Comparison of quince with vitamin B6 for treatment of nausea and vomiting in pregnancy: a randomised clinical trial

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To link to this article: http://dx.doi.org/10.1080/01443615.2017.1322046

Published online: 20 Jun 2017.
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ABSTRACT
This trial was performed to compare quince (Cydonia oblonga) fruit with vitamin B6 on 76 pregnant women with a gestational age of 6–14 weeks and mild-to-moderate nausea and vomiting (NVP) (40 in the quince and 36 in the B6 group). The ‘Pregnancy-Unique Quantification of Emesis’ (PUQE-24) scale was used to examine the severity of NVP. The quince syrup (1 tablespoon/TDS) or vitamin B6 tablets (20 mg/TDS) were used as intervention for 1 week. The mean (±SD) age was 27.5 (±5.2) years. The score of the PUQE was decreased from 9.5 (±2) at baseline to 5.2 (±2.3) on the 7th day and 5.3 (±2.6) on the 14th day (p < .001) in the quince group. In the other group, the scores were 8.4 (±1.8), 7.3 (±2.4) and 7.7 (±3.8), respectively (p = .001). The change in symptoms were more marked in the quince group (p < .001). Quince syrup seems to be a suitable treatment for NVP.

IMPACT STATEMENT
- What is already known on this subject: Pregnancy-induced nausea and vomiting (NVP) is one of the most common problems during gestation. Treatment is mainly symptomatic, ranging from dietary changes and oral pharmacological treatment to hospitalization in severe forms. In early pregnancy, the use of chemical drugs is avoided, so there is an increasing tendency to use alternative therapies. According to the literature review in Iranian Traditional Medicine (ITM), the quince fruit (Cydonia oblonga) can be useful in NVP. Quince has a wide range of pharmacological activities including antioxidant, antibacterial, antifungal, anti-inflammatory, hepatoprotective and antidepressant effects. ITM literature suggests some therapeutic effects of the quince fruit on important organs like brain, heart, liver and stomach.
- What the results of this study add: The results of this study demonstrated the significant efficacy of quince in comparison with vitamin B6.
- What the implications are of these findings for clinical practice and/or further research: This fruit is also safe to be administered in pregnant women suffering from NVP.

Introduction
Pregnancy-induced nausea and vomiting (NVP) is one of the most common problems during pregnancy with an approximate incidence of 70–85%. This medical condition can vary from mild to incapacitating, known as hyperemesis gravidarum (Einarson et al. 2012; Haji Seid Javadi et al. 2013).

This condition can impose negative impacts on the quality of the family and social life (Lacasse et al. 2008; Lua and Zakaria 2012). Psychological, emotional and economic issues may also arise as a result of these complications (Ozgoli et al. 2009). Treatment is mainly symptomatic, including dietary changes (Chortatos et al. 2013), oral pharmacological treatments and hospitalization with intravenous fluid replacement and nutritional therapy (Lee and Saha 2011). Vitamin B6 is used as the first-line treatment of NVP (Sahakian et al. 1991; Haji Seid Javadi et al. 2013); however, current studies support the use of metoclopramide and antihistamines such as doxylamine (Oliveira et al. 2014) and ondansetron (Einarson et al. 2004). In early pregnancy, chemical drugs are avoided as far as possible due to their potential teratogenic effects. So, there is an increasing tendency towards the use of alternative therapies (Haji Seid Javadi et al. 2013). According to some studies, ~50–65% of pregnant women use herbal remedies such as peppermint, ginger, cranberry and raspberry leaf for NVP (Holst et al. 2009; Hashem-Dabaghian et al. 2012).

According to a literature review on Iranian Traditional Medicine (ITM), Iranian physicians performed many experiments on maternal health and acquired important knowledge and professional skills in this field (Majeed 2005; Jafari-Dehkordi et al. 2013). Based on their viewpoints, Cydonia oblonga (commonly known as quince) is one of the medicinal herbs and its fruit can be useful in NVP (Razi 2000; Ibn 2005; Aliasl et al. 2015; Al-Snafi 2016).
The quince fruit is available in markets of some parts of Iran almost 6 months of the year and is usually used as a raw fresh fruit, jam or paste (Figure 1). It has a wide range of pharmacological activities such as antioxidant, antibacterial, antifungal, anti-inflammatory, renoprotective, hepatoprotective, antidepressant, hypolipidemic, anti-colicis, immunomodulatory, anti-allergic, anticancer, anti-Helicobacter pylori and anti-reflux effects (Tansaz et al. 2013; Zohalinezhad et al. 2015; Ashraf et al. 2016; Aliasl et al. 2016).

