Effect of Acupuncture on Nausea of Pregnancy: A Randomized, Controlled Trial

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***Objective*: To compare acupuncture with sham (placebo) acupuncture for treatment of nausea of pregnancy.**

***Methods*: In a subject- and observer-masked, randomized, controlled trial in the maternity unit at Exeter Hospital, we gave 55 women between 6 and 10 weeks' gestation genuine, traditional-style acupuncture or sham treatment with a cocktail stick on three or four occasions over 3 weeks. The main outcome measure was nausea score, as determined by subject report on a visual analogue scale in a daily diary. Anxiety and depression also were assessed.**

***Results*: Nausea scores decreased from a median of 85.5 (interquartile range 71.25–89.75) to 47.5 (interquartile range 29.25–69.5) in the acupuncture group and from 87.0 (interquartile range 73.0–90.0) to 48.0 (interquartile range 14.0–80.0) in the sham treatment group. There was strong evidence of a time effect ($P < .001$) but no evidence of a group effect ($P = .9$) or a group-time interaction ($P = .8$). Similarly, there was evidence of time effects in scores for anxiety and depression but no group differences. The study had a power of 95% to detect significant differences in nausea scores.**

***Conclusion*: Acupuncture was as effective in treating nausea of pregnancy as a sham procedure. (Obstet Gynecol 2001;97:184–8. © 2001 by The American College of Obstetricians and Gynecologists.)**

Nausea occurs in up to 80% of pregnant women.[1] A recent review found evidence that antiemetic medication was effective[2] but also some evidence of adverse events and very little evidence of the effect on fetal outcome. Because women wish to avoid the risk of teratogenic effects, they might reject drugs and use complementary medicine instead. One complementary therapy widely available is acupressure, commonly given in the form of pressure studs attached to wrist bands. A systematic review[3] concluded that acupressure might give relief to many women but that it was uncertain whether this was a specific effect of stimulation of the precise point or a generalized effect attributable to attention and intention. Acupuncture is a form of treatment that uses needles instead of pressure to stimulate points. It might be more effective than acupressure because it is a stronger stimulus. Literature searches of MEDLINE and EMBASE from their inceptions to July 1997, using the Ovid interface and searching for keywords "acup*" and "clinical trial," found several studies of acupressure but no previous studies of acupuncture for nausea of pregnancy. We therefore decided to test the hypothesis that acupuncture is superior to sham (or placebo) acupuncture in the treatment of nausea of early pregnancy.

Materials and Methods

We conducted a sham-controlled, subject- and observer-masked, randomized, controlled trial of acupuncture at the Royal Devon and Exeter Hospital maternity unit. All primiparous and multiparous women who were 6–10 weeks pregnant and complained of nausea, with or without vomiting, who approached a community midwife and who were willing to consider acupuncture were referred to the hospital and invited to participate in the study. We chose this early gestation period to permit treatment before the natural remission of symptoms would be expected. Women who had severe symptoms necessitating admission to the hospital were excluded, as were those who had acupuncture previ-

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Mrs Knight was partly supported by a National Health Service Executive South West Research and Development Project grant (Bristol, United Kingdom). We are grateful to Seirin Deutschland GmbH (Neu-Isenberg, Germany), for donating the acupuncture needles used in this study.

ously, those who had fear of needles, and those with severe bleeding disorders.

After women had given written informed consent, we collected baseline data and gave the women a list of self-help measures for treatment of nausea and vomiting written specifically for the trial, mainly concerning rest and choice of food. Participants were then randomly assigned to acupuncture or control groups by opening opaque, serially numbered envelopes containing a code (A or B) determined by computer-generated random numbers in blocks of four and prepared by staff not connected with the study. The acupuncturist opened the envelopes immediately before the first treatment session. The protocol included stratification of women into two groups with mild to moderate or moderate to severe nausea according to their rating of symptoms in the past week, using the scores from a pilot study in a convenience sample of pregnant women. However, all subjects' scores were moderate to severe.

The investigator and the acupuncture practitioner worked in different rooms. The investigator, who was responsible for recruitment, application of inclusion and exclusion criteria, and collection of baseline and outcome data, remained masked to the participants' group allocations. The acupuncturist made the decision of which treatment was represented by code A or B and did not reveal this decision until the analysis had been completed. The acupuncturist followed standardized procedures for all interactions with the women, ie, reception, history taking for diagnosis, removing needles and guide tubes, and pressing with cotton swabs. Women were treated in a relaxed, nearly supine position and remained masked to whether they were in the genuine or sham acupuncture group. The success of masking was tested at the second session by asking the question, "When you were invited to join the trial, you were told you had an equal chance of being assigned to one of two groups, either the specific point acupuncture group or the alternative treatment group. Did you know which group you were in?"

