

**A Systematic Review of the effect and safety  
of Ginger in the treatment of pregnancy-  
associated nausea and vomiting**

by  
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## ABSTRACT

**Background:** Nausea and vomiting during pregnancy (NVP) is a common medical condition. Due to possible harmful side-effects that conventional medicine may pose to the fetus, many mothers choose not to use it, and are left helpless against NVP. There is a need for alternative treatment to relieve NVP symptoms.

**Objectives:** This systematic review (SR) investigated current evidence regarding ginger for the treatment of NVP. The primary objective was to assess the effectiveness of ginger in treating NVP. The secondary objective was to assess the safety of ginger during pregnancy, by identifying adverse events or side-effects.

**Search strategy:** Electronic search of bibliographic databases (1966-February 2011).

**Selection criteria:** Randomized controlled trials (RCTs) of the efficacy of ginger by any route, as treatment for NVP in pregnant women regardless of their age or stage of pregnancy.

**Data collection and analysis:** The principal investigator and independent reviewer individually identified relevant studies, extracted data and assessed trial quality. Data analysis was performed using the RevMan5 software. Differences at the level of  $p < 0.05$  were considered to be statistically significant.

**Results:** Eleven RCTs involving 1176 pregnant women were included. The quality of evidence was low, hence the high risk of bias and imprecision of results. Ginger significantly improved the symptoms of nausea when compared to placebo, when comparing the results of this SR to past SRs, and taking into account a meta-analysis performed on two relatively large included studies (mean difference (MD) 1.20, 95% confidence interval (CI) 0.56-1.84,  $p = 0.0002$ ,  $I^2 = 0\%$ ). However, another meta-analysis on two smaller studies indicated no significant improvement in nausea. Ginger did not significantly improve nausea when compared to vitamin B6 (MD 0.34, 95% CI -1.52-2.20,  $p = 0.7$ ,  $I^2 = 91\%$ ). Similarly, ginger did not significantly reduce the number of vomiting episodes during NVP, when compared to placebo, although there was a trend

towards improvement (MD 0.72, 95% CI -0.03-1.46,  $p=0.06$ ,  $I^2=71\%$ ). Subgroup analyses performed seemed to favor the lower daily dosage of <1500mg ginger to possibly be more effective for the relief of nausea. Ginger did not pose a significant risk for spontaneous abortion when compared to placebo (RR 3.14, 95% CI 0.65-15.11,  $p=0.15$ ;  $I^2=0\%$ ), or to vitamin B6 (RR 0.49, 95% CI 0.17-1.42,  $p=0.19$ ,  $I^2=40\%$ ). Similarly, ginger did not pose a significant risk for the side effects of heartburn or drowsiness when compared to placebo or vitamin B6. When compared to dimenhydrinate, ginger posed a smaller risk for drowsiness (RR 0.08, 95% CI 0.03-0.18) and no increased risk for heartburn.

**Conclusions:** This review suggests *potential* benefits of ginger in reducing nausea symptoms in pregnancy (bearing in mind the limited number of studies, variable outcome reporting and quality of evidence). Ginger did not have a significant impact on vomiting episodes, nor pose a risk for side effects or adverse events during pregnancy. Based on evidence from this SR, ginger could be considered a harmless and *possibly* effective alternative option for women suffering from the symptoms of NVP. Large RCTs are necessary to confirm the possible benefit of ginger as treatment for NVP.

## OPSOMMING

**Agtergrond:** Naarheid en vomering tydens swangerskap (NVS) is 'n algemene mediese toestand. As gevolg van moontlike skadelike newe-effekte wat konvensionele medikasie kan veroorsaak vir die fetus, vermy baie moeders dit en word hulpeloos gelaat teen NVS. Dus is daar behoefte aan alternatiewe behandeling vir NVS.

**Doelwitte:** Hierdie sistematiese literatuuroorsig (SO) het huidige literatuur ondersoek wat verband hou met gemmer vir behandeling van NVS. Die primêre doelwit was om effektiwiteit van gemmer as behandeling vir NVS te assesseer. Die sekondêre doelwit was om veiligheid van gemmer tydens swangerskap te assesseer, deur ongunstige gebeure en newe-effekte te identifiseer.

**Soektogstrategie:** Elektroniese soektog van bibliografiese databasisse (1966-Februarie 2011).

**Seleksiekriteria:** Verewekansigde gekontroleerde proewe (RCTs) van gemmer deur enige roete as behandeling van NVS, in swanger vroue ongeag ouderdom of stadium van swangerskap.

**Dataversameling en -analise:** Die hoof navorser en 'n onafhanklike hersiener het individueel relevante studies geïdentifiseer, data ekstraksie onderneem en studie-kwaliteit geassesseer. Data-analise is uitgevoer deur die RevMan5 sagteware te gebruik. Verskille by die vlak van  $p < 0.05$  was beskou as statisties betekenisvol.

**Hoof resultate:** Elf RCTs waarby 1176 swanger vroue betrokke was, is ingesluit. Die studie-kwaliteit was swak, dus die hoë risiko vir sydigheid en onakkuraatheid van resultate. Gemmer het beduidend die simptome van naarheid verbeter in vergelyking met plasebo, wanneer die resultate van hierdie SO met vorige SO's vergelyk word, en die meta-analise in ag geneem word wat op twee relatiewe groot ingeslote studies uitgevoer is (gemiddelde verskil (MD) 1.20, 95% vertrouens interval (VI) 0.56-1.84,  $p=0.0002, I^2=0\%$ ). Kontrasterend, het 'n ander meta-analise van twee kleiner studies geen beduidende verbetering in naarheid aangedui nie. Gemmer het nie beduidend naarheid

verbeter wanneer dit met vitamien B6 vergelyk word nie (MD 0.34, 95% VI -1.52-2.20,  $p=0.7$ ,  $I^2=91\%$ ). Soortgelyk, het gemmer nie die aantal vomerings-episodes verminder, in vergelyking met plasebo nie, maar daar was wel 'n neiging na verbetering (MD 0.72, 95% VI -0.03-1.46,  $p=0.06$ ,  $I^2=71\%$ ). Die subgroup-analise blyk ten gunste te wees van die laer daaglikse dosis van <1500mg gemmer om meer effektief te wees vir die behandeling van naarheid.

Gemmer het nie 'n beduidende risiko ingehou vir spontane aborsie, wanneer dit vergelyk word met plasebo (relatiewe risiko (RR) 3.14, 95% VI 0.65-15.11,  $p=0.15$ ;  $I^2=0\%$ ), of vitamien B6 nie (RR 0.49, 95% VI 0.17-1.42,  $p=0.19$ ;  $I^2=40\%$ ). Soortgelyk, het gemmer nie 'n beduidende risiko ingehou vir nuwe-effekte van sooibrand of duiseligheid, wanneer dit vergelyk word met plasebo of vitamien B6 nie. Wanneer dit vergelyk word met dimenhidrinaat, het gemmer 'n kleiner risiko ingehou vir duiseligheid (RR 0.08, 95% VI 0.03-0.18) en geen verhoogde risiko vir sooibrand nie.

**Gevolgtrekkings:** Hierdie SO dui 'n *potensiële* voordeel van gemmer aan in vermindering van naarheid tydens swangerskap (inagnemend van die klein hoeveelheid studies, wisselende uitkomste-rapportering en studie-kwaliteit). Gemmer het nie 'n beduidende impak gehad op vomerings-episodes nie, en ook nie 'n risiko ingehou vir nuwe-effekte of ongunstige gebeure tydens swangerskap nie. Volgens bewyse uit hierdie SO, kan gemmer beskou word as 'n skadelose en *moontlike* effektiewe alternatiewe opsie vir vroue wat lei aan NVP. Groot skaalse RCTs is nodig om die moontlike voordeel van gemmer as behandeling vir NVS te bevestig.

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**Language care of this thesis was undertaken by: Erica Bethke**

## **CONTRIBUTIONS BY PRINCIPAL RESEARCHER AND FELLOW RESEARCHERS**

The principal researcher (Estelle Viljoen) developed the idea and the protocol. The principal researcher planned the systematic review, undertook data collection / extraction (with the assistance of an independent reviewer, Mrs Lorette Venter), captured the data for analyses, analysed the data with the assistance of a statistician trained in systematic reviews (Mr. Alfred Musekiwa), interpreted the data and drafted the thesis. Mrs Janicke Visser and Mrs Nelene Koen (Supervisors) provided input at all stages and revised the protocol and thesis.

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## LIST OF DEFINITIONS

**Bias:**<sup>1</sup> Bias is a systematic error, or deviation from the truth. Bias can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude – some are small and trivial compared to the observed effect, and some are substantial, so that an apparent finding may be entirely due to bias. Bias should not be confused with imprecision. Bias is a systematic error which will lead to the wrong answer on average when the same study is multiplied several times. Imprecision is a random error, meaning that multiple replications of the same study will produce different effect estimates due to sample variation, even if they would give the right answer on average.

**Blinding:**<sup>1</sup> Blinding (or masking) refers to the process by which study participants, health providers and investigators, including people assessing outcomes, are kept unaware of intervention allocation after inclusion of participants into the study. Blinding of study participants and personnel (double-blind) may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects the outcome. Effective blinding can also ensure that the compared groups receive the same amount of attention, ancillary treatment and diagnostic interventions.

**Chi-squared (Chi<sup>2</sup>) test:**<sup>1</sup> This is a formal test of heterogeneity and is included in the forest plots in Cochrane reviews. It assesses whether observed differences in results are comparable with chance alone. A low P-value (or a large Chi-squared statistic relative to its degree of freedom) provides evidence of the heterogeneity of the intervention effects (variation in effect estimates beyond chance). Care must be taken in the interpretation of the Chi<sup>2</sup> test, since it has an insignificant effect on the situation of meta-analyses when studies have a small sample size or are few in number. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result should not be taken as evidence of no heterogeneity. This is why a p-value of 0.10, rather than the conventional 0.05 is sometimes used to determine the statistical significance.

**Concealment of allocation:**<sup>1</sup> Allocation concealment seeks to prevent selection bias in intervention assignment by protecting the allocation sequence before and until assignment, and can always be successfully implemented regardless of the study topic.

**Confidence interval (CI):**<sup>1</sup> Study results are reported with a point estimate together with an associated confidence interval (CI). For example: “the odds ratio was 0.75 with a 95% confidence interval of 0.70 to 0.80. The CI describes the uncertainty inherent in this estimate and describes a range of values within which we can be reasonably sure that the true effect actually lies. If the CI is relatively narrow, e.g. 0.70 to 0.80, the effect size is known precisely. If the CI is wider, e.g. 0.60 to 0.90, the uncertainty is greater, although there may still be enough precision to make decisions about the utility of the intervention. If a CI is very wide, e.g. 0.50 to 1.10, it indicates that we have very little knowledge about the effect and that further information is needed.

A 95% CI is often interpreted as indicating a range within which we can be 95% certain that the true effect lies. This statement is a loose interpretation, but useful. The stricter interpretation of a CI is based on the hypothetical notion of considering the results that would be obtained if the same study were to be repeated many times. If a study were repeated infinitely, and on each occasion a 95% CI calculated, then 95% of these intervals would contain the true effect.

**Confounding:**<sup>1</sup> A confounder is a factor that can significantly affect validity and lead to incorrect conclusions being drawn. Two characteristics are confounded if their influences on the intervention effect can not be disentangled. For example, if a study aims to measure the effect of a drug on an illness, but the illness can also be influenced by dietary adjustments, then the dietary adjustments made by the participants could act as a confounding factor, since we cannot tell if the effects were due to the intervention or due to the dietary adjustments.

**Continuous data:**<sup>1</sup> Data which reflect each individual’s outcome as a measurement of a numerical quantity that can take any value in a specified range, e.g. weight, height.

**Dichotomous data:**<sup>1</sup> (Binary data) Data of which each individual's outcome is one of only two possible categorical responses (e.g. yes or no, present or absent).

**Fixed effect meta-analysis:** see meta-analysis

**Forest plot:**<sup>1</sup> A forest plot displays estimates and confidence intervals for both individual studies and meta-analyses. Each study is represented by a block at the point estimate of intervention effect with a horizontal line extending at each side of the block. The area of the block indicates the weight assigned to that study in the meta-analysis, while the horizontal line depicts the confidence interval (usually with a 95% level of confidence). The size of the block draws the eye towards the studies with larger weight (usually those with narrower confidence intervals) which dominate the calculation of the pooled result.

**Funnel plot:**<sup>1</sup> A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. The effect estimate is plotted on the horizontal plane, and the measure of the study size on the vertical axis. The name 'funnel plot' arises from the fact that the precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, the plot should approximately resemble a symmetrical (inverted) funnel.

**Heterogeneity:**<sup>1</sup> Any kind of variability or differences among studies included in a systematic review may be termed heterogeneity. Different types of heterogeneity exist. Variability in the participants, interventions and outcomes of studies is known as clinical diversity or clinical heterogeneity. Variability in study design and risk of bias is known as methodological diversity or heterogeneity. Variability in the intervention effects being measured in the different studies is known as statistical heterogeneity, and this is a consequence of clinical or methodological diversity, or both, among studies. Statistical heterogeneity occurs when the observed intervention effects differ more from each other than one would expect from random error (chance) alone.

**Human chorionic gonadotrophin (hCG):**<sup>2</sup> A hormone that is produced by the placenta during pregnancy. Large amounts are excreted in the urine, and this is used as the basis for most pregnancy tests.

**Hyperemesis gravidarum (HG):**<sup>2</sup> Severe vomiting during pregnancy. It starts in early pregnancy and may continue to produce marked dehydration and subsequent liver damage. Rarely, the condition worsens in spite of active treatment; under such circumstances it may be necessary to terminate the pregnancy.

**Incomplete outcome data:**<sup>1</sup> Any data that are missing from the study, can lead to risk of bias. When an individual participant's outcome data is not available, it is referred to as missing. Missing outcome data can be due to attrition (participants lost to follow-up, treatment withdrawals or trial group changes) or exclusions from the analysis. All the participants included in the study analysis should be exactly those who were randomized into the trial. If outcome data are missing in both intervention groups, but reasons for these are both reported and balanced across groups, then important bias would not be expected.

**Intention-to-treat analysis (ITT):**<sup>1</sup> Intention-to-treat (ITT) analysis aims to include all participants randomized into a trial, irrespective of what happened subsequently. ITT analyses are generally preferred as they are unbiased, and also because they address a more pragmatic and clinically relevant question. The principles of ITT are: i) Keep the participants in the intervention groups to which they were randomized, regardless of the intervention they actually received; ii) Measure outcome data on all participants; iii) Include all randomized participants in the analyses. There is no consensus about whether all three principles should be applied, and it is often difficult to apply these principles. Thus, especially in studies with an extended follow-up period and participants get lost to follow-up, it is difficult to perform a true ITT analysis without making imputations.

**Likert-type scale:**<sup>3</sup> (also referred to as a Likert scale) A psychometric scale commonly used in questionnaires which is a widely used scale in survey research. The term is often interchanged with 'rating scale' even though the two are not synonymous. When

responding to a Likert questionnaire item, respondents specify their level of agreement or disagreement on a symmetric agree-disagree scale for a series of statements. Thus the scale captures the intensity of their feelings. For example, a five-point Likert item could include “Strongly disagree / disagree / neither disagree or agree / agree / strongly agree”. The scale is named after its inventor, psychologists Rensis Likert.

**Mean difference (MD):**<sup>1</sup> The mean difference (more correctly ‘difference in means’) is a standard statistic which measures the absolute difference between the mean value in two groups in a clinical trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the control. It can be used as a summary statistic in meta-analysis when outcome measurements in all studies are made on the same scale.

**Meta-analysis:**<sup>1</sup> Meta-analysis is the use of statistical methods to summarize or combine the results of two or more independent studies. It can be used to combine the numerical results of all or some of the studies included in a systematic review. This yields an overall statistic, together with its confidence interval, that summarizes the effectiveness of the experimental intervention compared with the control intervention. Meta-analysis focuses on pair-wise comparisons of interventions, such as an experimental intervention versus a control intervention, or the comparison of two experimental interventions. The outcomes of two groups treated differently are known as the effect, the treatment effect or the intervention effect. The combination of intervention effects estimates across studies may incorporate an assumption that the studies are not all estimating the same intervention effect, but rather estimate intervention effects that follow a distribution across studies. This is then a **random-effects meta-analysis**. Alternatively, if it is assumed that each study is estimating exactly the same quantity, a **fixed-effect meta-analysis** is performed.

**Nausea and Vomiting of Pregnancy (NVP):**<sup>2</sup> A condition affecting many pregnant women, typically referred to as morning sickness, although it can occur any time of day or night. Nausea, vomiting, retching or a combination of these symptoms can occur.



**Odds ratio (OR):**<sup>1</sup> The ratio of probability that a particular event will occur to the probability that it will not occur, can be any number between zero and infinity. The value of 1 indicates that the estimated effects are the same for both interventions. Neither the OR nor the risk ratio for a study can be calculated if there are no events in the control group, nor if everybody in the intervention group experiences an event. In health care it is the ratio of number of people with the event to the number without. It is commonly expressed as a ratio of two integers. For example, an OR of 0.01 is often written as 1:100; an OR of 0.33 as 1:3; and OR of 3 as 3:1. OR describes the multiplication of the odds of the outcome occurring with the use of the intervention. OR is difficult to interpret, and it is simplest to first convert it into a risk ratio, and then interpret the risk ratio in the context of a typical common group risk.

**Point estimate:**<sup>1</sup> The results for both individual studies and meta-analyses are reported with a point estimate together with an associated confidence interval. The point estimate is the best guess of the magnitude and direction of the experimental intervention's effect compared to the control intervention.

**P-value:**<sup>1</sup> A p value is the probability of obtaining the observed effect (or larger) under a 'null hypothesis'. A 'null hypothesis' is the assumption of 'no effect of the intervention', or 'no differences in the effect of intervention between studies' (no heterogeneity). Thus, a p value that is very small indicates that the observed effect is very unlikely to be due to chance, and therefore provides evidence against the null hypothesis. P values less than 0.05 (5%), are often reported as 'statistically significant' – meaning there is a 5% chance of the observed effect being due to chance, and this being small enough to reject the null hypothesis. To avoid misinterpretations, review authors should always examine the effect estimate and its 95% confidence interval, together with the p value.

**Random effects meta-analysis:** see meta-analysis

**Randomization:**<sup>1</sup> Randomization means ordering subjects in the sample group in such a way that each subject would have the same chance of being selected for each intervention and that this allocation should be unpredictable. Randomization ensures that no biases,

conscious or unconscious, on the part of the researchers, influence the choice of subjects.<sup>4,5</sup>

**Randomized controlled trial (RCT):**<sup>1</sup> A clinical trial in which a test and control treatment are measured against each other by enrolment and follow-up of the test- and control-treated groups of individuals or other units. The individuals (or other units) followed in the trial are assigned prospectively to one of two (or more) alternate forms of health care, using random allocation or some quasi-random method allocation. If the authors state explicitly that the groups compared in the trial were established by random allocation, then the trial is classified as an RCT. If it is not clearly stated, but randomization cannot be ruled out, then the report is classified as a CCT (controlled clinical trial). The classification as RCT or CCT is based solely on what the author has written, not the reader's interpretation.

**Randomized cross-over trial:**<sup>1</sup> In a cross-over trial, all participants receive all interventions in sequence. They are randomized to an ordering of interventions, and each participant acts as their own control. The main concerns over risk of bias in cross-over trials are (i) whether the cross-over design is suitable; (ii) whether there is a carry-over effect; (iii) whether only first-period data is available; (iv) incorrect analysis; and (v) comparability of results with parallel-group trials.

**Review Manager version 5 (RevMan5):**<sup>1</sup> The Cochrane Information Management System (IMS) consists of two main components, the Cochrane review writing software, Review Manager (RevMan5), which can perform a variety of meta-analyses, and a central server for managing documents and contact details, Archie. RevMan5 is freely available for authors preparing a Cochrane review, and used by academic institutions.

**Risk Ratio (RR):**<sup>1</sup> Risk describes the probability with which a healthcare outcome (usually an adverse event) will occur. In research it is commonly expressed as a decimal number between 1 and 12, although it is occasionally converted into a percentage. It is simple to grasp the relationship between risk and the likely occurrence of events: in a sample of 100 people the number of events observed will on average be the risk

multiplied by 100. For example, when the risk is 0.1, every 10 people out of every hundred will have the event; when the risk is 0.5, about 50 people out of every hundred will have the event. RR describes the multiplication of the risk that occurs with the use of the experimental intervention. For example, a RR of 3 for a treatment implies that events with the treatment are three times more likely to occur, than events without the treatment.

**Side-effect:**<sup>2</sup> An unwanted effect produced by a drug in addition to its desired therapeutic effects.

**Selective outcome reporting:**<sup>1</sup> The selection of a subset of the original variables recorded, on the basis of the results, for inclusion in publication of trials. The particular concern is that statistically non-significant results might be selectively withheld from publication. The possibility of within-study selective outcome reporting can be examined for each study included in a systematic review, to detect risk of bias.

**Sensitivity analysis:**<sup>1</sup> A sensitivity analysis is a repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear. For example, if the eligibility of some studies in a meta-analysis is dubious because they do not contain full details, then a sensitivity analysis may involve undertaking the meta-analysis twice: first, including all studies, and second, including only those that are definitely known to be eligible.

There are many decision nodes in the systematic review process which can generate a need for a sensitivity analysis. Examples include: searching for studies, eligibility criteria, what data should be analyzed and analyses methods. Some sensitivity analyses can be pre-specified in the protocol, but often issues suitable for sensitivity analysis are only identified during the review process. When sensitivity analyses show that the overall result and conclusions are not affected by the different decisions that could be made during the review process, the results of the review can be regarded with a high degree of certainty.

**Sequence generation:**<sup>1</sup> This principle addresses the allocation process in a RCT. The starting point for an unbiased intervention study is the use of a mechanism that ensures that the same kinds of participants receive each intervention. Several interrelated processes need to be considered. Firstly an allocation sequence must be used that, if perfectly implemented, would balance prognostic factors, on average, evenly across intervention groups. Secondly, the most important among the practical aspects of the allocation sequence is the use of mechanisms to prevent foreknowledge of the next assignment.

**Standardized mean difference (SMD):**<sup>1</sup> This is a summary statistic in meta-analyses when the studies all assess the same outcome, but they measure it in a variety of ways, using different scales. In this circumstance it is necessary to standardize the results of the studies into a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. (In reality the intervention effect is a difference in means and not a mean in differences).  $SMD = [\text{difference between mean outcome in groups}] \text{ divided by } [\text{standard deviation of outcomes among participants}]$ . Thus, studies for which the difference in means is in the same proportion as the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements.

**Subgroup analysis:**<sup>1</sup> Subgroup analyses involve splitting all the participant data into subgroups, often so as to make comparisons between them. The aim is to investigate whether an intervention works differently in different subgroups. Subgroup analyses may be done for subsets of participants (e.g. males or females), or subsets of studies (e.g. different geographical locations). Subgroup analyses may be done as a means of investigating heterogeneous results, or to answer specific questions about particular patient groups, types of interventions or types of studies. When there are only two subgroups, the overlap of the CIs of the summary estimates in the two groups can be considered. Non-overlap of the CIs indicates statistical significance, but the CIs can overlap to a small degree and the difference may still be statistically significant.

**Systematic Review (SR):**<sup>1</sup> A SR attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view of minimizing bias, thus producing more reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a SR are: (i) a clearly stated set of objectives with pre-defined eligibility criteria for studies; (ii) an explicit, reproducible methodology; (iii) a systematic search that attempts to identify all studies that would meet the eligibility criteria; (iv) an assessment of the validity of the findings of the included studies, for example, through the assessment of risk of bias; (v) a systematic presentation and synthesis of the characteristics and findings of the included studies. Many systematic reviews contain meta-analyses (see meta-analysis).

**Visual analogue scale (VAS):**<sup>3</sup> A psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item the respondents specify their level of agreement to a statement by indicating a position along a continuous line between two endpoints. This continuous (or ‘analogue’) aspect of the scale differentiates it from discrete scales such as the Likert scale.

## LIST OF ABBREVIATIONS

<b>CI</b>	Confidence interval
<b>hcG</b>	Human chorionic gonadotropin
<b>HG</b>	Hyperemesis gravidarum
<b>ITT</b>	Intention-to-treat analysis
<b>MD</b>	Mean difference
<b>NVP</b>	Nausea and vomiting of Pregnancy
<b>OR</b>	Odds ratio
<b>RCT</b>	Randomized controlled trial
<b>RevMan5</b>	Review Manager version 5
<b>RR</b>	Risk ratio
<b>SMD</b>	Standardized mean difference
<b>SR</b>	Systematic review
<b>VAS</b>	Visual analogue scale

## **CHAPTER 1: BACKGROUND AND MOTIVATION FOR THE STUDY**

## **1.1 INTRODUCTION**

Nausea and vomiting are very common complaints during the early weeks of pregnancy. Due to the possible harmful side effects that conventional medicine may pose to the unborn fetus, many mothers choose not to use them, and are left helpless in the face of this burden. Pregnancy is a time when a woman should be in optimal health, and the feeling of nausea or even worse, actual vomiting, may lead to physical and psychological morbidity and complications during pregnancy.<sup>6</sup> These problems clearly call for an alternative treatment for nausea and vomiting during pregnancy.

## **1.2 DESCRIPTION OF THE CONDITION**

### **1.2.1 Nausea and Vomiting**

Nausea can be described as the feeling of being about to vomit.<sup>2</sup> This feeling often occurs in morning sickness during pregnancy, motion sickness or seasickness. Vomiting (emesis) occurs when the contents of the stomach are ejected through the mouth, by a reflex reaction controlled by the brain. This reflex reaction can be triggered by chemicals or drugs, irritating substances in the stomach or intestine, or from balance-disturbances in the inner ear.<sup>1</sup> Retching is described as repeated, unavailing attempts to vomit.<sup>2</sup>

It is very important to identify the correct cause of the nausea and vomiting, in order to treat it effectively. There are many conditions that may cause or worsen nausea and vomiting. These include gastrointestinal causes (gastroenteritis, gastroparesis, hepatitis, pancreatitis, appendicitis, helicobacter pylori (H.pylori), intestinal obstruction, biliary tract disease); metabolic causes (diabetic ketoacidosis, porphyria, Addison's disease, hyper- or hypothyroidism); neurological disorders (vestibular lesions, migraine headaches, tumours of the central nervous system); genitourinary tract (pyelonephritis, uremia, ovarian torsion, kidney stones, degenerating uterine leiomyoma); pregnancy related conditions (acute fatty liver of pregnancy, preeclampsia); drug toxicity or intolerance, infections, psychological and psychiatric disorders. All these are differential diagnoses or causes for nausea and vomiting other than pregnancy.<sup>6,7</sup>



### **1.2.2 Nausea and Vomiting of Pregnancy (NVP)**

NVP is commonly referred to as morning sickness (although it can occur at any time of the day or night), and affects about 80-90% of pregnant women in varying degrees.<sup>6,8</sup> Most of these women will experience both nausea and vomiting, and some only nausea without vomiting or retching, but vomiting alone is rare.<sup>8</sup> Symptoms usually appear at 4-9 weeks of gestation, reaching a peak at 7-12 weeks, and subsiding by week 16. About 15-30% of pregnant women's symptoms will persist beyond 20 weeks, or even up to the time of delivery.<sup>6,8</sup> NVP symptoms will appear before 10 weeks of gestation. When symptoms start later than this, it is probably due to another cause, as listed above, and it is very important to correctly diagnose and treat the cause.<sup>6</sup>

Hyperemesis gravidarum (HG) is severe and persistent vomiting during pregnancy, which can lead to dehydration, electrolyte disturbances and liver damage, possible fetal damage and in extreme cases, even to the death of the mother.<sup>2,6,9,10</sup> It is usually characterized by protracted vomiting, leading to malnutrition and a weight loss of more than 5% of the pre-pregnancy weight. Women with HG usually need to be hospitalized.<sup>6</sup> HG occurs in approximately 2% of pregnancies.<sup>6,8</sup>

### **1.2.3 Causes of NVP**

The exact cause of NVP remains unclear, and is probably multifactorial. Theories include the rapid increase in hormones such as estrogen and human chorionic gonadotropin (hCG),<sup>7</sup> or *H. pylori* infection, and psychological and genetic predisposition.<sup>7,8</sup>

During pregnancy many women report that they experience a heightened sense of smell and taste, and often complain of a metallic taste in the mouth. These can cause or aggravate NVP symptoms, and lead to aversions to certain types of food, especially strong tasting vegetables, meats and poultry. One theory is that this is a protective mechanism during pregnancy, to cause the mother to avoid potentially toxic or bacteria-containing foods that could harm her or the fetus.<sup>6</sup>

Generally it has been observed that women who suffer from uncomplicated NVP (thus, not HG) have better pregnancy outcomes than women who don't experience any NVP.<sup>6-8,11</sup> A meta-analysis conducted by Weigel and Weigel<sup>11</sup> indicates a strong significant association of NVP with a decreased risk of miscarriage, and no consistent associations with peri-natal mortality, especially in the first 20 weeks gestation.

