A Randomized Controlled Trial of Ginger to Treat Nausea and Vomiting in Pregnancy

Caroline Smith, PhD, MSc, Caroline Crowther, MD, FRANZCOG, Kristyn Willson, BSc (Hons), Neil Hotham, B Pharm, and Vicki McMillian, B Nursing

OBJECTIVES: To estimate whether the use of ginger to treat nausea or vomiting in pregnancy is equivalent to pyridoxine hydrochloride (vitamin B6).

METHODS: A randomized, controlled equivalence trial involving 291 women less than 16 weeks pregnant was undertaken at a teaching hospital in Australia. Women took 1.05 g of ginger or 75 mg of vitamin B6 daily for 3 weeks. Differences from baseline in nausea and vomiting scores were estimated for both groups at days 7, 14, and 21.

RESULTS: Ginger was equivalent to vitamin B6 in reducing nausea (mean difference 0.2, 90% confidence interval [CI] −0.3, 0.8), retching (mean difference 0.3; 90% CI −0.0, 0.6) and vomiting (mean difference 0.5; 90% CI 0.0, 0.9), averaged over time, with no evidence of different effects at the 3 time points.

CONCLUSION: For women looking for relief from their nausea, dry retching, and vomiting, the use of ginger in early pregnancy will reduce their symptoms to an equivalent extent as vitamin B6. (Obstet Gynecol 2004;103:639–45. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

Nausea and vomiting are common symptoms experienced by women in the first trimester of pregnancy and affect 50–80% of pregnant women.[1] Women often seek help from professionals and try numerous strategies to alleviate their symptoms, few of which suppress their symptoms to their satisfaction. There is a tradition of using ginger, an antiemetic herb in Chinese and Ayurvedic medicine, to treat nausea and vomiting. Many complementary medicines are perceived as being safe and natural, and many pregnant women choose to use these products or therapies during pregnancy.

From the Department of Obstetrics and Gynaecology, The University of Adelaide, The Department of Public Health, The University of Adelaide, and the The Women's and Children's Hospital, Adelaide, Australia.

Supported by The Women's and Children's Hospital Research Foundation and The Department of Obstetrics and Gynaecology, The University of Adelaide. Products were provided by Faulding Healthcare.

Evidence on the efficacy of ginger has been evaluated in 3 randomized controlled trials,[2–4] a Cochrane systematic review of interventions to treat nausea and vomiting in pregnancy,[5] and a systematic review of ginger for nausea and vomiting.[6] The 3 randomized controlled trials found ginger to be better than placebo. However, the duration of the study interventions were short, and the findings may have been influenced by symptoms regressing to a mean. The method of treatment allocation was not clearly described in 1 trial.[2] The Cochrane review currently includes 1 trial and concluded that 1 g of powdered ginger maybe helpful in alleviating symptoms.

The 3 clinical trials reported on pregnancy outcome and found no adverse effects arising from ginger for the mother and baby. Several sources of herbal information state that ginger is contraindicated during pregnancy, although evidence is lacking.[7] In animal studies, experimental data showed in utero exposure to ginger tea resulted in an increased early embryo loss with increased growth in surviving rat fetuses.[8] These findings have led to some concerns about the use of ginger extracts by pregnant women.

Evidence of efficacy exists for a range of treatments for nausea and vomiting in early pregnancy. Because of the medicines already available, it was considered that the evaluation of ginger in a placebo-controlled trial would be unethical. Vitamin B6 appears to be effective at reducing severe nausea from evidence described in the Cochrane systematic review on other treatments for nausea and vomiting in pregnancy. There was, however, no evidence of any reduction on vomiting.[5] Vitamin B6 is frequently used as a first line of treatment for women experiencing nausea and vomiting.

An active comparator of a treatment regularly used for nausea and vomiting was considered appropriate for this trial. We conducted a randomized controlled equivalence trial of the effectiveness of 1 g of ginger and the recommended dose (25 mg 3 times a day) of vitamin B6 to treat nausea and vomiting in early pregnancy.

