Original Article

Effect of a ginger extract on pregnancy-induced nausea:
A randomised controlled trial

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Abstract
Objective: To investigate the effect of a ginger extract (EV.EXT35) on the symptoms of morning sickness.
Design: Double-blind randomised placebo-controlled trial.
Participants: The participants included 120 women less than 20 weeks pregnant, who had experienced morning sickness daily for at least a week and had had no relief of symptoms through dietary changes.
Intervention: Random allocation of 125 mg ginger extract (EV.EXT35; equivalent to 1.5 g of dried ginger) or placebo given four times per day for 4 days.
Main outcome measures: Nausea, vomiting and retching as measured by the Rhodes Index of Nausea, Vomiting and Retching.
Results: The nausea experience score was significantly less for the ginger extract group relative to the placebo group after the first day of treatment and this difference was present for each treatment day. Retching was also reduced by the ginger extract although to a lesser extent. No significant effect was observed on vomiting. Follow-up of the pregnancies revealed normal ranges of birthweight, gestational age, Apgar scores and frequencies of congenital abnormalities when the study group infants were compared to the general population of infants born at the Royal Hospital for Women for the year 1999–2000.
Conclusion: Ginger can be considered as a useful treatment option for women suffering from morning sickness.

Key words: ginger, pregnancy, nausea, Zingiber officinale, morning sickness

Introduction
Nausea is likely to affect more than 50% of pregnant women as illustrated by a study of 7027 women in the USA, and frequently disrupts their family and work routines.1,2 Prescription drugs are usually avoided in early pregnancy due to fear of fetal abnormalities. There is consequently increasing interest in alternative therapies for this condition. Ginger (Zingiber officinale) has been used for thousands of years in Indian and Chinese traditional medicines for a number of actions, including anti-emetic effects, stimulation of digestion, relief of coughs and colds and an anti-inflammatory action.3 More recently, clinical trials have also demonstrated the anti-emetic effect of ginger in a number of contexts including women hospitalised for hyperemesis gravidarum,4 chemotherapy,5 motion sickness,6,7 and postoperative surgery.8,9 A recent Cochrane review on interventions for nausea and vomiting in early pregnancy reported an overall reduction in nausea from anti-emetic medications, and indicated that more research on ginger was required.10

We initially carried out a pilot study on 34 women who had morning sickness to compare two doses of ginger: 125 mg or 255 mg of ginger extract (EV.EXT35) three or two times a day, respectively, for 4 days. The pilot study showed no significant difference between the two doses but did show a trend towards better reduction in morning sickness with increased frequency of administration. We then conducted a randomised controlled trial comparing this ginger extract with placebo, using 125 mg administered four times a day to maximise the probability of a treatment effect. The primary objective was to compare nausea experience between the ginger extract and placebo groups.

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Methods

To be eligible, women were required to be less than 20 weeks pregnant, have had experienced morning sickness daily for at least a week which had failed to respond to dietary measures. Exclusion criteria included hospitalisation for dehydration during the current pregnancy, significant medical problems (hypertension, epilepsy or diabetes) and known allergy to ginger. Women who had used ginger, vitamin B6 or prescription drug therapies for nausea were required to have a 3-day wash-out period prior to entering the study. The random allocation sequence was generated by Eurovita Pty Ltd, Denmark, using randomisation blocks of six, and was placed in sealed envelopes and posted to us in at the hospital in Sydney where the trial was carried out. These envelopes were only opened when the last subject had completed the treatment. Participants, those administering the treatment and those assessing the outcomes were all blinded to the group assignment. Study medication was supplied as wax sealed capsules identical in appearance, the active treatment containing 125 mg ginger extract (equivalent to 1.5 g of dried ginger) and the placebo containing soya bean oil. Women were required to take study medication four times a day (8 a.m., 12 noon, 4 p.m., 8 p.m.) and to record their symptoms an hour after each capsule was swallowed using the Rhodes Index of Nausea, Vomiting and Retching (RINVR).11 The RINVR is an eight item 5-point Likert-type tool. It measures the frequency and duration, as well as the distress caused by the symptoms of nausea vomiting and retching. The RINVR was administered 1 h after treatment on the basis of previous studies which achieved an effect between 20 min and 1.5 h.17–9 Baseline symptoms were recorded the day after the first visit. Study medication was to be used for four consecutive days after the baseline day. The present study was approved by the South-eastern Sydney Area Health Service Ethics Committee and written informed consent was obtained.

Sample size and statistical methods

A total of 120 subjects were recruited for the present study. Our pilot study showed a standard deviation of approximately 3.5 for the nausea experience score. Based on a 5% significance level, a minimum total of 96 subjects were required to detect a difference between ginger extract and placebo of at least two points on the RINVR, with 80% power. However, assuming a 20% drop-out rate among study subjects, a target of 120 subjects was recruited.