One theory is that NVP may be caused by rapid hCG increase in the blood, possibly caused by a more robust placenta secreting high levels of hCG hormones,<sup>6</sup> and the more robust placenta then being more capable of completing a full term pregnancy. The improved pregnancy outcomes observed include lower incidences of miscarriages, preterm deliveries and stillbirths, fewer cases of low birth weight, growth retardation and mortality.<sup>7</sup>

Many proposals or theories have been suggested for identifying risk factors for experiencing NVP. These include younger maternal age, increased placental mass, genetic predisposition, previous HG, multipara, fetal gender, and *H. pylori* infection.<sup>6</sup> It also appears to be more common for urban women to experience NVP than rural women, and more housewives tend to experience it, than professional "white collar" women.<sup>7</sup> Results of studies are inconclusive though, and these remain only theories of risk factors for NVP.

Up to 85% of pregnant women will experience at least one symptom associated with gastro-intestinal reflux disorders, and usually more than one symptom occur simultaneously. These symptoms include heartburn, reflux, regurgitation, belching, flatulence, stomach bloating, indigestion, and a sensation of feeling a lump in the back of the throat. It has been shown that if women experience these together with NVP, they are more likely to classify their NVP as severe. *Helicobacter pylori* infection might aggravate any gastrointestinal condition, thus it is important that all patients with these above-mentioned symptoms and NVP should be tested for *H. pylori*.<sup>6</sup>

#### 1.2.4 Negative Effects of NVP and HG

Severe NVP and HG can lead to maternal malnourishment and weight loss, leading to negative fetal outcomes including low birth weight and preterm birth.<sup>6</sup> Maternal complications include acute renal failure, esophageal rupture and coagulopathy. One rare maternal complication of HG is Wernicke's encephalopathy, caused by thiamine (vitamin B1) deficiency, which causes symptoms such as ophthalmoplegia, ataxia, and mental confusion. It can also lead to stupor, coma and even maternal death if not treated promptly.<sup>8</sup>

Negative maternal consequences of NVP can continue even post delivery, including longer recovery time from pregnancy and labour, postpartum gallbladder dysfunction, aversions to foods which were associated with episodes of nausea and vomiting, muscle pain, nausea continuing after delivery, and typical psychological symptoms of post traumatic stress disorder (PTSD).<sup>6</sup>

NVP, especially HG, can be emotionally traumatic. It has a negative impact on the woman's physical and mental health. Even without vomiting or retching, nausea alone may have a negative effect on the woman's health status, as it affects her day-to-day activities and feelings. Many women with NVP believe it negatively affects their relationship with their spouse, compromises their parenting ability and professional performance, and up to 55% feel depressed.<sup>6,8,12</sup> A survey done by Smith et al<sup>13</sup> found that women with NVP reported low energy levels, a decrease in physical functioning and social functioning.

In extreme cases it may even lead to elective abortions as they feel they cannot continue the pregnancy under such unbearable circumstances,<sup>6,12</sup> and in one study approximately half of the respondents with NVP reported they were less likely to have another child after their experience with severe NVP.<sup>14</sup>

A study conducted to investigate the factors that determine medical treatment of NVP, concluded the following: women with NVP were more likely to obtain a prescription for an anti-emetic drug during the first prenatal visit if they worked outside the house, had

severe symptoms, or if it was not their first pregnancy. This study also showed that many health practitioners do not address the subject of NVP at the first prenatal visit during the early weeks of pregnancy, leaving the woman to her own devices.<sup>12</sup>

Aursenault et al<sup>15</sup> mentioned that NVP can be very costly to the patient and / or the medical scheme or health system of the relevant country. Doctor's visits, hospitalizations, time lost from work and the expenses of medicines or alternative therapies may all be reduced if NVP is treated early.

The negative effects of NVP described above, clearly show the importance of managing and treating NVP and HG as early as possible, and not considering NVP as merely an unpleasant part of pregnancy that has to be endured and suffered through.

## **1.2.5 Non-Pharmacological Treatment of NVP**

### **1.2.5.1 Lifestyle**

The following guidelines have been developed by the Motherisk NVP Helpline at Toronto's Hospital for Sick Children. This program has been counselling women with NVP for more than 16 years, and their guidelines are well researched and comprehensive.<sup>6</sup> Table 1 describes this program's recommendations.

Other recommendations to relieve NVP include not lying down directly after a meal, shortening food preparation time, eating foods that are appealing, eating in a comfortable place, avoiding warm odorous places, wearing comfortable clothing, drinking herbal tea with honey, or peppermint tea, sucking on a peppermint candy, and brushing teeth after a meal.<sup>6</sup> Sour liquids like lemonade are often better tolerated than water. Adequate amounts of sleep and rest are also needed, as fatigue may worsen NVP.<sup>6</sup> Emotional support from family, friends and medical staff is needed, as some women with NVP may become depressed as mentioned previously.<sup>6,7</sup>

**Table 1: The Motherisk NVP Helpline's Guidelines for Treating NVP.<sup>6</sup>**

- i. Maintain adequate hydration and electrolyte levels by drinking at least 2 liters of water per day.
- ii. Avoid an empty stomach, by having small frequent meals every 1-2 hours, consisting of bland foods.
- iii. Prevent a full stomach by avoiding large meals, not mixing liquids and solids, and avoid very fatty or oily food.
- iv. Avoid strong tasting, odorous foods (i.e. spicy, metallic tastes)
- v. Consume ice chips, popsicles and very cold beverages to help reduce metallic taste.
- vi. Snack on nuts and high protein foods between meals
- vii. Discontinue iron-containing prenatal multivitamins in early pregnancy and switch to children's chewable tablets and folic acid instead. Resume iron-containing prenatal vitamins after 12 weeks of gestation, when iron is most needed by mother and baby. Pregnant women with past or current anemia should not discontinue their prenatal vitamins but rather take them in divided doses
- viii. Eat simple dry and salty carbohydrates (i.e. crackers, toast, and biscuits) prior to getting out of bed in the morning.

### **1.2.5.2 Acupressure**

Acupressure is a complementary medicine technique often used in Chinese medicine. It is closely related to acupuncture, but instead of using dry needles, the pressure points in the body are directly stimulated with a finger, palm or electrical device. The most common acupressure location is the pericardium 6 or Neiguan point, located three fingerbreadths above the wrist, on the inside of the forearm. Applying direct pressure to the point with a finger, palm, or wearing a wrist band (i.e. "Sea Band", "ReliefBand") has

been shown to relieve nausea and vomiting symptoms.<sup>16</sup> Articles discussing this topic suggest that study results are inconclusive at this stage.<sup>6,7</sup> Despite a lack of evidence of efficacy, acupressure will not do harm and is not invasive, so it is a safe and easy option for pregnant women trying to manage their NVP symptoms.<sup>6,7</sup>

### **1.2.5.3 Ginger**

Ginger is currently considered as an effective non-pharmacological treatment of NVP.<sup>5,6,14</sup> Because ginger is the topic for this Review, it will not be discussed here, but in the paragraph 1.3 “Description of the intervention” on page 11.

### **1.2.6 Pharmacological Treatment of NVP**

During pregnancy many physiological changes occur, including gastro-intestinal mobility, plasma volume and glomerular filtration.<sup>17</sup> These factors all influence the distribution, absorption and excretion of drugs and due to this reason, not all drugs are safe during pregnancy. Many drugs cross the placenta by simple diffusion and can affect the fetus directly.<sup>17</sup> Several factors such as molecular size, lipid solubility and the protein binding ability of a specific drug can affect the rate of diffusion, and some drugs are actively metabolized by the placenta. These factors all determine the level of toxicity to the fetus.<sup>17</sup> Research on adverse drug effects during pregnancy is difficult due to the fact that it can be potentially very dangerous to the mother and fetus and would in effect be unethical to do experimental trials in this regard. The occurrence of adverse effects has thus been reported primarily by means of case reports from practitioners, epidemiological studies, both retrospective and prospective, and animal studies.<sup>17</sup> Evidence from these sources should be interpreted with care however, because of the inherent limitations of each. In addition, single case reports can be influenced by many other factors as well. Epidemiological studies often have difficulty with accurate data collection and a statistical correlation does not necessarily prove an etiological relationship. Animal studies are useful, but should be extrapolated to the human race with great care.<sup>17</sup>

### **1.2.6.1 Pyridoxine / Vitamin B6**

Vitamin B6 is a water soluble vitamin that functions as a coenzyme for amino acid, lipid and carbohydrate metabolism. It has been extensively researched for its antiemetic properties, and doses of 30-75 mg per day are effective for relieving NVP, according to two RCTs done on this subject.<sup>18,19</sup> The vitamin B6 dose can be adjusted according to need, using maternal weight and severity of NVP as guideline, and doses of up to 500mg per day can be safely used. The current recommendation however, is a maximum dose of up to 200mg per day, as suggested by the 2007 Motherisk NVP algorithm.<sup>6,7</sup>

### **1.2.6.2 Doxylamine / Pyridoxine combination**

A medication called Bendectin, combining doxylamine (antihistamine) and pyridoxine, was available from 1958 to 1983 and often prescribed for women with NVP. In 1983 the manufacturer voluntarily discontinued the product due to litigation and allegations of teratogenic effects (later proven to be false). After this event, a meta-analysis of 30 years of Bendectin data and birth defects has been conducted, proving the safety of the combination of doxylamine and pyridoxine.<sup>20</sup> Although Bendectin is no longer on the market, many compounding pharmacies will prepare the combination on request. A single doxylamine tablet (Unisom) can also be taken alone or in combination with pyridoxine. Pyridoxine-doxylamine is the only medication the U.S. Food and Drug Administration (FDA) has ever approved specifically for the treatment of NVP.<sup>6,7,14</sup>

### **1.2.6.3 Anti-emetics**

Phenothiazines have been reported to reduce NVP compared with a placebo, without increased risk to mother or fetus.<sup>6,15</sup> Cyclizine (e.g. Valoid) and Buclizine (e.g. Vomifene) are often prescribed for NVP in South Africa.<sup>21</sup>

### **1.2.6.4 Antihistamines**

H1 receptor antagonists (antihistamines) such as dimenhydrinate, and diphenhydramine, have been reported to be effective as treatment for NVP. Some types of antihistamines are

available in suppository formulation, and this makes them convenient for severe cases of nausea and vomiting, where the swallowing of a capsule might be difficult.<sup>6</sup>

#### **1.2.6.5 Corticosteroids**

Methylprednisolone (Medrol)<sup>21</sup> may be an effective therapy for HG. Corticosteroid therapy is generally considered safe during pregnancy.<sup>7</sup> However, a study published by the Motherisk program, has demonstrated a marginally increased risk for oral cleft incidences in infants exposed to corticosteroids during the first trimester of pregnancy.<sup>6</sup> This treatment should be reserved for when other treatments are ineffective, and only be administered after the 10th week of pregnancy.<sup>7,8,15</sup>

#### **1.2.6.6 Motility drugs**

Metoclopramide (e.g. Maxalon, Clopamon, Metalon, Perinorm) increases lower esophageal sphincter pressure and speeds up transit time through the stomach.<sup>6,21</sup>

#### **1.2.6.7 Acid reflux / Heartburn pharmacotherapy**

As described earlier, gastro-intestinal reflux disorders are common conditions during pregnancy, and can contribute to the severity of the pregnant woman's experience of NVP. With exacerbation of NVP symptoms due to heartburn and acid reflux, the use of acid-reducing agents such as H<sub>2</sub>-histamine blockers and proton pump inhibitors, will provide relief for many women.<sup>6</sup> Gaviscon is a popular antacid product among South African pregnant women.<sup>21</sup>

#### **1.2.6.8 Intravenous rehydration, enteral or parenteral nutrition**

When a woman suffering from NVP cannot keep any fluids down or she shows clinical signs of dehydration, despite the previously discussed treatments, she will require intravenous fluids. This is usually saline or lactated Ringer's solution, or some other dextrose-containing solution. It is very important to start supplementing thiamine soon, due to the theoretical risk of Wernicke's encephalopathy. When the woman continues to lose



weight and cannot keep food down, enteral tube feeding should be tried first, before total parenteral nutrition (TPN) is considered, as an absolute last resort.<sup>6,7</sup>

### 1.3 DESCRIPTION OF THE INTERVENTION

Ginger (*Zingiber Officinale Roscoe*) is a tropical plant with green and purple flowers and an aromatic underground stem, called a rhizome.<sup>10,22,23</sup>

The rhizome (also referred to as the roots) can be peeled and is used as a spice in cooking and baking, and has long been used in the traditional Chinese and Indian medicine, or so-called alternative or complementary medicine, with limited scientific evidence of its benefits or safety.<sup>10,22</sup> It can be used fresh, dried, powdered, as a tea, juice or oil. The oil can be taken orally or applied to the skin.

Raw ginger consists of approximately 9% lipids or glycolipids, and about 5-8% oleoresin (oily plant secretion). Ginger contains up to 3% essential oils, accounting for 20-25% of the oleoresin. Another 25% of the oleoresin consists of the pungent factors consisting mainly of gingerols. The main gingerol is [6]-gingerol, and this is more pungent than [8]- or [10]-gingerol. There are many other gingerols, including methylgingerol, gingerdiol, dehydrogingerdione, gingerdiones, diarylheptanoids, diterpenlactones and galanolactone.<sup>23</sup>

In the crude plant material of ginger, several other sulfonated compounds and shogasulfonic acids are found. These phenolic shogaols are much more pungent than gingerols, and are mainly found in the semi-dried ginger plant. Shogaols are rarely found in fresh ginger, as they are major degradation products of gingerols (gingerols are thermally labile, thus the shogaols will be released when the ginger is heated and dried). Zingerone is also a degradation product and this will cause the ginger product to smell bad as it ages.<sup>23</sup>

Gingerols are agonists of a capsaicin-activated receptor.<sup>23</sup> This means that gingerols can bind to this receptor and 'mimic' the effect of capsaicin. Capsaicin is the active and irritant component of chilli peppers.<sup>23</sup>

Both ginger and chilli peppers contain irritants (zingerone and capsaicin, respectively) that can cause sensations of warmth and burning. Repeated oral stimulation of zingerone can cause desensitization (in other words you get used to the taste), while repeated stimulation with capsaicin can cause either desensitization or sensitization (the burning feeling can get more and more intense).<sup>23</sup>

#### **1.4 PHARMACOLOGICAL PROPERTIES OF GINGER**

Ginger is an inexpensive and relatively safe natural remedy<sup>9</sup> with many reported benefits. The most common ailments currently being treated with ginger include nausea, vomiting, pregnancy-associated morning sickness, motion sickness and indigestion.<sup>22,25,26-28</sup> Many authors<sup>10,22,24,25,29</sup> also claim that ginger has antioxidant, anti-tumour and anti-inflammatory effects. A wide variety of disease conditions are being treated with ginger in Chinese and Ayurvedic medicine.<sup>24</sup> These include a variety of gastro-intestinal symptoms as mentioned above, also arthritis, rheumatism, cramps, dementia, fever, hypertension, infectious diseases, motion sickness,<sup>9</sup> asthma<sup>10</sup> and helminthiasis.<sup>24</sup> There is mixed scientific evidence for the use of ginger for nausea and vomiting associated with pregnancy.<sup>22</sup>

##### **1.4.1 *In-vitro* Effects of Ginger**

Chrubasik, Pittler and Roufogalis<sup>23</sup> conducted a comprehensive review of relevant literature to give an overview of the pharmacological and clinical effects of ginger. Their main findings on in-vitro experiments with ginger were that ginger can inhibit platelet aggregation, has anti-inflammatory effects, can protect against lipid peroxidation and tumour formation (it inhibited human leukemia cell viability), had antibacterial and anti-fungal properties, as well as destroying many species of worms.

#### **1.4.2 *In-vivo* Effects of Ginger on Animal Models**

Chrubasik et al<sup>23</sup> have reported that ginger has positive effects on the gastro-intestinal, cardiovascular and immune systems, as well as having central effects (may lead to motor un-coordination). Interestingly, these authors concluded that a combination of garlic and ginger is more beneficial for cardiovascular health, than the ginger alone.

Ginger is reported to be protective against tumour formation and lipid peroxidation.<sup>23</sup> It also has anti-pyretic, anti-inflammatory and analgesic effects, which may be useful in relieving musculoskeletal and osteo-arthritic pain.<sup>23</sup>

#### **1.5 POTENTIAL ADVERSE EFFECTS OF THE INTERVENTION**

Since 1994, The Food and Drug Administration (FDA) does not regulate herbal supplements strictly,<sup>30</sup> so these remedies can be bought over the counter without prescription and can differ in dosage and purity or strength.<sup>10,22,26,30</sup> Information is easily accessible to all on the internet, and consumers might be misled or ill-informed by quackery, and unknowingly overdose themselves with complementary or alternative medicine, such as ginger. The amounts ingested as spice in food is probably low enough to be safe, but when it is taken in supplement form for medicinal purposes, it might have different effects.<sup>26</sup> Herbal remedies can often interfere with the actions of mainstream medicines.<sup>25,30,31</sup> The ingestion of whole, fresh ginger has relatively few adverse effects, since it is not usually ingested in large enough amounts to cause any effects. Reported adverse effects may include stomach upsets or intestinal blockage when whole ginger is not chewed properly.<sup>26</sup>

High doses of concentrated ginger in the form of powder or herbal tinctures, however, can increase bleeding risk by decreasing platelet-aggregation, and also increase stomach acid production, especially if taken with other herbs or medicines with the same effect.<sup>22,25,30</sup> Thus, ginger supplementation can have additive or competitive interactions with some medicines.

Fagen<sup>9</sup> recommends not using large doses of ginger together with aspirin, warfarin or other anti-platelet drugs, antihypertensive drugs or hypoglycemic drugs, due to the possible additive effect. Very high doses of ginger powder (higher than 6g/day) can increase exfoliation of gastric epithelial cells which cause gastric irritation<sup>23</sup> and can lead to gastric bleeding.<sup>10</sup> Inhalation of ginger-dust may produce an IgE-mediated allergy.<sup>23</sup>

### **1.5.1 Possible Teratogenicity**

Teratogenic effects can be described as effects leading to structural abnormalities during the stage of embryogenesis.<sup>17</sup> Studies done on rats showed a higher risk for spontaneous abortions in pregnant rats being supplemented with ginger, possibly because of its blood-thinning properties. Doses of ginger tea up to 50g/liter posed no risk for maternal health but the embryonic loss was more than double that of the control group. Contrastingly, the fetuses who survived the exposure to the ginger tea were significantly heavier than the controls and their skeletal development was more advanced.<sup>23,25</sup>

Thus, theoretically ginger taken in large doses can be risky for pregnant women, but it should be kept in mind that the doses fed to experimental rats were very high in relation to their body weight. Human intake would almost certainly never be proportionately as high. The issue of the safety of ginger during pregnancy will be investigated as part of this systematic review.

### **1.5.2 Acute Toxicity**

The LD<sub>50</sub> (Median lethal dose, or Lethal dose 50%) is the dosage required to kill half of a tested population after a specified test duration.<sup>3</sup> For ginger oil the acute oral LD<sub>50</sub> in rats and the acute dermal LD<sub>50</sub> in rabbits exceeded 5g/kg body weight.<sup>23</sup>

Human dosages of ginger intake are much lower than these animal doses, with the average dose of ginger supplemented during trials being approximately 1g ginger per day.<sup>26</sup>

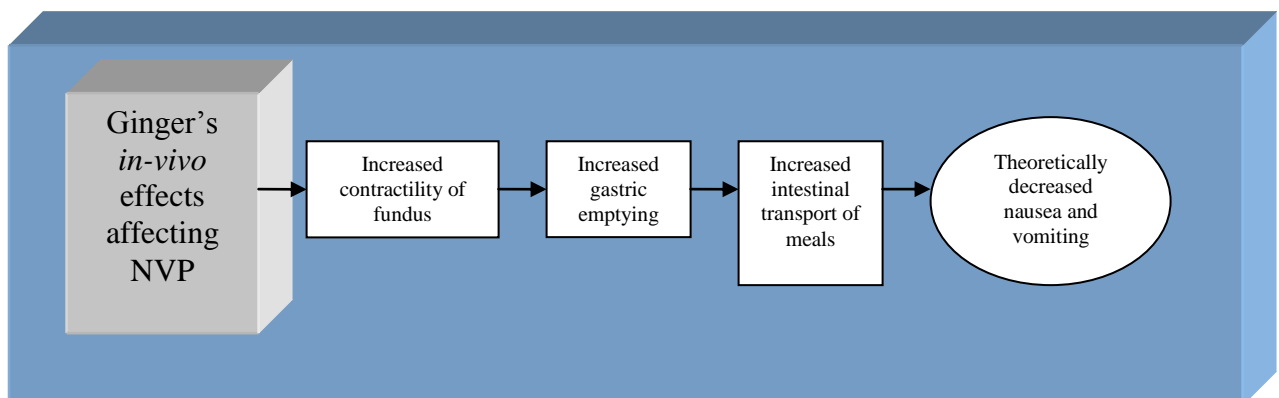
## 1.6 HOW THE INTERVENTION MIGHT WORK

Several studies have been performed on the use of ginger as an anti-emetic for use with post-operative nausea and vomiting, motion sickness and vertigo and chemotherapy-induced nausea and vomiting.<sup>22,25,27,32</sup> The ingestion of oral ginger in a fasting state or after food intake resulted in an increase in gastro-duodenal motility.<sup>23</sup> See figure 1.1.

### Further gastro-intestinal effects of ginger include:<sup>23</sup>

- The occurrence of induced gastric ulcers can be prevented by the ingestion of ginger extract. Roasted ginger used in the extract has a stronger anti-ulcer tendency than dry ginger.
- Ginger's effect on the digestive system is complex. It can increase bile secretion in rats, enhance pancreatic lipase activity, intestinal lipase, disaccharidases, sucrase and maltase activities.
- Ginger extracts and its anti-emetic constituents (shogaols and gingerols) demonstrate strong anti-emetic effects. It can enhance gastro-intestinal transport of a meal, and can significantly inhibit serotonin-induced diarrhea.

Thus, the possibility exists that ginger might alleviate pregnancy associated nausea and vomiting. When being researched, the concepts of nausea and vomiting are usually interlinked, and not studied separately.



Source: Chrubasik<sup>23</sup>

**Figure 1.1 Gastro-intestinal effects of ginger affecting nausea and vomiting**

## 1.7 EVIDENCE-BASED NUTRITION

The concept ‘evidence-based nutrition’ (EBN) can be defined as “the application of the best available systematically assembled evidence in setting nutrition policy and practice.”<sup>33</sup> There are vast numbers of research results available from studies, and if these results are interpreted alone, or out of the right context, then these findings are of little value, or could even be completely useless. The evidence-based approach would base a decision on a review of all the available scientific evidence there is on the subject. The evidence should also be current, using up-to-date methods and skills to acquire the results.<sup>26</sup>

Authorities or decision makers in communities need to have scientific information presented to them in a very clear and simple way, and this information needs to be based on research done on the relevant topic. This can be done by reviewing individual original research studies, or by reviewing reviews.<sup>33</sup> Nutritional epidemiology refers to public health issues related to nutrition in a community. Exposure to health risks in a community needs to be assessed and reported, to make it possible for authorities to make judgments according to these risk assessments. The goal is to reduce the burden of risk in the community, by minimizing the health risks associated with nutritional exposures.

In the private sector also, medical personnel need to make decisions based on evidence not only from one event or study done, but on the compilation of all the relevant evidence available, in order to offer their patients the best advice.

To conclude, there is a definitive need for evidence-based nutrition recommendations. The public often perceives nutritional guidelines as confusing and feel that experts change their minds, or that recommendations change with time. The confusion is probably not always validated, but it remains a concern as it can discredit the nutritional and research profession.<sup>33</sup>

## 1.8 DESCRIPTION OF SYSTEMATIC REVIEWS

There are different types of reviews, namely narrative or systematic. The difference between the two is the gathering of the individual studies to be included. In a systematic review, *all* the relevant studies available on the topic are included and interpreted to prevent publication bias, while in the narrative study, some studies might be left out, thus influencing the results.<sup>1,4</sup>

The Cochrane Handbook of Systematic Reviews defines a systematic review (SR) as “a review that attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.”<sup>1</sup>

Many SRs contain meta-analyses. A meta-analysis is defined as “the use of statistical methods to summarize the results of independent studies”. By combining the findings from all relevant studies, more precise estimates of the effect of treatment can be provided.<sup>1</sup>

Both systematic reviews and meta-analyses are used in Evidence-based practice, since both these methods allow for standardized methods of compiling new evidence in a structured way. According to Gray’s hierarchy of quality of evidence<sup>35</sup>, SRs of randomized controlled trials are the best quality evidence, and meta-analyses rank as very strong evidence according to Porter et al.<sup>34</sup>

A systematic review is a complete collection and objective analysis of all available relevant studies in a specific area. A meta-analysis is a statistical integration of separate studies which can be considered as combinable, to create a more statistically powerful tool.<sup>36,37</sup> Meta-analyses can form part of a systematic review, when the data included allows for this to be done.

## **1.8.1 Characteristics of a Systematic Review**<sup>33,35</sup>

### **1.8.1.1 Research question**

A vital starting point for any research is to state a clearly defined research question or objective, or set of objectives. The SR should have a very clear and well-formulated question, namely:

- The persons / patients of interest
- The intervention
- The control group
- The outcomes

Pre-defined eligibility criteria consisting of both inclusion and exclusion criteria should also be clearly stated after the research question.<sup>1,35</sup>

### **1.8.1.2 Reproducible methodology**

Any SR should have a very clear and explicit description of the exact steps that were followed during every stage of the review. It should be described in such a manner that the study can be repeated exactly.