0029-7844/04/$30.00
doi:10.1097/01.AOG.0000118307.19798.ec

Secondary hypotheses explored the safety, adverse pregnancy outcome, and tolerance of ginger compared with vitamin B6.

MATERIALS AND METHODS

The trial took place at The Women's and Children's Hospital in Adelaide, Australia, between July 2000 and March 2002. Women with nausea or vomiting were eligible for the trial if they were between 8 and 16 weeks pregnant, with dates confirmed by ultrasound. Women were excluded if they had any signs of clinical dehydration, if there were reasons to suspect their symptoms were not the result of pregnancy, or if they had any known allergy to ginger or vitamin B6. The previous use of antiemetics, ginger, or vitamin B6 did not exclude entry to the trial. Women could continue to use any existing medication or other measures other than ginger or vitamin B6 during the trial, and a record of use was made at the start and end of the trial.

The trial was promoted within the community by using the media, and referrals were made by general practitioners and other hospital health care providers. The study was approved by the hospital's research and ethics committee, and all women gave written, informed consent before enrolling in the trial.

Women were randomly allocated to receive either ginger or vitamin B6 in a blinded fashion. Women were instructed to take 1 capsule of ginger (350 mg) or 1 capsule of vitamin B6 (25 mg) 3 times a day for 3 weeks. All capsules were contained in an opaque brown soft gel capsule. Capsules were prepared by RP Scherer (Braeside, Victoria, Australia) with a certificate of analysis issued that ensured the products were standardized and quality controlled.

Demographic information, history of nausea and vomiting, and health status assessment was conducted with each woman before randomization. Women completed the Rhodes Index of Nausea and Vomiting Form 2[9] for 3 days as a baseline before randomization. Women who met the eligibility criteria were randomly assigned to a treatment group by logging onto the service at The University of Adelaide, Maternal and Perinatal Clinical Trials Unit. The computer-generated randomization schedule used balanced variable blocks and was prepared by a researcher not involved in the trial. Participation in the trial was for 3 weeks.

The primary outcomes assessed equivalence and examined any change in women's experience from nausea, dry retching, and vomiting from baseline at days 7, 14, and 21 by the Rhodes Index of Nausea and Vomiting Form 2[9] and change in health status measured by the MOS 36 Short Form Health Survey.[10] The Rhodes scale is a 5-point Likert scale ranging from 0 to 12, with larger scores indicating more symptoms. The Short Form 36 is a general outcome measure consisting of an 8 multiitem scale measuring physical functioning, physical role functioning, emotional role functioning, social functioning, bodily pain, mental health, vitality, and general health perceptions, with a higher score indicating better outcomes. An assessment of change in health status was made from baseline at day 21.

Secondary outcomes included the occurrence of any side effects and adverse pregnancy outcome. The standard definitions of pregnancy outcome from the South Australian Health Commission Pregnancy Outcome Unit[11] were used to examine the incidence of pregnancy outcome between study groups. The main pregnancy complications were defined as antepartum hemorrhage, pregnancy-induced hypertension, preeclampsia (hypertension 140/90 mm Hg or greater, proteinuria 0.3 g/L or greater from the 20th week of pregnancy) and preterm birth (less than 37 weeks of gestation). Perinatal outcome included stillbirth defined as death in a fetus of at least 400 g birth weight or 20 weeks of gestation and neonatal death defined as death of a liveborn infant within 28 days of birth. Data on pregnancy outcome include perinatal rates per thousand and are presented for South Australia. Data collected on congenital abnormalities from women in this trial were classified according to the diagnostic categories used by the register for coding of the Royal College of Paediatrics and Child Health Classification of Diseases (1979).[12] Pregnancy outcome data were collected from women 6 weeks after their expected date of delivery. Data were extracted from women's case notes for those women who gave birth at the Women's and Children's Hospital, or a telephone call was made by the study investigator (C.S.) to the woman at home.

