Effectiveness and Safety of Ginger in the Treatment of Pregnancy-Induced Nausea and Vomiting

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OBJECTIVE: **Conventional antiemetics are burdened with the potential of teratogenic effects during the critical embryogenic period of pregnancy. Thus, a safe and effective medication would be a welcome addition to the therapeutic repertoire. This systematic review was aimed at assessing the evidence for or against the efficacy and safety of ginger (*Zingiber officinale*) therapy for nausea and vomiting during pregnancy.**

DATA SOURCES: **Systematic literature searches were conducted in 3 computerized databases (MEDLINE, EMBASE, and Cochrane Library), and the reference lists of all papers located were checked for further relevant publications.**

METHODS OF STUDY SELECTION: **For the evaluation of efficacy, only double-blind, randomized controlled trials (RCTs) were included. All retrieved clinical data, including uncontrolled trials, case reports, observational studies, and RCTs, were included in the review of safety.**

TABULATION, INTEGRATION, AND RESULTS: **Six double-blind RCTs with a total of 675 participants and a prospective observational cohort study (n = 187) met all inclusion criteria. The methodological quality of 4 of 5 RCTs was high. Four of the 6 RCTs (n = 246) showed superiority of ginger over placebo; the other 2 RCTs (n = 429) indicated that ginger was as effective as the reference drug (vitamin B6) in relieving the severity of nausea and vomiting episodes. The observational study retrieved and RCTs (including follow-up periods) showed the absence of significant side effects or adverse effects on pregnancy outcomes. There were no spontaneous or case reports of adverse events during ginger treatment in pregnancy.**

CONCLUSION: **Ginger may be an effective treatment for nausea and vomiting in pregnancy. However, more observational studies, with a larger sample size, are needed to confirm the encouraging preliminary data on ginger safety (Obstet Gynecol 2005;105:849–56. © 2005 by The American College of Obstetricians and Gynecologists.)**

LEVEL OF EVIDENCE: **I**

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Nausea and vomiting (commonly referred to as morning sickness) are very common symptoms in pregnancy, affecting 70–85% and 40–50% of pregnant women, respectively.[1,2] It has been estimated that the financial burden of morning sickness on the American health system is more than 130 million dollars per year.[3,4] Usually morning sickness begins between the first and second missed menstrual period and may last until the end of the third month of pregnancy. However, approximately 20% of women experience nausea and vomiting for a longer period of time, and 2% of this group suffers until the end of the pregnancy. Moreover, a small number (0.3–3%) of all pregnant women experience a more severe form of morning sickness, namely hyperemesis gravidarum.[5]

Many medications are currently available for the treatment of morning sickness.[3,6] However, concerns about the potential teratogenic effects of drugs administered during the critical embryogenic period of pregnancy drastically limit their use. Consequently, many pregnant women use complementary and alternative therapies. These include vitamins, herbal products, homeopathic preparation, acupressure, and acupuncture.[7–9] A recent literature survey reports that the most commonly used natural drugs for the treatment of morning sickness are ginger, chamomile, peppermint, and raspberry leaf.[10] Among these, only ginger has been evaluated in controlled trials for the treatment of morning sickness.

Ginger, a rhizome of *Zingiber officinale* Roscoe (Fam. *Zingiberaceae*), has been widely used as a spice to enhance the flavor of food and beverage and for medical purposes, particularly to treat ailments such stomachache, diarrhea, and nausea.[11,12] Ginger is among the 20 top-selling herbal supplements in the United States, and its retail sales in the mainstream U.S. market in 2001 amounted to 1.2 million dollars.[13] German and European monographs are available, and both list nausea/vomiting as indications. Moreover, in 1997 the U.S. Pharmacopoeia approved ginger and powdered ginger monographs for inclusion in the National Formulary.

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Given the widespread use of ginger as an antiemetic drug, we systematically assessed the efficacy and safety of this herbal product in the treatment of nausea and vomiting in pregnancy.