### **1.8.1.3 Search for answers**

A systematic search should attempt to identify all studies that would meet the eligibility criteria.<sup>1</sup>

The literature suggests *Location of studies* using the 4S approach, referring to Systems, Synopses, Syntheses and Studies as the sources of literature. Systems include comprehensive, evidence-based resources, synopses are compilations of structured abstracts of high-quality studies, syntheses are systematic reviews, and studies are original research articles.<sup>35</sup>

### **1.8.1.4 Appraisal of evidence**

Appraisal of evidence (by selecting studies) is particularly important when the last 'S', namely Studies, are used as evidence. During this step the validity, importance and applicability of the individual studies to the SR should be questioned. Applying the



inclusion and exclusion criteria to select studies is part of the appraisal of evidence, as this is a way of deciding which studies are relevant and which are not.

#### **1.8.1.5 Assessment of study quality**

An assessment of the validity of the findings of the included studies should be done, for example, through the assessment of risk of bias. The Cochrane Handbook for Systematic Reviews recommends using the “Risk of bias tool” which includes six domains of possible bias. These domains include adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias.<sup>1</sup>

#### **1.8.1.6 Data extraction**

Extraction of the relevant data from each individual study is important, to select only the specific information out of each study which will be applicable to the SR. The reviewer needs to plan exactly how the relevant data will be presented and analyzed.

#### **1.8.1.7 Application of the results**

Once all the studies have been selected and applicable data have been extracted, this data must be analyzed to draw new or combined conclusions. When suitable, a meta-analysis can be performed on all or some of the included studies.

Systematic presentation of the findings is crucial, and a meta-analysis must always include a graphic visual display of the results. An SR will usually include tables that describe the ‘Characteristics of included studies’ and ‘Summary of findings’, when appropriate.

Because systematic reviews and meta-analyses are compiled of collaborations of studies of different sizes, this assignment of ‘weight’ or ‘importance’ is crucial. Statistically, smaller studies can be influenced more by chance than larger studies can, and should therefore make a smaller contribution to the results of the review. Two models are used in this regard, to determine how much weight should be assigned to each study.<sup>36</sup>

The “Fixed effects model” assumes that random variation is responsible for all variability between studies, and that all studies would yield the same results, if they were the same size. The “Random effects model” assumes that each study has different underlying variability, and assigns different weights to different studies. According to Egger<sup>36</sup> when heterogeneity is detected, it is best to use a random effects model to determine the importance of individual studies.

#### **1.8.1.8 Assessment of the outcomes**

In a systematic review or meta-analysis, assessing the outcomes would refer to interpreting the newfound results from the combined studies. This can then describe the general trend that was observed, and new hypotheses can be formulated.<sup>37</sup>

Discussion of the following topics should be done: limitations of the review, including all sources of possible bias; the strength of evidence; applicability of the results to the relevant population; and the implications of the newfound results on the relevant medical milieu.

#### **1.8.2 Limitations of Systematic Reviews**

Systematic reviews and meta-analyses aim to answer a question by pooling together answers from different sources. A big challenge for such an attempt is to agree on the comparability of the collected data, in terms of the design, conduct and presentation of data.<sup>4</sup> Issues such as size of studies, quality of the studies, randomization procedures and time spans should be comparable.<sup>37</sup>

Nutritional studies are more difficult, particularly when compared to pharmacological experimental studies, in respect of controlling exposures, and to make sure that all subjects receive exactly the same exposures. The outcome data used in different studies are not always the same either.<sup>33</sup>

Another challenge in conducting a SR is to obtain all the relevant literature and to ensure a thorough and complete collection of all studies done on the subject. If all available literature is not included, the summary estimate may be misleading.<sup>4</sup> When the original studies included in the SR are of poor quality, the findings of the SR or meta-analysis

conducted will also be of poor quality or weak strength of evidence.<sup>37</sup> It is the responsibility of the author of the SR to include honest assessments of the study quality, the possible methodological flaws, the risk of bias and the comparability of the studies. This will allow for readers to interpret the results with caution, when necessary, and to bear these shortcomings in mind when drawing conclusions.

Because of all these challenges, SRs can aid, but never replace sound clinical reasoning.

### **1.8.3 Goal of Systematic Reviews**

In medical practice there is a need for clear and explicit recommendations based on solid facts. Without conducting a SR on a subject, decisions on what should be recommended will be made on personal opinion or hearsay, or on individual trials or single pieces of evidence, which can lead to bias and inaccurate conclusions. The Cochrane Collaboration is an international initiative that aims to facilitate an evidence-based approach by bringing together scientific evidence on RCTs.<sup>4</sup> Its primary aim is to “help people make well-informed decisions about healthcare and health policy by preparing and maintaining high quality systematic reviews.” It is a non-profit organization and draws significantly on volunteer effort. The Cochrane Library is published on behalf of The Cochrane Collaboration and includes SRs done on medical topics.<sup>38</sup> Not all SRs done are necessarily included in the Cochrane Collaboration – good SRs can be conducted that are not Cochrane Reviews.

## **1.9 SUMMARY AND MOTIVATION FOR THE STUDY**

Nausea and vomiting during pregnancy can limit the mother’s nutritional intake, and have a negative impact on the developing fetus. Some anti-emetic drugs can be used, but may cause side effects and pose a possible threat to the developing fetus.<sup>9</sup> Adjustments to the mother’s dietary intake can play a role in the prevention or treatment of nausea and vomiting, but it is limited.<sup>9,10</sup> The use of natural remedies, such as ginger, for treating nausea and vomiting can be very beneficial for these women.

Currently no clear guidelines are available for ginger’s use in the treatment of pregnancy-associated nausea and vomiting, despite systematic reviews done on the subject to some

extent.<sup>26,39,40</sup> These reviews were published between 2000 and 2005, which included studies up to June 2004. The findings of these reviews were that ginger may be effective in treating pregnancy-associated nausea and vomiting, but that the safety aspect needed more research. In the meantime, additional studies have been conducted, prompting the researchers to ask these and other questions once more. This review involves the studies already included in the above-mentioned reviews, where they fulfilled the inclusion criteria for this review, and also includes the more recent studies, to establish whether any new discoveries have been made regarding the effectiveness and safety of using ginger as a treatment for pregnancy-associated nausea and vomiting. The findings could ultimately lead to clearer guidelines regarding the use of ginger for pregnancy-associated nausea and vomiting.

A systematic review of the available literature is needed to provide the best current evidence regarding possible benefits or risks for the clinical use of ginger to treat NVP. The results will be discussed and conclusions drawn to make recommendations for the practical use of ginger to treat nausea and vomiting during pregnancy.

## **CHAPTER 2: METHODOLOGY**

## **2.1 OBJECTIVES**

### **2.1.1 Purpose of the Study**

To investigate the current evidence regarding the efficacy and safety of ginger for the treatment of nausea and vomiting during pregnancy.

### **2.1.2 Specific Objectives**

#### *Primary objective*

The primary objective of this systematic review was to assess the effectiveness of ginger in the treatment of pregnancy-associated nausea and vomiting.

#### *Secondary objective*

The secondary objective of this systematic review was to assess the safety of orally administered ginger in the treatment of pregnancy-associated nausea and vomiting, by identifying adverse events or side effects (if any), and to classify them as major (serious complications detrimental to the mother or fetus), or minor (discomfort, but manageable side effects).

#### *Implementation objectives*

To make recommendations if possible, on the use of ginger to treat patients with pregnancy-associated nausea and vomiting, and the dosage, duration and form in which the ginger should be ingested.

The results will be published in the peer-reviewed literature. These recommendations can be made available to doctors, dieticians, homeopaths, gynaecologists and midwives to inform their clinical practice.

## **2.2 CRITERIA FOR CONSIDERING STUDIES FOR INCLUSION**

### **2.2.1 Types of Studies**

Randomized controlled trials (RCTs), involving human participants and investigating ginger for the treatment of pregnancy-associated nausea and vomiting were included in this systematic review. Trials were included despite lack of blinding or placebo treatment.

### **2.2.2 Types of Participants**

Women suffering from pregnancy-associated nausea and vomiting were included, with no restriction on their age or stage of pregnancy.

### **2.2.3 Types of Interventions**

Any form of ginger intervention (fresh root, dried root, powder, tablets, capsules, liquid extract, and tea) compared with an inert (placebo) or active ingredient, all via the oral route of administration, was included.

### **2.2.4 Types of Outcome Measures**

Outcome measures include:

- Symptom scores on the subjective feeling of nausea, measured by standardized scales or methods (e.g. Visual Analogue Scale (VAS) )
- The incidence of vomiting episodes, measured by daily recording
- The general response to the treatment, measured by standardized scales or methods (e.g the 5-point Likert-type scale)
- The occurrence of adverse events and side effects

*Effect modifiers and confounders*

- compliance with treatment

- any co-treatment that can influence ginger's effects (e.g. dietary, medicinal, herbal or physical intervention) was considered a confounder.

### **2.3 SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

Literature searches were conducted in computerized databases, by a qualified medical librarian (Ms. Wilhelmine Pool). Databases searched: Medline (accessed via Pubmed); EBSCO host (Elton B Stephen's Company), including Academic Search Premier (provides full-text coverage on biology, chemistry, engineering, physics, psychology, religion), CINAHL (nursing & allied health research database), and CAB abstracts (produced by CABI Publishing, this database covers the significant research and development literature in agriculture, forestry, human nutrition, veterinary medicine and the environment); CENTRAL (Cochrane Central Register of Controlled Trials); Science Direct; ISI Web of Science, ISAP (Index to South African Periodicals – National Library of South Africa); Proquest; Scopus (abstract and citation database of peer-reviewed literature); Africa Wide; SABINET (South African Bibliographic Information Network); Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com)) and Clinical trials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Studies were selected regardless of publication status. The author also searched for additional studies by searching the reference lists of the included trials and other articles identified by the electronic search. The dates for inclusion were from 1966 up to the most recent publications, the latest date of electronic searches done being 28 February 2011.

Search words used on first attempt: Pregnant\* AND (nausea OR vomiting OR morning sickness OR hyperemesis gravidarum) AND (ginger OR zingiber officinale roscoe). The only limitation was the stipulation that these searches should apply to humans.

In the Pubmed database this first attempt of search words lead to more than 40 000 references, mostly due to cases of vomiting relating to a variety of causes such as chemotherapy and many other illnesses, and many studies done on pregnant women, not necessarily with NVP, clearly irrelevant to our search. The search string was then further



refined to specifically identify trials related to this systematic review topic and a language filter was used to limit the studies to English publications.

The search word string was adapted to ‘pregnancy AND (nausea OR vomiting OR morning sickness OR hyperemesis gravidarum) AND (ginger OR zingiber officinale roscoe)’ to be more sensitive on the second attempt. This then referred only to nausea and vomiting due to pregnancy. The only limitation was the application to humans alone. Finally, an even stricter search strategy was employed to focus on the required study design and thus included only RCTs. The final complete search word string was:

Pregnan\* AND (nausea OR vomit\* OR morning sickness OR hyperemesis gravidarum) AND (ginger OR zingiber officinale roscoe) AND (clinical trial\* OR randomized control trial\* OR random allocation OR placebo\* OR random research OR comparative OR “evaluation stud\*” OR follow up OR prospective\* OR control\* OR volunteer\* OR single mask\* OR double mask\* OR treble mask\* OR tripl\* mask\* OR single-blind OR double-blind OR treble blind OR tripl\* blind\*). This search word string was implemented for Pubmed and the rest of the databases as well.

## **2.4 DATA COLLECTION AND ANALYSIS**

### **2.4.1 Selection of Studies**

The principal investigator (EV) and a second reviewer (LV, a qualified dietician) independently did the screening of titles and abstracts of studies identified by the search and applied the pre-specified criteria in order to identify eligible studies. This process was recorded on a specifically designed study eligibility form (Appendix 6.1). Where at least one author considered a study to be relevant, the full text was obtained with the help of the qualified medical librarian, and independently assessed for eligibility. Disagreements were resolved by discussion until consensus was reached between the reviewers. Where there was missing information or clarity was needed, the authors of the primary studies were contacted via e-mail. Studies that at first were thought to be relevant, but later excluded, are discussed in the section ‘Excluded studies’ together with the reasons for exclusion.

### **2.4.2 Data Extraction and Management**

The principal investigator and reviewer independently undertook the data extraction from the full text of the selected studies, using a specifically designed standardized, pre-piloted data extraction form (Appendix 6.2).

For each study, the following items were recorded: administrative details, study methodology, participant characteristics, setting of study, interventions, outcomes, study findings and limitations, ethical approval and funding sources.

Disagreements or uncertainties concerning the data extraction and methodological quality were discussed and resolved and consensus was reached in all cases. There were uncertainties in three articles, and the researchers were contacted via email to answer these queries. One author could not be reached, and two responded with answers to the queries. During the process of data analysis, the author and statistician detected some missing information from two studies, and the relevant authors were contacted with the queries. There was no response in this regard. (See Appendix 6.3, Letters to research authors).

After discussion of all issues, the two sets of corresponding data were then merged into one standard table for each study, to summarize all relevant information. (This data is presented later: refer to Table 3.3, Characteristics of included studies).

## **2.5 ASSESSMENT OF METHODOLOGICAL QUALITY OF INCLUDED STUDIES**

The principal investigator and the independent reviewer independently assessed the components of each of the included studies for risk of bias, using a pre-piloted Risk of bias tool to record judgments and comments (see Appendix 6.4). The recommended tool for assessing the risk of bias, as described in the Cochrane Handbook for Systematic Review of Interventions<sup>1</sup> (Table 2.1) was used to evaluate the potential sources of bias in the methodology of the included trials. The methodological domains of the trials were evaluated and classified as adequate, inadequate or unclear, as described below. The specific detailed criteria appear in Appendix 6.5. The domains of the methodology that were assessed are sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity (Table 2.1). Assessment was done by answering a pre-specified question about the adequacy of the study in relation to the entry, in such a way that the judgment of ‘yes’ can be indicative of low risk of bias, ‘no’ can be indicative of high risk of bias, and ‘unclear’ can be indicative of uncertain risk of bias. Disagreements between the author's and the reviewer's judgments were resolved by discussion, and consensus was reached in all cases.

**Table 2.1 The Cochrane Collaboration's tool for assessing risk of bias**

<b>DOMAIN</b>	<b>DESCRIPTION</b>	<b>REVIEW AUTHOR'S JUDGEMENT</b>
<b>Sequence generation</b>	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
<b>Allocation concealment</b>	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during enrolment	Was allocation adequately concealed?
<b>Blinding of participants, personnel and outcome assessors</b>	Describe all measures used to blind study personnel and participants from knowledge of which intervention relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
<b>Incomplete outcome data</b>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared to total randomized participants), reasons for attrition / exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed, regarding the amount, nature and handling of incomplete data?
<b>Selective outcome reporting</b>	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports or the study free of suggestion of selective outcome reporting?
<b>Other sources of bias</b>	State any important concerns about bias not addressed in the other domains of the tool.	Was the study apparently free of other problems, not covered elsewhere in the table, that could put it at a high risk of bias?

*Source: Higgins<sup>1</sup>*

## **2.6 MEASURES OF TREATMENT EFFECT**

### **2.6.1 Dichotomous Data**

Dichotomous outcomes like adverse events, nausea and vomiting, were expressed as risk ratios (RR) with 95% confidence intervals (CI).

### **2.6.2 Continuous Data**

Continuous outcomes such as symptom scores (for example, as measured by a VAS), were expressed as mean differences (MD) with 95% CI's.

### **2.6.3 Incidence data**

Incidence outcomes such as the incidence of nausea and vomiting would have been expressed as incidence rate ratios (IRR) with 95% confidence intervals, but none of the outcomes were reported in the form of incidence rates.

### **2.6.4 Dealing with Duplicate Publications**

Often, the same research paper was identified by different electronic databases. It was then checked to make sure that it was indeed the same paper, and only one was then included. The original paper (or the oldest version) was used in the case of duplicate publications.

### **2.6.5 Assessment of Heterogeneity**

Heterogeneity was assessed by both the visual inspection of the forest plots (where non-overlapping of confidence intervals indicated the likelihood of heterogeneity) and by using the Chi<sup>2</sup>-test for heterogeneity. Differences at the level of  $p < 0.05$  were considered to be statistically significant. Heterogeneity was quantified using the I<sup>2</sup> test, using the following guidelines for interpretation of I<sup>2</sup> statistic values:<sup>1</sup>

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

### **2.6.6. Assessment of Reporting Biases**

The investigators undertook to assess funnel plots to explore the possibility of small study bias where at least ten included studies would be included per analysis. (*As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the test is too low to distinguish chance from real asymmetry.*<sup>1)</sup>) Different explanations for funnel plot asymmetry would be considered, such as publication bias, the effect of different study sizes and poor study design.

### **2.6.7 Data Synthesis or Meta-analysis**

Data were analyzed using Review Manager 5 (RevMan 2008) software. A random effects model of meta-analysis was used in the presence of moderate heterogeneity of treatment effects, and a fixed effect model in the absence of heterogeneity. The Mantel-Haenszel (M-H) method of meta-analysis was used for dichotomous outcomes and the Inverse-Variance (IV) method was used for continuous outcomes.

### **2.6.8 Subgroup Analysis and Investigation of Heterogeneity**

In the presence of significant statistical heterogeneity, an attempt to investigate potentially influential study characteristics had been planned, should sufficient studies exist, by conducting subgroup analyses with respect to the following:

- different dosages administered in the various studies (low dosage of < 1.5g ginger per day versus high dosage of  $\geq 1.5$ g ginger per day).
- different durations of intervention in the various studies (short treatment of < 7days versus long treatment of  $\geq 7$  days)

### **2.6.9 Sensitivity Analysis**

The investigators had planned to perform sensitivity analyses, should sufficient studies exist, in order to explore the influence of the following factors on effect size:

- study quality (allocation concealment versus none)
- source of funding (industry versus other)

## 2.7. ETHICS AND LEGAL ASPECTS

Since this is a systematic review and not a trial involving human participation, no ethical approval was needed. The Health Research Ethics Committee of Stellenbosch University was informed of the proposed systematic review and did register the project for record purposes (see Ethics letter, Appendix 6.6).

The protocol was also submitted to the PROSPERO register (International Prospective Register of Systematic Reviews) and published on the register. PROSPERO is an international database of prospectively registered systematic reviews on health and social care. The registration number is CRD42011001237, <http://www.crd.york.ac.uk/PROSPERO>.

## **CHAPTER 3: RESULTS**



### 3.1 DESCRIPTION OF STUDIES

#### 3.1.1 Results of the Search

Across all searched databases [CINAHL, Cochrane Library, Medline (via Pubmed), Science Direct, Academic Search Premier, CAB abstracts, Web of Science, Proquest, Africa Wide, ISAP and Scopus], 240 titles were identified, using the final search word string as described in chapter 2. Table 3.1 indicates the number of titles identified in each database.

**Table 3.1 Summary of electronic database search**

Database	Amount of titles found
CINAHL	59
Cochrane	1
Medline (accessed via Pubmed)	15
Science Direct	5
Academic Search Premier	15
CAB abstracts	11
Web of science	89
Proquest	12
Africa Wide	9
ISAP (SA journals on SABINET)	1
Scopus	23
<b>TOTAL</b>	<b>240</b>

Seventy six titles were rejected on the initial screen because of repetitions. It then left 164 titles, from which the abstracts were requested for further review by the principal investigator (EV) and an independent reviewer (LV) (Mrs. Lorette Venter: qualified and registered dietician).

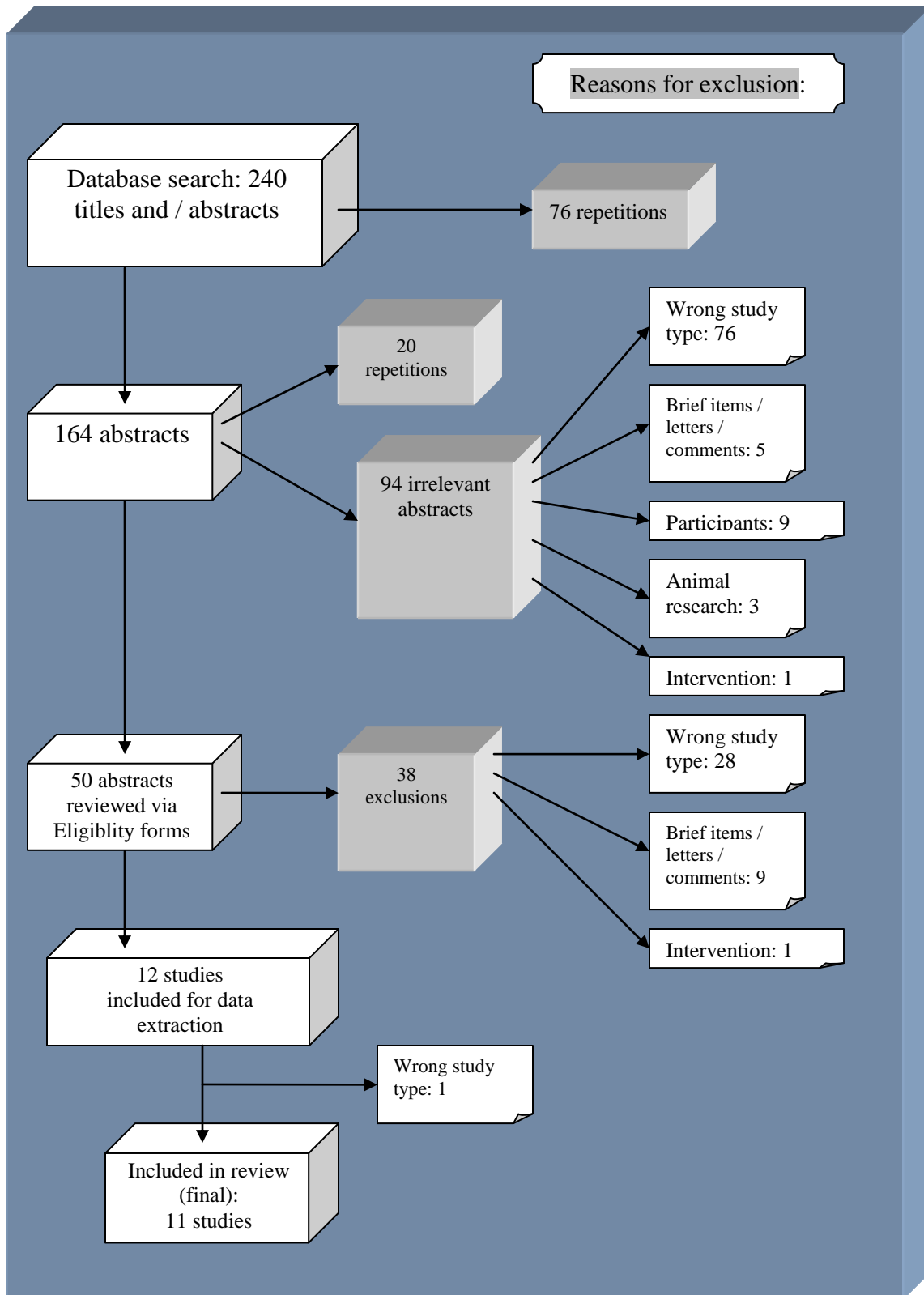
Another 20 repetitions were detected, which left 144 abstracts for assessment. Ninety-four abstracts were excluded for the following reasons: study type other than RCT (n=76); participants other than pregnant women with NVP (n=9); brief items / commentary / letters (n=5); animal research (n=3) and intervention other than ginger (n=1).

Fifty studies were identified by both the investigator and independent reviewer as possibly relevant to the SR, and these studies were again assessed independently.

The investigator and reviewer then reviewed the abstracts of the 50 studies identified, and applied the pre-specified criteria in order to identify eligible studies. This process was recorded on a specifically designed and pre-piloted Eligibility form (Appendix 6.1). This closer inspection of the abstracts revealed another nine titles as being part of a comment / brief summary / short article or letter, and therefore not a research article. This left 41 studies, of which 28 were excluded due to study type other than RCT, and 1 due to intervention other than ginger.

The remaining 12 abstracts were considered relevant and eligible for the SR and the author requested the full texts. The reference lists of these full text articles were reviewed to search for more possible relevant titles. The 15 titles that were found using this method were repetitions of titles already included in the initial electronic searches.

One of the 12 studies was at first thought to be relevant, but later excluded due to study type. This study is described in section 3.1.2. “Excluded studies,” together with the rest of the excluded studies, as well as the reasons for their exclusion (see appendix 6.4: “Table of excluded studies”). Thus a total of 11 studies were included in this SR (Figure 3.1), which are all described under section 3.1.4 “General Description of the Included Studies.”



**Figure 3.1 Summary of study selection**

### 3.1.2 Excluded Studies

The main reason for exclusion of studies (N=133) was study type other than RCT (N=105); followed by no abstract or full text published, only brief summaries, letters or comments on research articles (N=14); subjects other than pregnant women with NVP (N=9); animal research (N=3) and subjects not receiving ginger as intervention (N=2). (see “Table of excluded studies”: Appendix 6.7). One study (Portnoi<sup>41</sup>) was originally thought to be relevant and included for data extraction, but excluded on closer inspection. This observational study compared the efficacy of different forms of ginger taken by pregnant women with NVP, who called in to the Motherisk Program’s call centre for advice on managing their symptoms. As this is not a RCT, it could not be included in this SR.

### 3.1.3 Included Studies

Eleven studies<sup>42-52</sup> met the aforementioned inclusion criteria and were included in this SR. Their study IDs and reference numbers are listed in Table 3.2.

**Table 3.2 Study ID and reference index of included studies (n=11)**

Study ID (alphabetical order)	Reference
Basirat 2009	42
Chittumma 2007	43
Ensiyeh 2009	44
Fischer-Rasmussen 1991	45
Keating 2002	46
Ozgoli 2009	47
Pongroj paw 2007	48
Smith 2004	49
Sripramote 2003	50
Vutyavanich 2001	51
Willetts 2003	52

### 3.1.4 General Description of the Included Studies

Included studies were published from 1991 to 2009. Key data of the included studies is summarized in Table 3.3, and the main findings, as reported by the relevant authors, are briefly described below.

**Basirat:**<sup>42</sup> The study done by Basirat et al was a double-blind parallel RCT in Iran. It included 65 pregnant women, of which 62 completed the trial. Participants received either ginger biscuits (500mg ginger per biscuit) or placebo biscuits, 5 times per day for 4 days (total of 2500mg ginger per day) for 4 days. No other anti-emetics were allowed during the trial. Outcomes included the severity of nausea, number of vomiting episodes and the patients' general response to the treatment. The severity of nausea was measured on the baseline day before treatment started, and again once per day at bedtime on days 1-4 of the treatment. A visual analogue scale was used, consisting of a 10 centimetre scale of 0–10, 0 being no nausea, and 10 being the worst nausea. The number of vomiting episodes were measured on the baseline day to record the number of episodes during the previous 24 hours, and recorded on days 1-4 as the vomiting occurred. The general response to treatment was measured on day 7, using a 5-point Likert type scale where patients had to indicate if they felt much worse, worse, the same, better or much better. The results showed that the ginger biscuits provided significantly greater relief from the severity of nausea ( $p=0.01$ ), and to some extent vomiting ( $p=0.24$ ). Vomiting incidences were reduced in both groups, but no significant differences were detected between the groups. Side effects were experienced only in the ginger group, namely dizziness and heartburn.