The first hypothesis tested whether ginger and vitamin B6 were equivalent in terms of reducing nausea and vomiting symptoms, and this would be indicated by a difference between the groups of no greater than 2 points in the change from baseline of the Rhodes index of nausea and vomiting scale favoring vitamin B6. A difference of more than 2 points on this scale indicates a clinically meaningful reduction in the severity, frequency, or distress from these symptoms.

The sample size calculation was based on data from an initial pilot study. To reject the null hypothesis of a worse reduction in symptoms than 2 points with a power of 80% and a significance level of 5%, a minimum sample size of 113 women per group was required, assuming a standard deviation of 3 and an observed mean difference of 1 (calculated by using nQuery Advisor; Statistical Solutions, Saugas, MA). With adjustment for a withdrawal rate of 25% and losses to follow-up in an earlier

nausea and vomiting trial,[13] a minimum of 141 women per group were required.

The second hypothesis was that ginger was equivalent to vitamin B6 in improving the health status of women, as indicated by a difference in improvement between the groups of no more than 4 points on the Short Form 36 favoring vitamin B6. The equivalence difference of 4 in Short Form 36 scores was based on our previous nausea and vomiting study,[13] where differences in health status of 8 points were found between active and placebo treatments.

Women recorded their own primary outcome scores, and data were entered by an experienced data entry operator blind to treatment group. Analysis was by intention to treat using SPSS for Windows (SSPSS, Chicago, IL) and SAS 8.2 (SAS Institute, Cary, NC). Each symptom of nausea, dry retching, and vomiting was summed into a subscale describing women's experience. Mixed model analysis of variance (with a random intercept for each subject) was performed as a comparative repeated measures analysis to assess whether the difference in symptom reduction between the treatment groups was constant with respect to time (no treatment by time interaction). Estimated mean changes from baseline in symptoms and Short Form 36 scores were calculated from mixed model analysis of variance after adjusting for any potential confounders. Equivalence of these mean changes was assessed using one-sided *t* tests with 90% confidence intervals (CIs). The χ^2 or Fisher exact test was used for comparing binary variables, and 95% CIs were reported. A *P* value of less than .05 was used to demonstrate statistical significance.

