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Does Ginger Help with Symptoms of Nausea in Early Pregnancy?

By Mary Hardy, MD, and Jay Udani, MD

NAUSEA IN EARLY PREGNANCY AFFECTS UP TO 80% OF GRAVID women and can be a significant cause of morbidity during pregnancy.[1] A severe form of nausea and vomiting of pregnancy (NVP), hyperemesis gravidarum, can cause 1-3% of women to become malnourished or dehydrated and may require hospitalization.[2] Many women are reluctant to use conventional medication for the control of NVP due to the uncertainty of risk to the fetus. Thus, pregnant women, who often perceive CAM therapies to be safer than conventional medication, are very interested in the use of these modalities to control nausea.

Ginger has been shown to decrease nausea from many different etiologies[3] and has been recommended as an intervention for nausea and vomiting in early pregnancy as well.[4] In fact, almost 52% of obstetrician/gynecologists included in a recent survey recommend ginger for NVP[5] and their patients are taking both the advice and the ginger. In one qualitative study, pregnant women were 4.4 times more likely to use an herbal remedy than an OTC or prescription medication.[5] A survey performed by the Motherisk Program in Toronto, a group that specializes in assessing risk of drug use during pregnancy, demonstrated that 61% of their sample used CAM therapies to decrease NVP with ginger tea (50.7%), acupressure (46%), and vitamin B_6 (29%) being the most commonly used therapies.[6]

Perceived safety of ginger appears to be an important component of a women's decision to use ginger during pregnancy. Women who called the Motherisk Program agreed strongly with statements that reflected their reluctance to use drugs and concerns that drug use might harm their babies. Their use of CAM therapies, including ginger, did not appear to be directed by their medical providers as these women were five times more likely to cite friends and family as their source of information about CAM than their doctor or pharmacist (40% vs. 8%).[6]

As medical providers interested in the health of women, it behooves us to become educated about the common therapies our

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patients use so that we may more effectively advise them. The most common herbal therapy used by pregnant women is ginger. This fact, coupled with the publication of some new clinical trials, warrants a review of the use of ginger for NVP.

History/Tradition

Ginger is a perennial plant with thick underground stems called rhizomes, which are used for medical and culinary purposes. The aboveground stem can grow to heights of 24 feet. Ginger is native to southern Asia, but now is cultivated extensively throughout the tropics. The very best quality ginger is grown in Jamaica, but more than 80% of the ginger imported to the United States is reported to come from China and India.[7]

Medicinal use of ginger has been broadly documented in cultures as diverse as Indian, Chinese, Arabic, Greek, and Roman. It is cited in ancient Ayurvedic, Sanskrit, and Chinese texts as early as the fourth century B.C. for conditions such as stomachache, diarrhea, nausea, cholera, hemorrhage, and toothache.[8,9] In traditional Chinese medicine, a distinction is made between fresh ginger (sheng jiang) and dried ginger (gan jiang).[10] Both are considered warming herbs, although dried ginger is thought to be "hotter" than fresh.

In addition to its medicinal applications, ginger also is widely used as a spice in foods, beverages, candies, and liqueurs, and also is used commonly in many cosmetic products. The Chinese use fresh ginger in many dishes, not only for its spicy flavor and perfume, but also as a yang ingredient—to balance cooling (or yin) dishes. Five-spice powder and many curries contain dried ginger and thus large amounts are eaten with food in Asian and Indian countries.

Pharmacology

The pharmacologically active components of ginger include an oleoresin and pungent "principles." The oleoresin (5-8% of total matter) contains an essential aromatic oil (1-2%) consisting mainly of sesqueterpene lactones, such as zingiberene.[11] The pungent or hot "principles" are phenolic compounds, primarily gingerols, which are a mixture of closely related compounds differentiated by the number of carbon atoms in their side chain ([6], [8], [10]-gingerol).[12] Shogaols, more pungent and more bitter, seem to form from gingerols mainly as a result of drying.[7] The constituents that likely account for ginger's antiemetic effect are the shogaols and gingerols[12,13]

Ginger has many other pharmacologic effects, including anti-inflammatory, antipyretic, analgesic, and antioxidant actions.[11] Ginger also has been reported in vitro to affect platelet aggregation via its inhibition of platelet thromboxane.[14] No adverse effects on human platelet function or episodes of bleeding have been confirmed clinically.[11]

