Interactive case report

Treating nausea and vomiting during pregnancy: case outcome

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Five weeks ago (31 January, p 276) we presented the case of Ms Reynolds, a 25 year old woman who presented to her general practitioner when eight weeks pregnant complaining of nausea and vomiting with light headedness. After an unsuccessful trial of prochlorperazine, she asked about alternatives to conventional drugs, and we suggested a trial of vitamin B-6 (pyridoxine) to relieve her symptoms (7 February, p 337). Because of the paucity of evidence for or against the use of vitamin B-6, we suggested an n of 1 trial as an objective way to assess whether it was effective. The table shows that vitamin B-6 did not have a significant treatment effect compared with placebo for Ms Reynolds's four most important symptoms. After being shown the results of her n of 1 study, Ms Reynolds stopped taking vitamin B-6.

Vitamin B-6 in the form of pyridoxal-5-phosphate acts as an important coenzyme in the transamination of amino acids, with deficiency leading to polyneuropathy and convulsions.² Vitamin B-6 has an important role in protein metabolism and transporting many amino acids across cell membranes. The mode of action in alleviating nausea in pregnancy is not known. No clear relation has been found between indicators of vitamin B-6 status and nausea and vomiting.²

Nausea and vomiting are the commonest symptoms experienced in the first trimester of pregnancy, affecting 70-85% of women.³ Hyperemesis gravidarum, persistent vomiting that is sufficient to cause fluid and electrolyte disturbance, is much less common, with an incidence of 3.5/1000 deliveries.³ Despite the relative lack of evidence, use of complementary or alternative medicines, including vitamins and herbal remedies, is popular. One study found that nearly a third of pregnant women use such remedies, with 13% of women specifically taking them to alleviate symptoms of nausea and vomiting in pregnancy.¹ In most instances patients do not tell their doctors that they are taking complementary medicines.¹

An n of 1 trial in a patient with hyperemesis gravidarum showed that prednisolone 50 mg daily was no more effective than ascorbic acid.⁴ The results of our n of 1 trial—that vitamin B-6 had no clinically important effect on vomiting—concurred with those of a systematic review, based on evidence from three randomised controlled trials.⁵ Vitamin B-6 was also ineffective in

Main symptom scores* for nausea and vomiting in pregnancy after five pairs of treatment with vitamin B-6 or placebo in n of 1 trial

Symptom	Mean score (95% CI)		Mean difference (95% CI)
	Vitamin B-6	Placebo	
Vomiting	3.2 (2.1 to 4.3)	3.9 (2.7 to 5.1)	-0.7 (-2.4 to 1.0)
Dizziness	4.2 (2.6 to 5.8)	4.1 (2.5 to 5.7)	0.1 (-1.1 to 1.3)
Activity (daily tasks)	3.6 (2.7 to 4.5)	3.8 (3.0 to 4.6)	-0.2 (-0.5 to 0.1)
General wellbeing	3.8 (2.5 to 5.1)	3.1 (1.9 to 4.3)	0.7 (-0.5 to 1.9)

*Based on measure yourself medical outcome profile (MYMOP),¹ with lower score indicating better outcome.

alleviating our patient's three other most important symptoms of dizziness, daily activities, and general wellbeing. We believe an n of 1 trial is a useful means of helping patients decide on which treatment to take in situations where evidence is poor or equivocal.

We thank Ms Reynolds for taking part in this study.

Funding: This study was funded through an extended South and West Deanery registrar contract for NH through the Division of Primary Health Care, University of Bristol, and Dean Lane Family Practice, Bristol.

Competing interests: None declared.

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BMJ 2004;328:503-6

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This is the final part of a 3 part case report, which describes the outcome and summarises the comments made by readers during the case presentation

Commentary: Patient's perspective

Sally Reynolds with the support of Nicola Harker

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At first I just felt so unwell that I would have taken anything. I was really disappointed that prochlorperazine hadn't worked; I felt so tired and unwell. I was really happy to do this trial because someone was taking an interest in my symptoms. I felt that I was being given a treatment and being monitored just to see if it helped me, rather than just being given the routine treatment that might not work. I found the daily questionnaire really helped because I could see if my symptoms were

getting better or worse. Before that it just felt all the same.

It was nice that I chose which symptoms were the most important to measure. This was a difficult pregnancy for me, and I was finding it difficult to cope with feeling ill and looking after my daughter. Even though the medication didn't work in the end, I don't regret doing the trial. It was helpful that someone took an interest in how I was feeling.

Commentary: Obstetrician's perspective—therapeutic trial and error?