**Chittumma:**<sup>43</sup> Chittumma et al conducted a double-blind parallel RCT in Thailand. One hundred and twenty-six women were included, and 123 completed the trial. They received either ginger root powder capsules (325mg per capsule, 2 capsules 3 times per day, resulting in a total of 1950mg ginger per day), or vitamin B6 capsules (12.5mg per capsule, 2 capsules 3 times per day, total 75mg vitamin B6 per day) for 4 days. Some participants continued to use other medicines throughout the trial, including some other ginger products. Dietary advice was given to both groups before start of treatment, on

guidelines for reducing nausea and vomiting. Outcomes included a change in nausea and vomiting scores and the occurrence of side effects. The nausea and vomiting scores included 3 physical symptoms of the Rhode's score: episodes of nausea, duration of nausea, and number of vomits. These scores were taken on baseline day, and at noon of each day of the 4 days of treatment. Results showed that ginger is more effective in relieving NVP than vitamin B6 ( $p < 0.05$ ). Side effects included heartburn (both groups), sedation (both groups), arrhythmia (only in the ginger group) and headaches (only in the vitamin B6 group). The authors concluded that the side effects were minor and not significantly different between the two groups ( $p = 0.795$ ).

**Ensiyeh:**<sup>44</sup> The study conducted by Ensiyeh et al was a RCT done in Iran. Seventy pregnant women were included and 69 finished the trial. They were randomized to receive either ginger root powder capsules (500mg ginger per capsule, twice per day, total 1000mg per day), or vitamin B6 capsules (20mg vitamin B6 per capsule, twice per day, total of 40mg vitamin B6 per day) for 4 days. Dietary advice was given to both groups before start of treatment, on guidelines for reducing nausea and vomiting. Outcomes included the severity of nausea, vomiting incidences, the women's response to treatment, and the occurrence of side effects. The severity of nausea was measured on the baseline day before treatment started, and again three times per day (morning, noon and bedtime) on days 1-4 of the treatment. A visual analogue scale was used, consisting of a 10 centimetre scale of 0–10; 0 indicating no nausea, and 10 indicating the worst nausea. The number of vomiting episodes were measured on the baseline day to record the number of episodes during the previous 24 hours, and recorded on days 1-4 as the vomiting occurred. The general response to treatment was measured on day 7, using a 5-point Likert type scale where patients had to indicate if they felt much worse, worse, the same, better or much better. The occurrence of side effects was measured for up to 12 weeks after delivery, to include any adverse pregnancy outcomes as well. The results showed that the ginger is more effective than vitamin B6 for relieving the severity of nausea ( $p < 0.024$ ), and equally effective for reducing the number of vomiting episodes. The general response to treatment was better in the ginger group ( $p = 0.52$ ). No side effects occurred and spontaneous abortions occurred in both groups, but the authors felt

that the number of subjects was not large enough to draw conclusions about these adverse events.

**Fischer-Rasmussen:**<sup>45</sup> This was a double-blind randomized cross-over trial done in Denmark, and included 30 pregnant women who were hospitalized, suffering from HG. Twenty-seven women completed the trial. Patients received either ginger root capsules (250mg ginger per capsule, 4 times per day, total of 1000mg ginger per day), or placebo capsules (250mg lactose powder per capsule, 4 times per day, total 1000mg lactose per day). Each treatment was given for 4 days, and the wash-out period between the two treatments was two days. No other anti-emetic medications were allowed, but intravenous fluids were given to prevent dehydration. Outcomes included the preference of treatment period (assessed after concluding both treatments), and the relief scores (point-system regarding nausea, vomiting, change in body weight, personal opinion about the treatment), and the outcome of the pregnancy. The results showed that ginger was more effective than the placebo in eliminating or minimizing HG ( $p=0.035$ ). No side effects were reported, and 1 spontaneous abortion occurred, non-significant.

**Keating:**<sup>46</sup> This double-blind RCT done in the USA by Keating et al included 26 pregnant women, of which 21 completed the trial. They received either a tablespoon of ginger syrup (250mg ginger, honey and water) or placebo syrup (lemon oil, honey and water) 4 times per day in hot or cold water, resulting in 1000mg ginger per day, for 14 days. Dietary advice was given to both groups before start of treatment, on guidelines for reducing nausea and vomiting. Outcomes included the level of nausea, and the number of vomiting episodes. Baseline scores were measured before treatment started. The level of nausea was recorded daily for days 1-14 in a diary, using a numerical scale 1-10. The vomiting episodes were recorded daily as they occurred. The results showed that ginger had a greater effect on the relieving of NVP, but due to the small study sample the results were not statistically analyzed. The authors concluded that ginger syrup may be more effective than placebo syrup in the treatment of NVP. No adverse outcomes were reported.

**Ozgili:**<sup>47</sup> This RCT done in Iran included 70 pregnant women of whom 67 finished the trial. They were randomized to receive either a ginger root capsule (250mg ginger per capsule, 4 times per day, total 1000mg ginger per day), or a placebo capsule (250mg lactose powder per capsule, 4 times per day, total 1000mg lactose per day) for 4 days. Dietary advice was given to both groups before start of treatment, on guidelines for reducing nausea and vomiting. Outcomes included the nausea intensity and vomiting incidences. A baseline day pre-treatment questionnaire was completed using a visual analogue scale of 0-10 to indicate nausea intensity, and again twice per day on each treatment day. The vomiting incidences were measured on the baseline day, and recorded on days 1-4 of treatment as the vomiting occurred. The results showed that ginger was more effective than the placebo in improving symptoms of NVP ( $p < 0.05$ ), without any reported side effects or adverse events.

**Pongrojpraw:**<sup>48</sup> This RCT done in Thailand was done on 170 pregnant women, and 151 completed the trial. They received either ginger capsules (500mg ginger per capsule twice per day, total 1000mg ginger per day) or dimenhydrinate capsules (50mg per capsule, twice per day, total 100mg dimenhydrinate per day) for 7 days. Outcomes included the degree of nausea, number of vomiting incidences, and the occurrence of side effects. The degree of nausea was measured on baseline day and twice per day (morning and evening) on days 1-7 of treatment, by using a visual analogue scale of 0-10. The vomiting incidences were recorded on baseline day for the previous 24 hours, and again on days 1-7 as vomiting occurred. The occurrence of side effects was measured at the follow-up on day 7. Side effects reported were drowsiness (more in the dimenhydrinate group than the ginger group,  $p < 0.01$ ) and heartburn (more in the ginger group than the dimenhydrinate group,  $p = 0.403$ ). The results showed that ginger is as effective as dimenhydrinate in the treatment of NVP, with fewer side effects.

**Smith:**<sup>49</sup> Smith et al conducted a RCT in Australia which included 291 pregnant women of which 235 completed the trial. They received either ginger capsules (350mg per capsule, 3 times per day, total 1050mg ginger per day) or vitamin B6 capsules (25mg per capsule, 3 times per day, total 75mg vitamin B6 per day), for 21 days. Participants were allowed to continue with other medications throughout the trial. The first outcome



measured was the women's experience of nausea, dry retching and vomiting, and this was measured on days 0,7,14 and 21 using the Rhodes Index of Nausea and Vomiting Form 2 (a 5-point, 5-item Likert type scale). The second outcome measured was the change in the women's health status, measured on days 0 and 21 on the Medical Outcomes Survey 36 Short form (an 8 multi-item scale, the higher score indicating a better outcome). The third outcome measured was the occurrence of side effects and adverse pregnancy outcomes. Belching occurred more in the ginger group than the vitamin B6 group. Adverse events compared well with national standards and were considered non-significant. The results indicated that ginger is equivalent to vitamin B6 in improving nausea (MD=0.2), dry retching (MD=0.3) and vomiting (MD=0.5) in pregnancy. All p-values were <0.001.

**Sripramote:**<sup>50</sup> This double-blind RCT conducted in Thailand included 138 pregnant women, of whom 128 finished the trial. They were randomized to receive either ginger powder capsules (500mg per capsule, 3 times per day before meals, total 1500mg per day), or vitamin B6 capsules (10mg per capsule, 3 times per day, total 30mg vitamin B6 per day), for 3 days. Dietary advice was given to both groups before start of treatment, on guidelines for reducing nausea and vomiting. Outcomes measured were improvement in nausea symptoms, number of vomiting episodes per day, and occurrence of side effects or adverse events. The nausea symptoms were measured on the baseline day, and three times per day on days 1-3 of treatment (morning, noon, bedtime), by using a visual analogue scale 0-10. The number of vomiting episodes was measured on day 0 for the previous 24 hours, and again daily as they occurred on days 1-3 of the treatment. The occurrence of side effects was recorded during the treatment and reported at the follow-up on day 7. Side effects included heartburn (more in the ginger group than the vitamin B6 group) and drowsiness (more in the vitamin B6 group than the ginger group). The results indicated that both ginger and vitamin B6 were effective for treating NVP (p<0.001), and there were no significant differences between the two treatments' efficacy.

**Vutyavanich:**<sup>51</sup> This double-blind RCT conducted in Thailand included 70 women, and 67 completed the trial. They received either ginger root capsules (250mg per capsule 4 x

per day, total 1000mg ginger per day) or placebo capsules (250mg placebo per capsule, 4x/day), for 4 days. The placebo was not specified. Dietary advice was given to both groups before start of treatment, on guidelines for reducing nausea and vomiting. The outcomes measured were improvement in nausea symptoms (measured on baseline day, and twice per day on days 1-4 of treatment, using a visual analogue scale 0-10); the number of vomiting episodes (recorded daily as it occurred); and the severity of nausea after 1 week (measured on day 7 with a 5-item Likert scale indicating if the patient felt much worse, worse, the same, better or much better); as well as the occurrence of side effects or adverse pregnancy outcomes. Headaches occurred in both groups, and only in the ginger group did heartburn, abdominal discomfort and diarrhea for 1 day occur. Spontaneous abortions occurred in both groups, but the difference between the occurrences in the two groups was not significant ( $p=0.615$ ). The results showed that ginger was more effective than the placebo in relieving the severity of nausea in pregnancy ( $p=0.014$ ).

**Willett's:**<sup>52</sup> Willett's et al conducted a double blind RCT in Australia, including 120 women of whom 99 finished the trial. They were randomized to receive either ginger extract capsules (125mg ginger extract per capsule, 4 times per day, total 1000mg per day), or placebo capsules (consisting of soy bean oil, 4 times per day, the amount not specified), for 4 days. Outcomes measured were nausea experience reduction, vomiting and retching (measured using the Rhodes Index of Nausea, Vomiting and Retching tool) and birth outcomes. The results show that ginger was more effective than the placebo for improving symptoms of nausea and retching during pregnancy, but no difference in the vomiting episodes were observed. No p-values were provided.

### 3.1.5 Characteristics of Study Settings

Ten (90.9%) of the eleven included trials were designed as parallel group studies. Only one study<sup>45</sup> had a cross-over design.

Four studies<sup>43,48,50,51</sup> were done in Thailand; three studies<sup>42, 44, 47</sup> were done in Iran, two<sup>49,52</sup> in Australia, one in Denmark<sup>45</sup> and one in the USA.<sup>46</sup>

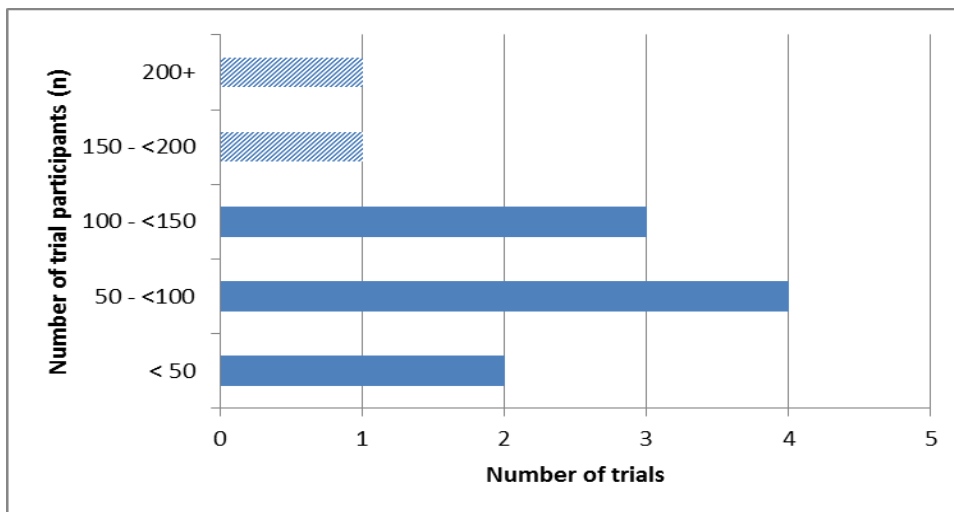
Seven studies<sup>42,43,44,48,50,51,52</sup> were done at antenatal clinics at hospitals, two<sup>45,49</sup> at University hospitals, one<sup>47</sup> in several health centres and city hospitals, and one in a private practice office.<sup>46</sup> Thus, only one trial<sup>47</sup> was a multi-centre trial.

### 3.1.6 Funding

Three studies<sup>46,49,52</sup> were funded by pharmaceutical companies; two studies<sup>42,50</sup> were funded by the research ethics council from the relevant hospital where the study was conducted. Two studies<sup>44,47</sup> acknowledged individual persons involved in their research ethics councils, and the remaining four studies<sup>43,45,48,51</sup> did not provide any information on funding.

### 3.1.7 Characteristics of Participants

A total of 1176 participants were included in the respective studies, ranging from 26 in the smallest trial<sup>46</sup> to 291 participants in the largest trial.<sup>49</sup> Only 2 trials<sup>48,49</sup> recruited more than 150 participants (Figure 3.2). All the included trials included pregnant women who were before or at 20 weeks gestation. The inclusion criteria for this review do not specify a stage of pregnancy, or maternal age. Ten of the eleven included studies<sup>42-44,46-52</sup> (90.9%), included women suffering from NVP, and one study<sup>45</sup> (9.1%) included women suffering from HG.



**Figure 3.2: The number of trials by number of included participants**

### 3.1.8 Characteristics of the Interventions

The study intervention (ginger) was clearly described in each included study. Most of the studies (n=8) (72.7%)<sup>43,44,45,47,48,49,50,51</sup> used ginger powder capsules as intervention, ranging from 1000mg to 1950mg ginger per day. One study<sup>42</sup> (9.1%) used Ginger biscuits as intervention, with a total dose of 2500mg ginger per day. One study<sup>46</sup> (9.1%) used a total of 1000mg ginger syrup per day, dissolved in water; and one study<sup>52</sup> (9.1%) used 1000mg ginger extract per day, in capsule form.

The dosage that was used in the majority of the included clinical trials<sup>44,45,46,47,48,51,52</sup> was 1000 milligram (mg) of ginger powder per day. This was also the lowest dose, and thus theoretically the safest dose. The remaining studies used 1050mg per day,<sup>49</sup> 1500mg per day,<sup>50</sup> 1950mg per day<sup>43</sup> and 2500mg per day.<sup>42</sup> The majority of the studies used a duration of 4 days.<sup>42,43,44,45,47,51,52</sup> The remaining studies used a duration of 3 days,<sup>50</sup> 7days,<sup>48</sup> 14 days<sup>46</sup> and 21 days.<sup>49</sup>

The comparator was clearly described in most of the included studies.<sup>43-50,52</sup> A placebo was used as the control in 6 studies. Two studies<sup>45, 47</sup> used lactose as the placebo, one used lemon oil<sup>46</sup> and one used soy bean oil.<sup>52</sup> One study<sup>42</sup> used placebo biscuits but did not specify the content of the biscuit, and one study<sup>51</sup> did not specify the content of the placebo capsule. Four studies used Vitamin B6 as active comparator. Two studies<sup>43,49</sup> used 70mg per day, one<sup>44</sup> used 40mg per day and one<sup>50</sup> used 30mg per day. The remaining study<sup>48</sup> used 100mg Dimenhydrinate per day as active comparator. See table 3.3 for details.

**Table 3.3 Table of characteristics of included studies**

Study ID	Risk of bias	NPB/ NME (treatment)	Intervention (Ginger dose per day)	Comparator * (dose per day)	LT	Main outcome measures	Main results
Basirat 2009 <sup>42</sup>	High	65 / 62 (32G, 30C)	Ginger biscuits (500mg 5 times daily = 2500mg / day)	Placebo biscuit (5 biscuits per day, dose not specified)	4 days	Severity of nausea (VAS 0-10); number of vomiting episodes; general response to treatment (5-item Likert scale)	Ginger in biscuit form was more effective than placebo in relieving severity of nausea in pregnancy, and to some extent, vomiting
Chittumma 2007 <sup>43</sup>	High	126 / 123 (61G, 62C)	Ginger powder capsules (325mg x2, three times daily, = 1950mg/day)	Vitamin B6 capsules (12.5mg x2, three times daily =75mg/day)	4 days	Change in nausea and vomiting scores (3 symptoms on Rhodes index); occurrence of side effects)	Ginger was more effective than vitamin B6 for relief from NVP
Ensiyeh 2009 <sup>44</sup>	High	70 / 69 (35G,34C)	Ginger powder capsules (500mg 2x/d =1000mg /day)	Vitamin B6 capsules (20mg twice per day =40mg/day)	4 days	Severity of nausea (VAS 0-10); number of vomiting episodes; general response to treatment (5-item Likert scale); occurrence of side effects or adverse pregnancy outcome	Ginger was more effective than vitamin B6 for relieving the severity of nausea, and was equally effective for decreasing the number of vomiting episodes in pregnancy
Fischer-Rasmussen 1991 <sup>45</sup>	Moderate	30 / 27 (27G,27C) (cross-over **)	Ginger powder capsules (250mg 4 times per day =1000mg /day)	Placebo capsules (lactose) (250mg 4 times per day =1000mg / day)	4 days	Preference of treatment period; relief scores (4-point scoring system); outcome of pregnancy	Ginger was more effective than placebo in relieving symptoms of HG
Keating 2002 <sup>46</sup>	High	26 / 21 (12G, 9C)	Ginger syrup in water (250mg 4 times per day =1000mg/day)	Placebo syrup (lemon oil) 4x/day (dose not specified)	14 days	Level of nausea (numerical scale 1-10); number of vomiting episodes	Ginger syrup may be more effective than placebo syrup in the treatment of NVP. No side effects or adverse pregnancy outcomes occurred
Ozgoli 2009 <sup>47</sup>	Moderate	70 / 67 (32G,53C)	Ginger powder capsules (250mg 4 times per day =	Placebo capsules (lactose) (250mg 4 x/d	4 days	Nausea intensity (VAS 0-10); number of vomiting incidences	Ginger was more effective than the placebo in improving symptoms of NVP, without any side effects or adverse events

<b>Pongroj-paw 2007</b> <sup>48</sup>	High	170 / 151 (77G,74C)	1000mg/day) Ginger powder capsules (500mg 2x/d =1000mg /day)	1000mg/day) Dimenhydrinate capsules (50mg 2x/d = 100mg/day)	7 days	Degree of nausea (VAS 0-10); number of vomiting incidences; occurrence of side effects	Ginger was as effective as dimenhydrinate in the treatment of NVP, and has fewer side effects
<b>Smith 2004</b> <sup>49</sup>	High	291 / 235 (120G,115 C)	Ginger capsules (350mg 3times per day = 1050mg/day)	Vitamin B6 capsules (25mg 3 x/d =75mg/day)	21 days	Nausea, vomiting and dry retching on days 0,7,14,21 (Rhodes Index of Nausea and Vomiting Form2) (5-point Likert scale); change in health status on day 0,21 (MOS 36 Short Form Health Survey, 8-multi-item scale, higher core = better outcome); occurrence of side effects and adverse pregnancy outcomes	Ginger was equivalent to vitamin B6 in improving nausea, vomiting and dry retching in pregnancy
<b>Sripromote 2003</b> <sup>50</sup>	High	138 / 128 (64G,64C)	Ginger powder capsules (500mg 3x/d =1500mg/day)	Vitamin B6 capsules (10mg 3x/d =30mg/day)	3 days	Severity of nausea (VAS 0-10); number of vomiting incidences; occurrence of side effects	Both ginger and vitamin B6 were effective in improving symptoms of NVP, no difference between the two treatments' efficacy
<b>Vutyavanich 2001</b> <sup>51</sup>	High	70 / 67 (32G,35C)	Ginger powder capsules (250mg 4x/day =1000mg/day)	Placebo capsules (not specified) (250mg 4x/day = 1000mg/day)	4 days	Severity of nausea (VAS 0-10); number of vomiting episodes; general response to treatment after 1 week(5-item Likert scale); occurrence of side effects and adverse pregnancy outcomes	Ginger was more effective than placebo for relieving NVP
<b>Willetts 2003</b> <sup>52</sup>	Mode- rate	120 / 99 (48G, 51C)	Ginger extract capsules (125mg4x/d =1000mg/day)	Placebo capsules (soy bean oil 4x/d) (dose not specified)	4 days	Used RINVR to measure frequency, duration, distress caused by nausea, vomiting and retching; long term follow-up for birth outcome	Ginger is more effective than placebo for nausea and retching during pregnancy. No difference was seen in vomiting symptoms

\* **Comparator:** includes placebo and active ingredients. \*\*Cross-over design RCT. All the other studies were parallel design RCT's.

**RCT:** Randomized controlled trial; **NVP:** Nausea and vomiting of pregnancy; **HG:** Hyperemesis gravidarum; **NPB:**Number of patients at beginning of trial; **NPE:** Number of patients at end of trial; **LT:** Length of treatment; **G:** patients in Ginger group; **C:** patients in comparator group **VAS:** Visual analogue scale; **MOS:** Medical outcome study; **RINVR:** Rhodes Index of Nausea, Vomiting and Retching. 5-point Likert type tool with 8 items.

### 3.1.9 Characteristics of outcome measures

#### 3.1.9.1 Nausea

Nausea (the feeling of being about to vomit) is a subjective feeling, thus, another person cannot be aware of this feeling unless the patient tells him that she feels nauseated, and the degree of distress caused by this feeling cannot be observed. For this reason, several tools have been developed to reliably measure nausea. A tool often used by the included studies is called the Rhodes Index of Nausea and Vomiting (RINV). It is also referred to as the Rhodes Index of Nausea, Vomiting and Retching (RINVR).<sup>53</sup> After the completion of pilot studies to test validity and reliability of the original tool, the RINV, the developers of the tool realized the need to include symptom measurement of dry heaving or retching as well. Retching refers to no actual ejection of vomit, but similar gastric contractions occur during these heaves, and are similarly distressing for the patient.<sup>53</sup>

The RINVR tool was originally developed for the assessment of nausea and vomiting in cancer patients receiving chemotherapy. The pilot studies and tests were however, performed on patients with nausea and vomiting, regardless of cancer diagnosis.<sup>53</sup>

The included studies<sup>42,44,47,48,51</sup> which used the Visual analogue scale (VAS) described the measurements as 0 being no nausea, and 10 being the most severe condition of nausea. The scale is divided into increments of 1 centimeter on which the patient plots the relevant number according to her feeling of nausea. Table 3.4 describes the different tools that the included studies used as measures for nausea as the outcome.

**Table 3.4 Outcome measure: Nausea**

Nausea-grading scales used in included studies (Subjective)	Studies	Scales
Visual analogue scale (VAS)	Basirat 2009, Ensiyeh 2009, Ozgoli 2009, Pongroj paw 2007, Sripramote 2004, Vutyavanich 2001	0-10 (centimetres)
Numerical scale	Keating 2002	1-10
3 Physical symptoms of Rhodes' score: episodes of nausea, duration of nausea, number of vomits)	Chittumma 2007	Change in nausea and vomiting scores
Point-system regarding nausea, vomiting, change in body weight, patient's opinion about the treatment.	Fischer-Rasmussen 1991	Point system
Rhodes Index of Nausea and Vomiting Form 2 (RINV)	Smith 2004	5-point, 5-item Likert-type scale.
Rhodes Index of Nausea, Vomiting and Retching (RINVR)	Willets 2003	8-item, 5-point Likert-type tool.

### 3.1.9.2 Vomiting

In contrast to nausea, vomiting is a readily observable occurrence which can be measured or reported without information from the patient. Still, the distress caused by vomiting cannot be observed by another person, and remains a subjective feeling. The RINVR tool, as described above, can also be used to measure vomiting incidence and distress caused by this event.<sup>53</sup> Because the outcome 'Vomiting incidences' simply requires the number of vomiting episodes, it can easily be recorded by the patient or an observer. Table 3.5 describes the tools the different included studies used to measure the vomiting incidences outcome.



**Table 3.5 Outcome measure: Vomiting incidences**

Vomiting recording method used in included studies (Objective)	Studies	Recording method
Participant records the number of vomiting episodes as they occur during the treatment period.	Basirat 2009, Ensinyeh 2009, Keating 2002, Ozgoli 2009, Pongroj paw 2007, Sripramote 2003, Vutyavanich 2001	Recorded daily, as vomiting occurred
Three physical symptoms of Rhodes' score: episodes of nausea, duration of nausea, number of vomits	Chittumma 2007	Change in nausea and vomiting scores
Point-system regarding nausea, vomiting, change in body weight, patient's opinion about the treatment.	Fischer-Rasmussen 1991	Point system
Rhodes Index of Nausea and Vomiting Form 2 (RINV)	Smith 2004	5-item, 5-point Likert scale
Rhodes Index of Nausea, Vomiting and Retching (RINVR)	Willets 2003	8-item, 5-point Likert-type tool

### 3.1.9.3 General response to treatment

It often occurs in RCTs that one of the outcomes includes a subjective measure of symptoms or quality of life – as is seen in this SR. Gyuatt et al<sup>3</sup> did a comparative study of Likert scales and VAS instruments to determine if these were reliable tools to measure subjective feelings or symptoms, and quality of life responses from participants. Their conclusions were that these two tools resulted in comparable responses, and could be of great benefit for use in clinical trials. Their easy administration and interpretation makes it user-friendly for the participants as well as the interpreters.<sup>3</sup>

The SF-36 Health Survey is a multi-purpose short-form health survey that measures functional health and well-being from the patient's point of view. It consists of 36 questions referring to the following indicators of health: functioning at the behavioural level, perceived well-being, social life and central life roles and direct personal perception of total health.<sup>54</sup> Many versions of this survey exist, for disease- or age-specific purposes, and these are all available in many different languages and formats, including online formats for easy administration.<sup>55</sup> Table 3.6 describes the tools the different included studies used to measure the general response to treatment outcome.