Mechanism of Action

Ginger's mechanism of action for the prevention and treatment of nausea is not clear. Studies have shown increased gastric motility,[8] but not increased gastric emptying.[15] Ginger enhances salivary and gastric secretion, and has documented antispasmodic effects associated with its fat-soluble components, such as galanolactone, and its ability to antagonize serotonin receptor sites.[7] Unlike other anti-emetics, ginger's mechanism of action is not CNS-mediated.[16]

Clinical Studies

Ginger has been tested as an anti-emetic in a number of clinical scenarios including for the control of nausea associated with sea/motion sickness, surgery, and chemotherapy as well as pregnancy.[3] A search of the medical literature revealed seven trials of ginger specifically for the treatment of NVP. One qualitative trial[5] and

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one observational trial[17] were found. The other five trials are controlled clinical trials. Four tested ginger against a placebo[18-21] and one tested ginger against vitamin B_6.[22]

In a qualitative study on self-directed use of anti-emetic herbs in NVP, 26 of 27 women interviewed used herbs during their pregnancies.[5] Six women reported using ginger (three alone and three in combination with peppermint) with moderate success. Some women reported heartburn or aversion to the smell or taste of ginger. This study provides interesting insight into a group of pre-identified users of herbs for NVP, but this study design does not permit us to draw any conclusions about the efficacy of ginger for this indication.

In a much larger observational prospective cohort trial conducted by the Motherisk Program, 187 women who called Motherisk for counseling regarding safety of ginger use in pregnancy were matched with similar controls who did not use ginger.[17] All women were followed throughout their pregnancies and for up to 12 months after delivery. Although women were not advised to take any particular form or dose of ginger, the patients used a wide variety of ginger preparations, including fresh herb, tea, cookies, and other foods, e.g., candied ginger. However, dried ginger capsules were the most popular preparation used (49% women). Most women used ginger alone and one-third combined it with other anti-emetic drugs. Almost half rated ginger as totally ineffective in controlling their symptoms. However, capsules were significantly more likely to be rated as effective than all other forms of ginger therapy combined ($P < 0.001$). Observational data again cannot draw conclusive inferences about causality and/or efficacy of a given therapy. Despite that limitation, this design provides useful data about safety and fetal outcome as well some indications about patterns of use and response to ginger during early pregnancy.

The oldest controlled clinical trial found in the literature enrolled 30 hospitalized women with hyperemesis gravidarum in a randomized, double-blind, crossover trial. Dried ginger capsules (250 mg) or placebo were given to patients four times per day for four days.[18] After a two-day washout period, patients were then given four days of the other substance. Subjective measures of relief were significantly greater with ginger (70.4%, $P = 0.003$). Objective measures backed these findings significantly as well ($P = 0.035$). Although, this trial showed a decrease in nausea and vomiting after 10 days of treatment with ginger, several issues exist that may limit the broad application of these data. The number of women studied was small ($n = 30$), they were hospitalized with relatively severe symptoms and they were receiving a great deal of additional therapy. This group is not typical of the large majority of women who suffer from NVP, but it is encouraging that even in this group of more severely affected women ginger was able to show a benefit.

Following this trial, a group in Thailand, where ginger is used extensively as a folk treatment and dietary spice, conducted a trial to address these issues in less severely ill women.[19] Seventy women complaining of first trimester nausea at an outpatient obstetrical visit were enrolled in this study. They were given a dried ginger powder (250 mg four times a day for four days) that had been prepared by the investigators from fresh ginger root. Nausea as assessed by a visual analog scale (VAS) was significantly lower in the treatment group by day 2 and continued to decrease for the next two days ($P = 0.014$). Episodes of vomiting also decreased for the treatment group (1.4 vs. 0.3; $P < 0.001$). Subjectively, 28 of 32 treated women also reported an improvement in symptoms compared with only 10 of 35 placebo patients. Ginger apparently was effective after a short treatment time, but it is a weakness of this trial that women were not followed for a longer time. Thus, this trial does not tell us anything about the durability of a response to ginger. However, it was a well-designed and executed trial.

Keating and Chez, who suspected that ginger could be given in a more easily absorbed form, tested a commercially available ginger syrup, rather than a dried ginger capsule, for effectiveness in controlling first trimester nausea.[20] A syrup that contained the equivalent of 250 mg of ginger root was consumed by 26 women four times a day for two weeks. By the tenth day, the treatment group reported a better clinical response than the placebo group. This was a small pilot study and no statistical analysis was performed. However, the trend was consistent with the other published studies that favored treatment with ginger. This more unusual formulation was well accepted by the patients.