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About 70% of pregnant women experience nausea and vomiting. This troublesome condition has been recognised in medical literature since the days of Hippocrates, who noted that it began soon after conception and continued until the end of the fourth month. Despite the longevity of our knowledge of this association, our understanding of the mechanism of this condition and its possible physiological protective role has advanced little. Indeed, sickness in pregnancy, like pre-eclampsia, remains a "disease of theories." Many hypotheses have been advanced, ranging from psychological disturbance to nutritional deficiencies, disturbed thyroid function, and excessively high concentrations of chorionic gonadotropin.

Our ability to treat nausea and vomiting in pregnancy is hampered by our lack of knowledge, and treatment has been empirical, focusing on the symptoms rather than the cause and compounded by concerns for teratogenicity and a placebo effect. But perhaps there is no single cause. Could nausea and vomiting in pregnancy be a generic physical response to a variety of functional and physiological disturbances invoked by pregnancy? If so, it is not surprising that we have failed to identify reliably effective treatments. Perhaps this is the ideal condition for an n of 1 trial, as it is the individual's response to a range of possible treatments that is important.

Diet and lifestyle modifications are generally the first line treatments. Iron supplements should be avoided since they can cause nausea and vomiting. The woman will require reassurance and support from family, friends, and health professionals. Antihistamines and phenothiazines are safe to use and usually give some improvement in symptoms,^{1,2} but the size of improvement can be variable. Newer drugs such as ondansetron may be effective, but safety data are limited.¹ Pyridoxine seems to be safe and is effective in reducing nausea, but there is no consistent effect on vomiting.³ There is also some evidence of benefit from alternative and natural remedies such as acupressure and ginger root extract.² When sickness progresses to hyperemesis treatment focuses on rehydration, thiamine supplementation (to prevent Wernicke's

encephalopathy), antiemetic therapy, thromboprophylaxis, and increasingly corticosteroids.⁴

What of Mrs Reynolds, the subject of the case report? Her case is not entirely typical since her sickness started later in pregnancy than is usual at 8 weeks and because she had not had this problem in previous pregnancies. Her history suggests that social or psychological factors were absent. She did not benefit from prochlorperazine, but it is important that antiemetics are taken regularly rather than on an as required basis and this should be clarified with her. It is also important to consider whether she was vomiting up the drugs. In this situation suppositories can be helpful.

Her condition seems to have progressed and was affecting her ability to function. However, she had no evidence of dehydration (absence of postural hypotension) and no ketonuria, features present when vomiting has progressed to hyperemesis. As sickness in pregnancy and hyperemesis are diagnoses of exclusion, it is essential to consider alternatives before embarking on further treatment. In particular, thyrotoxicosis (although transient gestational thyrotoxicosis, which is self limiting, often accompanies hyperemesis), urinary tract infection, and a twin or molar pregnancy (as there is an association with hyperplacentation) should be excluded. Thus, before proceeding, it would be useful to check thyroid function, urea and electrolytes, and liver function tests, pelvic ultrasound, and urine culture and sensitivity.

If other problems are excluded then an n of 1 trial of the conventional and alternative treatments is justified. In the context of nausea and vomiting in pregnancy, however, this trial and error approach will perhaps tell us more about what doesn't work than what does

Competing interests: None declared.

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Commentary: n of 1 learning

Ed Peile

How should we start to look at the learning that this interactive case has stimulated? Should we look again at the web discussants? We could appreciate the diversity of disciplinary backgrounds and nationalities of contributors. We could categorise the learning threads: as the case progressed, I have commented both on the breadth and the depth of learning that was evident in rapid responses. But are we missing something? I think we are missing the parallel message from the clinical topic for educationalists. We were learning about n of 1 trials; about systematically evaluating an individual response to an approach intended to help a difficult problem.

Look again at the individual learners who responded on *bmj.com*. They focused on widely different aspects of the case—some on pharmacotherapeutics, others on alternative medicine, yet others on research methodology. They offered references to the evidence base, personal anecdotes, and distillations of experience. What stimulated one reader left others cold, and herein I suspect lies the value of the broad group learning—something for everyone, or at least for many different learners if they are prepared to delve.

Learning is an n of 1 area. In the classroom,¹ the medical school lecture theatre, and the postgraduate group, there are so many fundamental differences underpinning learners' understanding that it is safest to think of each learner as different from every other in the group. We can look at learners' preferences in several ways as learning style inventories abound. They may help us appreciate the different ways in which we take in our information, interpret it, process it, and store it, but the realisation dawns that there are so many cognitive and non-cognitive profiles that groupings are virtually useless. I come back to thinking of teaching and learning exchanges as one on one processes that may take place in a crowd.