**Table 3.6 Outcome measure: General response to treatment**

Opinion about treatment	Studies	Scale
Patients' general idea or response to the treatment	Basirat 2009, Ensiyeh 2009, Vutyavanich 2001	5-point Likert scale (much worse, worse, same, better, much better)
Relief scores including women's opinion about the treatment	Fischer-Rasmussen 1991	Point-system
Change in women's health status	Smith 2004	MOS SF-36 Health Survey (8 multi-item scale, higher score=better outcome)

MOS SF: Medical outcome survey Short form

#### 3.1.9.4 Adverse events and side effects

Adverse events and side effects reported in the studies are listed in Table 3.7. During assessment of side effects, it should be kept in mind that any event occurring during pregnancy should be interpreted with care. Pregnancy is a condition that affects many physiological functions in a woman's body which can lead to a wide variety of symptoms occurring, and often the spectrum differs from person to person. Thus, many of the symptoms that are often seen as the side effects to an intervention could actually be related to the condition, rather than to the treatment.<sup>56</sup>

The judgments made on the seriousness of the reported side effects or adverse events are the review author's own subjective judgments, also taking into account the fact that some of these events do occur in any normal pregnancy as well, without interventions.

**Table 3.7 Outcome measure: Adverse events and side effects**

Adverse events or side effects reported  (Sorted from least to most commonly reported, first major then minor events)	Author's judgment if effect is minor* or major**	Studies
Allergic reaction	<i>Major</i>	Willets 2004
Arrhythmia	<i>Major</i>	Chittuma 2007
Dehydration	<i>Major</i>	Willets2004
Spontaneous abortion	<i>Major</i>	Ensiyeh 2009, Fischer-Rasmussen 1991, Vutyavanich 2001
Abdominal discomfort	Minor	Vutyavanich 2001
Belching	Minor	Smith 2004
Burning sensation after capsule ingestion	Minor	Smith 2004
Diarrhea	Minor	Vutyavanich 2001
Dry retching after capsule ingestion	Minor	Smith 2004
Vomiting after capsule ingestion	Minor	Smith 2004
Headaches	Minor	Chittuma 2007, Vutyavanich 2001
Drowsiness	Minor	Basirat 2009, Chittuma 2007, Pongroj paw 2007, Sripramote 2003
Heartburn	Minor	Basirat 2009, Chittuma 2007, Pongroj paw 2007, Sripramote 2003, Vutyavanich 2001, Willets 2004



\*minor (discomfort, but manageable side effects)

\*\*major (serious complications, possibly detrimental to the mother or fetus)



## 3.2 RISK OF BIAS IN INCLUDED STUDIES

Appendix 6.8 includes tables with the details of the specific risk of bias judgments per each included study across the six methodological quality domains. These domains included adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias.




### 3.2.1 Adequate Sequence Generation

Random sequence generation was adequate (Yes, ) in nine<sup>42-46,49-52</sup> of the eleven studies (81.8 %, Figure 3.2). It was unclear (Unclear, ) in two<sup>47,48</sup> studies (18.2 %), and no studies posed a high risk of bias in this domain.

### 3.2.2 Allocation Concealment




The concealment of allocation was adequate (Yes, ) in five<sup>42,43,46,51,52</sup> of the eleven studies (45.5%), unclear (Unclear, ) in the remaining six<sup>44,45,47-50</sup> studies (54.5%) and no studies posed a high risk of bias in this domain.

### 3.2.3 Blinding

Blinding of participants and personnel was adequate (Yes, ) in five<sup>45,47,50-52</sup> of the eleven studies (45.5%), unclear (Unclear, ) in two<sup>44,48</sup> studies (18.2%), and inadequate (No, ) in four<sup>42,43,46,49</sup> studies (36.4%).

There were four studies<sup>42,43,46,49</sup> in which participants could identify the treatment that they were taking, and the review author considered this as ‘unblinding’, and posing a high risk for bias.

### 3.2.4 Incomplete Outcome Data

Five<sup>42,45-47,52</sup> of the eleven studies (45.5%) had addressed incomplete data adequately (Yes, ), five<sup>43,44,48-50</sup> studies (45.5%) were unclear (Unclear, ), and one<sup>51</sup> study (9.1%) was inadequate (No, ) in this domain.

### 3.2.5 Selective Reporting

The author did not have access to any of the included studies' protocols, thus no comparison could be made between original outcome goals and actual described outcomes, but in ten<sup>42-45,47-52</sup> of the eleven studies (90.9%) no apparent selective outcome reporting was found (Yes, **+**). In one<sup>46</sup> study (9.1%), there was selective outcome reporting detected (No, **-**), when an outcome was clearly stated in the beginning of the study, but not described later in the article.

### 3.2.6 Other Potential Sources of Bias

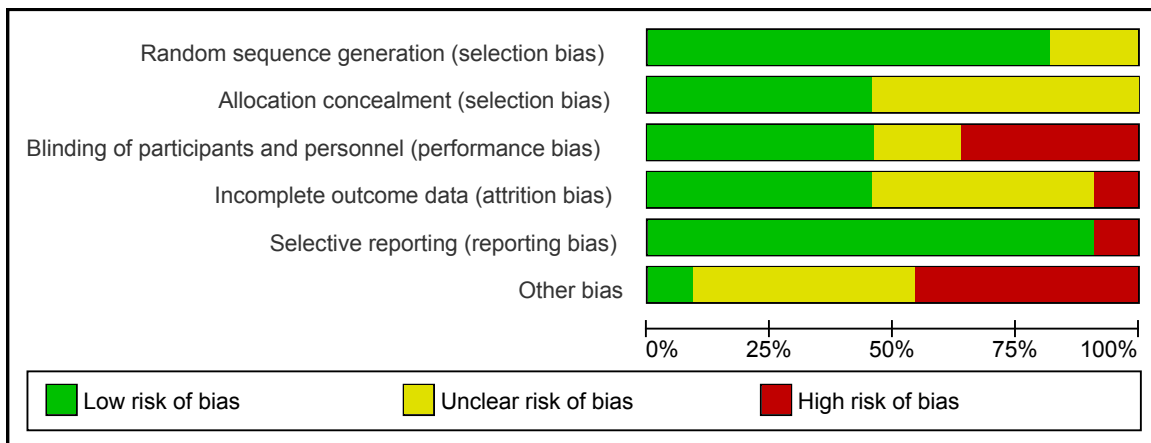
Only one<sup>42</sup> of the eleven studies (9.1%) had no risk of other bias (Yes, **+**). Five<sup>45-47,49,52</sup> of the studies (45.5%) had an unclear risk of other bias (Unclear, **?**), and five<sup>43,44,48,50,51</sup> studies (45.5%) had a high risk of other bias (No, **-**). The high risk studies all included dietary counseling as part of their treatment in both the experimental and the control groups. The author considered this as a confounding factor, since change in outcome scores could be affected by the dietary adjustments made, rather than the intervention itself. No reporting was done on the dietary measures in any of these mentioned studies.

The quality assessments of the trial methodology reported for each of the included 11 trials are demonstrated in Figure 3.3. The author and reviewer judgments about each methodological quality assessment factor across all included studies (Figure 3.4) indicate high risk of bias in “blinding” and “other bias” categories.

There were insufficient studies per comparison and outcome to permit the use of funnel plots to assess publication bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Basirat, 2009	+	+	-	+	+	+
Chittumma Jan 2007	+	+	-	?	+	-
Ensiyeh Dec 2009	+	?	?	?	+	-
Fischer-Rasmussen Jan 1991	+	?	+	+	+	?
Keating Sep 2002	+	+	-	+	-	?
Ozgoli 2009	?	?	+	+	+	?
Pongrojpraw Sep 2007	?	?	?	?	+	-
Smith April 2004	+	?	-	?	+	?
Sripramote Sep 2003	+	?	+	?	+	-
Vutyavanich April 2001	+	+	+	-	+	-
Willetts April 2003	+	+	+	+	+	?

**Figure 3.3 Methodological quality summary: judgments about each methodological quality item for each included study**



**Figure 3.4 Methodological quality graph: judgments about each methodological quality item presented as percentages for all included studies (n=11)**

Individual studies were assessed for methodological quality by the author and the independent reviewer, using the six domains in the Cochrane Risk of Bias tool, as previously described in Chapters 2 and 3. See table 2.1 for the specific criteria on how the judgments were made for each included study, and Appendix 6.8 for details on the judgments. Table 3.8 provides a summary of the risk of bias conclusions for each study.

**Table 3.8 Risk of bias summary: review authors' judgments within each study**

Study ID	Risk of bias
Basirat 2009	High risk of bias
Chittumma 2007	High risk of bias
Ensiyeh 2009	High risk of bias
Fischer-Rasmussen 1991	Moderate risk of bias
Keating 2002	High risk of bias
Ozgoli 2009	Moderate risk of bias
Pongroj paw 2007	High risk of bias
Smith 2004	High risk of bias
Sripramote 2003	High risk of bias
Vutyavanich 2001	High risk of bias
Willetts 2003	Moderate risk of bias

### 3.3 METHODOLOGICAL QUALITY OF GROUPS OF STUDIES

The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) has developed a system for grading the quality of evidence. For purposes of systematic reviews, the GRADE approach defines the quality of evidence for each individual outcome reported in a SR as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. Quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect

estimates and risk of publication bias. The Cochrane Collaboration has adopted these principles of the GRADE system.<sup>1</sup>

Taking into account that this SR included only 11 studies, which were split into 3 groups according to their comparators, and the largest group consisted of only 6 studies, no GRADE assessment was done. Meta-analyses performed on selected outcomes included at the most 3 studies per analyses. These small study numbers have lead to the decision that GRADE assessment were beyond the scope of the SR at this stage.

*Referencing in the remaining part of the results section is done following the Cochrane format (i.e. Author and Year) for included studies, to enable easy identification of relevant studies.*

### **3.4 EFFECTS OF INTERVENTIONS**

The primary outcomes for this review were as follows:

To assess the effectiveness of ginger in the treatment of pregnancy-associated nausea and vomiting, by assessing:

- 1) Symptomatic relief of nausea
- 2) Number of vomiting episodes
- 3) General response to treatment

The secondary objective of this systematic review was to assess the safety of ginger in the treatment of pregnancy-associated nausea and vomiting, by assessing:

- 1) adverse events or side effects (if any),
- 2) and to classify them as major (serious complications detrimental to the mother or fetus), or minor (discomfort, but manageable side effects).

The included studies were split into three groups, according to the comparison substance used. Placebo was used in six studies, and this was considered as a control substance. However, four studies used Vitamin B6 and one study used Dimenhydrinate as



comparator, and these two substances were considered active ingredients, and not controls. The analyses were done separately as these were different comparisons and they could not be pooled in one meta-analysis.

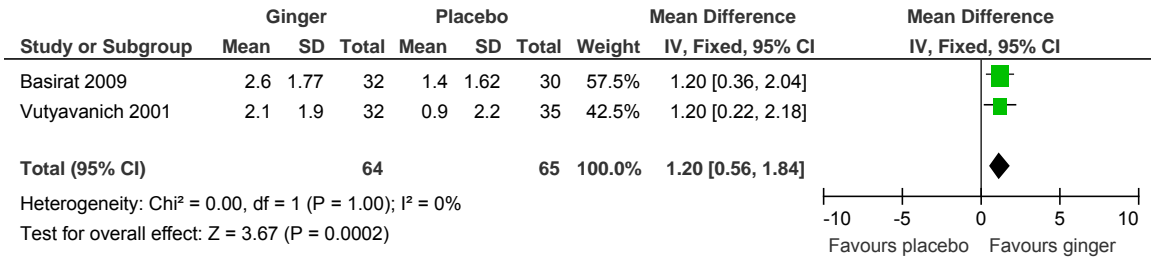
Subgroup analysis addressing dosage and duration aspects were performed for the primary objectives, namely the effectiveness of ginger for reduction in nausea and vomiting. Sensitivity analysis had been planned to explore the influence of study quality and source of funding, however, no sensitivity analyses could be performed as a result of an insufficient number of studies per comparison group.

### **3.4.1 Comparison 1: Ginger versus Placebo**

There were six studies assessing the effect of ginger versus placebo (Basirat 2009, Fischer-Rasmussen 1990, Keating 2002, Ozgoli 2009, Vutyavanich 2001, Willets 2003) of which one study (Fischer-Rasmussen 1990) was a crossover design and the remaining five studies were parallel group randomized controlled trials.

#### **3.4.1.1 Improvement in nausea symptoms**

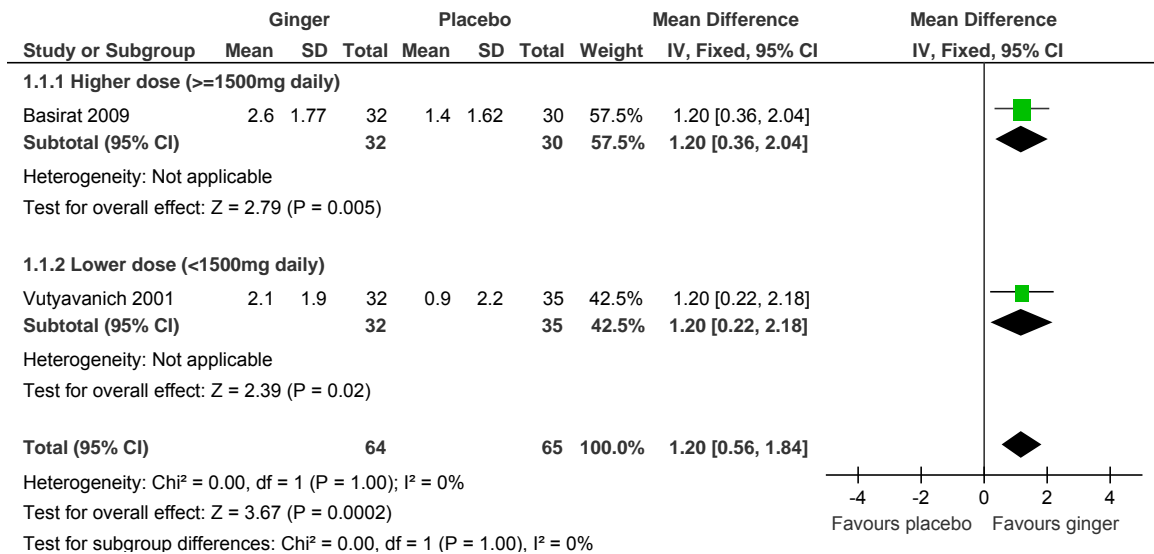
All six studies assessing the effect of ginger versus placebo reported this outcome but their results could not all be pooled in a meta-analysis. Two studies (Basirat 2009, Vutyavanich 2001) reported the reduction in the visual analogue scale of post-therapy minus baseline nausea as mean standard deviation (MSD) and their results were pooled in a meta-analysis. Ginger significantly decreased nausea symptoms when compared to the placebo (MD 1.20, 95% CI: 0.56 to 1.84,  $p=0.0002$  Figure 3.5) and there was no significant heterogeneity detected between the two studies ( $\text{Chi}^2=0.00$ ,  $p=1.00$ ,  $I^2=0\%$ , Figure 3.5)



**Figure 3.5: Forest plot of the improvement in nausea symptoms measured by change in VAS scores (ginger versus placebo)**

**3.4.1.1.1 Improvement in nausea symptoms: subgroup analyses regarding dose**

There were no significant subgroup differences between the higher dose ( $\geq 1500$  mg daily) and the lower dose ( $< 1500$  mg daily) with respect to the improvement in nausea symptoms (change in VAS scores) as shown in the figure below (Chi<sup>2</sup>=0.00, p=1.00, I<sup>2</sup>=0%, Figure 3.6). This implies there was no dose-response effect on this outcome.

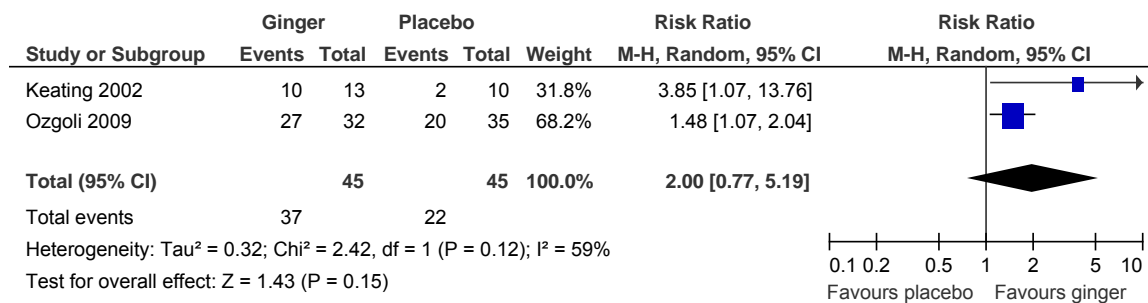


**Figure 3.6: Forest plot of the improvement in nausea symptoms (ginger versus placebo): subgroup analysis regarding dose ( $\geq 1500$  mg versus  $< 1500$  mg)**

No subgroup analysis with respect to duration was undertaken, as the two studies had the same duration of 4 days.

One study (Willets 2003) reported the trend in mean nausea experience scores for both the ginger and placebo groups in the form of a figure only, from which no MSD values could be extracted. No treatment effect could therefore be calculated. The author was contacted via e-mail to enquire about the missing data, but did not respond (see Appendix 6.3 “Letters to the authors”).

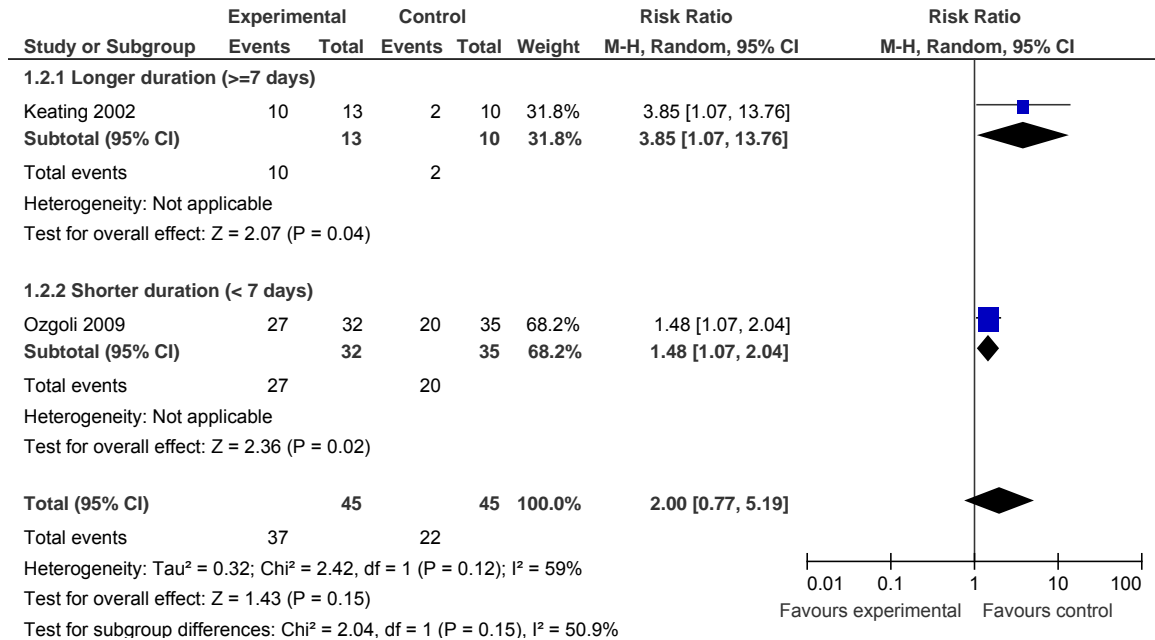
Two studies (Keating 2002, Ozgoli 2009) reported this outcome in terms of the number of women showing improvement in nausea symptoms (again measured by VAS scores). Meta-analysis of the results from these two studies shows that ginger failed to significantly decrease nausea symptoms when compared to the placebo (RR 2.00, 95% CI: 0.77 to 5.19,  $p=0.15$ , Figure 3.7) and there may be moderate heterogeneity between the two studies ( $\text{Chi}^2=2.42$ ,  $p=0.12$ ,  $I^2=59\%$ , Figure 3.6).



**Figure 3.7: Forest plot of the improvement in nausea symptoms, measured by the number of participants showing significant improvement**

#### 3.4.1.1.2 Improvement in nausea symptoms: subgroup analyses regarding duration

There were no significant subgroup differences between the longer duration ( $\geq 7$  days) and the shorter duration ( $< 7$  days) with respect to the improvement in nausea symptoms (number showing significant improvement) as shown in the figure below ( $\text{Chi}^2=2.04$ ,  $p=0.15$ ,  $I^2=50.9\%$ , Figure 3.8).



**Figure 3.8: Forest plot of the improvement in nausea symptoms (number showing significant improvement): subgroup analysis regarding duration ( $\geq 7$  days versus <7 days)**

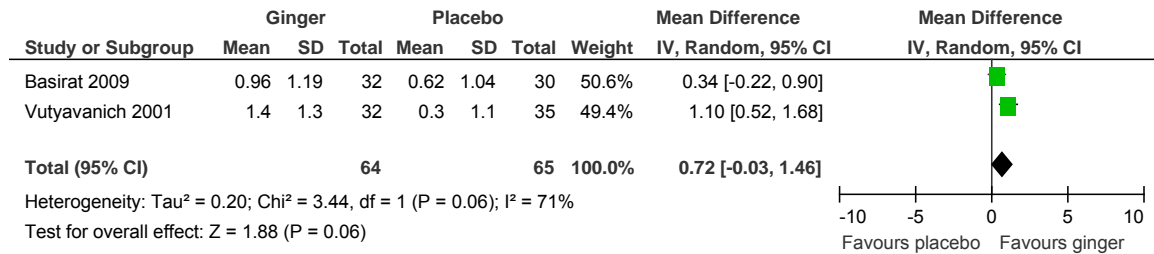
No subgroup analysis with respect to dose was undertaken, as the two studies had the same dosage of 1000 mg/day.

The remaining study (Fischer-Rasmussen 1991) was a crossover study which reported the relief scores on symptoms of a combination of nausea, vomiting, change in body weight, and patient's opinion about the treatment. The observed values for the relief scores were reported for each patient during the two periods of the crossover study in the form of a table. These values were used in calculating the MD and its standard error (SE) using a paired analysis and the 95% CIs were calculated using the generic-inverse variance method in RevMan 5. A significantly greater relief of the symptoms was found after ginger treatment compared to the placebo (MD 3.52, 95%CI: 0.27 to 6.77).

### 3.4.1.3 Reduction in the number of vomiting episodes

All six studies in this comparison reported a reduction in the number of vomiting episodes, but not all their results could be pooled in a meta-analysis. Two studies (Basirat

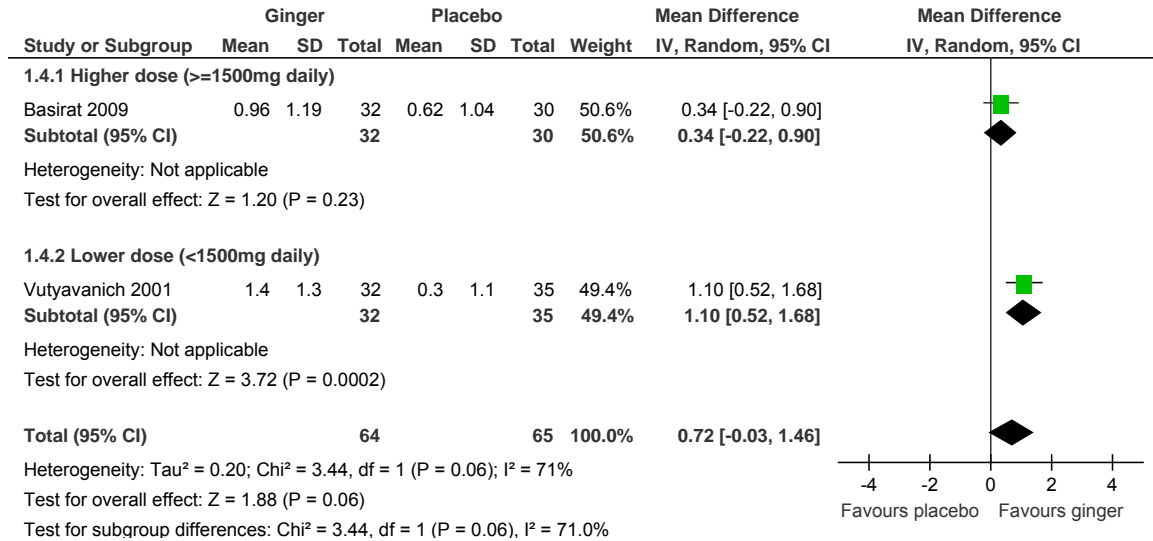
2009, Vutyavanich 2001) reported this outcome in the form of MSD, and their results could be pooled in a meta-analysis. According to the meta-analysis, ginger failed to significantly reduce the number of vomiting episodes compared to the placebo, although it did approach significance (MD 0.72, 95% CI: -0.03 to 1.46,  $p=0.06$ , Figure 3.7) and statistically significant heterogeneity was detected between the two studies ( $\text{Chi}^2=3.44$ ,  $p=0.06$ ,  $I^2=71\%$ , Figure 3.9).



**Figure 3.9: Forest plot of the reduction in the number of vomiting episodes (ginger versus placebo)**

#### 3.4.1.3.1 Reduction in the number of vomiting episodes: subgroup analyses regarding dose

There were no significant subgroup differences between the higher dose ( $\geq 1500$  mg daily) and the lower dose ( $< 1500$  mg daily) with respect to the reduction in the number of vomiting episodes as shown in the figure below ( $\text{Chi}^2=3.44$ ,  $p=0.06$ ,  $I^2=71\%$ , Figure 3.10). No dose-response effect was found on this outcome.



**Figure 3.10: Forest plot of the reduction in the number of vomiting episodes (ginger versus placebo): subgroup analyses regarding dose ( $>1500$ mg versus  $< 1500$ mg)**

No subgroup analysis with respect to duration was undertaken, as the two studies had the same duration of 4 days.

One study (Fischer-Rasmussen 1990) reported vomiting in conjunction with nausea scores (as mentioned above, in section 3.1.1.1 Improvement in nausea symptoms).

One study (Keating 2002) reported the number of women who stopped vomiting by day 6 of treatment. Treatment with ginger failed to significantly reduce the number of women who stopped vomiting by day 6, when compared to the placebo treatment (RR 3.33, 95% CI: 0.91 to 12.26).

One study (Ozgoli 2009) reported that incidence of vomiting decreased by 50% in the ginger group and 9% in the placebo group, but this information is insufficient for calculation of a treatment effect.

One study (Willets 2003) only reported that there was no significant difference between ginger extract and placebo groups for any of the vomiting symptoms but failed to give any values for the calculation of a treatment effect, as mentioned earlier.

### **3.4.1.3 Patients' subjective responses to treatment**

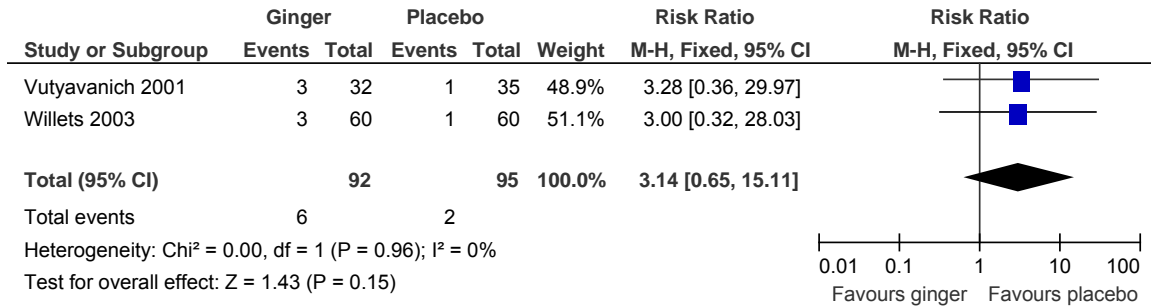
Only one study (Basirat 2009) measured this outcome using a Likert scale on which the women indicated improvement in symptoms. Ginger failed to significantly increase the number reporting improvement compared to the placebo (RR 1.25, 95% CI: 0.96 to 1.63).

