Ginger for Nausea and Vomiting in Pregnancy: Randomized, Double-Masked, Placebo-Controlled Trial

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***Objective*: To determine the effectiveness of ginger for the treatment of nausea and vomiting of pregnancy.**

***Methods*: Women with nausea and vomiting of pregnancy, who first attended an antenatal clinic at or before 17 weeks' gestation, were invited to participate in the study. During a 5-month period, 70 eligible women gave consent and were randomized in a double-masked design to receive either oral ginger 1 g per day or an identical placebo for 4 days. Subjects graded the severity of their nausea using visual analog scales and recorded the number of vomiting episodes in the previous 24 hours before treatment, and again during 4 consecutive days while taking treatment. At a follow-up visit 7 days later, five-item Likert scales were used to assess the severity of their symptoms.**

***Results*: All participants except three in the placebo group remained in the study. The visual analog scores of post-therapy minus baseline nausea decreased significantly in the ginger group (2.1 ± 1.9) compared with the placebo group (0.9 ± 2.2, $P = .014$). The number of vomiting episodes also decreased significantly in the ginger group (1.4 ± 1.3) compared with the placebo group (0.3 ± 1.1, $P < .001$). Likert scales showed that 28 of 32 in the ginger group had improvement in nausea symptoms compared with 10 of 35 in the placebo group ($P < .001$). No adverse effect of ginger on pregnancy outcome was detected.**

***Conclusion*: Ginger is effective for relieving the severity of nausea and vomiting of pregnancy. (Obstet Gynecol 2001;97: 577–82. © 2001 by The American College of Obstetricians and Gynecologists.)**

Nausea and vomiting are common in early pregnancy.[1] Although the condition is not life threatening, it can cause considerable distress to pregnant women and their families. Moreover, it can cause temporary disability in a high proportion of employed women, and as many as 25% of nauseous pregnant women require time off from work.[2] The cause of nausea and vomiting in pregnancy is still unknown. As a consequence, a wide variety of treatments have been used empirically.[1,3] However, the use of drugs for this condition is limited because of the concern for potential teratogenic effects.[1] Natural products such as ginger, red raspberry, and wild yam have been suggested as alternative treatments, but data on their efficacy are limited.[1]

In one study, ginger was found to be superior to dimenhydrinate in reducing motion sickness.[4] In another study, ginger was found to significantly reduce postoperative emetic sequelae.[5] Only one trial of ginger in nausea of pregnancy was identified by an online search of the National Library of Medicine's MEDLINE database from 1990 to 2000, using the search terms "nausea and vomiting and ginger" and "hyperemesis gravidarum and ginger." Cochrane Database of Systematic Reviews on CD-ROM (Issue 1, 2000) also was searched but no additional trials were identified. In addition, citations and bibliographies of all retrieved papers were reviewed to find any trial not found in the automated search.

The only study reported so far was a randomized, double-blind, cross-over trial of ginger in hospitalized patients with hyperemesis gravidarum.[6] The purpose of the present study was to further evaluate the effectiveness of ginger in a randomized, double-masked, parallel design, involving a larger group of subjects with less severe manifestation of nausea and vomiting.

Materials and Methods

The study was approved by the ethical committee of the Faculty of Medicine, Chiang Mai University (Chiang Mai, Thailand) and the procedures followed were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki of

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1975, revised in 1983. Subjects were recruited consecutively from the antenatal clinic at Maharaj Nakorn Chiang Mai University Hospital (Chiang Mai, Thailand). They were included in the study if they first attended the clinic before 17 weeks' gestation and had nausea of pregnancy, with or without vomiting. Subjects were excluded if they: (1) had other medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea or vomiting; (2) were mentally retarded; (3) had language or geographic barriers; (4) had taken other medication in the past week that might aggravate or alleviate nausea or vomiting, such as iron tablets or antiemetics; (4) were unable to take the medication as prescribed; (5) were unable to return for a follow-up visit within 1 week; or (6) refused to participate in the trial.

Consenting subjects underwent general physical examinations and routine obstetric evaluations. They were then randomized into two groups. Those in the ginger group received one 250-mg capsule three times daily after meals and one capsule before bedtime for 4 days. Those in the placebo group received identical-looking capsules and the same regimen. All subjects were advised to divide their meals into frequent small ones rich in carbohydrates and low in fat and not to take any other medications outside the trial. Subjects were requested to return in 1 week to assess their responses to treatment. Those who did not return were contacted by telephone or mail. Compliance was assessed by pill count, by monitoring attendance at scheduled visits, and by asking subjects whether the drugs were taken.