At each woman's first visit the practitioner made a traditional Chinese medical diagnosis. Using the symptoms and examination of tongue and pulse, we allocated each woman to one of the following three categories and treated her at the appropriate points (all needled bilaterally, unless midline point or where stated): stomach and spleen qi xu, for nausea, stuffiness in the chest, and lassitude, with pale white, moist tongue, and "slippery" pulse. Points used were stomach 36 (below the knee), conception vessel 12 (central upper abdomen), spleen 4 (medial border of foot, right side only), and pericardium 6 (medial surface of wrist); stomach fire, for lump in throat, heartburn, metal taste in mouth, constant hunger, sour regurgitation, constipation, nausea and vomiting immediately after eating, with red tongue with a yellow, cracked coat, and "rapid, slippery, full" pulse. Points used were stomach 44 (forefoot), conception vessel 12, and pericardium 6; and heat in heart and disharmony of liver, for nausea, bitter taste, restlessness, insomnia, vivid dread, thirst, dark urine, red tongue with red spots on tip and yellow coat, and "rapid, slippery, wiry pulse." Points used were conception vessel 12, stomach 34 (superior to patella), and pericardium 6.

Such categories are standard in traditional Chinese medicine, although formal validity and interrater reliability have not been established. The categories and points for treatment are in common use in China and were confirmed by consultation with a midwife who uses these treatments regularly in a health service antenatal clinic and with the Integrated Chinese Medicine acupuncture training college (Reading, UK).

We used 40 × 0.25-mm needles (Seirin, Japan) inserted to a depth of 0.5–1.0 cm with the assistance of a guide tube. We then removed the guide tube to manipulate the needle and elicit Deqi, the dull aching sensation associated with correct needling, and determined the moment of insertion (during inspiration or expiration) and the technique of manipulation to achieve tonification or reduction, according to traditional Chinese theory. Finally, the guide tube was replaced over the needle, and the combination of needle and guide tube was covered with 10-cm-square white, soft, opaque adhesive dressing to hold the needle at the correct angle and position.

Sham treatment consisted of tapping a blunt cocktail stick, supported by a plastic guide tube, over a bony prominence in the region of each acupuncture point during expiration (specific locations were, on the left side, the radial styloid, tibial tuberosity and fifth or sixth rib 8 cm from the midline, and on the right side, the medial malleolus). After removing the cocktail stick, we left the guide tube in position but concealed it by a 10-cm-square white, soft, opaque adhesive dressing, like a tent. Because this form of intervention might produce a physiologic response, it is labeled sham rather than placebo. In the design stage, we considered using a no-treatment group but rejected it because we believed it would affect recruitment adversely.

Needles or shams were left in position for about 15 minutes. Both genuine and sham acupuncture were given twice in the first week and once weekly for 2 weeks. The minimum number of treatments regarded as fulfilling the requirements of the protocol was three.

The primary outcome was measured by using a visual analogue scale consisting of a 100-mm line with vertical lines at each end marked 0 and 100 and labeled

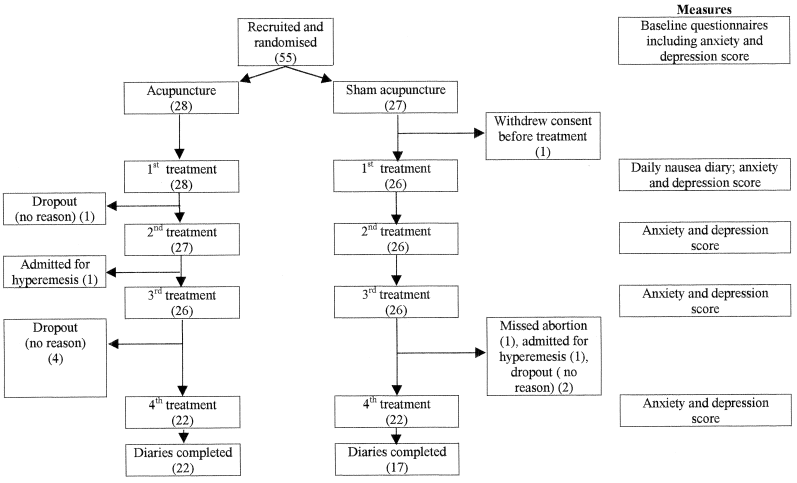

Figure 1. Flowchart for acupuncture trial for nausea of pregnancy.