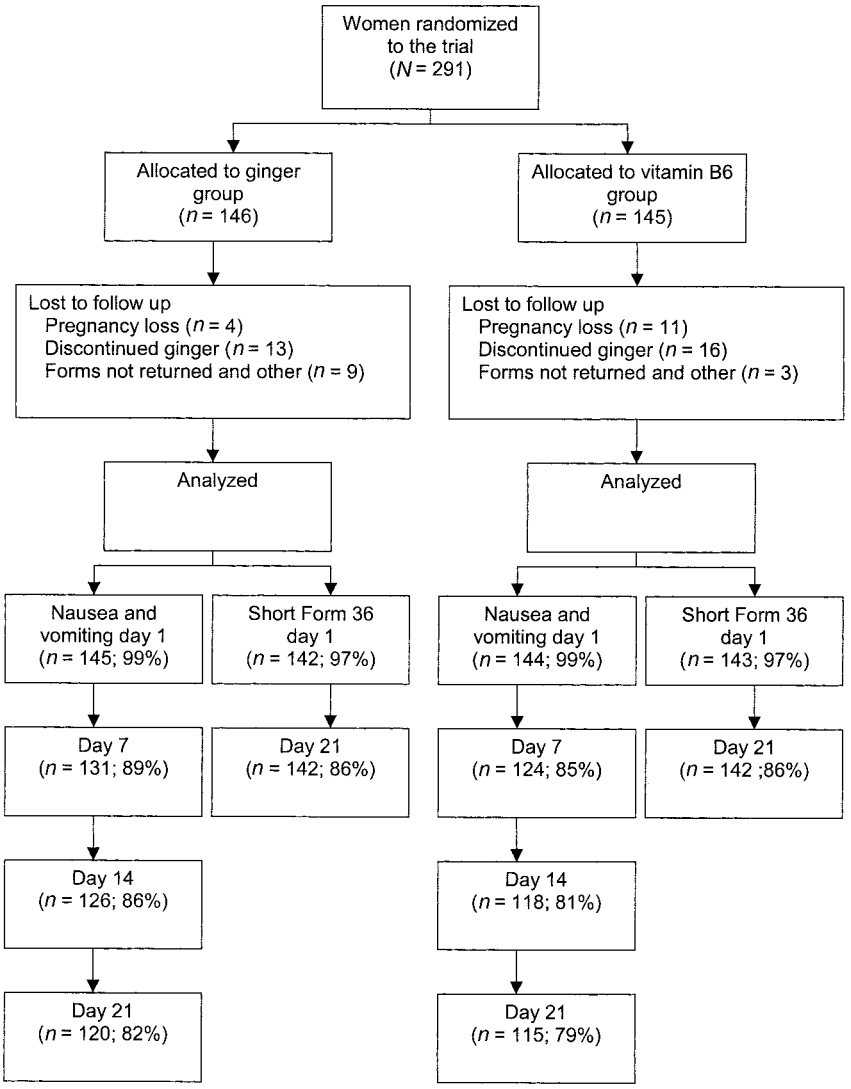

Figure 1. Trial profile: Randomization and return of nausea and vomiting and Short Form 36 questionnaires at day 1, 7, 14, and 21.

Smith. Ginger Equivalence Trial. Obstet Gynecol 2004.

Table 1. Baseline Characteristics of Women by Treatment Group at Trial Entry

	Ginger (n = 145)		Vitamin B6 (n = 146)	
Age (y)*	29.6	5.2	28.4	5.4
BMI (kg/m^2)*	25.6	6.1	25.9	5.8
Gestational age (wk) (median and range)	8.5	8–15	8.6	8–15
Parity (≥ 20 wk)†				
0	49	34	56	39
≥ 1	97	66	89	61
Smoked at trial entry†	12	8	12	8
Employed outside the home†	90	61	92	63
Use of antiemetic†	33	44	42	56

BMI = body mass index.
* Data are presented as mean and standard deviation.
† Data are presented as number and percentage.

RESULTS

There were 146 women randomized to ginger and 145 women to vitamin B6 (Figure 1). The groups were balanced in relation to the main demographic variables, nausea and vomiting, and Short Form 36 scores (Table 1). Nausea was experienced by 288 (99%) women, 287 women (98%) dry retched, and 175 women (60%) vomited before joining the trial. Nausea and vomiting data forms were returned from 255 (87%) women at the end of the first week of the trial, and data were received from 241 (82%) women at the end of the third week of the trial (Figure 1). The return rate for the Short Form 36 was 87% from 241 women. There appeared to be an imbalance in the use of antiemetics before joining the trial. The primary analyses of equivalence were adjusted for this variable. Seventy-five women (25%) reported using an antiemetic; these included metoclopramide (78%), prochlorperazine (12%), promethazine theoclate (5%), and ondansetron (4%). There were no differences in the use of medication between groups, and no data were available on the dosage used.

There was no evidence of a treatment by time interaction for any of the nausea and vomiting symptoms; therefore, we assessed equivalence on the change from baseline averaged over the 3 time points. Ginger was therapeutically equivalent to vitamin B6 for improving nausea, dry retching, and vomiting (Table 2).

When a comparison was made between the proportion of women reporting to be completely free of their symptoms, no differences were found between study groups at any time during the trial. Women's perception of an overall reduction in their symptoms was not found to differ between groups. Sixty-eight women (53%) reported an improvement taking ginger, and 69 (55%) reported an improvement with vitamin B6 (relative risk 0.97; 95% CI 0.77, 1.21). At the end of the intervention, the use of antiemetics was reported by 51 women (20%).