Before the trial began, a research nurse who was not responsible for patient care used a table of random numbers to prepare the treatment assignment. The treatment codes were kept in sequence in a sealed black envelope that could not be read through. As each subject entered the trial, she received the next envelope in the sequence, which determined her assignment. A list that revealed drug codes given to patients was kept strictly confidential in one safe place by a research nurse and was not accessible to the physicians. Neither the physicians nor the patients knew the identity of the drugs administered.

The ginger and identical-looking placebo capsules were prepared by a pharmacist from the Faculty of Pharmacology, Chiang Mai University. Briefly, fresh ginger root was chopped into small pieces, baked at 60C for 24 hours, and then ground into powder. Ginger powder was weighed and packed into 250-mg capsules. Excess powder was wiped off the capsule surface with a clean dry cloth. Quality control was done by randomly weighing the content of the capsule and by performing bacteriologic cultures. Both placebo and ginger capsules were similarly packed in an envelope containing 18 capsules each. Before the trial began, ginger and placebo capsules were given to 10 volunteers (resident physicians) for 4 consecutive days. They were then asked whether they knew if they were taking ginger or placebo. Although three correctly identified what they were taking, they were not certain of their selections.

The primary outcome in this study was the improvement in nausea symptoms. Because nausea is a subjective symptom, two independent measurement scales were used to quantify the changes in severity: a visual analog scale and a Likert scale. For the visual analog scales, patients were asked on their first visit to grade the severity of their nausea over the past 24 hours (baseline scores) by marking an "X" corresponding to their perceived states on a 10-cm vertical line, ranging from 0 = no nausea to 10 = nausea as bad as it could be. On the following 4 days of treatment, recordings of the severity of nausea were made twice daily at noon and at bedtime. To obtain an objective measurement, we measured the markings on each of the visual analog scales in centimeters. The average daily nausea scores and the mean nausea scores over the 4 days of treatment for each subject were then calculated. Finally, we compared the median change in the severity of nausea (post-therapy minus baseline scores) in the ginger and the placebo groups by Wilcoxon rank-sum test. At the 1-week follow-up visit, five-item Likert scales (much worse, worse, same, better, much better) were used to assess the patients' response to treatment. Fisher exact test was used to compare the change in the severity of nausea in the two groups.

Patients were also asked to record the number of vomiting episodes in the 24 hours before treatment, and then on each subsequent day of the treatment. The change in the number of vomiting episodes in the two groups was compared by Wilcoxon rank-sum test. The proportion of subjects with vomiting before and after treatment were compared by χ^2 tests. Other secondary outcome measures included the occurrence of side effects and adverse effects on pregnancy outcomes such as abortion, preterm birth, congenital anomaly, perinatal death, and mode of delivery.

In a pilot study using Likert scales on 20 subjects, all cases reported improvement with ginger, whereas only 1 of 10 did so in the placebo group. Given a probability of type I error of 1% (two-tailed) and a type II error of 10% (ie, a power of 90%), we calculated that fewer than 10 subjects were required to show this treatment effect. However, in such a small study, randomization may result in substantial imbalance and may not yield comparable groups. We calculated that if the pilot study gave an overestimation of the treatment effect, that is, the improvement in the ginger group was in fact only