ITM literature suggests that quince has some therapeutic effects on important organs like the brain, heart, liver and stomach. It is known as a brain, heart, liver and cardiac tonic, and also as a ‘mofarreh’ (gives people cheerfulness and vitality). In addition, this fruit is known to be a stomach tonic, improving nausea and vomiting, pica, hangover and appetite (Aghili 2004; Ibn Sina 2005).

While there are considerable ITM recommendations for the benefits of quince in NVP, none of the previous clinical studies has investigated this therapeutic effect. This study was performed in order to compare the efficacy of the quince syrup with vitamin B6 in NVP.

Materials and methods

Patients and protocol

This multicentric, randomised, controlled clinical trial was carried out between March 2013 and August 2013 in five clinical centers in Tehran and Qom (Iran) after receiving approval from the Ethics Committee of Tehran University of Medical Sciences. Furthermore, the trial was registered in the Iranian Registry of Clinical Trials with the number IRCT2012081110559N1.

To estimate 1.8 differences of the Pregnancy-Unique Quantification of Emesis (PUQE) scores between the two groups, considering type I error of 0.05, type II error of 0.2 and PUQE standard deviation of 2.7, the sample size was calculated as 35 patients in each group. The effect size was considered as 0.7 based on the results of our pilot study and the formula of comparing two means was used to calculate the sample size.

The initial sample consisted of 110 pregnant women aged 18–40 years with a gestational age of 6–14 weeks who had mild-to-moderate nausea (PUQE score = 3–12) with or without vomiting, requiring treatment. The subjects were excluded if they had severe nausea and vomiting during pregnancy requiring fluid therapy and hospitalization, nausea and vomiting of pregnancy due to secondary causes such as peptic ulcer, hepatitis, pyelonephritis, pancreatitis, cholecystitis, appendicitis, gastroenteritis, urinary tract infection, central nervous system disorders, gastroesophageal reflux disease, hyperthyroidism, multiple pregnancy, ectopic pregnancy, molar pregnancy, pregnancy complications such as bleeding, threatened abortion, history of chronic diseases, history of drug addiction, alcoholism and smoking, drug allergy, and taking anti-nausea medication (vitamin B6, metoclopramide, etc.) at least 48 hours before visiting the clinic.

The aim and the details of the study were explained to the subjects and written consent was obtained from those who accepted the terms of the study. Then, 90 patients were randomly assigned into two groups, each including 45 patients, who either received ‘the quince syrup’ (Group A) or ‘vitamin B6’ (Group B). Blocks of 4 (AABB, ABAB, BABA, BBAA, ABBA, BAAB) were selected randomly to create the randomisation list. Patients were instructed not to consume any other forms of quince or other herbal preparations during the study.

Preparation of syrup

The quince syrup was prepared in the laboratory of the Pharmacy Department, Faculty of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran. Forty kilograms of the quince fruit was bought from the market of Tehran (capital of Iran). It has been deposited in the Herbarium of Faculty of Pharmacy (Tehran University of Medical Sciences) under the voucher number: PMP: 641. The syrup was traditionally prepared as described in ‘Qarabadin-e-Kabir’ (a reference of traditional pharmacy) (Aghili 2008). The juice of fresh quince pulps was boiled with sugar with the ratio of 1/2.8. Eleven litres of concentrated syrup was produced. The concentrated syrup was standardised based on total phenols and gallic acid content (Folin–Ciocalteu method) (Singleton et al. 1999). Each 1 g of concentrated syrup contains 2 mg total phenols as gallic acid equivalents. Quality control tests, including measurements of heavy metals and microbial contamination, were conducted based on the United States Pharmacopeia guideline. The further safety assessment was not conducted in the present study because previous studies on quince have demonstrated its safety and no side effects have been yet reported for therapeutic doses of quince (Fleming 2009; Al-Snafi 2016).

Standard questionnaire

In this study, the PUQE-24 was used for evaluation of the efficacy of treatment. The PUQE scale, which is designed to measure the severity of NVP, is composed of three questions which measure the duration of nausea and frequency of vomiting and retching in the last 24 hours through a five-point Likert scale. Each question is scored from one to five and the total score is between 3 and 15. A score of ≤6 indicates mild nausea, 7–12 shows moderate nausea and vomiting, and ≥13 suggests severe nausea and vomiting. The PUQE-24 scale is
derived from the Rhodes scale which was validated by Ebrahimi et al. in Iran (Ebrahimi et al. 2009; Clark et al. 2012).