One hundred twenty women with NVP unresponsive to dietary intervention were enrolled in a double-blind, placebo-controlled trial that tested the effect of 125 mg standardized ginger extract (equivalent to 1.5 g dried ginger) given four times a day for four days.[21] No other characterization of extract, such as content of shogaols or gingerols, was reported. Although a placebo effect was noted for the main outcome measures, statistically significant decreases in the experience of nausea were recorded on all four days of the trial except day 3 (P values not reported). There also was a decrease in retching without a change in the number of episodes of vomiting between the two groups. Twenty-one subjects did not complete the trial and were not included in the

analysis. Four patients, all in the active treatment group, withdrew due to intolerance of study medication, presumably due to heartburn and/or reflux. One participant taking ginger reported an allergic reaction. Sixteen additional patients withdrew or were lost to follow up before the end of the trial. No increase in fetal malformation, gestational age, or apgar scores were noted. No increased rate of post-partum hemorrhage was reported.

This study included a large number of women, was well-designed, tested a number of outcomes, and was well-executed. The only flaws in this study were the 17.5% dropout rate, the fact that these patients were not included in an intention-to-treat analysis, and the incomplete reporting of key statistics. The short duration of this trial does not contribute to our knowledge of the long-term utility of ginger for NVP. A higher rate of adverse events was reported in this trial, which may reflect the relatively high dose (equivalent to 5 g/d fresh ginger) delivered by the extract. This suggests that the increase in adverse events reported may have been related to the preparation or increased dose of ginger.

Another group from Thailand performed a randomized, double-blind trial in which ginger was tested against B_6, a presumed active therapy, instead of placebo.[22] In this trial, 138 women enrolled before 16 weeks of gestation were randomized to receive either 500 mg dried ginger or 10 mg vitamin B_6 three times per day for one week. Nausea was measured using VAS and the number of episodes of vomiting was noted over the four days of the trial. Both treatments decreased nausea significantly from baseline ($P < 0.001$). The decreases were greater with ginger than B_6, but this difference was not statistically significant. Similar results were seen with number of episodes of vomiting as well. Heartburn and sedation were reported equally in both groups and occurred less than 10% of the time. This study compared the effect of ginger to a presumed active control (B_6) and found them to be equivalent. Thus, ginger is only as good as B_6 is felt to be. The large number of women included in this trial is a strength, while the short duration does not tell us anything about a long-term effect of ginger. The dose here was somewhat lower than in other trials (750 mg/d vs. 1,000 mg/d), but still seemed to be effective.

Limitations of Clinical Studies

Generally, trials favor treatment, which would encourage use for NVP. Most have used dried ginger and this seems to be the preferred preparation. However, at least two other forms have shown efficacy, an extract and a syrup. Two short-term intervention trials showed rapid onset of the effect of ginger, but did not provide information about long-term use or risk. Not all studies addressed fetal outcome, but in those studies that did, no increased rate of harm to fetus was shown. Preparations appeared to be well tolerated with a small number of women complaining of gastrointestinal upset.

Safety

Fresh ginger in amounts used in foods is generally considered to be safe.

Although some authorities raise a concern about dried ginger and the adverse risk to fetus[10,11,23] others do not categorically restrict use.[13,24] No data in vitro,[25-27] in animal studies,[28] or in the human clinical trials discussed here support this ban for doses equivalent to 1 g/d of dried ginger root. No increases in major fetal malformations or fetal loss in excess of baseline rates were noted.

Further, it has been postulated that ginger could, as a thromboxane synthetase inhibitor, interfere with testosterone binding and sexual differentiation in the fetus.[29] This thesis has never been supported with data and it is rejected outright by some experts.[5]

Summary

Ginger does seem to be helpful in treating NVP in early pregnancy. Preferred treatment seems to be capsules and recommended dose for efficacy and safety is 1 g/d of dried ginger in 3-4 divided doses. Ginger foods, syrups, or teas also should be encouraged if a patient prefers these dosage forms as they are well tolerated. Ginger works quickly and appears, at the recommended doses, to be safe for use in routine pregnancies. For more severe forms of NVP, ginger could be included as one intervention in a comprehensive treatment plan and could provide additional benefit. ❖

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Do Estrogen and Progestin Increase Colon Cancer Risk?

Source: Chlebowski RT, et al; Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;350:991-1004.