"no nausea" and "nausea worst imaginable" at each end, respectively. This measure has been validated.[4] Women marked the scale daily, at a fixed time they determined themselves, to represent the worst experience of nausea in the previous 24 hours. We asked the women to record how many times they had vomited in the previous 24 hours and to write any adverse effects of their treatment on the reverse of the diary. We used the Hospital Anxiety and Depression scale as a secondary outcome measure in view of the clinical association among anxiety, depression, and nausea. Participants completed the scale at baseline and immediately after the last treatment.[5] Within 2 weeks of completion of treatment we telephoned women to ask how effective overall they believed the treatment was, using a five-point Likert-type scale ranging from very much worse (1) to very much better or cured (5).

We calculated sample size by using data from the study by Hyde[6] in which the difference for nausea scores between acupressure and control groups was 0.9 ± 0.9 (mean ± standard deviation). Using a standardized difference of 1.0 in a standard nomogram,[7] we calculated that a sample size of 55 subjects would have 95% power to discriminate between acupuncture and control, with a two-sided hypothesis and alpha of 5%.

We did intent-to-treat analysis according to the predetermined trial protocol. The primary analysis consisted of a comparison of nausea scores on the third day after each scheduled treatment, on the basis that those scores would show an effect of acupuncture at its maximum. For missing data we carried forward the last available score. We then did a repeated measures analysis of variance using procedure GLM in SAS version 6.12 (SAS Institute, Cary, NC). We conducted similar analyses for anxiety and depression scores and analyzed the remaining diary data in an exploratory manner. The East Devon and Exeter Local Research Ethics Committee granted ethical approval of the trial.

Results

We recruited and randomly assigned 55 subjects to the groups. As shown in Figure 1, five women withdrew for medical reasons or dropped out before the second treatment. Six other women did not have a fourth treatment session.

The groups were well balanced for baseline variables (Table 1). In response to the question about masking, one woman in each group believed she might have had sham treatment, whereas all others believed they had received acupuncture or were not sure. Women reported a total of 19 adverse events, including, in the acupuncture group, two cases each of tiredness, sleep disturbance, and heaviness of arms and one case each of more energy, altered taste, bruising, pressure in nose, and headache; and in the sham group, two cases each of tiredness and altered taste and one case each of increased vomiting, flatulence, vivid dreams, and feelings of coldness.

Table 1. Baseline Characteristics

	Acupuncture (n = 28)	Sham procedure (n = 27)
Age (y), mean (range)	30.7 (22–40)	30.3 (22–40)
Parity		
Nulliparous	14	9
Multiparous	14	18
Gestational age (wk)	7.8 ± 1.0	8.0 ± 1.0
Maternal weight (kg)	62.6 ± 11.4	68.3 ± 11.7
Smoker	2	2

Data are given as n or mean ± standard deviation, except for maternal age.

Table 2. Nausea Scores After Four Sessions of Acupuncture or Sham Acupuncture

Assessment and group	Median	Interquartile range
Day 1		
Acupuncture	85.5	71.25–89.75
Sham	87.0	73.0–90.0
3 days after session 1		
Acupuncture	63.0	50.75–86.5
Sham	69.0	45.0–87.0
3 days after session 2		
Acupuncture	65.0	36.25–79.5
Sham	61.0	30.0–80.0
3 days after session 3		
Acupuncture	44.0	29.0–77.25
Sham	53.0	25.0–80.0
3 days after session 4		
Acupuncture	47.5	29.25–69.5
Sham	48.0	14.0–80.0

For the nausea scores at baseline and 3 days after each treatment (Table 2), Mauchly's test of sphericity failed, having a low P value; therefore, we based conclusions on the multivariate tests of hypotheses. (Results from the univariate tests were very similar.) The data were not normally distributed, but the extreme P values obtained suggested that the conclusions were sound. There was strong evidence of a time effect ($P < .001$) but no evidence of a group effect ($P = .9$) or a group-time interaction ($P = .8$). Therefore, there is strong evidence that the scores changed over time but no evidence of any group differences in overall level or in the nature of the changes. After removing the data for the five women who dropped out of the study early or for medical reasons, there were still no differences in the conclusions. A closer inspection of the data showed that the most pronounced average reduction in nausea scores was between days 1 and 2. The median change for the acupuncture group was −15 with an interquartile range of −31 to −3. In this group 21 nausea scores decreased, one did not change, five increased, and the other was not known. In the sham group, the median change was −8 with an interquartile range of −14.75 to 0.25. In this group 18 nausea scores decreased, two did not change, six increased, and one was not known.

