptoms but the findings are not conclusive. One trial compared ginger with acupressure. Ginger again looked promising but the evidence was not very conclusive. For the comparison of ginger with vitamin B6 there are some higher-quality studies, but little evidence of a difference in the severity of symptoms between groups. There were few data for the comparisons of ginger with doxylamine–pyridoxine or antihistamine or metoclopramide, and little evidence suggesting any difference between groups. Overall, ginger might be better than placebo in reducing the severity of symptoms, but these data are limited to less severe symptoms.

Acupressure, acupuncture and nerve stimulation

Use of either acupuncture or acupressure was explored in 18 RCTs and one case series study. The quality of evidence available varied between low to high risk of bias. Comparisons with placebo were equivocal: two studies involving acupressure (both had mild symptoms and low risk of bias) reported better outcomes, but the remainder found no evidence of a difference or did not report NVP symptoms. The evidence for nerve stimulation was also mixed. Comparisons of traditional Chinese acupuncture and herbal medicine with Western medicine were at high risk of bias and impossible to emulate within the NHS. Overall, acupressure may reduce symptoms of nausea and retching in women with mild–moderate symptoms, but data were limited and inconclusive.

Aromatherapy

The evidence from two trials available for aromatherapy was at unclear risk of bias. There was no evidence of a difference compared with placebo or routine antenatal care.

Vitamin B6

Five studies considered the effectiveness of pyridoxine (vitamin B6), and they were at low risk of bias or risk of bias was unclear. Participants in all studies had mild to moderate symptoms at baseline. Comparisons of vitamin B6 preparations with placebo generally reported evidence of reduced symptoms of nausea, especially for women with more severe symptoms, and vomiting. Higher doses of vitamin B6 resulted in a greater improvement in symptoms. There was no evidence to suggest that vitamin B6 and metoclopramide as a combination treatment had an advantage over metoclopramide alone. Overall, there is a suggestion that vitamin B6 might be better than placebo in reducing the severity of symptoms especially at higher doses.

Vitaman B6 (pyridoxine)/doxylamine combination

Four studies compared the effectiveness of vitamin B6 and antihistamine with either placebo or ondansetron (and placebo). Two trials were at low risk of bias and two were at unclear risk of bias. Diclectin® [Duchesnay Inc.; doxylamine succinate (10 mg) plus pyridoxine hydrochloride (10 mg) slow release tablet] (vitamin B6 and antihistamine combination) appears more effective than placebo. Ondansetron appears more effective at reducing nausea than pyridoxine plus doxylamine, but with equivocal evidence for vomiting. Pre-emptive treatment with Diclectin before symptoms of NVP begin in women at high risk of severe NVP recurrence appears to result in a reduced risk of moderate–severe NVP compared with women who take Diclectin once symptoms begin.

Antihistamines

Of the three studies, two were at high risk of bias whereas one was at low risk. Participants in all studies had mild symptoms. Use of antihistamines resulted in an improvement compared with placebo or no treatment over a range of symptoms. The addition of vitamin B6 does not appear to improve effectiveness.

Dopamine antagonists

Dopamine antagonists were used in one trial (low risk of bias) and one poor-quality non-randomised study. There is limited evidence suggesting that promethazine is as effective as metoclopramide in reducing the symptoms of NVP.

Serotonin antagonists

Five trials and one case series study compared serotonin antagonists (ondansetron) against a range of alternatives. Three trials tested ondansetron against metoclopramide; symptoms were classified as mild to moderate in two trials and severe in one trial. The remaining two trials compared ondansetron with antihistamines with symptoms being moderate to severe. Only one trial was at low risk of bias. The studies comparing ondansetron with metoclopramide had mixed results, with both drugs improving symptoms. A study with low risk of bias found ondansetron more effective at reducing vomiting compared with metoclopramide after 4 days. Both ondansetron and antihistamine improve symptoms with no difference between effects. Overall, ondansetron reduces the severity of symptoms.

Intravenous fluids

Two studies were identified. One compared different compositions of i.v. solution (dextrose saline vs. saline only), which was at low risk of bias and one compared i.v. fluids containing vitamins with diazepam. I.v. fluid improves reported symptoms. Dextrose saline may be more effective at improving nausea over time for those with moderate nausea. Diazepam appears to be more effective than i.v. fluids alone at reducing nausea on day 2, but there was no evidence post treatment for those with moderate–severe nausea.

Transdermal clonidine

Evidence from one study with unclear risk of bias suggests that the use of transdermal clonidine patches looks promising for the treatment of severe HG.

Outpatient/day case management

The two studies of day case management were at low and high risk of bias respectively. Day case management of women with moderate to severe symptoms is feasible and acceptable, and as effective as inpatient management for some women.