Abstract: Although the Women's Health Initiative (WHI) trial of estrogen plus progestin in postmenopausal women identified more overall health risks than benefits among women in the hormone group, the use of estrogen plus progestin was associated with a significant decrease in the risk of colorectal cancer. The researchers analyzed features of the colorectal cancers that developed and their relation to the characteristics of

the participants. In the WHI trial, 16,608 postmenopausal women who were 50-79 years of age and had an intact uterus were randomly assigned to a combination of conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo. The main outcome measures were the incidence, stages, and types of colorectal cancer, as determined by blinded central adjudication. There were 43 invasive colorectal cancers in the hormone group and 72 in the placebo group (hazard ratio, 0.56; 95% confidence interval, 0.38-0.81; P = 0.003). The invasive colorectal cancers in the hormone group were similar in histologic features and grade to those in the placebo group but with a greater number of positive lymph nodes (mean ± SD, 3.2 ± 4.1 vs. 0.8 ± 1.7; P = 0.002) and were more advanced (regional or metastatic disease, 76.2% vs. 48.5%; P = 0.004). In exploratory analyses, women in the hormone group with antecedent vaginal bleeding had colorectal cancers with a greater number of positive nodes than women in the hormone group who did not have vaginal bleeding (3.8 ± 4.3 vs. 0.7 ± 1.5 nodes, P = 0.006). Relatively short-term use of estrogen plus progestin was associated with a decreased risk of colorectal cancer. However, colorectal cancers in women who took estrogen plus progestin were diagnosed at a more advanced stage than those in women who took placebo.

■ Comments by Dónal P. O'Mathúna, PhD

COLORECTAL CANCER IS THE SECOND LEADING CAUSE of death from cancer in the United States. Studies have failed to provide evidence of any intervention reducing the risk of colorectal cancer. A variety of interventions have been tested for their efficacy in inhibiting the development or recurrence of colorectal polyps, which can be an early sign of colorectal cancer. Hopes that high-fiber diets would be of benefit here were set back by two studies reported in 2000 that failed to show benefit.[1] However, calcium, celecoxib, aspirin, and sulindac have been shown to inhibit the development or recurrence of colorectal polyps.

Observational studies of women taking postmenopausal hormone therapy have suggested a reduced incidence of colorectal cancer. These findings have not been confirmed in a randomized controlled trial. The Women's Health Initiative (WHI) randomized trial compared the outcomes of postmenopausal women taking estrogen plus progestin to those taking placebo. The highly publicized reports in 2002 noted the higher risk to benefit ratio with hormone therapy.[2] However, the trial also found that taking estrogen plus progesterone was associated with a significantly lower risk of colorectal cancer. The present report examines in further detail both this association and the features of the colorectal cancers that occurred during the WHI trial.

As noted in the abstract, significantly fewer cases of colorectal cancer occurred in the hormone group compared to placebo. However, few of these cases were of rectal cancer (eight taking hormones compared to 11 receiving placebo) making the results more clearly applicable to colon cancer (35 cases in the hormone group and 61 with placebo).

Of concern, though, was how the cancers discovered in the hormone group were more advanced and more likely to have lymph-node involvement, despite being similar in histological features and grade. The hormone group also contained more women with metastatic colorectal cancers. The reasons for these differences are unknown. The researchers noted that women in the hormone group more commonly experienced vaginal bleeding than those in the placebo group. This may have led these women to delay seeking medical attention since the early symptoms of colorectal cancer are often attributed to other, less serious causes. This suggests that women taking postmenopausal hormone therapy might benefit from routine bowel screening, despite the fact that their risk of colorectal cancer is reduced by the therapy.

A limitation with this study (as with the whole WHI study) is that 42% of the hormone group stopped their medication for some period during the study and 38% of those taking placebo similarly stopped their tablets. Also, women in both groups reported off-protocol use of postmenopausal hormones: 6% of those taking the study intervention and 10% of the placebo group.

This report reveals the importance of analyzing secondary results carefully and thoroughly before drawing firm conclusions. The initial finding of lower incidence of colorectal cancer in those taking postmenopausal hormone therapy must be balanced against the more advanced nature of the cancers that are discovered. For this reason, current data do not support the use of postmenopausal hormone therapy to reduce the risk of colorectal cancer. ❖

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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;

2. identify risks and interactions associated with alternative therapies;

3. discuss alternative medicine options with patients; and

4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

13. Which of the following mechanisms is thought to be responsible for ginger's anti-emetic activity?

a. CNS depression
b. Increased gastric motility
c. Increased gastric emptying
d. None of the above

14. Therapeutic doses of ginger are considered safe in pregnancy.

a. True
b. False

15. Ginger appears to prevent and/or treat nausea in all of the following situations *except*:

a. seasickness.
b. anesthesia-induced nausea.
c. food poisoning.
d. chemotherapy-induced nausea.