SOURCES

Literature searches were performed to identify all clinical reports regarding the efficacy and safety of ginger in pregnancy. Three electronic databases, MEDLINE, EMBASE, and Cochrane Library, were searched (all from their respective inceptions to June 2004) using the search terms "ginger" and "*Zingiber officinale*." No language restrictions were imposed. Citations and bibliographies of all retrieved papers were reviewed for further relevant publications not found in the electronic searches. Additionally, several manufacturers of ginger-containing preparations were asked to contribute published or unpublished material, and web sites devoted to providing information for pregnant women were visited.

STUDY SELECTION

For the evaluation of efficacy, only double-blind, randomized controlled trials (RCTs) of the oral administration of a monopreparation of ginger for the treatment of the symptoms of pregnancy-related nausea and vomiting (morning sickness and hyperemesis gravidarum) were included. All retrieved clinical data, including uncontrolled trials, case reports, and observational studies, were included in the review of safety. For papers not reporting enough information, the authors were contacted to provide additional data. The methodological quality of each study was assessed using the scoring system developed by Jadad and colleagues (Box: "**Jadad Score:** Instrument Used to Assess Methodological Quality of Clinical Trials").[14] All reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. Disagreements about the assessment of data were resolved by discussion, and consensus was reached in all cases. A meta-analysis was considered but proved to be not feasible. Because of the different measures used to assess the outcomes and because of the different control groups in the trials, a clinically meaningful pooling of the data was not possible.

RESULTS

The searches identified 33 potentially relevant trials,[15–47] but only 6 double-blind RCTs[15–20] met the aforementioned inclusion criteria and were included in this systematic review. The flow chart provides an overview of all included and excluded trials (Fig. 1). The assessment of their methodological quality revealed a maximal score for 5 of 6 studies. Four RCTs[15–17,19] compared the efficacy of ginger to placebo, whereas 2 trials[18,20] compared the efficacy of ginger to vitamin B6 (used as a reference compound). Key data are summa-

Jadad Score: Instrument Used to Assess Methodological Quality of Clinical Trials

Each "yes" scores 1 point; each "no" 0 points:

- Study described as randomized (this includes the use of words such as *random, randomly,* and *randomization*)?
- Study described as double-blind?
- Description of withdrawals and dropouts?
- Method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc.)?
- Method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?

Deduct 1 point if:

- Method to generate the sequence of randomization described and inappropriate (patients were allocated alternately, or according to their date of birth, hospital number, etc.)?
- Method of double-blinding described and inappropriate (comparison of tablet versus injection with no double dummy, etc.)?

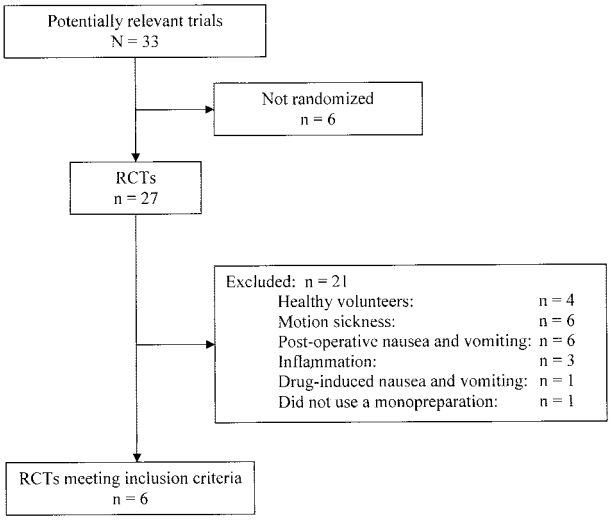

Fig. 1. Flowchart of studies included and excluded. RCTs, randomized controlled trials.