### **3.4.1.4 The occurrence of adverse events**

Four studies (Basirat 2009, Keating 2002, Ozgoli 2009, Vutyavanich 2001) reported that none of the participants experienced any adverse events from ginger during the treatment period.

One study (Fischer-Rasmussen 1990) reported that one patient had a spontaneous abortion and one patient asked for a legal abortion. Because this trial had a crossover design and all patients received both treatments, no treatment effect could be calculated for the occurrence of spontaneous abortion after the treatment period.

Two studies (Vutyavanich 2001, Willets 2003) reported results on spontaneous abortions (major adverse event) and their results were pooled in a meta-analysis. No significant difference in the occurrence of spontaneous abortions was found between the ginger and placebo treated groups (RR 3.14, 95% CI: 0.65 to 15.11,  $p=0.15$ , Figure 3.8) and there was no statistically significant heterogeneity detected between the two studies ( $\text{Chi}^2=0.00$ ,  $p=0.96$ ,  $I^2=0\%$ , Figure 3.11). The confidence interval is wide (with upper limit 15.11) as the numbers of events in both treatment arms are too small.



**Figure 3.11: Forest plot of the occurrence of spontaneous abortions (ginger versus placebo)**

One study (Willets 2003) reported results on treatment intolerance (minor side effect) and there was no statistically significant difference found between the ginger and placebo treated groups (RR 9.00, 95%CI: 0.50 to 163.58).

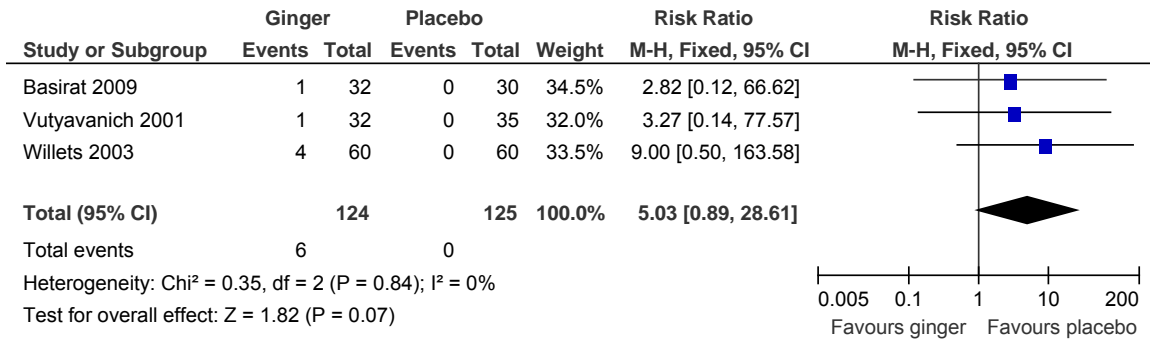
One study (Willets 2003) reported results on worsening of symptoms requiring medical assistance (minor side effect). There was no statistically significant difference found between the ginger and placebo treated groups (RR 0.50, 95%CI: 0.05 to 5.37).

#### 3.4.1.5 The occurrence of side effects

Three studies (Fischer-Rasmussen 1990, Keating 2002, Ozgoli 2009) reported that none of the participants experienced any side effects from ginger during the treatment period.

Three studies (Basirat 2009, Vutyavanich 2001, Willets 2003) reported heartburn (minor side effect) and their results were pooled in a meta-analysis. No significant difference in the occurrence of heartburn was found between the ginger and placebo treated groups (RR 5.03, 95% CI: 0.89 to 28.61, Figure 3.12) and no statistically significant heterogeneity was detected between the two studies (Chi<sup>2</sup>=0.35, p=0.84, I<sup>2</sup>=0%, Figure 3.12).





**Figure 3.12: Forest plot of the occurrence of heartburn (ginger versus placebo)**

One study (Basirat 2009) reported results on drowsiness (minor side effect) and there was no statistically significant difference found between the ginger and placebo treated groups (RR 2.82, 95% CI: 0.12 to 66.62).

One study (Vutyavanich 2001) reported results on headache (minor side effect) and there was no statistically significant difference found between the ginger and placebo treated groups (RR 1.31, 95% CI: 0.44 to 3.89).

One study (Vutyavanich 2001) also reported results on abdominal discomfort and diarrhea (minor side effects) and the frequencies were the same for each of these side effects (one in the ginger group and none in the placebo group). These two side effects were represented in the same calculation of treatment effect which found no statistically significant difference between the ginger and placebo treated groups (RR 3.27, 95% CI: 0.14 to 77.57).

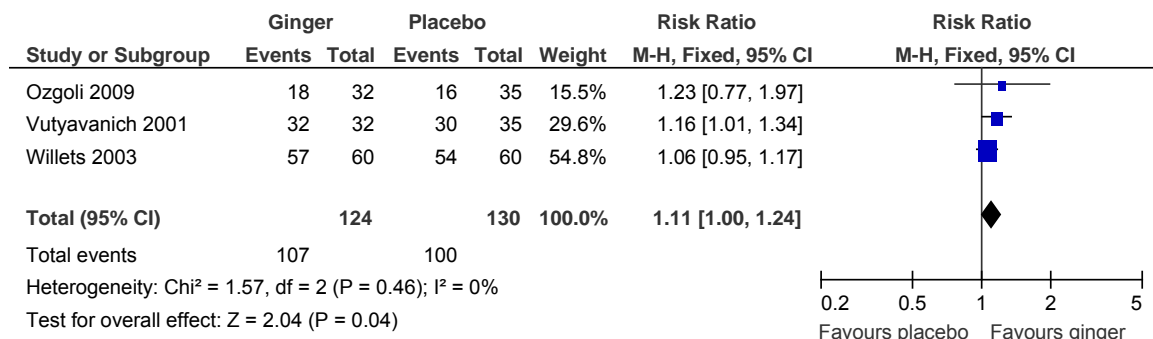
One study (Willets 2003) reported results on dehydration and allergic reaction to the treatment (major side effects), and the frequencies were the same for each of these side effects (one in the ginger group and none in the placebo group). These two side effects were represented in the same calculation of treatment effect which found no statistically significant difference between the ginger and placebo treated groups (RR 3.00, 95% CI: 0.12 to 72.20).

One study (Willets 2003) also reported results on worsening of symptoms requiring pharmaceutical treatment (minor side effect) and there was no statistically significant

difference found between the ginger and placebo treated groups (RR 0.33, 95% CI: 0.01 to 8.02).

### 3.4.1.6 Effect modifiers and confounders

Four studies (Basirat 2009, Ozgoli 2009, Vutyavanich 2007, Willets 2003) reported on compliance with treatment, but their results could not all be pooled in a meta-analysis. One study (Basirat 2009) reported that all of the women who finished the study complied with their respective treatments. Results from the remaining three studies (Ozgoli 2009, Vutyavanich 2007, Willets 2003) were pooled in a meta-analysis, and this indicated that the women taking ginger were more likely to comply with treatment compared to those taking the placebo (RR 1.11, 95% CI: 1.00 to 1.24,  $p=0.04$ , Figure 3.13) and there was no statistically significant heterogeneity between the three studies ( $\text{Chi}^2=1.57$ ,  $p=0.46$ ,  $I^2=0\%$ , Figure 3.13).



**Figure 3.13: Forest plot of participants' compliance with treatment (ginger versus placebo)**

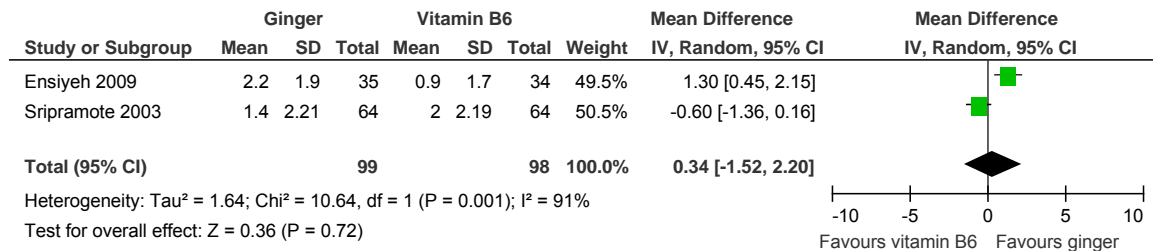
Co-treatment that could influence ginger's effects was considered as a possible confounder. The three studies (Basirat 2009, Ozgoli 2009, Vutyavanich 2007) that assessed this outcome reported that none of the participants took any other medication for nausea or vomiting.

### 3.4.2 Comparison 2: Ginger versus Vitamin B6

Four of the included studies assessed the effect of ginger versus vitamin B6 (Chittumma 2007, Ensiyeh 2009, Smith 2004, Sripramote 2003).

#### 3.4.2.1 Improvement in nausea symptoms

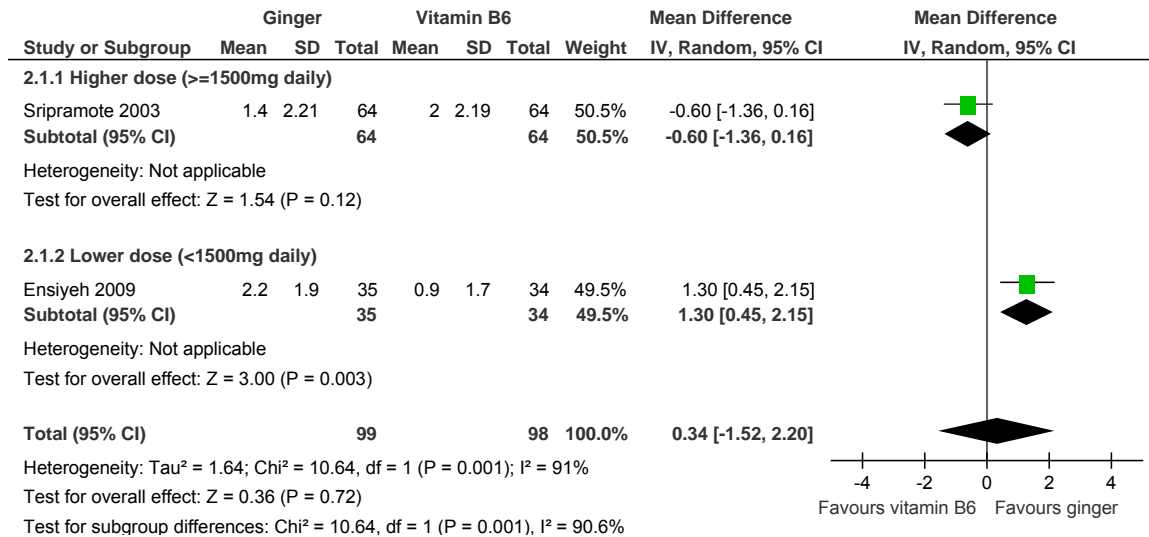
All four studies assessing the effect of ginger versus vitamin B6 reported this outcome, but their results could not all be pooled in a meta-analysis. Two studies (Ensiyeh 2009, Sripramote 2003) reported the reduction in the VAS scores of post-therapy minus baseline nausea as MSD and their results were pooled in a meta-analysis. According to this meta-analysis, ginger failed to significantly decrease nausea symptoms when compared to vitamin B6 (MD 0.34, 95% CI: -1.52 to 2.20,  $p=0.72$ , Figure 3.14) and significant heterogeneity was detected between the two studies ( $\text{Chi}^2=10.64$ ,  $p=0.001$ ,  $I^2=91\%$ , Figure 3.14).



**Figure 3.14: Forest plot of the improvement in nausea symptoms, as measured by change in VAS scores (ginger versus vitamin B6)**

#### 3.4.2.1.1 Improvement in nausea symptoms: subgroup analyses regarding dose

There were significant subgroup differences between the higher dose ( $\geq 1500$  mg daily) and the lower dose ( $< 1500$  mg daily) with respect to the improvement in nausea symptoms (change in VAS scores) as shown in the figure below ( $\text{Chi}^2=10.64$ ,  $p=0.001$ ,  $I^2=90.6\%$ , Figure 3.15). This implies there was a dose-response effect on this outcome in favour of lower dosage. The different dosages between the two studies may be the source of heterogeneity detected in this meta-analysis.



**Figure 3.15: Forest plot of the improvement in nausea symptoms as measured by the change in VAS scores (ginger versus Vitamin B6): subgroup analysis regarding dose ( $\geq 1500$ mg versus < 1500mg)**

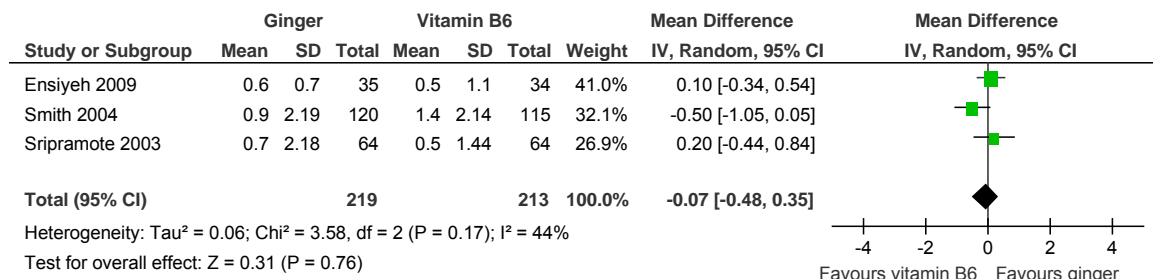
No subgroup analysis with respect to duration was undertaken, as the two studies had the similar short durations of 4 days and 3 days.

One study (Smith 2004) reported the reduction in nausea symptoms from baseline using the Rhodes Index of Nausea (ranging from 0 to 12, with larger scores indicating more symptoms). The results were reported in the form of mean standard errors (MSE) and these values were used in calculating the SDs. The means and SDs were used in calculating the mean difference (MD) and its 95% CIs. There was no statistically significant improvement of nausea symptoms with ginger treatment compared to vitamin B6 treatment (MD -0.3, 95% CI: -0.85 to 0.25).

The remaining study (Chittumma 2007) reported the reduction in nausea vomiting scales (episodes of nausea, duration of nausea, and number of vomits) using a modified Rhodes' score. The results were reported in form of MSD and were used in calculating the MD which showed that ginger treatment significantly improved the nausea and vomiting symptoms compared to vitamin B6 treatment (MD 0.70, 95% CI: 0.20 to 1.20).

### 3.4.2.2 Reduction in the number of vomiting episodes

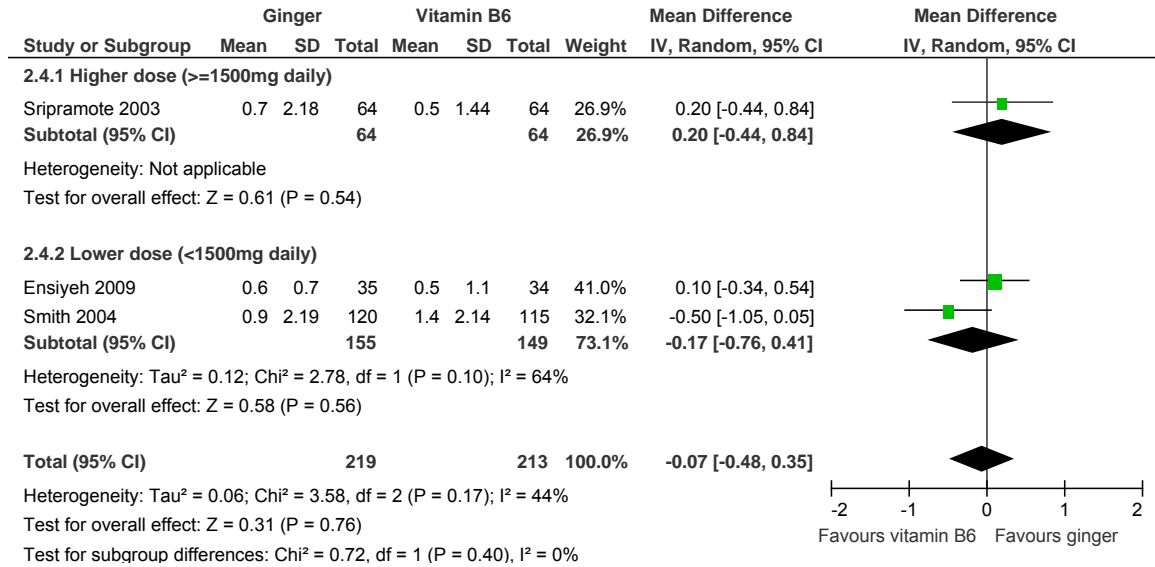
All four studies in this comparison group reported a reduction in the number of vomiting episodes, but not all the results could be pooled in a meta-analysis. Results from three studies (Ensiyeh 2009, Smith 2004, Sripramote 2003) were reported in the form of MSD which were pooled in a meta-analysis. According to this meta-analysis, ginger failed to significantly reduce the number of vomiting episodes when compared to vitamin B6 (MD -0.07, 95% CI: -0.48 to 0.35,  $p=0.76$ , Figure 3.16) and there may have been moderate heterogeneity between the three studies ( $\text{Chi}^2=3.58$ ,  $p=0.17$ ,  $I^2=44\%$ , Figure 3.16).



**Figure 3.16: Forest plot of the reduction in the number of vomiting episodes (ginger versus vitamin B6)**

#### 3.4.2.2.1 Reduction in the number of vomiting episodes: subgroup analyses regarding dose

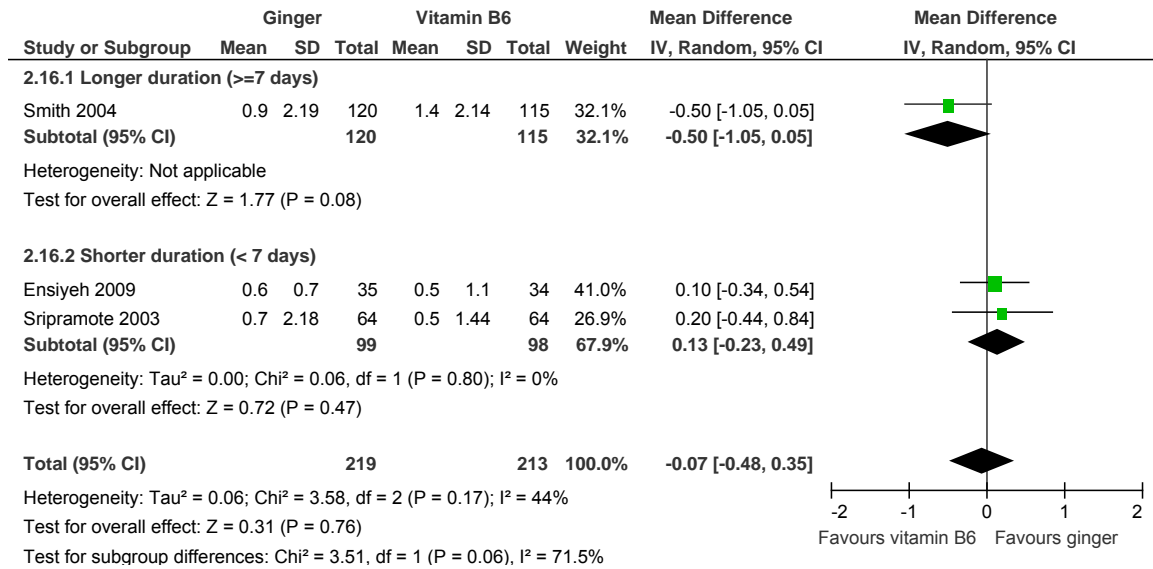
There were no significant subgroup differences between the higher dose (>1500 mg daily) and the lower dose (<1500 mg daily) with respect to the reduction in the number of vomiting episodes as shown in the figure below ( $\text{Chi}^2=0.72$ ,  $p=0.40$ ,  $I^2=0\%$ , Figure 3.17). This implies there was no dose-response effect on this outcome.



**Figure 3.17: Forest plot of the reduction in the number of vomiting episodes (ginger versus vitamin B6): subgroup analysis regarding dose (>1500mg versus <1500mg)**

**3.4.2.2.2 Reduction in the number of vomiting episodes: subgroup analyses regarding duration**

There were no significant subgroup differences between the longer duration ( $\geq 7$  days) and the shorter duration ( $< 7$  days) with respect to the reduction in the number of vomiting episodes as shown in the figure below ( $\text{Chi}^2=3.51$ ,  $p=0.06$ ,  $I^2=71.5\%$ , Figure 3.18). This implies there was no duration-response effect on this outcome.

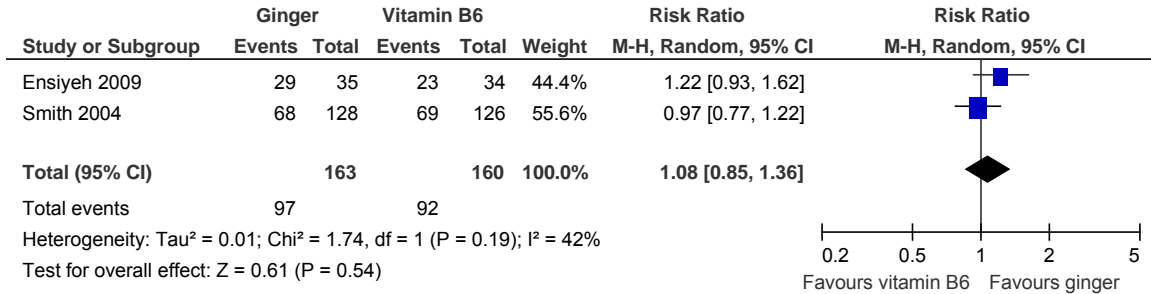


**Figure 3.18: Forest plot of the reduction in the number of vomiting episodes (ginger versus vitamin B6): subgroup analysis regarding duration ( $\geq 7$  days versus  $< 7$  days)**

The remaining one study (Chittumma 2007) reported vomiting in conjunction with nausea as mentioned above.

### 3.4.2.3 Patients' subjective responses to treatment

Only two studies (Ensiyeh 2009, Smith 2004) measured this outcome using a Likert scale and reported the number of participants who indicated improvement of NVP symptoms during treatment. Ginger failed to significantly increase the number reporting improvement compared to the placebo (RR 1.08, 95% CI: 0.85 to 1.36,  $p=0.54$ , Figure 3.19) and there may have been moderate heterogeneity between the three studies ( $\text{Chi}^2=1.74$ ,  $p=0.19$ ,  $I^2=42\%$ , Figure 3.19).

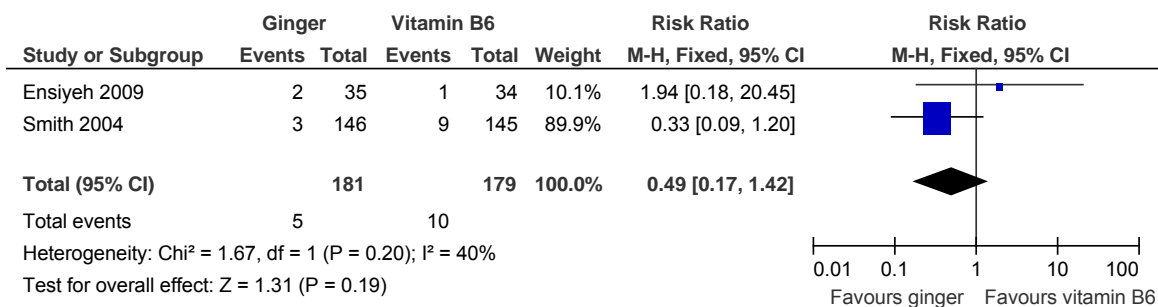


**Figure 3.19: Forest plot of the participants' general response to treatment (ginger versus placebo)**

### 3.4.2.4 The occurrence of adverse events

Two studies (Chittumma 2007, Sripramote 2003) reported that none of the participants experienced any adverse events from either ginger or vitamin B6 during the treatment period.

Two studies (Ensiyeh 2009, Smith 2004) reported results on spontaneous abortions (major adverse events) and their results were pooled in a meta-analysis. No significant difference in the occurrence of spontaneous abortions was found between the ginger and vitamin B6 treated groups (RR 0.49, 95% CI: 0.17 to 1.42,  $p=0.19$ , Figure 3.20) and there was no statistically significant heterogeneity detected between the two studies ( $\text{Chi}^2=1.67, p=0.20, I^2=40\%$ , Figure 3.20).



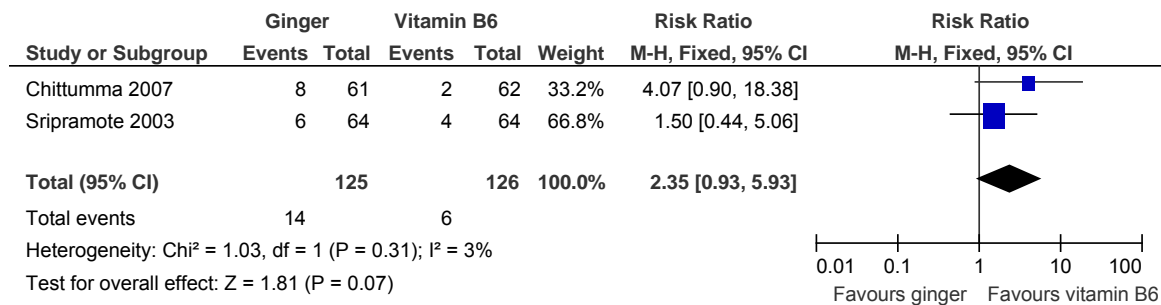
**Figure 3.20: Forest plot of the occurrence of spontaneous abortions (ginger versus vitamin B6)**



### 3.4.2.5 The occurrence of side effects

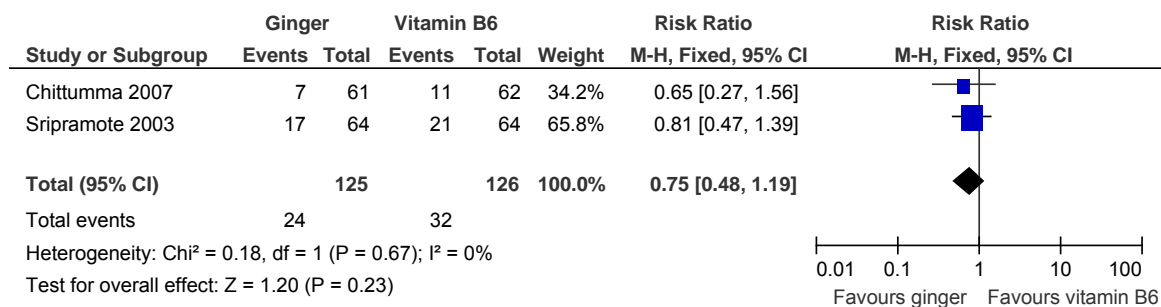
Only one study (Ensiyeh 2009 ) reported that none of the participants experienced any side effects of either ginger or vitamin B6 during the treatment period.