Overall, women's health status improved during 3 weeks of the trial (Table 3). However, there was insufficient evidence to demonstrate ginger was equivalent to vitamin B6 in improving the health status of women,

Table 2. Change in Nausea, Dry Retching, and Vomiting From Baseline (Averaged Over Time)

	Ginger		Vitamin B6			
Change in symptoms	Change in score	Standard error	Change in score	Standard error	Difference of means (90% confidence interval)	P
Nausea	−3.6	0.2	−3.9	0.2	0.2 (−0.3, 0.8)	< .001
Dry retching	−0.5	0.1	−0.7	0.1	0.3 (−0.0, 0.6)	< .001
Vomiting	−0.9	0.2	−1.4	0.2	0.5 (0.0, 0.9)	< .001

P values are for equivalence testing, and a difference in means > +2 indicates nonequivalence.

Table 3. Change in Mean SF-36 Domains From Baseline by Treatment Group

	Ginger		Vitamin B6		Difference of means, (standard error) (90% confidence interval)	
SF-36 domain	Change in score	Standard error	Change in score	Standard error		P
Social function	7.0	2.1	5.3	2.1	1.7 (−3.1, 6.6)	.03
Vitality	2.2	1.6	5.9	1.6	−3.7 (−7.3, −0.1)	.45
Physical function	1.4	1.7	2.3	1.7	−0.8 (−4.8, 3.2)	.10
Physical role function	6.1	2.7	3.0	2.7	3.2 (−3.1, 9.5)	.03
Bodily pain	4.9	1.7	5.0	1.7	−0.1 (−4.0, 3.8)	.05
Mental health	2.1	1.4	2.9	1.4	−0.8 (−4.0, 2.3)	.05
Emotional role function	7.7	3.9	10.4	3.9	−2.7 (−11.8, 6.4)	.41
General health perception	0.9	1.3	3.1	1.3	−2.2 (−5.2, 0.9)	.16

SF-36 = Medical Outcome Study 36-item Short-Form Health Survey.
P values are for equivalence testing, and a difference in means more negative than −4 indicates nonequivalence.

Table 4. Pregnancy Outcome by Study Group

Outcome	Ginger (n = 146) [n (%)]	Vitamin B6 (n = 145) [n (%)]	Rate per 1,000 births in South Australia	P
Spontaneous abortion	3 (2)	9 (6)	NA	.07
Therapeutic abortion	2 (1)	2 (1)	NA	.7
Stillbirth	0 (0)	3 (2)	7.4 per 1000	.1
Neonatal death	0 (0)	0 (0)	3.2 per 1000	1.0
Live birth	143 (98)	135 (93)		.03
Congenital abnormality				
Cardiovascular	0 (1)	1 (1)	170 (9.5)	.3
Gastrointestinal	1 (1)	1 (1)	89 (5.0)	.9
Urogenital	2 (1)	4 (3)	169 (9.5)	.4
Pregnancy outcome			n = 18,394 (%)	
APH/abruption, placenta praevia	5 (3)	5 (3)	622 (3)	.9
PIH	5 (4)	4 (3)	1,671 (9)	.7
Preeclampsia	6 (4)	4 (3)	NA	.6
Preterm birth	5 (3)	3 (2)	NA	.5
Gestational age at delivery (wk)*	39.0 (2.1)	38.9 (2.4)	NA	.8
Placental weight (kg)*	0.6 (0.7)	0.6 (0.2)	NA	.4
Birth weight (kg)	3.4 (0.6)	3.4 (0.7)	NA	.9
Male	57 (40.0)	59 (43.7)	51.3	.5
Birth length (cm)*	50.0 (3.0)	49.8 (5.1)	NA	.7
Head circumference (cm)*	34.4 (1.9)	34.7 (2.3)	NA	.2

NA = not available; APH = antepartum hemorrhage; PIH = pregnancy-induced hypertension.
Figures are number and percentage or mean and standard deviation.
* Rate per 1,000 total births.

with only 2 of the 8 Short Form 36 domains demonstrating statistically significant equivalence.