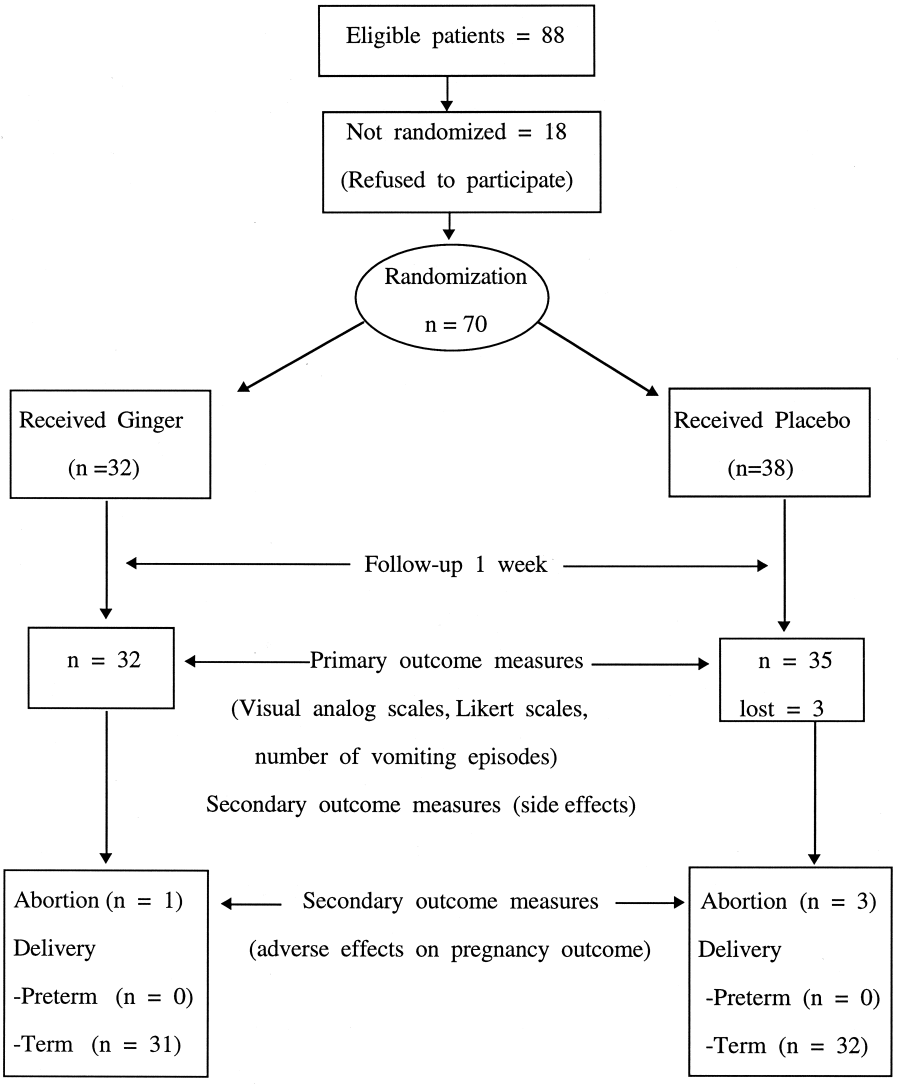

Figure 1. Trial profile summarizing participant flow, numbers, and timing of randomization assignment, interventions, and outcome measures.

70% (instead of 100%) and that in the placebo group was as high as 30% (instead of 10%), we would still be able to detect this difference with a power of 0.9 and $\alpha = .05$ by using a sample size of 31 subjects per group. To allow for a 10% dropout rate, a total sample size of 70 was projected.

Stata Statistical Software (Stata Corporation, College Station, TX) was used for data analysis and the statistical tests were considered significant at $P < .05$. Analysis was performed by excluding those who were lost to follow-up. In addition, effectiveness was assessed by intent-to-treat analysis.

Results

Between October 1, 1998, and February 28, 1999, 992 new obstetric patients attended the antenatal clinic at Maharaj Nakorn Chiang Mai University Hospital, of whom 88 met eligibility criteria. Seventy women consented to participate in the study (Figure 1). Thirty-eight subjects were assigned to placebo and 32 to ginger. Three placebo subjects (7.9%) did not return for follow-up visits and were excluded from the study. Differences in baseline characteristics of the two groups were not statistically significant (Table 1).

The median change in nausea scores (baseline minus average posttherapy nausea scores for all subjects) in the ginger group was significantly greater ($P = .014$) than that in the placebo group (Table 2). To account for the three missing patients in the placebo group, we assumed that their nausea scores changed as much as subjects with the best improvement. Intent-to-treat analysis was then performed using Wilcoxon rank-sum test. The result showed that there was a significantly greater reduction in nausea scores in the ginger group than in the placebo group only on day 4 of treatment ($P = .0348$).

Table 1. Baseline Characteristics

Characteristic	Placebo ($n = 35$)	Ginger ($n = 32$)
Age (y)	28.6 ± 5.5	28.3 ± 5.8
Parity		
Nulliparous	16 (45.7%)	13 (40.6%)
Multiparous	19 (54.3%)	19 (59.4%)
Gestational age (wk)	10.3 ± 2.6	10.4 ± 2.3
Baseline nausea scores (cm)	4.7 ± 2.1	5.4 ± 2.1
Episodes of vomiting in previous 24 h (median [range])	2 (0–6)	3 (1–10)
Education		
Primary school	14 (40.0%)	14 (43.8%)
Secondary school	15 (42.9%)	16 (50.0%)
University	6 (17.1%)	2 (6.2%)
Occupation		
Employee	20 (57.1%)	18 (56.2%)
Housewife	9 (25.7%)	9 (28.1%)
Merchant	2 (5.7%)	2 (6.3%)
Agricultural	0	3 (9.4%)
Civil servant	4 (11.5%)	0

Data are presented as mean ± standard deviation or *n* (%).