16. Ginger capsules are better tolerated than ginger foods, syrups, or teas.

a. True
b. False

16. Recent data from the Women's Health Initiative found a lower incidence of colorectal cancers in women taking postmenopausal hormone therapy. However, colorectal cancers in women who took estrogen plus progestin were diagnosed at a more advanced stage than those in women who took placebo.

a. True
b. False

Answers: 13. b, 14. a, 15. c, 16. b, 17. a

News Briefs

Choice Increases CAM Usage by Insured Cancer Patients

New research shows that a substantial number of insured cancer patients will use alternative providers if they are given the choice.

Researchers at the University of Washington in Seattle wanted to evaluate complementary and alternative medicine (CAM) provider utilization by cancer patients in Washington. The state requires the inclusion of alternative practitioners in private, commercial insurance products.

For the study, the researchers looked at year 2000 claims data from two large Washington State insurance companies. Of 357,709 claimants, 7,915 claimants had a cancer diagnosis. Among the cancer patients, 7.1% had a claim for naturopathy, acupuncture, or massage; and 11.6% had a claim for chiropractic during the study year. The use of naturopathy and acupuncture were more common, and the use of chiropractic was less common for cancer patients compared with those without cancer.

Most of the cancer patients also had at least one

conventional provider claim during the year. Factors associated with non-chiropractic alternative provider use were female gender, the presence of metastatic cancer, hematologic malignancy, and the use of chemotherapy. Increased use of naturopathic physicians accounted for much of this trend. Musculoskeletal pain was the most common diagnosis at the CAM provider visit. Billed amounts for alternative services were less than 2% of the overall medical bills for cancer patients.

Overall, the cost of the CAM treatment is modest compared with conventional care charges, the researchers say. "For individuals with cancer, CAM providers do not appear to be replacing conventional providers but instead are integrated into overall care," they conclude. Their findings were published in the April 1 print issue of the journal *Cancer*, but were released in late February on the journal's web site.

Osteoarthritis Initiative Begins Participant Enrollment

A major initiative to learn about the biological markers for osteoarthritis (OA) has begun recruiting in four centers in the United States.

The Osteoarthritis Initiative (OAI) is a public-private partnership between the National Institutes of Health, including the National Center for Complementary and Alternative Medicine, and industry. Women and men at risk for developing OA and those with early disease are eligible to participate. They must be 45-79 years old, and have one or more of the following to be volunteers in the study:

- Overweight
- Hand osteoarthritis
- Knee pain during the past year (Note: They don't have to have current knee pain to join.)
- Previous knee injury

This study is not for those who have rheumatoid arthritis, have joint replacements in both knees, are unable to walk without assistance, or can't have a MRI (magnetic resonance imaging) of the knee.

After an initial screening, the four centers around the United States plan to each enroll and follow 1,250 adults for five years. Biological specimens (blood, urine, DNA), images (X-rays and magnetic resonance scans), and clinical data will be collected annually.

The four clinical centers, selected in the summer of 2002, include the University of Maryland School of Medicine/Johns Hopkins University in Baltimore, the Ohio State University Medical Center in Columbus, the University of Pittsburgh, and the Memorial Hospital of Rhode Island/Brown University in Pawtucket. A data-coordinating center at the University of California, San Francisco, oversees the study conduct and will manage the resulting data. The Ohio State University and University of Pittsburgh centers enrolled their first participants the week of Feb. 23, and centers in Maryland and Rhode Island began enrollment in late March and early April.

Participants will be asked to do the following for the study:

- Complete a telephone interview to confirm their eligibility.
- Attend two initial visits that will include a knee X-ray and knee MRI scan, knee exam, strength testing, an interview, and lab tests.
- Return to the clinic for a once-a-year follow-up visit for the next four years.

They will not be required to take medications or change their eating or exercise habits.

The OAI is a federal contract funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Center for Complementary and Alternative Medicine, National Institute on Aging, Office of Research on Women's Health, National Institute of Dental and Craniofacial Research, and National Center on Minority Health and Health Disparities, all part of the Department of Health and Human Services' National Institutes of Health. Private funding partners include Merck Research Laboratories, Novartis Pharmaceuticals Corp., and Pfizer. Private sector funding for the OAI is being managed by the Foundation for the National Institutes of Health.

For full details about the OAI, visit The OAI: A Knee Health Study at http://www.oai.ucsf.edu/clinics.asp. For general questions, visit www.niams.nih.gov/ne/press/2001/07_17qa.htm. The NIAMS Office of Communications and Public Liaison (301-496-8190) or the NIA Communications Office (301-496-1752) can also be contacted for information. ❖

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