The majority of women tolerated both medications well. Women in both groups reporting dry retching after swallowing (ginger 52% versus B6 56%), or vomiting after ingestion (ginger 2% versus B6 1%), or a burning sensation (ginger 2% versus B6 2%). Women taking ginger (9%) reported belching more frequently compared with women taking vitamin B6 (0%; $P < .05$). Data on blinding were available from 138 women (47%); of these, 55 women (40%) reported they were unsure to which group they were allocated. Among the 83 women who gave an opinion, 76% of women who thought they were taking ginger were in the ginger group, compared to 65% of women who thought they were taking vitamin B6 and were allocated to the vitamin B6 group ($P < .001$).

Pregnancy outcome data were collected from 291 women (100%). Of these, 272 (93%) gave birth to 278 infants delivered after 20 weeks of pregnancy. There were 6 sets of twins. Four women terminated their pregnancy. Twelve (4.1%) women experienced a spontaneous abortion in the first or second trimester, 3 (1%) women experienced a stillbirth, and there were no neonatal deaths (Table 4). No differences were found between study groups.

No differences in congenital abnormalities were detected between study groups. In total, 9 babies (3%) were born with a major or minor congenital abnormality (Table 4). Among women receiving ginger, 3 babies were born with a congenital abnormality, and in the vitamin B6 group, 6 babies were born with a congenital abnormality. There were 6 cases of urogenital disorders; 1 of these was for undescended testes, 1 case for hypospadias, and 4 were for minor kidney abnormalities. The remaining congenital malformations were 2 cases of minor gastrointestinal abnormalities and 1 case of a minor congenital heart defect. In the year 2000, there were 770 (4.3%) birth defects notified in South Australia; this included minor and major malformations.[14]

The overall risk of pregnancy complications did not differ by study group (Table 4). No differences were found between study groups for any other birth outcome. The mean birth weight for babies in the trial was 3.4 kg (standard deviation 0.6 kg), with no differences in the mean birth weight found between study groups. We also examined birth weight by sex for surviving fetuses and found there were no differences between study groups.

DISCUSSION

Evidence from 2 systematic reviews concluded that ginger may be helpful and that further high-quality trials were needed.[5,6] Our results suggest there was a beneficial effect for women taking ginger in this trial, with

women reporting a reduction in their nausea and vomiting. Findings from our trial testing equivalence are not easily compared with other placebo-controlled trials evaluating the effectiveness of ginger for nausea and vomiting in early pregnancy. Our trial required women to take the trial medication for 3 weeks, and our results are influenced less by women's symptoms regressing to a mean. Women's participation in the trial for 3 weeks may also reflect more accurately women's use of these measures to manage rather than cure their nausea and vomiting. We found insufficient evidence to demonstrate equivalence of ginger with vitamin B6 on improving women's health status. This may have arisen from insufficient power to demonstrate equivalence.

Herbal products are generally perceived as "being natural and free of side effects." We monitored adverse effects systematically from women's case notes and patient self-report. Most of the side effects reported by women were associated with problems swallowing, a frequent problem reported by pregnant women. Vitamin B6 was slightly better tolerated. This report was demonstrated by women taking ginger reporting belching after ingestion. Previous studies suggest that higher doses of ginger may be associated with heartburn.[4] The manufacture of both products attempted using an identical soft gel capsule was a specific attempt to blind the medication.