Two studies (Chittumma 2007, Sripramote 2003) reported the side effect of heartburn (minor side-effect) and their results were pooled in a meta-analysis. No significant difference in the occurrence of heartburn was found between the ginger and vitamin B6 treated groups (RR 2.35, 95% CI: 0.93 to 5.93,  $p=0.07$ , Figure 3.21) and there was no statistically significant heterogeneity detected between the two studies ( $\text{Chi}^2=1.03$ ,  $p=0.31$ ,  $I^2=3\%$ , Figure 3.21).



**Figure 3.21: Forest plot of the occurrence of heartburn (ginger versus vitamin B6)**

The above-mentioned two studies (Chittumma 2007, Sripramote 2003) also reported drowsiness (minor side effect) and their results were pooled in a meta-analysis. No significant difference in the occurrence of drowsiness was found between the ginger and vitamin B6 treated groups (RR 0.75, 95% CI: 0.48 to 1.19,  $p=0.23$ , Figure 3.22) and there was no statistically significant heterogeneity detected between the two studies ( $\text{Chi}^2=0.18$ ,  $p=0.67$ ,  $I^2=0\%$ , Figure 3.22).



**Figure 3.22: Forest plot of the occurrence of drowsiness (ginger versus vitamin B6)**

One study (Chittumma 2007) reported results on arrhythmia (major side effect) and there was no statistically significant difference found between the ginger and vitamin B6 treated groups (RR 0.51, 95% CI: 0.05 to 5.46)

One study (Smith 2004) reported results on belching (minor side effect). Ginger significantly increased the risk of belching compared to vitamin B6 (RR 27.18, 95%CI: 1.63 to 453.06). One study (Smith 2004) reported results on dry retching after capsule ingestion (minor side effect) and there was no statistically significant difference found between the ginger and vitamin B6 treated groups (RR 0.93, 95%CI: 0.76 to 1.15).

One study (Smith 2004) also reported results on vomiting after ingestion of capsule (minor side effect), and there was no statistically significant difference found between the ginger and vitamin B6 treated groups (RR 1.51, 95%CI: 0.26 to 8.91). This study (Smith 2004) also reported results on burning sensation after ingestion of capsule (minor side effect), and there was no statistically significant difference found between the ginger and vitamin B6 treated groups (RR 1.01, 95%CI: 0.21 to 4.91).

#### **3.4.2.6 Effect modifiers and confounders**

Only one study (Chittumma 2007) reported on compliance with treatment, and a treatment effect was calculated. There was no statistically significant difference in the number of women who complied with treatment between the ginger and vitamin B6 treatment groups (RR 0.98, 95%CI: 0.91 to 1.06).

Only one study (Chittumma 2007) reported on co-treatment that could influence ginger's effects and a treatment effect was calculated. There was no statistically significant difference in the number of women who took other medications for nausea and vomiting between the ginger and vitamin B6 treatment groups (RR 0.25, 95%CI: 0.03 to 2.21).

#### **3.4.3 Comparison 3: Ginger versus Dimenhydrinate**

Only one included study (Pongroj paw 2007) assessed the effect of ginger versus dimenhydrinate.

#### **3.4.3.1 Improvement in nausea symptoms**

This study (Pongrojpraw 2007) reported a reduction in the VAS scores of post-therapy minus baseline nausea in the form of a figure only, from which no MSD values could be extracted. No treatment effect could therefore be calculated. The author was contacted via e-mail to enquire about the missing data, but did not respond (see Appendix 6.3 “Letters to Research Authors”).

#### **3.4.3.2 Reduction in the number of vomiting episodes**

This study (Pongrojpraw 2007) reported a reduction in the number of vomiting episodes in form of a figure from which the values for mean (SD) could not be extracted accurately. No treatment effect could therefore be calculated, as mentioned above.

#### **3.4.3.3 Patients’ subjective responses to treatment**

This outcome was not reported.

#### **3.4.3.4 The occurrence of adverse events and side effects**

No adverse events were reported. The study reported results on drowsiness (minor side effect). Dimenhydrinate significantly increased the risk of drowsiness compared to ginger (RR 0.08, 95% CI: 0.03 to 0.18).

The study also reported results on heartburn (minor side effect) and there was no statistically significant difference found between the ginger and dimenhydrinate treated groups (RR 1.44, 95% CI: 0.65 to 3.20).

#### **3.4.3.5 Effect modifiers and confounders**

Compliance with treatment and co-treatments that could influence ginger’s effects was not reported.

## **CHAPTER 4: DISCUSSION**

## **4.1. GENERAL**

The majority of the included RCTs and other study types in general (not included in this SR) indicate the possibility that ginger may be effective for the treatment of NVP. However, the small sample sizes and few study numbers analyzed per outcome, as well as differences in dosage and duration of treatment lead to high levels of inconsistency and heterogeneity in the results of the review. Unfortunately, many of the included studies did not present data in a usable form for inclusion in meta-analysis, or similar outcomes were reported differently and could not be pooled together. These factors limit the strength of evidence and cause uncertainty when interpreting the results. Therefore, these results can not be generalized to the pregnant population with confidence.

The assessment of nausea remains a subjective modality, despite standardized objective measurement tools specifically designed for this purpose. The outcomes of nausea improvement and general response to treatment (and also in most cases the occurrence of side effects) were based on the patient's own report thereof. The findings of this SR should be considered in context with general medical and nutritional management of pregnant women with NVP.

## **4.2 PRIMARY OUTCOMES**

### **4.2.1 Symptomatic Relief of Nausea**

Ginger versus placebo was assessed in six of the included studies.<sup>42,45,46,47,52</sup> Individually, all six studies concluded that ginger was more effective than the placebo in relieving the intensity of nausea, or NVP in general. One meta-analysis performed on two relatively large studies<sup>42,51</sup> (the total combined number of participants were 135) showed significant improvement of NVP with ginger when compared to the placebo. A meta-analysis on two other studies<sup>46,47</sup> (total number of participants were 96) showed that that ginger did not significantly improve NVP compared to the placebo. The single crossover design study<sup>45</sup> showed significantly greater relief from ginger than from the placebo, and the treatment effect of the remaining study<sup>52</sup> could not be calculated. These few studies could lead to a simple 'majority vote' that ginger might significantly improve nausea symptoms when

compared to the placebo, but the reality is that this evidence is too little and of too poor quality to draw conclusions. When taking into account that other SRs<sup>26,39,40,58</sup> and individual studies also concluded that ginger had beneficial effects on nausea during pregnancy, it is probably safe to assume that ginger has potential as a possible anti-emetic drug-alternative during pregnancy. The subgroup analyses performed in this SR found no duration-response effect to relieve nausea. The results of the subgroup analyses should however be interpreted with care, bearing in mind the limited number of studies included in these analyses. The theoretical physiological mechanism by which ginger affects the digestive system also supports this theory. Ginger can increase gastric contractility, speeding up gastric emptying, and therefore increasing the gastro-intestinal transit time of meals, which can decrease the feeling of nausea.<sup>23</sup> This topic is discussed in chapter 1.

Four studies<sup>43,44,49,50</sup> assessed ginger versus vitamin B6 for the treatment of NVP. The majority of this limited evidence showed that ginger does not seem to improve nausea symptoms significantly when compared to vitamin B6, or at best the two treatments could be considered as equally effective. The subgroup analysis found no dose-response effect to relieve nausea.

The study comparing ginger to dimenhydrinate concluded that ginger was as effective as dimenhydrinate in relieving symptoms of NVP, but no treatment effect could be calculated for any of the primary outcomes in this single study, thus no conclusions can be drawn from this limited evidence.

#### **4.2.2 Number of Vomiting Episodes**

Although three studies<sup>45,47,51</sup> of the six studies that assessed ginger versus placebo concluded individually that ginger was more effective than placebo in reducing the number of vomiting episodes, the remaining evidence and meta-analysis performed lead to the conclusion that ginger did not significantly reduce the number of vomiting episodes during NVP when compared to the placebo. The subgroup analysis performed indicated that the lower dosage of <1500mg ginger per day could possibly be more

effective than the higher dosage of  $\geq 1500\text{mg}$  (again, bearing in mind the limited value of the subgroup analyses).

A meta-analysis of three studies<sup>44,49,50</sup> showed that ginger did not significantly reduce vomiting episodes when compared to vitamin B6. One study<sup>43</sup> reported the nausea and vomiting symptoms together, which could influence the vomiting results, and significantly favoured ginger. Based on currently available evidence, the review author concluded that ginger does not seem to reduce the number of vomiting episodes significantly when compared to vitamin B6. The subgroup analysis performed found no duration-response effect.

#### **4.2.3 General Response to Treatment**

Only 3 of the 11 studies included in this SR reported on this outcome. One study<sup>42</sup> reported that ginger did not significantly result in better responses to the treatment, when compared to the placebo. A meta-analysis of two studies<sup>44,49</sup> showed that ginger did not significantly increase the number reporting improvement when compared to vitamin B6. Due to the small number of studies reporting this outcome, no conclusions can be drawn in this regard.

### **4.3 SECONDARY OUTCOMES**

#### **4.3.1 Adverse Events or Side effects**

Four studies<sup>42,46,47,51</sup> reported no adverse events when comparing ginger to placebo. Spontaneous abortion was reported in two studies,<sup>45,52</sup> both administering 1000mg ginger per day, but the difference was insignificant between the occurrences during treatment with ginger compared to treatment with the placebo.

Also, during the crossover trial<sup>45</sup> it cannot be determined which of the treatment groups would be the cause of abortion, since each participant received each intervention.

To conclude, ginger does not appear to pose a significant risk for spontaneous abortion during pregnancy when compared to the placebo, but due to the very large confidence intervals of most of the analyses, no firm conclusions can be drawn.

Heartburn, dizziness, headache, abdominal discomfort and diarrhea, allergic reaction, dehydration, and worsening of symptoms were reported as side effects in studies comparing ginger and placebo. No significant differences were found between the two treatment groups in any of these cases. Also, as discussed earlier, it should be kept in mind that many of these symptoms do occur spontaneously in pregnancy, due to physiological changes occurring in the body during this time. To conclude, ginger does not seem to pose a significant risk for side effects during pregnancy, when compared to placebo. Again, large CIs prevent firm conclusions from being drawn.

Two studies<sup>43,50</sup> reported that no adverse events occurred in either ginger or vitamin B6 groups. Two studies<sup>44,49</sup> reported spontaneous abortion occurring, and no significant difference was found between ginger and vitamin B6 groups. According to this evidence, ginger does not pose a greater risk for spontaneous abortion, when compared to vitamin B6.

One study<sup>44</sup> reported that no side effects occurred in either ginger or vitamin B6 groups. Two studies<sup>43,50</sup> reported heartburn and drowsiness as side effects, but no significant difference was found between the two groups. One study<sup>49</sup> reported belching as side effect, and it was shown to be significantly increased by ginger, when compared to vitamin B6. Due to its very large CI, no firm conclusion can be drawn on this effect.

Arrhythmia, dry retching, vomiting after ingestion, and burning sensation after ingestion was reported in studies comparing ginger and vitamin B6, but there was no significant difference between the two treatment groups for any of these side effects. To conclude, there is no increased risk for side effects occurring during ginger treatment, when compared to vitamin B6 treatment, but due to large CIs we cannot be absolutely sure of the treatment effect.



Only one study<sup>48</sup> compared ginger and dimenhydrinate. This study showed a significantly increased risk of drowsiness in the dimenhydrinate group, compared to ginger. Heartburn was also reported, but no significant difference was found between the two groups. This single study concluded that ginger posed less of a risk for the side effect of drowsiness, when compared to dimenhydrinate.

#### **4.3.2 Classification of Adverse Events or Side effects as Major or Minor**

The author made subjective judgments to classify the occurring side effects as major (serious complications detrimental to the mother or fetus), or minor (discomfort, but manageable side effects). These judgments can be viewed in Table 3.7. The events classified as major were arrhythmia, spontaneous abortion, allergic reaction to treatment, and dehydration. All the other events were classified as minor. According to the evidence as described above, ginger does not pose a risk for any side effects or adverse events occurring, thus no risk for any serious complications detrimental to the mother or fetus.

#### **4.3.3 Effect Modifiers and Confounders**

Women taking ginger were more likely to comply with the treatment, than those taking the placebo. No conclusions can be drawn from the studies comparing ginger and vitamin B6, as only one study reported this outcome.

### **4.4 OVERALL COMPLETENESS AND QUALITY OF EVIDENCE**

Eleven RCTs involving 1176 pregnant women were included in this SR. The search strategy was as inclusive as possible. Literature included in the review was researched in Europe, Australia, Iran, Thailand and the USA, thus including a wide spectrum of different continents and cultures.

The methodological quality of the included studies was varied. All studies were either at moderate risk for bias, or at high risk for bias, mainly due to lack of blinding. The overall quality of evidence was low, due to heterogenic data (regarding the dose, duration and control treatments, as well as the outcome measures) hence the high risk of bias and

the imprecision of results, as seen in the wide confidence intervals obtained from the statistical analyses.

The small study numbers per comparison group have lead to the decision that GRADE assessment were beyond the scope of the SR at this stage.

#### **4.5 POTENTIAL BIASES IN THE REVIEW PROCESS**

Publication bias is always a concern when a SR is conducted, as it is known that studies with a negative result are often not published, and therefore more easily missed or overlooked during the study search and selection process. This may lead to misleading overall results and overestimation of effects in systematic reviews. Ginger is considered as a complementary and/or alternative medicine (CAM).<sup>57</sup> The publication of literature on CAM therapies might be suboptimal.<sup>26,57</sup> The electronic database search was limited to studies published in English, leading to studies published in another language being overlooked.

As with all SRs, there was potential for bias at all stages of the reviewing process. Minimizing bias was attempted by having two persons independently assess quality and extract data, but these were still subjective judgments which could have differed from another review team's judgments.

#### **4.6 AGREEMENTS AND DISAGREEMENTS WITH OTHER REVIEWS**

Recent SRs done on the same subject include Ernst,<sup>26</sup> Betz,<sup>32</sup> Borrelli,<sup>39</sup> Jewel<sup>40</sup> and Matthews.<sup>58</sup> The Cochrane review by Jewel et al has been updated and replaced by the Cochrane review done by Matthews et al.

*Borrelli et al*<sup>39</sup> conducted a SR in 2005 similar to this one, also evaluating the effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. They included six studies<sup>35, 36, 39, 40, 41, 42</sup> (all of which are also included in this SR). The conclusion was that ginger may be a safe and effective option for the treatment of nausea and vomiting in pregnancy. They based their conclusion on the fact that results

of the studies were largely positive, and the absence of adverse effects on pregnancy outcome. Meta-analyses were not performed. They recommended that randomized clinical trials with larger sample sizes be conducted to confirm the issue of safety of ginger during pregnancy.

**Ernst and Pittler**<sup>26</sup> did a SR in 2000 on the efficacy of ginger for nausea and vomiting, not necessarily related to pregnancy, but including different causes for the nausea and vomiting. They included six trials, namely three trials done on post-operative nausea and vomiting, one on seasickness, one on chemotherapy-induced nausea, and one study on NVP (the study done by Fischer-Rasmussen<sup>45</sup>, on hyperemesis gravidarum). Meta-analyses were not performed. They concluded that ginger is a promising anti-emetic herbal remedy, but the clinical data are insufficient to draw firm conclusions. The majority of their studies reported that 1 gram of ginger powder per day alleviated clinical nausea, resulting from diverse causes. As Borelli et al recommended, these authors also felt that there is a need for more observational studies with larger sample sizes, especially to confirm ginger safety.

**Betz et al**<sup>32</sup> conducted a SR in 2005 on ginger's clinical role as an anti-emetic against kinetosis, post-operative nausea and vomiting, as well as NVP and HG. They concluded that no clear evidence was found for ginger as treatment for kinetosis and post-operative nausea and vomiting, but the evidence for ginger as treatment for NVP was encouraging. They warned that ginger should, for the time being, be administered in controlled clinical studies only, until safety has been proven. They observed that a dosage of up to 6g per day resulted in few or no side effects.

**Fugh-Berman and Kronenberg**<sup>57</sup> performed a review in 2002 of RCTs done on women of reproductive age who use complementary and alternative medicine (CAM). This included women with premenstrual syndrome, dysmenorrhea, infertility and a range of pregnancy-associated problems including NVP, pain, cramping and edema. The interventions included a range of vitamins, minerals, herbs, dietary changes, exercise, massage and acupuncture. Meta-analyses were not performed. The authors concluded that both ginger and vitamin B6 have potential as treatment for nausea during pregnancy and

should be investigated further, and also that acupuncture point stimulation (by acupressure) has great potential as a non-invasive treatment for NVP, as also described by Steele et al.<sup>16</sup>

*Matthews et al*<sup>58</sup> published a SR in 2010, this is an updated version of the SR done by Jewel et al which was published in 2003. This SR reviewed interventions for nausea and vomiting in early pregnancy. The interventions included acupressure, acustimulation, acupuncture, ginger, vitamin B6, and several anti-emetic drugs. Due to the heterogeneity in participants, interventions, outcomes and comparison groups, the findings could not be pooled. Twenty-seven trials were included, of which nine trials<sup>43,44,46-52</sup> examined the use of ginger for NVP. These nine studies are also included in this current SR. Their conclusion was that “the use of ginger products may be helpful to women, but the evidence of effectiveness was limited and not consistent.”

To conclude, the findings of this current SR compare well with the findings of the five above-mentioned reviews. None of these SR's were able to statistically pool their results into meta-analyses, due to the heterogeneity in participants, interventions, outcome measures and comparison groups. This clearly shows the need for more research on the topic, with larger studies and standardization of methods and materials. All these reviews did agree that ginger may be effective for the treatment of NVP, but data is insufficient to draw firm conclusions regarding the dosage and duration of treatment. They all also agree that ginger seems to be a safe option during pregnancy, with only minor side effects occurring, but again insufficient data prevent firm conclusions from being drawn.

Chrubasik et al<sup>23</sup> and Betz et al<sup>32</sup> have observed that doses of up to 6g per day resulted in few or no side effects, but because this SR did not observe these high daily doses, this recommendation cannot be seconded. Animal studies done on this subject have explored the issue of safety and dosage in more detail than any human studies performed in this regard. Two studies performed on rats have yielded contradictory results. The study done by Weidner and Sigwart<sup>59</sup> concluded that ginger extract in doses of up to 1000mg/kg body weight administered to pregnant rats, during the early weeks of pregnancy and

organogenesis, caused no maternal nor fetal toxicity or complications, and was thus safe during pregnancy.

In contradiction, the study conducted by Wilkinson,<sup>60</sup> also performed on rats, concluded that ginger tea of up to 50g per litre posed no risk for maternal toxicity, but the embryonic loss in the treatment group was double that of the control group. Strangely, the surviving fetuses exposed to ginger were heavier and had more advanced skeletal development. Of course, as with most animal studies, it should be kept in mind that experimental animals are exposed to proportionately much higher dosages than human intake would be.

#### **4.7 STRENGTHS AND LIMITATIONS OF THIS SYSTEMATIC REVIEW**

One of the strengths of this SR is that it includes more studies than any other previous SR has done on this topic. A major limitation however, is the introduction of publication bias by excluding foreign language reports in the search for studies. This was done to minimize the search items. The majority of studies had a small sample size and patients were recruited from a single site, introducing bias related to small study effects.

None of the eleven studies included in this SR described any form of chemical or chromatographic tests to verify the exact composition of the active compounds in the ginger preparations. Six studies<sup>42,45,47,48,49,52</sup> gave no description of the preparation or testing of the ginger formulae, and the remaining 5 studies<sup>43,44,46,50,51</sup> described the preparation of the formulae, but no testing of the final product. One study (Vutyavanich 2001<sup>51</sup>) mentioned that they considered this absence of chemical or chromatographic testing as a limitation of their study.

##### **4.7.1 Confounding Factors**

###### **4.7.1.1 Dietary advice given in some studies**

Many of the included studies<sup>43,44,46,47,50,51</sup> mentioned in their methodology that dietary advice was given to all the participants, in both the experimental and the control groups.

This advice was given before the starting of treatment, and the advice was to eat smaller meals more regularly, and to decrease fatty foods and increase starchy foods, in order to manage their nausea and vomiting symptoms better. None of these studies gave any further information on the dietary advice – they did not follow up on this to see which of the participants followed the advice, or to what extent any of the dietary adjustments were made.

Because the advice was given to both the experimental and the control groups, one could argue that it ‘balances out’ and would not confound any results. But one could also argue that some participants might have followed the dietary advice religiously, and could have made really drastic dietary adjustments which could have improved their NVP symptoms significantly, whether on treatment or on placebo. This should then be taken into account when considering the results of that study, as the dietary changes could be a confounding factor.

As with all nutritional research studies, it is difficult to control every exposure and it is almost impossible to keep all dietary exposures identical for all participants.

#### **4.7.1.2 The use of other medications during some trials**

Two studies<sup>43,49</sup> allowed the participants to continue using medication throughout the trials. The study done by Chittumma<sup>43</sup> allowed the participants to continue with other medicines, which included medicines for headaches and the common cold, other ginger products, and also anti-emetics. The study by Smith et al<sup>49</sup> allowed the use of any existing medicines, except for ginger and vitamin B6 products. Many women (75%) reported using anti-emetics during the course of this trial. The researchers documented the use before and after the trial, and the analyses were adjusted to accommodate this factor. One could argue that as long as the medicine was used continuously throughout the trial, then the intervention would still be the only change, thus any changes in NVP symptoms occurring could still be attributed to the intervention. But still many medications (especially anti-emetics) can have an influence on gastro-intestinal factors,

which can contribute to, or lessen the symptoms of NVP, thus acting as a confounding factor.

#### **4.7.1.3 Adjustment of control intervention**

The study done by Pongrojpa<sup>48</sup> compared ginger and dimenhydrinate. In the methodology of the study, the authors mention that they decreased the dosage of the dimenhydrinate to improve patient compliance, due to the unpleasant side effect of drowsiness. The usual dose for dimenhydrinate is 50mg three times daily, and they decreased it to 50mg twice daily, to prevent patient drop-outs. This could have affected results, as the usual dose is the one that will be taken in real life situations. When considering the analysis for this specific outcome, it showed a significantly increased risk of drowsiness in the dimenhydrinate group, compared to the ginger group (RR 0.08, 95% CI 0.03, 0.18). Thus, ginger poses less of a risk for the side effect of drowsiness, when compared to dimenhydrinate – and the risk would be even less when compared to the usual larger daily dose.

#### **4.7.2 Limitations of the Intervention Itself**

Ginger has a very characteristic and recognizable taste, which makes it difficult to mask during trials. Even when the ginger is in powdered form contained inside a capsule, the taste may still be recognized when ‘belching’. Also, due to the somewhat uncomfortable side effects of heartburn and belching, the taste or smell of ginger can be aggravated. In a few of the included studies, it was mentioned that some of the participants could correctly identify what they were taking, when asked after completion of the trial. This fact could act as a potential confounder, as it can be considered ‘unblinding’.

A possible solution to this problem is to do pre-trial testing, as was done in the study by Vutyavanich et al,<sup>52</sup> to test if the patients are able to identify the treatment before the start of the trial.

The comparator compound can also have limitations. Vitamin B6 or pyridoxine has been shown to be an effective emetic when used together with doxycycline.<sup>6,7</sup> Individual

studies have indicated that vitamin B6 on its own can also be effective against NVP.<sup>18,19</sup> The RCT performed by Vutyavanich et al<sup>19</sup> concluded that 30mg of vitamin B6 per day is effective against nausea, but not against vomiting during pregnancy. Sahakian et al<sup>18</sup> concluded that 75mg vitamin B6 per day is effective for both nausea and vomiting during pregnancy. SRs on this subject are lacking, and two SRs done on different treatments for NVP<sup>39,57</sup> have concluded that there are insufficient studies available on vitamin B6 and NVP to draw conclusions about efficacy. This could be a possible subject for future research.

#### **4.6.3 Differences between Protocol and Review**

- Language restriction in search method: Initially no language restriction was planned, but later we restricted it to English language, to make the search more practical.
- Sensitivity analyses were planned, if practical and possible. However, due to the small number of studies per comparison, no sensitivity analyses could be performed.
- Classification of the identified adverse effects and side effects (if any) as major or minor was planned in the protocol. The statistical analyses performed concluded that ginger did not pose a significant risk for side effects or adverse events when compared to any of the comparator groups, and therefore the classification was not explored further.
- It was envisaged that clear conclusions would be drawn and recommendations made about the duration and dosage of ginger for the treatment of NVP, and that these recommendations would be available to doctors, gynaecologists, midwives and dieticians. Recommendations were made according to the results obtained from the subgroup analyses, but should however, be interpreted with care, due to the limited number of studies included per comparison group.



## **CHAPTER 5: CONCLUSION**

## 5.1 AUTHOR'S CONCLUSIONS

The present literature indicate that there is little known about the exact cause and treatment of NVP.<sup>42-52,56,58</sup> Currently there is only weak evidence suggesting a significant benefit from ginger supplementation for symptom relief in this regard. A review of RCTs on Complementary and alternative medicine (CAM) usage in women of reproductive age reported that women are more frequent users of CAM than men.<sup>57</sup> Women who are trying to conceive and pregnant women are also regular users of CAM. Therefore there is a definitive need for clear recommendations on CAM usage with regard to dosage and duration of treatment, especially for pregnant women.

According to the comparisons made and analyses done in this SR, no firm conclusions can be drawn due to the small study numbers per comparison, and also the relatively small sample sizes in the studies. Taking these limitations into account, the investigators still came to the following conclusions:

There appears to be a trend towards a lessening of nausea when treating NVP with ginger, compared to placebo, but ginger does not appear to improve nausea symptoms when compared to vitamin B6. Vomiting episodes are not significantly reduced by ginger, when compared to placebo or to vitamin B6. No improvement has been observed in terms of the patients' general response to ginger treatment. The few subgroup analyses performed addressing dosage and duration aspects, indicated a favoring of the lower dosage of <1500mg of ginger per day for reduction in nausea, and no duration-response effect was observed. The subgroup analyses should however, be interpreted with extreme caution due to the limited number of studies per group.

There appears to be no significant indication of harm, since the evidence concluded that ginger during the first trimester of pregnancy does not pose a significant risk for side effects or adverse events, including spontaneous abortion during pregnancy, when compared to placebo or vitamin B6. In fact, ginger poses less of a risk for the side effect of drowsiness, when compared to dimenhydrinate, and was observed to be as effective as dimenhydrinate.

When looking at these apparently positive results, and the absence of side effects and adverse events, ginger may *possibly* be considered an effective and safe option for women suffering from NVP. However, when the statistical analyses done in the SR are taken into account, it can be seen that ginger actually did not have a significant impact on the vomiting episodes, and it did not pose a risk for side effects or adverse events during pregnancy. Thus, even though there is not enough evidence to draw conclusions with absolute certainty, the review authors conclude that the use of ginger products may be helpful to pregnant women to relieve nausea, but the evidence of the effectiveness and safety was limited and not consistent. It can be considered a harmless (and possibly effective) alternative option for women suffering from the unpleasant symptoms of NVP, who choose not to use conventional medication during pregnancy.