**Treatment and assessments**

The participants were asked about their demographics, pregnancy characteristics and the baseline severity of nausea and vomiting according to PUQE-24. Patients were instructed to complete the questionnaires. The block randomisation method was used to allocate the patients into the quince or vitamin B6 group. The experimental group received one tablespoonful of the quince syrup and the control group received vitamin B6 (20 mg pills) three times a day before each meal for one week.

This dosage regimen of quince syrup was determined according to Iranian traditional medicine books and usage of quince extract for the same indication (Aghili 2008). Patients were asked not to take any additional medications during the study.

All of the participants were advised to avoid fatty foods and divide their meals into frequent smaller meals. They were also asked to fill out the PUQE-24 questionnaire for 14 days (7 days treatment and 7 days follow-up). The participants were also requested to report other secondary outcomes, including the occurrence of side effects such as heartburn, arrhythmia, headache and sleep conditions.

**Statistical analyses**

Data analyser was blinded about the groups A and B. Descriptive statistics are summarised as mean with standard deviation and percentage. Mann–Whitney U-test was used to compare the PUQE-24 score between the two groups at the beginning and at the end of the first week.

Chi-square ($\chi^2$) test was used to compare the qualitative variables between the two groups. The data analysis was performed using SPSS software (v.16, Chicago, IL), and $p$-values < .05 were considered statistically significant.

**Results**

From the 90 pregnant women who were included in the trial, 76 completed the interventions (Figure 2). Fourteen patients were lost to follow-up: five in the quince group and nine in the B6 group. The main reason for dropping out of the study was the lack of effect, using another antiemetic drug, personal reasons and failure to follow-up.

The baseline characteristics are presented in Table 1. The two study groups were statistically similar in terms of age, BMI, education, occupation, gravidity, parity and gestational age. The PUQE scores at baseline and 7 and 14 days after the intervention are shown in Table 2. The results showed a significant decrease in nausea and vomiting scores in both groups compared before and after the treatment. Although the PUQE score was significantly higher in the quince group ($p = .01$) at the beginning of the study, it was decreased in the quince group ($p < .001$) more than the B6 group ($p = .001$). In other words, a greater improvement of symptoms was seen in the quince group. No adverse effect was reported during the study.

**Discussion**

The use of medicines during pregnancy is limited due to concerns about birth defects. It is clear that medication during pregnancy must be supported by scientific evidence. Recent evidence has shown some side effects for medications that were known to be safe in pregnancy, such as cleft lip due to prednisone intake before the tenth week (Lee and Saha 2011). Trade dyskinesia can be caused by metoclopramide. Constipation, diarrhoea, fatigue and headache are some side effects of ondansetron, and oesophageal reflux and heartburn.

![Consort flow diagram](image-url)
Table 1. Demographic data of the patients in both groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quince syrup (Group A) (n = 40)</th>
<th>Vit B6 (Group B) (n = 36)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year) (mean ± SD)</td>
<td>27.35 ± 5.19</td>
<td>27.81 ± 5.45</td>
<td>.7</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± SD)</td>
<td>24.22 ± 1.30</td>
<td>24.90 ± 2.02</td>
<td>.09</td>
</tr>
<tr>
<td>Education No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>8 (20%)</td>
<td>11 (30.6%)</td>
<td>.4</td>
</tr>
<tr>
<td>High school</td>
<td>15 (37.5%)</td>
<td>14 (38.8%)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>17 (42.5%)</td>
<td>11 (30.6%)</td>
<td></td>
</tr>
<tr>
<td>Occupation, No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housekeeper</td>
<td>34 (85%)</td>
<td>30 (83.3%)</td>
<td>.6</td>
</tr>
<tr>
<td>Employee</td>
<td>6 (15%)</td>
<td>6 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Gravidaity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (42.5%)</td>
<td>17 (47.3%)</td>
<td>.6</td>
</tr>
<tr>
<td>2</td>
<td>15 (37.5%)</td>
<td>13 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>8 (20%)</td>
<td>6 (16.6%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (Nullipara)</td>
<td>22 (55%)</td>
<td>19 (52.8%)</td>
<td>.7</td>
</tr>
<tr>
<td>1</td>
<td>14 (35%)</td>
<td>15 (41.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (10%)</td>
<td>1 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>0 (0%)</td>
<td>1 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (day) (mean ± SD)</td>
<td>61.18 ± 14.42</td>
<td>67.75 ± 16.02</td>
<td>.6</td>
</tr>
</tbody>
</table>

*Chi-square test.