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Table 1. Clinical Trials Reporting the Effectiveness of Ginger in Treatment of Pregnancy-Related Nausea and Vomiting

Study	JS	Design	NPS/NPE (Patient Treatment)	Period of Gestation (wk)	Ginger Dosage	Control Treatment (Dosage)	LT	Main Outcome Measures	Main Results
Fischer-Rasmussen, 1991[15]	3	Randomized double-blind cross-over trial	30/27 (14G, 13C)	< 20	250 mg 4 times daily	Placebo	4 d	Severity and relief of nausea and vomiting (4-point scoring system); change in body weight	Ginger was better than placebo in diminishing or eliminating the symptoms of hyperemesis
Vutyavanich, 2001[16]	5	Randomized double-blind trial	70/67 (32G, 35C)	< 17	250 mg 4 times daily	Placebo	4 d	Severity of nausea and vomiting (visual analogue scale and Likert scale); number of vomiting episodes; occurrence of side and adverse effects on pregnancy	Ginger was more effective than placebo in reducing the severity of nausea and vomiting; no adverse effect was detected
Keating, 2002[17]	5	Randomized double-blind trial	26/23 (13G, 10C)	< 12	250 mg 4 times daily	Placebo	2 wk	Duration and severity of nausea and vomiting (10-point scale)	Ginger was more effective than placebo in reducing nausea and stopping vomiting
Sripramote, 2003[18]	5	Randomized double-blind trial	138/128 (64G, 64C)	< 17	500 mg 3 times daily	Vitamin B6 (10 mg; 3 times a day) (30 mg)	3 d	Severity of nausea (visual analogue scale), number of vomiting episodes, and occurrence of adverse effects	Significant reductions of nausea score and vomiting episodes were observed in ginger and vitamin B6 groups
Willetts, 2003[19]	5	Randomized double-blind trial	120 (60G, 60C)	< 20	125 mg of ginger extract 4 times daily	Placebo (soy bean oil)	4 d	Nausea, vomiting, and retching (Rhodes Index); occurrence of side and adverse effects on pregnancy.	Ginger was more effective than placebo in reducing nausea and retching; no effects on vomiting symptoms
Smith, 2004[20]	5	Randomized double-blind trial	291/235 (120G, 115C)	> 8, < 16	350 mg 3 times daily	Vitamin B6 (25 mg; 3 times a day) (75 mg)	3 wk	Nausea, retching, and vomiting at days 7, 14, 21 (Rhodes Index, Form 2[9]); change in health status (MOS 36-Item Short Form Health Survey)	Ginger was as effective as vitamin B6 in reducing nausea, dry retching, and vomiting compared with baseline

JS, Jadad Score; NPS/NPE, number of pregnancies at the start of trial/number of pregnancies at the end of trial; LT, length of treatment; G, patients in the ginger group; C, patients in the control group; MOS, Medical Outcomes Study.

rized in Table 1, while the main results are described below.

The first double-blind, crossover RCT included 30 pregnant women who needed hospitalization for hyperemesis gravidarum before the 20th week of gestation.[15] Twenty-seven woman completed the trial. Patients received either ginger (250 mg) or placebo (lactose, 250 mg) 4 times a day for 4 days; the washout period was 2 days. No indication on the source of the ginger powdered root was reported. Other antiemetic medications

were withdrawn. Outcomes included degree of nausea and vomiting, change in body weight, adverse effects on pregnancy, and pregnancy outcomes. The degree of nausea and vomiting was evaluated by using 2 relief and severity scoring systems. The relief score aimed to evaluate the efficacy of ginger, whereas the severity score was used to exclude a potential beneficial effect of ginger to the second period of treatment (placebo). The results showed that ginger was better than placebo in diminishing or eliminating the symptoms of hyperemesis gravidarum.