The patterns in the scores for anxiety and depression were similar overall to those for the nausea scores (Table 3). In each case there was evidence of non-normality, and Mauchly's test of sphericity failed, having a low P value. The results of the multivariate tests were as follows. For the anxiety score there was evidence of a time effect ($P = .0062$) but no evidence of a group effect ($P = .4$) or a group-time effect ($P = .20$). For the depression scores there was evidence of a time effect ($P = .002$) and again no group ($P = .9$) or group-time interaction ($P = .5$). Both scores appeared on average to decrease during the course of the study, and the drop was more pronounced for the depression scores, which on average started at higher values. Although the average behavior of all three sets of scores was similar, there was no clear correlation structure among the three sets of measures.

The median rating of global effectiveness of the treatments was 4 (range 3–5) for both groups, indicating an overall level of satisfaction with the treatment.

Discussion

Three or four sessions of acupuncture or sham acupuncture given over 3 weeks produced notable decreases in nausea of early pregnancy but with no difference between the groups.

There are several potential sources of bias in this study. Limitations on availability of the acupuncturist, together with social and work commitments of the participants, interfered somewhat with optimal spacing of treatment sessions. We gave the second treatment late (more than 1 week from the first) in four women, the third treatment earlier than the second week in one case, and the fourth treatment in less than two weeks after the second treatment in eight cases. Acupuncture treatment might have been less than ideal because the protocol did not allow for variation in treatment in subsequent sessions in patients who had failed to respond. The sham procedure might not have been completely inactive: acupuncture is believed to induce its effects, at least in pain control, by stimulating A-delta

Table 3. Anxiety and Depression Scores at Treatment Sessions

Assessment	Group	Median	Interquartile range
Anxiety			
1	Acupuncture	8	6–9
	Sham	10	7–13
2	Acupuncture	8.5	6–9
	Sham	8	6–11
3	Acupuncture	7	6–9
	Sham	7	5–10
4	Acupuncture	7	4–9
	Sham	8	5–9
Depression			
1	Acupuncture	9.5	8–15
	Sham	11	8–14
2	Acupuncture	9	7–11
	Sham	9	7–12
3	Acupuncture	8.5	7–12
	Sham	8	7–11
4	Acupuncture	7	5–11
	Sham	8	6–10

nerve fibers in skin and muscle.[8] It is possible that the sham procedure, although applied briefly, also could have stimulated A-delta fibers. Women failed to record systematically data on vomiting; therefore, it is possible that we missed an effect, although two previous studies have shown effects on nausea without effects on vomiting, and none has shown reduced vomiting with no effect on nausea.[3]

The first systematic review of the literature of acupuncture, acupressure, and electrical stimulation for nausea[9] included seven studies of acupressure for nausea of pregnancy. It reached a positive conclusion that all forms of stimulation of the relevant acupuncture point were effective for all forms of nausea. In a review limited to trials in nausea of pregnancy,[3] two studies found acupressure to be superior to no treatment, three found it superior to dummy acupressure, and one found it not superior to dummy acupressure. It is notable that results of the last study, which was the most rigorous,[10] were negative. The investigators randomized 161 women to receive correct acupressure, acupressure to an incorrect point, or no treatment for 7 days. A research assistant, who was masked to the group allocation, telephoned the women daily. The results showed no benefit from genuine or sham acupressure. The reviewer[3] concluded that many women benefit from pericardium 6 stimulation, but because they probably would know whether they were receiving the active intervention, the findings might be due only to the placebo effect. Our negative findings support this conclusion.

This intervention was popular with our subjects, all of whom were grateful and looked forward to their next treatments. They particularly enjoyed the opportunity to discuss their problems with midwives and to have their symptoms recognized and accepted by professionals. It is noteworthy that the major decline in nausea scores occurred between the first and second days. Moreover, the spread of nausea scores was less on day 1 than on subsequent days. On day 1 the interquartile range was approximately 70–90 for each group, whereas on subsequent days it was approximately 50–80. We believe this sudden reduction in nausea is unlikely to have occurred because of natural remission of symptoms during pregnancy. The reduction would be compatible with a placebo effect, with an effect of advice contained in the leaflet, or with the tendency for participants to overstate the severity of their symptoms at baseline. The latter effect might be particularly likely because the women recorded initial scores under supervision of the researcher but recorded subsequent scores at home. Thus, the major improvement shown by both groups may be an artifact or a mind-body effect. The reduction in scores for anxiety and depression between first and second treatments was small, but there might have been other relevant psychological changes at the same time that were not monitored. To identify reasons for the time effects seen in this trial, further studies specifically using an additional attention control group are necessary.

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Received March 27, 2000.
Received in revised form September 8, 2000.
Accepted October 12, 2000.

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