Table 2. PUQE scores at baseline, 7th and 14th days after intervention.

<table>
<thead>
<tr>
<th>PUQE score (Men ± SD)</th>
<th>Quince syrup (n = 40)</th>
<th>Vit B6 (n = 36)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.55 ± 2.05</td>
<td>8.44 ± 1.87</td>
<td>.01</td>
</tr>
<tr>
<td>Week 1</td>
<td>5.22 ± 2.39</td>
<td>7.30 ± 2.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Week 2</td>
<td>5.38 ± 2.60</td>
<td>7.72 ± 3.80</td>
<td>.001</td>
</tr>
<tr>
<td>Score change up to 7th day</td>
<td>4.3 (2.9)</td>
<td>1.1 (2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score change up to 14th day</td>
<td>4.1 (2.8)</td>
<td>0.7 (3.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Mann–Whitney U-test.
**Wilcoxon signed rank test.

may be the side effects of ginger (Lee and Saha 2011). Therefore, it is important to determine safe and easy treatments for pregnant women. As mentioned earlier, complementary therapies are becoming increasingly popular and the pregnant women are one of the most wide user groups (Hashem-Dabaghian et al. 2012).

The results of this study indicated significant advantages of the quince syrup over vitamin B6 in NVP without any side effects. What we know about the effects of quince in NVP is based upon the ITM literature. There are some possible explanations for this result according to the ITM and the quince fruit has tonic properties on the brain, heart, liver and stomach. It is also worth pointing out that it is foetus protective as well (Aghili 2004; Ibn Sina 2005).

The present study was the first clinical trial to evaluate the effect of the quince fruit in NVP, so there is no work on the quince fruit to be compared. The results of some other herbal therapies on NVP are mentioned and compared with the results of this study. For example, Pasha et al. studied the effects of mint oil aromatherapy on NVP but did not approve its efficacy compared with placebo. Although the intensity of nausea reduced during the intervention in the mint group (especially on the fourth night), the difference was not statistically significant (p-value = .577) (Pasha et al. 2012). In our study, the quince fruit was significantly more effective than vitamin B6.

Ginger is a plant which is frequently studied in this disorder. Chittumma et al. demonstrated that both ginger and vitamin B6 significantly reduced nausea and vomiting. The average change of the nausea score in the ginger group was 0.7 points more than the vitamin B6 group (p < .05) (Chittumma et al. 2007). Sripramote et al. showed that ginger and vitamin B6 similarly reduced the intensity of nausea and number of vomiting episodes (p = .13, p = .49). In addition, there were some minor side effects in both groups such as sedation and heartburn (Sripramote and Lekhyananda 2003).

The results of a systematic review and meta-analysis of the efficacy and safety of ginger in the treatment of NVP showed that 1500 mg/day ginger was effective in nausea but did not have a significant impact on vomiting episodes (Viljoen et al. 2014).

Another systematic review showed that ginger improved NVP better than placebo, and similar to vitamin B6 and dimenhydrinate (Dante et al. 2013). From the perspective of ITM masters, ginger is warm in nature and its use is limited during the first trimester of pregnancy due to its emmenagogue effects (Aghili 2004; Azam 2004; Ibn Sina 2005). In this study, we did not observe any side effects. In addition, no side effects have been yet reported for therapeutic doses of the quince fruit (Fleming 2009; Al-Snafi 2016; Aliasl et al. 2016).

Strengths and limitations

In most clinical studies evaluating NVP, the treatment duration was 4 days without follow-up reports while in the present study, the intervention was conducted for 7 days and then the patients were followed up for one week. As one of the limitations of the present study, future studies are suggested to have a double-blind design.

Conclusions

We found that the quince (Cydonia oblonga) syrup was significantly effective in nausea and vomiting during pregnancy when compared with vitamin B6. Due to the beneficial effects of quince besides its safety, a therapeutic role is
expected for this fruit in nausea and vomiting during pregnancy in the future.

However, large standardised randomised controlled trials are necessary to determine the appropriate dose and duration of treatment, and the reliability of the quince.

Acknowledgements

This work was supported by a grant from Research Institute for Islamic and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran.

Disclosure statement

No potential conflict of interest was reported by the authors. None of the funding bodies had any influence in the design, implementation, analysis or interpretation of the data in the study.

Funding

This work was supported by a grant from Research Institute for Islamic and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran.

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