All 32 women in the ginger group and 33 of 35 (94.3%) in the placebo group had one or more vomiting episodes during the 24 hours before treatment (Fisher exact test, $P = .17$). After 4 days of treatment, the proportion of women who had vomiting in the ginger group (12 of 32, 37.5%) was significantly less (Pearson $\chi^2 = 5.334$, $P = .021$) than that in the placebo group (23 of 35, 65.7%). When the average number of vomiting episodes over the 4 days of treatment was subtracted from the corresponding baseline value for each patient, and the overall change in the number of vomiting episodes for subjects in the two groups was compared, we found a greater reduction in the number of vomiting episodes in the ginger group than in the placebo group (Table 3). Intent-to-treat analysis was performed by assuming that the three missing patients in the placebo group had reductions in the number of their vomiting episodes as high as the best subject in the ginger group. The same conclusion was obtained (Table 3).

On follow-up visits, five-item Likert scales were used to assess patients' subjective response to treatment. Twenty-eight of 32 (87.5%) ginger-treated women reported that their symptoms improved, compared with only 10 of 35 (28.6%) in the placebo group (Fisher exact test, $P < .001$) (Table 4). If we arbitrarily assign the best outcomes to the three missing members of the placebo group and performed analysis by intention-to-treat, the proportion of women who reported improvement in the ginger group was still significantly higher than that in the placebo group (Fisher exact test, $P < .001$).

Compliance, as assessed by pill count, revealed that 30 of 35 (85.7%) in the placebo group took at least eight of the prescribed capsules, compared with 32 of 32 (100%) in the ginger group. Twenty-seven of 35 (77.1%) in the placebo and 28 of 32 (87.5%) in the ginger group had 100% compliance. No subjects in this trial took any other medications for nausea or vomiting. All women in the placebo group (except three who defaulted from the study) returned for follow-up visits on time, whereas two in the ginger group (6.3%) came back 1 week later than their scheduled appointments. Headache occurred in five women (14.3%) in the placebo group and six (18.8%) in the ginger group. One patient in the ginger group had abdominal discomfort, one had heartburn, and another had diarrhea for 1 day. These side effects were reported as minor and did not preclude them from taking their prescribed medication.

There were three spontaneous abortions in the placebo group (8.6%) and one (3.1%) in the ginger group (Fisher exact test, $P = .615$). Term delivery occurred in 32 of 35 (91.4%) and 31 of 32 (96.9%) in the placebo and the ginger groups, respectively. There were four (11.4%) cesarean deliveries in the placebo group and six (18.8%) in the ginger group (Fisher exact test, $P = .509$). No infants had any congenital anomalies recognized and all were discharged in good condition.

Discussion

Ginger, known scientifically as *Zingiber officinale*,[7] is a perennial native to many Asian countries. It is widely

Table 2. Nausea Scores

	Day 0–day 1	Day 0–day 2	Day 0–day 3	Day 0–day 4	Day 0–average day 1 to 4
Placebo ($n = 35$)	0.3 ± 1.9	0.8 ± 2.7	1.3 ± 2.4	1.5 ± 2.9	0.9 ± 2.2
Ginger ($n = 32$)	0.9 ± 2.1	1.5 ± 2.1	2.6 ± 2.5	3.4 ± 2.5	2.1 ± 1.9
*P**	.078	.054	.031	.005	.014
Intent-to-treat analysis					
Placebo ($n = 38$)	0.8 ± 2.5	1.3 ± 3.0	1.8 ± 3.0	2.0 ± 3.4	1.5 ± 2.8
Ginger ($n = 32$)	0.9 ± 2.1	1.5 ± 2.1	2.6 ± 2.5	3.4 ± 2.5	2.1 ± 1.9
*P**	.2753	.2156	.1453	.0348	.0820

Data are presented as mean ± standard deviation of the difference (baseline minus posttherapy) in nausea scores.
* Wilcoxon rank-sum test.