Nine outcome scores were evaluated for women taking ginger compared with women taking placebo. The following were the symptom scores for the outcomes of nausea, vomiting and retching, defined within each of three domains of symptoms: experience, occurrence and distress from symptom. The primary outcome was nausea experience, while the remaining eight scores (vomiting experience through to retching distress) constituted the secondary outcomes. Analysis was carried out separately for each of the nine outcome variables. Each outcome variable was measured four times a day over 5 days, including the baseline day. Regression models using generalised estimating equations were used to test for differences between ginger extract and placebo.12 The models included the treatment effect (treat), the day effect (day 0–day 4), the time effect (hour 1–hour 4), the treatment–day interaction (TXD1–TXD4) and the treatment–time interaction (TXH2–TXH4).

For each day post-baseline, the effect of ginger extract compared to placebo was calculated from the model estimates as the difference between the estimate for the particular day and that for its interaction with treatment. The standard error of this difference parameter was computed from the variance-covariance matrix for the model, thus providing the 95% confidence interval of the difference parameter. A level of 0.05 was used to determine statistical significance.

Results

Between March 1999 and November 1999, 264 women were screened and 120 were recruited for the study mainly via the outpatient antenatal clinic at the Royal Hospital for Women (Fig. 1). Demographics and baseline symptoms were analysed for all 120 women. Twenty-one women, however, were excluded from the final analysis due to insufficient data (12 for adverse events and nine due to non-compliance). Adverse events included spontaneous abortion (n = 4 women; three in the ginger extract group, one in the placebo group), intolerance of the treatment (n = 4; all in the ginger extract group), worsening of treatment requiring further medical assistance (n = 3; one in the ginger group, two in the placebo group) and allergic reaction to treatment (n = 1; ginger extract group).

There were no statistical differences in the baseline demographics (ethnic group, employment, parity, weeks of gestation and body mass index) between the two groups apart from age. The average age for the women in the ginger extract group was 33 years (range 22–43) and for placebo, 31 years (range 19–44). One hundred and three (86%) women in this study were Caucasian, nine (7.5%) were Asian, seven (5.8%) were Hispanic and one (0.8%) was Aboriginal. The average period of gestation was 9 weeks (range 5.5–18 weeks). One hundred and eleven (92%) were in their first trimester and nine (8%) were in their second. Ninety-eight women (82%) had not drunk any alcohol and 114 (96%) had not smoked during their pregnancy. The largest proportion, 68 women, (58%) had nausea throughout the day with only 13 women (11%) who had symptoms only in the morning. Forty-six women (39%) who participated had constant nausea. Sixty-nine women (58%) reported vomiting episodes.

Figure 2 displays the difference between treatments in the pattern of nausea experience across consecutive days. It illustrates trends in the mean nausea score for baseline and days 1–4. For both the ginger extract and placebo groups, there was a noticeable reduction in overall nausea experience score from baseline to day 1, which then appears to remain
Ginger is effective for morning sickness

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consistent through to day 4. It also appears from Fig. 2 that, compared to placebo, mean nausea experience score may be lower with ginger extract in the middle of the day (1 p.m.).

Regression models were used to investigate the observed patterns displayed in Fig. 2. From the parameter estimates of the fitted model for nausea experience there was no significant difference between the ginger extract and placebo groups at baseline (P-value = 0.515 for treat). The effect of ginger extract relative to placebo was calculated from the model estimates as a difference parameter for each day post-baseline, with its 95% confidence interval. Figure 3 displays the results of these calculations for the nausea experience score. It shows that except for day 3, the difference parameter for each day post-baseline, was significantly less than zero. However, the wide confidence intervals compared to the baseline effect, may suggest insufficient sample size for more accurate assessment of post-baseline effects. Although Fig. 3 shows a significant ginger effect on day 4, this result is likely confounded by a regression-to-the-mean effect (Fig. 2) and may require further investigation. Similar results were found for nausea occurrence and nausea distress.

Figure 1 Study flow diagram.
There was no significant difference between ginger extract and placebo groups for any of the vomiting symptoms. For retching symptoms, the ginger extract group was shown to have significantly lower symptom scores than the placebo group for the first 2 days only.

Follow-up assessment

Antenatal and postnatal assessments were carried out on the 81 women who completed the main study. Of these women who were exposed to ginger there were two spontaneous abortions, one stillborn, one neonatal death and one lost to follow-up or who declined to give consent to follow-up. A total of 81 women gave birth, and with two pairs of twins this resulted in 83 infants. Outcomes were compared with the July 1999–June 2000 data for the general infant population delivered at the Royal Hospital for Women in Sydney as well as previous studies (Table 1). There was one stillbirth

Table 1 Follow up data is for the main studies compared with hospital statistics (expected numbers) and data from previous studies