Vutyavanich et al[16] evaluated the effectiveness of ginger on pregnancy-induced nausea and vomiting in a double-masked, placebo-controlled RCT. Sixty-seven (70 at the beginning of the trial) women before the 17th week of gestation who manifested nausea (with or without vomiting) and did not take any other medication in the week before the study were evaluated. Subjects received either 250 mg ginger or placebo 4 times daily for 4 days. Ginger preparations were obtained from fresh ginger root, which was chopped into small pieces, baked at 60°C for 24 hours, and then ground into powder. Outcomes included change in nausea symptoms and number of vomiting episodes. Occurrence of side effects and adverse effects on pregnancy outcomes, such as abortion, preterm birth, congenital anomaly, perinatal death, and mode of delivery, were also taken into account. The degree of nausea and the number of vomiting episodes were recorded 24 hours before treatment, as well as twice daily (nausea) or one time daily (vomiting) each subsequent day of treatment. To avoid the subjectivity of nausea symptoms, 2 independent measurement scales, a visual analogue scale (objective) and a 5-item Likert scale (subjective), were used to quantify the changes in severity. The results showed a significantly (time-dependent) greater reduction in nausea score and in the number of vomiting episodes in the ginger group than in the placebo group. Reductions of nausea score and vomiting episodes were significant compared with placebo only on day 3 and day 2 of treatment, respectively.

The third double-blind RCT included 23 pregnant women (26 at the beginning of the trial), in the first trimester of pregnancy, with nausea and with or without vomiting.[17] Patients received either a tablespoon of syrup containing 250 mg ginger or placebo syrup 4 times daily for 2 weeks. Ginger rhizome juice was obtained via a carbon dioxide supercritical extract of dried ginger rhizome. The level of nausea and number of vomiting episodes were recorded daily in a diary and quantified on a numerical scale of 1 to 10. The effect of ginger on pregnancy weight, but not on pregnancy outcomes, was also analyzed. After 9 days, treatment, nausea levels were reduced in 77% and 20% of patients in the ginger and placebo groups, respectively. Moreover, 67% of women in the ginger group and 20% of women in the placebo group (who were vomiting daily at the beginning of the treatment) stopped vomiting by day 6.

One hundred thirty-eight (128 completed the trial) pregnant women before 17 weeks of gestation[18] were enrolled in the fourth double-blind RCT. Patients requested antiemetics for the nausea symptoms and did not take any other medication in the week before the study. Subjects received either a 500-mg capsule of ginger or 10-mg capsule of vitamin B6 orally 3 times daily. Ginger preparations were obtained from fresh middle-aged ginger root, which was chopped into small pieces, dried in sunlight, and ground into powder. Outcomes included change in nausea symptoms and number of vomiting episodes and occurrence of adverse effects (drowsiness, palpitations, heartburn, and mouth dryness). Effects of ginger on pregnancy outcomes were not analyzed. The degree of nausea (using the visual analogue scale) and the number of vomiting episodes were measured 24 hours before treatment, as well as 3 times daily on each subsequent day of treatment. Both ginger and vitamin B6 significantly reduced the degree of nausea and the number of vomiting episodes. The reductions of nausea score and nausea episodes were significant after a 1-day treatment.

A double-blind, placebo-controlled RCT evaluated the effectiveness of a ginger extract (EV.EXT35) on 120 women with morning sickness before 17th week of gestation.[19] Subjects received either 125 mg of ginger extract (equivalent to 1.5 g of dried ginger) or placebo (soy bean oil) 4 times daily for 4 days. No data were reported on the preparation of the ginger extract. Outcomes included the frequency, duration, and distress caused by the symptoms of nausea, vomiting, and retching. Secondary outcomes included gestational age, birth weight, and occurrence of side effects and adverse effects on pregnancy outcomes such as abortion, stillbirth, congenital abnormalities, and neonatal death. Pregnancy-related symptoms were recorded 24 hours before and during the 4 days of treatment (4 time a day) using the Rhodes Index of Nausea, Vomiting, and Retching (an 8-item, 5-point Likert-type tool). The follow-up of the study included 81 women (women from the placebo and ginger groups who were given an 18-day ginger supply following the end of the trial). Outcomes were compared with the general infant population delivered at the Royal Hospital for Women in Sydney. The results showed a significant reduction in nausea experience, occurrence, and distress in the ginger and in the placebo groups. However, the reduction of nausea scores was significantly higher in the ginger than in the placebo group. Similar results were observed for retching symptoms. There was no significant

difference between ginger extract and placebo groups for any of the vomiting symptoms.