Table 3. Number of Vomiting Episodes

	Day 0–day 1	Day 0–day 2	Day 0–day 3	Day 0–day 4	Day 0–average day 1 to 4
Placebo (n = 35)	−0.03 ± 1.3	0.3 ± 1.4	0.4 ± 1.3	0.4 ± 1.8	0.3 ± 1.1
Ginger (n = 32)	0.4 ± 1.5	1.4 ± 1.3	1.7 ± 1.5	2.3 ± 1.5	1.4 ± 1.3
P*	.153	.001	<.001	<.001	<.001
Intent-to-treat analysis					
Placebo (n = 38)	0.1 ± 1.4	0.5 ± 1.5	0.6 ± 1.4	0.6 ± 1.8	0.5 ± 1.3
Ginger (n = 32)	0.4 ± 1.5	1.4 ± 1.3	1.7 ± 1.5	2.3 ± 1.5	1.4 ± 1.3
P*	.378	.007	.002	<.001	<.001

Data are presented as mean ± standard deviation of the change in the number of vomiting episodes (baseline minus posttherapy).
* Wilcoxon rank-sum test.

cultivated for its aromatic rhizome, which can be used as a spice to enhance the flavor of food (eg, gingerbread, tarts, cookies, marmalades) and beverages (eg, ginger ale and ginger beer).[6] The rhizome of ginger also is valued as a herbal medicine for the relief of gastrointestinal distress.[7] The efficacy of ginger is believed to be due to its aromatic, carminative, and absorbent properties.[1,6]

In Thailand, ginger has long been recommended as folklore treatment for nausea and vomiting of pregnancy. Unfortunately, few scientific data can substantiate this claim. There is no commercially available ginger capsule in Thailand. The products available contain only 3.85%–6.6% ginger powder mixed with sucrose in a ratio of approximately 1:1, to be dissolved in 150–250 mL of hot water as beverages. Like other herbal products, ginger contains complex mixtures of ingredients whose levels can vary considerably depending on many factors such as intraspecies variation, which may be related to the country of origin, and environmental factors such as climate, growing conditions, and the time of harvesting.[8] Postharvesting factors such as storage conditions and processing may also result in a loss of thermolabile-active constituents.[8] In addition, the active ingredients responsible for the therapeutic effect of ginger are not adequately known. As such there are many problems when quality aspects are considered. To ensure the quality of ginger capsules in this study, we used only fresh ginger roots as starting materials and they were processed by a pharmacist who used good manufacturing practice. Microbiologic cultures were done and capsule content was weighed randomly. However, chemical and chromatographic tests were not carried out to determine the exact composition of our preparation. It is, therefore, not possible to directly compare our products with fresh ginger or the common powdered ginger in terms of potency or dosage.

Table 4. Symptoms Assessed by Likert Scales

Symptom rating	Placebo (n = 35)	Ginger (n = 32)
Much worse	0	0
Worse	9 (25.7%)	0
Same	16 (45.7%)	4 (12.5%)
Better	9 (25.7%)	8 (25%)
Much better	1 (2.9%)	20 (62.5%)

Data are presented as n (%); Fisher exact test, $P < .001$.

We can find only one randomized cross-over trial of ginger for hyperemesis gravidarum in the English literature.[6] In that study, 19 of 27 (70.4%) women preferred the period in which they received ginger compared with 4 of 27 (14.8%) women receiving placebo, and 4 of 27 (14.8%) were unable to state any preference. There was also a significant reduction in the number of vomiting episodes in the ginger group. We found a significant improvement in nausea scores in subjects who received ginger compared with those who received placebo. Ginger also significantly reduced the mean number of vomiting episodes during the 4 days of treatment.

In the present study, visual analog scales were used to quantify the change in the severity of nausea, because these scales gave an objective measure of the severity of nausea. Moreover, the scales have construct validity and are reproducible.[9–11] It is reassuring that another independent scale (ie, five-item Likert scale) also confirmed the results obtained from visual analog scales. We chose a study period of 4 days because a previous study[6] showed that the effect of ginger was evident within a few days of treatment and too long a period would result only in a higher rate of subject noncompliance and loss to follow-up.

Backon[12] cautioned that ginger could affect the binding of testosterone to its receptor. If ginger was used during pregnancy, it could theoretically alter sex steroid-dependent differentiation of the fetal brain. In this trial and the previous study by Fischer-Rasmussen et al,[6] the duration of treatment was short and the dosage used was very low. In fact, the dosage of 1 g per day was far below that used in recipes for cakes or tarts, which amounts to up to 30 g. It is reassuring that both trials, involving a cumulative total of 59 patients who

received ginger, consistently showed that there were no significant side effects. Adverse effects of ginger on pregnancy outcome were not detected either. Nevertheless, it is possible that rare but significant adverse effects, such as certain congenital anomaly, can go undetected due to the limited number of subjects studied so far.

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