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of infants (n = 83)</th>
<th>Expected number‡</th>
</tr>
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<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Stillborn</td>
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<td>0–1</td>
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<tr>
<td>Neonatal death</td>
<td>1</td>
<td>0–1</td>
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<tr>
<td>Premature (28–31 weeks)</td>
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<td>2</td>
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<tr>
<td>Congenital abnormalities</td>
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<td>0–1</td>
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<tr>
<td>Ventricular septal defect</td>
<td>1</td>
<td>0–1</td>
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<tr>
<td>Talipes</td>
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<td>1–2</td>
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<tr>
<td>Syndactyly</td>
<td>1</td>
<td>0–1</td>
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<tr>
<td>Polyactyly</td>
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<td>0–1</td>
</tr>
<tr>
<td>Birth characteristics</td>
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<td></td>
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<tr>
<td>Mean (95% confidence interval)</td>
<td></td>
<td></td>
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<tr>
<td>Gestational age (weeks)</td>
<td>39.3 (39.0–39.6)</td>
<td>38.8 (38.7–38.9)</td>
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<tr>
<td>Birthweight (g)</td>
<td>3428 (3335–3521)</td>
<td>3324 (3303–3345)</td>
</tr>
<tr>
<td>Apgar score</td>
<td>9–10</td>
<td>Not available</td>
</tr>
</tbody>
</table>

The ‘expected numbers’ ‡are calculated from data of 3983 infants born at the Royal Hospital for Women from July 1999–June 2000.
and one neonatal death out of 83 births, which is a similar frequency to the overall rates seen at the Royal Hospital for Women that year. The rates of birth defects were similar to the general population and were all minor. These included one with talipes, one premature birth at 28 weeks, and one with syndactyly of the second and third toes. The birthweights, gestational ages and Apgar scores seen for the babies whose mothers were exposed to ginger in the present study were similar to those seen in the rest of the hospital population over the same period of time. Of the babies whose mothers were involved in the study, only one baby had an Apgar score of less than seven at 5 min. The remaining 82 babies (98.8%) had an Apgar score of more than seven at 5 min. There was also no difference in the rates of postpartum haemorrhages. In summary, from the data we have collected, babies whose mothers were exposed to ginger during our study did not appear to be at increased risk of fetal abnormalities or low birthweight.

Discussion

We found ginger to be of some benefit in the treatment of pregnancy-induced nausea, particularly in the early days of use. To our knowledge, no similar study has been published with as many subjects. This study confirms the presence of a placebo effect in the relief of nausea but still detects some benefit of ginger in improving morning sickness. The withdrawal of four subjects in the ginger group was likely due to the reflux and heartburn caused by the dose of ginger used in the present study. Comments by the study subjects were recorded in the case report forms.

The follow-up data from the present study will contribute to the body of published reports on pregnant women exposed to ginger. Women in the treatment arm of this trial took ginger for 8 days and those in the placebo arm took ginger for 4 days. In addition, all were given 2 weeks supply following the end of the trial. Only the data for 4 days was analysed. Hence, the findings of the follow-up assessment should be viewed with caution. No direct attempt can be made to infer cause or association between the findings and the use of ginger over the 8-day period of the principal study.

The present study is consistent with other published trials showing that ginger is an effective treatment for nausea. However, unlike other studies we did not demonstrate an effect on vomiting. The main adverse event in this trial was reflux and heartburn. Heartburn has been reported in a number of previous trials. In the treatment of photopheresis-induced nausea subjects were given 1.5 g of ginger, and three out of 11 reported to have heartburn (27%). In another study for the prevention of postoperative nausea and vomiting 3/36 (8%) subjects taking 1.0 g, and 1/36 (3%) subjects taking 0.5 g ginger had heartburn. In the present study 1.5 g was used. It is difficult to extrapolate from these limited numbers; however, it seems likely that higher doses correlate with more heartburn.

Two contrasting studies examining the effect of ginger in pregnant rats have been carried out. One has shown that the effect of ginger tea (20 or 50 g/L) on pregnant rats was to significantly increase early embryonic loss and to increase growth in surviving fetuses. In contrast, teratogenic studies have been carried out in rats on a similar ginger extract to the present study (at doses of 100–1000 mg per kg) and although embryonic loss was examined, no toxic effects were observed. In the present study there were three in the ginger group (of 60) who had spontaneous abortions, although one of these had not begun taking the treatment. Of the published studies, there was one spontaneous abortion out of 32 in the ginger group. There was one spontaneous abortion of 27 of the cross-over design study. Again these are limited numbers, however, there is not a great deal of difference between these trials or with the background spontaneous abortion rate. In addition, the present study shows no obvious increased risk of fetal abnormalities or abnormal birthweights in babies exposed to ginger in pregnancy. These results are consistent with no abnormalities having been detected in the previous two studies. The evidence from the clinical trials to date does not seem to point to ginger being unsafe to take.

Ginger is also known to decrease thromboxane synthesis although not in vivo. It was reassuring to see that women exposed to ginger did not have an increased risk of antenatal or post-partum haemorrhage.

In conclusion this ginger extract was a more effective treatment than placebo for nausea and retching during pregnancy. Follow-up of the babies appears to show no increased risk of fetal abnormalities compared with the general obstetric population, although it is clear that more data needs to be collected in this area. Future studies should examine a lower dose of this ginger extract.

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References