There is insufficient data describing the safety of ginger in the first trimester of pregnancy.[15,16] Recent experimental data in an animal model reported in utero exposure to ginger tea resulted in an increased early embryo loss with increased growth in surviving fetuses in rats.[8] For this animal study to be applicable to human consumptions, the concentrations used were 20 g/L and 50 g/L. This was based on ginger tea that would be made up by women at home, made from grated ginger added to boiling water and infused for 10 minutes. Findings from our trial, however, suggest that outcomes in an animal model appear not to be transferable to the human model; however, the sample size of this equivalence trial was able to detect only large differences in measures of pregnancy outcome. For example, if ginger were to increase the rate of spontaneous abortion from 6% to 7%, a sample size of over 19,000 women would be needed. Clearly, our trial was underpowered to enable firm conclusions to be made on the safety of ginger in pregnancy.

Pregnancy outcome data have been reported in clinical trials evaluating the use of ginger in pregnancy. A meta-analysis of data on reported miscarriage from 505 women participating in the 4 trials reports a relative risk 0.63, 95% CI 0.27, 1.47. These data suggest there continues to be insufficient evidence to make a definitive statement on the safety of ginger in pregnancy. Data describing the safety of antiemetics such as Maxalon (Derma Tech Laboratories, Seven Hills, NSW, Australia) is likewise based on a small number of trials. The meta-analysis of data from the Cochrane review reports a statistic with wide confidence intervals, with insufficient evidence of any significant effect.

Firm evidence on the safety of ginger in pregnancy is essential and further systematic research on the risks and benefits of ginger during pregnancy would be of great clinical relevance. In the interim, there is a need for improved dissemination of information on the safety and efficacy of ginger to women, health professionals and complementary therapists.

Nausea and vomiting in early pregnancy remain a significant public health problem that has physiological, emotional, social, and economic consequences to women, their families, and society. For women looking for a reduction from their nausea, dry retching, and vomiting, the use of ginger in early pregnancy will reduce the severity of their symptoms and presents them with an alternative choice of treatment for the management of their symptoms.

REFERENCES

1. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of it's frequency, intensity and pattern of change. Am J Obstet Gynecol 2000;182:931–7.
2. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 1990;38:19–24.
3. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: a randomized double-masked, placebo-controlled trial. Obstet Gynecol 2001;97: 577–88.
4. Willetts KE, Ekangaki A, Eden JA. Effect of ginger extract on pregnancy induced nausea: a randomized controlled trial. Aust N Z J Obstet Gynaecol 2003;43:139–44.
5. Jewell MD, Young G. Interventions for nausea and vomiting in early pregnancy (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons.
6. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized controlled trials [review]. Br J Anaesth 2000;84:367–71.
7. Newall CA, Anderson LA, Phillipson JD. Herbal Medicines: a guide for health care professionals. London, UK: The Pharmaceutical Press; 1996.
8. Wilkinson JM. Effect of ginger tea on the fetal development of Sprague-Dawley rats. Reprod Toxicol 2000;14: 507–12.
9. Rhodes VA, Watson PM, Johnson MH. Development of a reliable and valid measure for nausea and vomiting. Cancer Nurs 1984;7:33–41.

10. Ware JE, Sherbourne CD. The MOS 36 Item Short Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
11. South Australian Health Commission Maternal Data. Pregnancy outcome in South Australia 1997. Adelaide: South Australian Health Commission; 1998.
12. Classification of diseases. London (UK): Royal College of Paediatrics and Child Health; 1979.
13. Smith C, Crowther C, Beilby J Acupuncture to treat nausea and vomiting in early pregnancy: a randomized controlled trial. Birth 2002;29:1–9.
14. Annual Report of the South Australian Birth Defects Register. Adelaide, South Australia: Women's and Children's Hospital; 2000.
15. Ernst E. Herbal medicinal products during pregnancy: are they safe [review]? BJOG 2002;109:227–35.
16. Natural medicines comprehensive database. Stockton, (CA): The Research Faculty; 1998.

Address reprint requests to: Caroline Smith, School of Health Sciences, The University of South Australia, GPO Box 2471, Adelaide SA 5001, Australia; e-mail: caroline.smith@unisa.edu.au.

Received July 1, 2003. Received in revised form December 11, 2003. Accepted January 7, 2004.