Corticosteroids

The evidence available for corticosteroids was at low (three trials), unclear/high risk of bias (three studies) or weak (one case study). There was no evidence of a difference between either placebo or promethazine, but corticosteroids appeared to reduce vomiting episodes when compared with Phenergan® (Sanofi-Aventis) suppositories or metoclopramide.

Nasogastricenteral/jejunostomy feeding

Two case series studies of nasogastric and jejunostomy feeding were identified for treatment of severe HG. Both were poor quality. Enteral feeding may be an effective but extreme method of supporting women suffering from very severe symptoms.

Gabapentin

One very small study which examined gabapentin therapy in women with HG was identified. Given the reported cases of congenital anomalies among the seven exposed infants, more research is needed.

Cost-effectiveness

No relevant economic studies were identified by the systematic review and the economic analysis was limited by lack of data. Estimates of costs for each therapy (both pharmacological and non-pharmacological) were derived and used to illustrate the benefits that would be implied if a more costly treatment was chosen over a less costly one. These data were set against the limited evidence base. For treatments initiated by women themselves, weekly costs of treatment ranged from £0.12 (vitamin B6) to £90 (hypnotherapy). For care prescribed by clinicians as third-line interventions, costs of treatment ranged from £1994 to £2115 (depending on combination of antiemetics and steroids used) if patients were admitted as inpatients. The total cost data were used to estimate the implied value for the benefits of treatment should a decision be made to adopt one treatment over another. The implied valuation showed the additional benefits that a more expensive treatment would need to provide in order to be considered a worthwhile use of resources. For patient-initiated interventions, the implied valuations ranged from 1.01 : 1.00 (vitamin B12 vs. vitamin B6) to 41 : 1 (hypnotherapy vs. ginger). For vitamin B12 versus vitamin B6, the interpretation is that vitamin B12 would need to provide at least 1% more in benefits to be considered cost-effective. Implied values were calculated for all comparators and related to evidence on clinical effectiveness, where available. These simple data on costs may be of use to stakeholders when judging what treatments to use.

Strengths and limitations

The main strength of the review was the comprehensively systematic approach to identifying studies investigating NVP and HG, which allowed us to identify all relevant studies across all levels of severity. This is a departure from the preplanned inclusion criteria of severe nausea and vomiting only, but it reflects the very limited evidence on severe symptoms and the fact that the overall quality of the evidence is either low or very low for all of the treatment comparisons made in the review for all severities. Quality was downgraded due to clinical heterogeneity, imprecision, a sparseness of data, or a combination of these factors. There was considerable variation as to how nausea and vomiting outcomes were recorded and considerable variation reporting of severity. This prevented the conduct of the planned meta-analysis and economic modelling. Another major limitation was the lack of comparisons of interventions of relevance to the NHS. Thus, we were restricted to a narrative review that, at best, was able to consider direction of effect.

Conclusions

Implications for health care

There appears to be evidence that some treatments (ginger, vitamin B6, antihistamines, metoclopramide) were better than placebo for mild symptoms, but there is little on the effectiveness of treatments in more severe NVP/HG. Evidence on differences in effectiveness were available for few other comparisons. Of note, however, was the finding that symptoms tended to improve after a few days (even with placebo). Therefore, if symptoms have not improved or not improved sufficiently after a short time, a change of treatment could be considered. Also of note was that day case management for moderate–severe symptoms is feasible, acceptable and as effective as inpatient care for some women. Overall, uncertainty exists about most of the estimates reported in the review and further research is very likely to have an important impact on our confidence in the findings of the review. The findings from the review provide little other evidence to help inform recommendations on the use of treatments for severe NVP/HG.

Recommendations for research

The main gaps in the evidence base are the lack of direct comparative studies of relevant treatments to the UK NHS and the consequent lack of robust data to estimate cost-effectiveness. The key research recommendations in order of importance are:

1. A RCT including economic evaluation to determine which second-line, hospital-prescribed therapy (i.v. rehydration with antihistamines, dopamine receptor antagonists or serotonin receptor antagonists) should be adopted as mainstream provision in the UK NHS.
2. A RCT including economic evaluation to test the use of subsequent treatments, such as steroids, as a third-line therapy. This could examine indication, effectiveness and dose of corticosteroids versus serotonin receptor antagonists (ondansetron).
3. A RCT including economic evaluation to determine which second-line, GP-prescribed therapy (e.g. vitamin B6–antihistamine combination vs. dopamine receptor antagonist) should be adopted in UK primary care.
4. In addition to the use of objective symptom scoring systems like the PUQE, consideration is needed as to what are the core outcomes of importance to women and further work.
5. The longer-term critical fetal and maternal outcomes (death, congenital abnormality) of all therapies used in the NHS need to be monitored and analysed to guide further research into stratified care.

Study registration

This study is registered as PROSPERO CRD42013006642.

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