The most recent double-blind RCT involved 291 women (235 subjects completed the trial) between 8 and 16 weeks of gestation.[20] Subjects received either ginger (350 mg) or vitamin B6 (25 mg) 3 times daily for 3 weeks. Women were allowed to use other medications during the trial (25% used an antiemetic, no data on the dosage used). No information was reported on the preparation of the ginger powder. Outcomes included both change in nausea, dry retching, and vomiting episodes (from baseline at days 7, 14, and 21, measured by the Rhodes Index of Nausea and Vomiting, Form 2,[9] 5-point Likert scale) and improvement in health status (measured by the Medical Outcomes Study 36-Item Short Form Health Survey). The baseline pregnancy-related symptoms were recorded for 3 days before treatment. Secondary outcomes included the occurrence of side effects and adverse pregnancy outcomes such as antepartum hemorrhage, pregnancy-induced hypertension, preeclampsia, perinatal and neonatal death, preterm birth, and congenital abnormalities. The results showed that ginger was therapeutically equivalent to vitamin B6 in alleviating nausea, dry retching, and vomiting. However, 20% of the pregnant women still continued to use antiemetics at the end of the trial. A significant difference was found in the percentage of women reporting belching while using ginger compared with those using vitamin B6 (9% and 0% for ginger and vitamin B6 groups, respectively).

Five of the 6 RCTs[15,16,18–20] described above and 1 prospective observational cohort study (described in detail below)[21] specifically evaluated ginger safety in pregnancy. Four RCTs, as well as the observational study, investigated ginger-induced adverse effects on pregnancies[16,18–21] and on the fetus (pregnancy outcomes).[15,16,19–21] Pregnancy outcomes, collected after the delivery, included antepartum hemorrhage, preeclampsia, preterm birth, perinatal and neonatal death, congenital abnormalities, and birth weight. There were no reports of adverse events during ginger treatment.

Adverse effects on pregnancies were observed in 4 of 6 clinical trials[16,18–20]. These included headache,[16] diarrhea and abdominal discomfort,[16] drowsiness,[18] reflux,[19] and heartburn.[16,18–20] The follow-up of RCTs[15,16,19,20] showed no difference in the occurrence of spontaneous abortions, stillbirth, term delivery and cesarean deliveries, neonatal death, gestational age, and congenital abnormalities between women who were exposed to ginger and women exposed to vitamin B6[20] or placebo.[15,16] Similar results were found when the effect of ginger on pregnancy outcomes was compared with the general population.[18]

The observational cohort comparative study involved the enrollment of 187 pregnant women exposed to ginger and 187 women exposed to nonteratogen drugs (which were not antiemetics) in the first trimester of pregnancy.[21] Among the 187 women exposed to ginger, 39% used ginger concurrently with an antiemetic drug. All subjects answered a structured questionnaire that elicited information about medical indication for ginger use, dosage, frequency of administration, and timing of exposure, as well as maternal demographics and obstetric history. After the delivery, women were questioned regarding the course of the pregnancy, the health of the child, the specific details of the exposure to ginger, and any other exposures or use of drugs during the pregnancy. Outcomes included the incidence of major malformations (congenital anomalies and social acceptability of the individual), rates of spontaneous or therapeutic abortions, live births and stillbirths, gestational age at birth, and birth weight. Dosage and origin of ginger were not documented. No statistically significant differences between the 2 groups regarding live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age were found. A significant difference was detected in the rates of low birth weight infants, ie, those weighing less than 2,500 g (1.6% and 6.4% in the ginger and comparison groups, respectively; $P < .05$), despite the presence of 8 sets of twins in the ginger group.