JENS SCHLUFTER/PIGETTY IMAGES

Learning could benefit from n of 1 approaches

Think about the way we evaluate the success of medical teaching. The most common way is to seek individual feedback after the session. We then tend to aggregate the scores and apply the principle of "the common good" in determining the proportion of learners who rated the session highly. It might be better sometimes not to aggregate but to regard the session as a series of n of 1 experiments, and to look to see where individual learners have advanced their understanding. Medical educators need to think qualitatively as well as quantitatively.

Competing interest: None declared.

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Commentary: General practitioners are wary of treating sickness in pregnancy

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Sickness in pregnancy causes symptoms that vary from mild to so severe that hospital admission is required. It is associated with an appreciable loss of time from work¹ and disruption of normal social activities,² and it has been the stated reason for 25-29 terminations of pregnancy every year in the United Kingdom.³ However, many general practitioners in the United Kingdom feel frightened of suggesting any treatment to women presenting with pregnancy sickness because they believe that it would be ineffective and could cause fetal abnormalities.

There were 20 rapid responses after the first part of the case history, some of which discussed the use of nutritional and complementary therapies. The problem is that few data exist on the effectiveness

and safety of such therapies for pregnancy sickness. There were fewer responses after the second part of the history, which perhaps suggests that doctors are not used to the idea of n of 1 trials in general practice.

Pregnancy sickness is difficult to measure, and the methods described in the case report might not have been sensitive enough to detect any improvement resulting from treatment with pyridoxine. One respondent also suggested that the treatment intervals should have been longer.

The Rhodes score, which was first used to assess nausea and vomiting during cancer chemotherapy, has been proposed as the method of choice for assessing treatments for pregnancy sickness.⁴ This score gives a

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validated and quantifiable measure of the severity of the condition.

Advice is needed

No drugs are licensed for treating pregnancy sickness in the United Kingdom. However, evidence based guidelines approved by the Society of Obstetricians and Gynaecologists of Canada state that diclectin (pyridoxine 10 mg and doxylamine 10 mg) should be the initial treatment as it has the greatest evidence to support its efficacy and safety in pregnancy.⁵

In the absence of such a guideline in the United Kingdom, general practitioners are left to give reassurance and general advice. They occasionally resort to prescribing, as in this case history, often using

something like prochlorperazine or metoclopramide, for which there are few data on effectiveness or safety in pregnancy.

Competing interests: RG is a trustee of the charity pregnancysicknesssupport, which has received an unrestricted educational grant from Duchesnay of Canada.

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Commentary: Statistical aspects

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The main issue in this study is the use of an n of 1 trial for the evaluation of treatments for nausea and vomiting in pregnancy. These trials are used to decide what treatment benefits an individual patient and are a more scientific method of decision making than the usual method used by general practitioners: asking the patient to return if the first treatment doesn't work and trying a second one.¹ As I have pointed out before, R A Fisher, one of the greatest statisticians, discussed at length an n of 1 trial investigating whether a woman could tell whether milk was added before or after the tea,² and this has even become the title of a book.³ They are usually used in chronic illness, such as arthritis, to evaluate the best long term treatment for a patient. A recent good example showed that paracetamol may be used instead of non-steroidal anti-inflammatory drugs in some patients with osteoarthritis.⁴

However it is worth mentioning a few problems associated with n of 1 trials.⁵ In terms of design an investigator needs to decide:

- How many treatment periods
- How long to treat within each period.

Since nausea in pregnancy obviously has a limited duration, few treatment periods will be available, and a compromise will have to be made about the number of periods compared with the length of each one. The trial had only five pairs of treatment periods, and so did not have much power to detect an effect unless it was large. However, that is what we would be hoping for in this case. To accommodate even five pairs of treatment periods within the time span, the treatment was given for only two days, and several respondents commented that two days of active treatment is unlikely to be enough to correct a vitamin deficiency.

N of 1 trials are crossover trials, and like crossover trials they are also vulnerable to carry over effects, where the effect of treatment extends to the next treatment period. This may be a problem in this case, because if the treatment did in fact cure the deficiency, it is unlikely to reappear again after two days.

An interesting problem (discussed at length by statisticians since it affects the P value) is what Ms Reynolds knew of the allocation. Was she simply told that she was going to be treated for 25 days with either vitamin B-6 or placebo allocated at random or did she know that there were five matched periods? Despite these caveats, it would be nice to see more general practitioners conducting these type of trials.

Competing interests: None declared.

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Endpiece

Paris and London consultants 1815

The French physicians and surgeons display a degree of attention and zeal in the execution of their duties truly exemplary. Their public professional duties are ever the primary consideration, for which the trifling salary they receive is a pitiful remuneration while in the London hospitals, it is too evident that public appointments are generally considered but the stepping stones to practice and private emolument.

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