CONCLUSION

This systematic review suggests that ginger may be a safe and effective option for the treatment of nausea and vomiting in pregnancy. This finding corroborates the results of previous inconclusive analyses based on less extensive data.[3,48] These studies were from Australia (2 studies), Thailand (2 studies), Canada (1 study), and Denmark (1 study). Whether or not demographic or social/cultural similarities and differences among these populations can be generalized to the universe of pregnant women worldwide cannot be extrapolated from the present review. According to the Jadad score,[14] the quality of the RCTs retrieved was good to excellent: adequate blinding of participants and investigators, appropriate method to generate the sequence of randomization, and the presence of adequate control conditions. However, several shortcomings have been noted.

Two clinical trials compared ginger with vitamin B6. Both studies concluded that ginger was as effective as vitamin B6 in reducing nausea and the number of vomiting episodes.[18,20] However, it should be noted that the efficacy of vitamin B6 in the treatment of nausea and vomiting in pregnancy is not compelling.[3] Moreover, a number of studies demonstrated that placebo treatment

is useful in the relief of nausea.[19,49] For these reasons, these comparative studies[18,20] should be viewed with caution. Also, it should be noted that in one study[20] 20% of women used conventional antiemetics during the trial. Four clinical studies compared the efficacy of ginger with that of a placebo.[15–17,19] These studies were of good methodological quality: women did not take other medications during the trial,[15–17,19] the compliance of the subjects was checked,[15–17,19] the severity of pregnancy-related symptoms was recorded more than once per day,[16,19] and an objective measurement of the nausea severity was obtained using 2 independent measurement scales.[15,16] One of the main problems in crossover trials is the possibility of a carryover effect of the active substance in the second treatment. In the study performed by Fischer-Rasmussen et al,[15] a severity score was used both to avoid a carryover effect of ginger and to objectify the symptoms of hyperemesis. In all clinical trials, ginger was taken 3 or 4 times a day, independently of the occurrence of nausea and/or vomiting. Moreover, although the single acute dose of ginger varied in each study, the daily dose was approximately 1 g in 5 of the 6 studies reviewed (with periods ranging from 8 to 20 weeks).

A prospective observational cohort study and the follow-up of 4 RCTs (reported above) consistently showed that there are no significant side effects or adverse effects on pregnancy outcomes.[15,16,19,21] This is consistent with the results of the majority of animal studies,[12] although a mutagenic activity has been documented for an ethanolic ginger extract in vitro.[50] However, the short duration of treatment periods and the small number of patients taking ginger (n = 303) in RCTs may have been insufficient to properly test the safety of the ginger with regard to pregnancy outcomes. Moreover, the cohort study had a small sample size (n = 187) and was based on a self-selected sample of women who called a help line and may have differed in some ways from the general population. An increase both in the mean of the birth weight of the babies and in the occurrence of multiple pregnancies (twins) has been observed in the pregnancies exposed to ginger. The increased birth weight is in line with clinical studies reporting a lower birth weight in infants of women experiencing nausea and vomiting during pregnancy.[51] However, the correlation between nausea and birth weight has been recently questioned.[52,53] The mechanism of the action of ginger on pregnancy symptoms has not been fully identified although several hypotheses have been proposed. It has been reported that symptoms of nausea and vomiting during pregnancy improved in direct correlation to the improvement in pregnancy-induced gastric dysrhythmias.[54] Therefore, ginger-induced reduction of pregnancy symptoms may be due to a direct effect of the drug on the gastrointestinal tract. The activity of ginger has been attributed to nonvolatile pungent components, namely shogaols and gingerols.[55]

In conclusion, considering the largely positive results of RCTs and the absence of adverse effects on pregnancy outcomes, ginger may be an effective treatment in managing nausea and vomiting symptoms during pregnancy. However, more observational studies and also larger randomized clinical trials to make a definite statement on the safety of ginger in pregnancy are needed.

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