## 5.2 RECOMMENDATIONS FOR PRACTICE

Due to this SR's unclear findings, no specific recommendations can be made on the dosage or duration of the ginger treatment. As described in chapter 3, the dosage that was used in the majority of the included clinical trials<sup>44,45,46,47,48,51,52</sup> was 1000mg of ginger powder per day. This was also the lowest dose, and thus theoretically the safest dose. The majority of the studies used this dose for a duration of 4 days.<sup>42,43,44,45,47,51,52</sup>

Due to the possible positive effect for some women, and the fact that no significant adverse events or side effects were demonstrated in this SR, the authors would recommend that medical personnel working with pregnant women (including general practitioners, gynaecologists, midwives, nurses and dieticians) be informed about the *possible* benefit that 1000mg of ginger per day can have on NVP during the first trimester of pregnancy. The evidence<sup>44-48,51,52</sup> suggests taking the dose in three to four divided doses during the day, irrespective of mealtimes. Due to the absence of harmful effects on the mother or baby, it can, based on the current available evidence be considered a safe and 'natural' alternative to other anti-emetics. The mother should be informed that no guarantees can be given that this treatment will bring relief of symptoms, but at least evidence suggests that there is no risk of damage to the fetus involved.

Currently in South Africa ginger capsules are not widely available, but there are quite a few ginger products on the market, including ginger tea and ginger lollipops specifically aimed at pregnant women (the 'Mama' range, from Purity), ginger biscuits, and a variety of different teas with ginger blends, as well as ginger ale or ginger beer soft drinks. Fresh, ground or crushed ginger is also readily available.

Medical personnel can advise mothers to use ginger freely in their cooking, to drink ginger tea and soft drinks, and have dry ginger biscuits as needed. The amounts of ginger powder found in teas, soft drinks and biscuits are difficult to determine, and each manufacturing company will have to be contacted for this information. When considering the fact that 1000mg of ginger powder is equal to 3ml (just more than half a teaspoon), ingesting 1000 mg of powdered ginger fresh in food is unlikely because of its strong and pungent taste. However, it is clear that the safety aspect needs to be researched further, in order to specify the recommended dosage and duration of use.

### **5.3. RECOMMENDATIONS FOR FUTURE RESEARCH**

As other authors have indicated, it is recommended that further research be done on this subject, since the current recommendations are vague due to the small study numbers and sample sizes. Larger scale studies (RCTs) need to be conducted, and GRADE assessments could be included in future SR's.

#### **5.3.1 Standardization of Methods and Materials**

The way that the outcome data were measured and reported was inconsistent in most of the studies included in this review, and this should be kept in mind when interpreting the results. Future research should aim for consistent outcome measures among different studies, and the tools with which outcomes are measured should be standardized to suit the needs of interventions for nausea and vomiting in pregnancy. For instance, a standardized visual analogue scale can be developed for nausea intensity, or the Rhode's Index for Nausea and Vomiting can be included in all studies measuring NVP. With these clearer outcome measures, and more and larger studies, hopefully some clear-cut conclusions can be made with regard to the dosage and duration of treatment.

Differences among studies' interventions also contribute to problems when analyzing the results. Differences in the dosage, duration, quality and composition of the ginger powder or ginger extract may influence results. If studies are to be reproducible, the ginger composition and dosages need to be standardized.<sup>61</sup> High-performance liquid-chromatography is a well-established method for determining the concentrations of the active components of ginger (namely 6-gingerol, 6-shaogal, 8-gingerol and 10-gingerol) in dietary supplements, as used by Schwertner et al,<sup>61</sup> and can be considered as an option for use in future clinical trials. As mentioned in chapter 4, none of the 11 included studies reviewed in this SR, did any form of chemical or chromatographic testing on the ginger formulae administered to the participants.

The authors recommend that future research on this subject take into account the dietary factor as well, and standardize the dietary advice provided to the trial participants, as dietary and lifestyle adjustments can also affect the symptoms of NVP. Future SRs done on this topic should also attempt to include all studies regardless of the published language.

The physiological cause of NVP, as well as the mechanisms of action for ginger's effects on NVP are still relatively unknown<sup>57</sup> and could be a topic of interest for future research.

### **5.3.2 Funding of Research**

Unfortunately, herbs, vitamins and other natural products (including ginger) have limited patent potential and funding will therefore remain a problem for any CAM product. Industry-sponsored research will probably be limited and researchers will need funding from the relevant government or private institutions.<sup>57</sup>

### **5.3.3 Labeling of Ginger Supplementation**

CAM therapies are often presumed to be safe because they are natural products from plant origin, but the isolated and concentrated components might have different effects than in its original state.<sup>57</sup> Lack of labeling legislation or product quality control might lead to very high dosages being ingested, when a consumer buys a ginger supplement

over the counter. A study done in the USA by Schwertner et al<sup>61</sup> on the variation in concentration and labeling of ginger root dietary supplements found that there is a very wide variation in the composition of the active compound, namely gingerol, and the suggested serving sizes of these ginger root capsules, from different manufacturers. Serving size recommendations were not found on all products in this study, and those that did make recommendations, varied from 0.25g to 4.77g ginger per day. This study also found that many supplements claim to contain certain amounts of active compounds in specific quantities (namely 6-gingerol, 6-shaogal, 8-gingerol and 10-gingerol) but then the high-performance liquid chromatography revealed that these claims were false or incorrect in many cases. The cause of the variation in these compounds is not known, but might be due to the source of the ginger, the age of the fresh product used for processing, processing methods, exposure to heat or other environmental factors.<sup>61</sup>

Many dietary supplements are imported from other countries into South Africa and therefore this problem should also be of concern in our country. Future research should aim to establish a safe upper limit for daily ginger ingestion and distribute this information to CAM manufacturing companies. The recommendation for the daily ingested dose should be expressed in many ways, including the amount of fresh ginger per day, of ginger extract per day, of ginger root powder per day, and amounts of 6-, 8-, or 10-gingerol or 6-shoagaol per day.

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**APPENDICES**

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**APPENDIX 6.1: Eligibility form**

**Eligibility Form: A Systematic review of the effects and safety of Ginger in the treatment of pregnancy-associated nausea and vomiting.**

Study ID: \_\_\_\_\_

Reviewer ID : \_\_\_\_\_

<b>Type of Study</b>			
Is the study a Randomised Controlled Trial?	YES ↓	UNCLEAR ↓	NO ↓
Go to next question			Exclude: Study type
<b>Trial Intervention</b>			
Was the intervention treatment with ginger (e.g. fresh, powdered, extract, tea, liquid)?	YES ↓	UNCLEAR ↓	NO ↓
Go to next question			Exclude: Intervention
Was a proper control used (placebo, other dietary intervention; pharmacological strategy, etc.)?	YES ↓	UNCLEAR ↓	NO ↓
Go to next question			Exclude: No proper control
<b>Trial Participants</b>			
Were the trial participants pregnant women?	YES ↓	UNCLEAR ↓	NO ↓
Go to next question			Exclude: Animal research
Do the trial participants present with nausea and / or vomiting?	YES ↓	UNCLEAR ↓	NO ↓
Go to next question			Exclude
<b>Other</b>			
Any other reasons for excluding study?	NO		YES
Specify:	↓		↓
	Include, subject to clarification of 'unclear points'		Exclude: Specified reason
<b>Final decision:</b>	<b>Include</b>	<b>Unclear</b>	<b>Exclude</b>

**APPENDIX 6.2: Data extraction form****Data Extraction Form****A. Source**

Review author ID	
Study ID	
Title	
Authors (1 <sup>st</sup> six)	
Contact details	
Published	Yes / No
If yes, provide citation:	Journal name Year; Volume (Issue): page
Source: e.g. Medline / Cochrane ...	
Type of publication	Full paper / Abstract / Dissertation / Unpublished report

**B. Methods**

Ethics approval obtained	Yes	No	Unclear	Not reported
	If yes, which board?			
Study design	Parallel-group RCT		Randomized cross-over trial	
Patients blinded	Yes	No	Unsure	
Investigators blinded	Yes	No	Unsure	
Study duration				

**C. Participants**

Total number	
Country and setting	

**D. Interventions**

	Intervention	Control
Specific treatment		
Dose per tablet, and frequency of administration (e.g. 100mg ginger powder per tablet, 2 tablets daily)		
Duration of intervention and follow-up period (e.g. 1 month intervention; follow-up 1 week after termination of intervention)		
Route of administration		
Concomitant treatments (e.g. dietary advice / medication)	Yes	No
If yes:	Description:	
	Reason(s) for usage	
	Did this treatment confound the effect of ginger's treatment? Yes / No	
	Was a proper control put in place for the confounder? Yes / No	

**E. Outcomes**

	Description of outcome	Time collected	point(s)	Unit of measurement
Outcome 1				
Outcome 2				
Outcome 3				
Outcome 4				

**F. Results**

		Intervention	Control
Nr of participants randomised			
Nr of randomized participants who finished the trial			
Missing participants	Number		
	Reason(s)		
Changes in clinical outcomes:			
All-cause mortality			
Adverse events: Serious			
Adverse events: Non-serious			

**G. Miscellaneous**

Correspondence required? If yes, what should be asked?	
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**H. Limitations (as mentioned by authors)**

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**I. Final Conclusion**

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## Appendix 6.3 Letters to Research Authors

### Letter 1: Regarding Ensiyeh 2009

from [Estelle Viljoen](mailto:estelleviljoen00@gmail.com) [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
to [enciehjenabi@yahoo.ca](mailto:enciehjenabi@yahoo.ca)  
date Sun, Apr 17, 2011 at 10:47 AM  
subject Ginger RCT  
mailed-by gmail.com

Good day,

I am currently busy with a Systematic Review on the efficacy of ginger for the treatment of pregnancy-induced nausea and vomiting. Your study "Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: a randomized controlled trial", 2007, is included in my review. I have two questions, if you would please be so kind as to clarify this for me?

1. Was only verbal informed consent given, or written as well?
2. Regarding the follow-up period of 7 days - is it 7 days after the baseline day, or 7 days after the termination of the treatment?

Thank you, I look forward to hearing from you.

Regards,

Estelle Viljoen (Dietician, Masters degree student at University of Stellenbosch, South Africa)

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from [enciehjenabi](mailto:enciehjenabi@yahoo.ca) [enciehjenabi@yahoo.ca](mailto:enciehjenabi@yahoo.ca)  
to Estelle Viljoen <[estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)>  
date Sun, Apr 17, 2011 at 7:36 PM  
subject Re: Ginger RCT  
signed-by yahoo.ca

Hi

1-verbal informed  
2-7 days after the termination of treatment  
yours sincerely  
Ensiyeh Jenabi

---



from **Estelle Viljoen** [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
to encieh jenabi <[enciehjenabi@yahoo.ca](mailto:enciehjenabi@yahoo.ca)>  
date Sun, Apr 17, 2011 at 9:13 PM  
subject Re: Ginger RCT  
mailed-by [gmail.com](mailto:)

Thank you for your fast response!  
regards,  
Estelle Viljoen

---

**Letter 2: Regarding Pongroj paw 2007**

from **Estelle Viljoen** [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
to [pongroj paw@hotmail.com](mailto:pongroj paw@hotmail.com)  
date Sun, Apr 17, 2011 at 9:50 PM  
subject Ginger RCT  
mailed-by [gmail.com](mailto:)

Good day,

I am currently busy with a Systematic Review on the efficacy of ginger for the treatment of pregnancy-induced nausea and vomiting. Your study "A randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy", 2007, is included in my review. I have a question, if you would please be so kind as to clarify this for me?

1. In your article you talk about 'post-treatment' days, but I can only find results for the 7 days of treatment. When you refer to , for example, "days 3-7 **post** treatment", do you mean days 3-7 **during** treatment?

Thank you, I look forward to hearing from you.

Regards,

Estelle Viljoen (Dietitian, and Masters degree student at University of Stellenbosch, South Africa

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from **DENSAK PONGROJPAW** [pongroj paw@hotmail.com](mailto:pongroj paw@hotmail.com)  
to [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
date Mon, Apr 18, 2011 at 4:38 AM [hide details Apr 18](#)  
subject RE: Ginger RCT  
mailed-by [hotmail.com](mailto:)

Dear Estelle Viljoen .

Thank you very much for your interest. In the method, the pregnant were given medication ( ginger or dimenhydrinate ) for 7 days. On the following 7 days ,the records were taken and they came for the next visit at the end of Day 7 .So,I mean 3-7 day during Rx.I apologise for making you questioned.

Best Regards.

**Densak Pongroj paw, M.D.**

Associate Professor  
Maternal Fetal Medicine Division  
Department of Obstetrics and Gynecology  
Faculty of Medicine ,Thammasat University,  
Pathumthani, THAILAND 12120  
Tel: (662) 02-926-9343  
Mobile: 081-987-8817  
Fax: (662) 02-926-9485  
E-mail: [pongrojpaaw@hotmail.com](mailto:pongrojpaaw@hotmail.com)

from [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)

reply-to           estelleviljoen00@gmail.com  
to                   DENSAK PONGROJPAW <[pongrojpaaw@hotmail.com](mailto:pongrojpaaw@hotmail.com)>  
date                Mon, Apr 18, 2011 at 10:32 AM  
subject            Re: Ginger RCT  
mailed-by         gmail.com

Thank you very much for your fast response and clear answer.  
Regards,  
Estelle

Sent via my BlackBerry from Vodacom - let your email find you!

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**Letter 3: Regarding Smith 2004 (no response from author)**

from Estelle Viljoen [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
to caroline.smith@unisa.edu.au  
date Mon, Apr 18, 2011 at 4:49 PM  
subject Ginger RCT  
mailed-by gmail.com

Good day,

I am currently busy with a Systematic Review on the efficacy of ginger for the treatment of pregnancy-induced nausea and vomiting. Your study "A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy", 2004, is included in my review. I have two questions, if you would please be so kind as to clarify this for me?

1. The fact that the women were allowed to continue with other medications, including anti-emetics, sounds like a confounder. But then, you account for this by saying that it was the same between the two groups, and the analyses were adjusted accordingly. Also the fact that it was used straight through the treatment period - I guess it could then be justified because the ginger would still then be the only 'changing factor'?? ... Am I correct in making these conclusions?
2. Regarding the "Discontinued ginger" mentioned in Figure 1 - could you please elaborate on this? It confuses me that it is mentioned at both the ginger and the Vit B6 groups?

Thank you, I look forward to hearing from you.

Regards,

Estelle Viljoen (Dietitian, and Masters degree student at University of Stellenbosch, South Africa)

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**Letter 4: Regarding Pongroj paw 2007, missing information. (No response from author)**

from **Estelle Viljoen** [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
 to [pongroj paw@hotmail.com](mailto:pongroj paw@hotmail.com)  
 date Mon, Sep 26, 2011 at 1:27 PM  
 subject more specific question regarding Ginger RCT  
 mailed-by [gmail.com](mailto:gmail.com)

Good day,

I am currently busy with a Systematic Review on the efficacy of ginger for the treatment of pregnancy-induced nausea and vomiting. Your study "A Randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy", 2007, is included in my review. I have a question regarding missing data, if you would please be so kind as to clarify this for me?

- Some results are reported in terms of figures, but with no actual values for mean (SD). This is specifically in the improvement in nausea symptoms, and the reduction in the number of vomiting episodes.

Can you kindly provide the actual values of means (SD) in the tables provided in 1 and 2 below?

Thank you , I look forward to hearing from you.  
 Estelle Viljoen

1. Reduction in nausea symptoms as measured by VAS scores (day 1-7).

Ginger			Dimenhydrinate		
Mean	Standard Deviation (SD)	n	Mean	Standard Deviation (SD)	n
?	?	?	?	?	?

2. Reduction in the number of vomiting episodes (day 1-7).

Ginger			Dimenhydrinate		
Mean	Standard Deviation (SD)	n	Mean	Standard Deviation (SD)	n
?	?	?	?	?	?

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**Letter 5: Regarding Willetts 2007, missing information. (No response from author)**

from **Estelle Viljoen** [estelleviljoen00@gmail.com](mailto:estelleviljoen00@gmail.com)  
 to [j.eden@unsw.edu.au](mailto:j.eden@unsw.edu.au)  
 date Mon, Sep 26, 2011 at 1:29 PM  
 subject more specific questions regarding the ginger RCT  
 mailed-by [gmail.com](mailto:estelleviljoen00@gmail.com)

Good day,

I am currently busy with a Systematic Review on the efficacy of ginger for the treatment of pregnancy-induced nausea and vomiting. Your study "Effect of a ginger extract on pregnancy-induced nausea: a randomized controlled trial", 2003, is included in my review. I have a question regarding missing data, if you would please be so kind as to clarify this for me?

- Some results are reported in terms of figures, but with no actual values for mean (SD). This is specifically in the improvement in nausea symptoms, and the reduction in the number of vomiting episodes.

Can you kindly provide the actual values of means (SD) in the tables provided in 1 and 2 below?

Thank you, I look forward to hearing from you  
 Estelle Viljoen

1. Reduction in nausea symptoms as measured by VAS scores (day 1-7).

Ginger			Dimenhydrinate		
Mean	Standard Deviation (SD)	n	Mean	Standard Deviation (SD)	n
?	?	?	?	?	?

2. Reduction in the number of vomiting episodes (day 1-7).

Ginger			Dimenhydrinate		
Mean	Standard Deviation (SD)	n	Mean	Standard Deviation (SD)	n
?	?	?	?	?	?

## APPENDIX 6.4: Methodological quality / Risk of bias Tool

STUDY ID \_\_\_\_\_ Reviewer ID \_\_\_\_\_

For each of the included studies, each domain will receive a judgment of "Yes" (low risk of bias), "No" (high risk of bias) or "Unclear" (unclear risk of bias).

ITEM	Judgment	Description
<p><i>Sequence generation</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelopes shuffling etc</li> <li>• <b>Inadequate:</b> investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number</li> <li>• <b>Unclear:</b> insufficient information to permit judgment of the sequence generation process</li> </ul>		
<p><i>Allocation concealment</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> Participants and the investigators enrolling participants cannot foresee assignment</li> <li>• <b>Inadequate:</b> participants and investigators enrolling participants can foresee upcoming assignment</li> <li>• <b>Unclear:</b> insufficient information to permit judgment of the allocation concealment or the method not described</li> </ul>		
<p><i>Blinding</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> blinding of either the participants, key study personnel or outcome assessor, and unlikely that the blinding could have been broken. No blinding in the situation where non-blinding is not likely to introduce bias</li> <li>• <b>Inadequate:</b> no blinding, incomplete blinding and the outcome is likely to be influence by lack of blinding</li> <li>• <b>Unclear:</b> insufficient information to permit judgment of adequacy or otherwise of the blinding</li> </ul>		
<p><i>Incomplete outcome data</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups</li> <li>• <b>Inadequate:</b> reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data</li> <li>• <b>Unclear:</b> insufficient reporting of attrition or exclusions</li> </ul>		
<p><i>Selective Reporting</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> a protocol is available which clearly states the primary outcome as the same as in the final trial report. If no protocol: the outcomes are clearly stated and then reported adequately.</li> <li>• <b>Inadequate:</b> the primary outcome differs between the protocol and final trial report. No clear outcome statement or reporting.</li> <li>• <b>Unclear:</b> no trial protocol available or there is insufficient reporting to determine if selective reporting is present</li> </ul>		
<p><i>Other forms of bias</i></p> <ul style="list-style-type: none"> <li>• <b>Adequate:</b> there is no evidence of bias from other sources</li> <li>• <b>Inadequate:</b> there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity)</li> <li>• <b>Unclear:</b>insufficient information to permit judgment of adequacy or otherwise of other forms of bias</li> </ul>		

**APPENDIX 6.5: Criteria for methodological components**

<b>SEQUENCE GENERATION</b>	
<b>Was the allocation sequence adequately generated? [Adequate sequence generation?]</b>	
<p><b>Criteria for a judgement of 'YES'</b></p> <p>(i.e. low risk of bias)</p>	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> <li>• Referring to a random number table;</li> <li>• Using a computer random number generator;</li> <li>• Coin tossing;</li> <li>• Shuffling cards or envelopes;</li> <li>• Throwing dice;</li> <li>• Drawing of lots;</li> <li>• Minimization*.</li> </ul>
<p><b>Criteria for the judgement of 'NO'</b></p> <p>(i.e. high risk of bias)</p>	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> <li>• Sequence generated by odd or even date of birth;</li> <li>• Sequence generated by some rule based on date (or day) of admission;</li> <li>• Sequence generated by some rule based on hospital or clinic record number.</li> </ul> <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> <li>• Allocation by judgement of the clinician;</li> <li>• Allocation by preference of the participant;</li> <li>• Allocation based on the results of a laboratory test or a series of tests;</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p>(uncertain risk of bias).</p>	<p>Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.</p>
<b>ALLOCATION CONCEALMENT</b>	
<b>Was allocation adequately concealed? [Adequate allocation concealment?]</b>	
<p><b>Criteria for a judgement of 'YES'</b></p>	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to</p>



(i.e. low risk of bias)	<p>conceal allocation:</p> <ul style="list-style-type: none"> <li>• Central allocation (including telephone, web-based and pharmacy-controlled randomization);</li> <li>• Sequentially numbered drug containers of identical appearance;</li> </ul>
<p><b>Criteria for the judgement of 'NO'</b></p> <p>(i.e. high risk of bias)</p>	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> <li>• Using an open random allocation schedule (e.g. a list of random numbers);</li> <li>• Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);</li> <li>• Alternation or rotation;</li> <li>• Date of birth;</li> <li>• Case record number;</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p>(uncertain risk of bias).</p>	<p>Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed</p>
<p><b>BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS</b></p> <p><b>Was knowledge of the allocated interventions adequately prevented during the study? [ Blinding?]</b></p>	
<p><b>Criteria for a judgement of 'YES'</b></p> <p>(i.e. low risk of bias)</p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;</li> <li>• Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;</li> </ul>
<p><b>Criteria for the judgement of 'NO'</b></p> <p>(i.e. high risk of bias)</p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;</li> <li>• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p>(uncertain risk of bias).</p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• Insufficient information to permit judgement of 'Yes' or 'No';</li> <li>• The study did not address this outcome.</li> </ul>

<b>INCOMPLETE OUTCOME DATA</b>	
<b>Were incomplete outcome data adequately addressed?</b>	
<p><b>Criteria for a judgement of 'YES'</b></p> <p><b>(i.e. low risk of bias)</b></p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• No missing outcome data;</li> <li>• Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);</li> <li>• Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;</li> <li>• For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;</li> <li>• For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;</li> </ul>
<p><b>Criteria for the judgement of 'NO'</b></p> <p><b>(i.e. high risk of bias)</b></p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;</li> <li>• For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;</li> <li>• For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;</li> <li>• 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p><b>(uncertain risk of bias).</b></p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided);</li> <li>• The study did not address this outcome.</li> </ul>
<b>SELECTIVE OUTCOME REPORTING</b>	
<b>Are reports of the study free of suggestion of selective outcome reporting? [Free of selective reporting?]</b>	
<p><b>Criteria for a judgement of 'YES'</b></p> <p><b>(i.e. low risk of bias)</b></p>	<p>Any of the following:</p> <ul style="list-style-type: none"> <li>• The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;</li> </ul>

<p><b>Criteria for the judgement of 'NO'</b></p> <p>(i.e. high risk of bias)</p>	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>• Not all of the study's pre-specified primary outcomes have been reported;</li> <li>• One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;</li> <li>• One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);</li> <li>• One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p>(uncertain risk of bias).</p>	<p>Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.</p>
<p><b>OTHER POTENTIAL THREATS TO VALIDITY</b></p> <p>Was the study apparently free of other problems that could put it at a risk of bias? [Free of other bias?]</p>	
<p><b>Criteria for a judgement of 'YES'</b></p> <p>(i.e. low risk of bias)</p>	<p>The study appears to be free of other potential sources of bias</p>
<p><b>Criteria for the judgement of 'NO'</b></p> <p>(i.e. high risk of bias)</p>	<p>There is at least one important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> <li>• Had a potential source of bias related to the specific study design used; or</li> <li>• Stopped early due to some data-dependent process (including a formal-stopping rule); or</li> <li>• Had extreme baseline imbalance; or</li> <li>• Has been claimed to have been fraudulent; or</li> </ul>
<p><b>Criteria for the judgement of 'UNCLEAR'</b></p> <p>(uncertain risk of bias).</p>	<p>There may be a risk of bias, but there is either:</p> <ul style="list-style-type: none"> <li>• Insufficient information to assess whether an important risk of bias exists; or</li> <li>• Insufficient rationale or evidence that an identified problem will introduce bias.</li> </ul>

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**APPENDIX 6.6: Ethics Letter**



UNIVERSITEIT • STELLENBOSCH • UNIVERSITY  
jou kennisvennoot • your knowledge partner

11 April 2011

**MAILED**

Ms E Viljoen  
Human Nutrition  
3rd Floor  
Clinical Building

Dear Ms Viljoen

**A Systematic Review of the effect and the safety of Ginger in the treatment of pregnancy associated nausea and vomiting.**

**ETHICS REFERENCE NO: N11/04/127**

**RE : ETHICAL REVIEW NOT REQUIRED**

Thank you for your application. The application is for a systematic review using only data that is available in the public domain therefore the cluster head for Research Ethics has considered this proposal to be exempt from ethical review.

This letter confirms that this project is now registered and you can proceed with the work.

Yours faithfully

**MS CARLI SAGER**

**RESEARCH DEVELOPMENT AND SUPPORT**

Tel: +27 21 938 9140 / E-mail: [carlis@sun.ac.za](mailto:carlis@sun.ac.za)

Fax: +27 21 931 3352

11 April 2011 15:54

Page 1 of 1



Fakulteit Gesondheidswetenskappe - Faculty of Health Sciences



Verbind tot Optimale Gesondheid - Committed to Optimal Health

**Afdeling Navorsingsontwikkeling en -steun - Division of Research Development and Support**

Posbus/PO Box 19063 - Tygerberg 7505 - Suid-Afrika/South Africa  
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**Appendix 6.7: Table of Excluded Studies**

Reason for exclusion: Study type other than RCT (n=105)
<b>Abascal K, Yarnell E.</b> Clinical Uses of Zingiber officinale (Ginger). <i>Alternative &amp; Complementary Therapies</i> , 2009; 15 (5): 231-237.
<b>All A, Gilani AH.</b> Medicinal value of ginger with focus on its use in nausea and vomiting of pregnancy. <i>International journal of food properties</i> 2007;10 (2):269-275.
<b>Allen R.</b> Are we failing women? Advice for nausea and vomiting in pregnancy. <i>Pract Midwife</i> 2001; 4 (4):20-22.
<b>Al-Achi, A.</b> A current look at ginger use: complementary medicine. <i>Journal of Modern Pharmacy</i> , 2002;10 (4).
<b>Anderson FWJ, Johnson CT.</b> Complementary and alternative medicine in obstetrics. <i>Int J Gynecol Obstet</i> 2005; 91(2):116-124
<b>Anon.</b> Ginger root effective against pregnancy-related nausea and vomiting: freshness and quality may hold the key to benefits. <i>Acupuncture Today</i> , 2001 Nov; 2 (11): 1, 24.
<b>Anon.</b> Herbal medicine during pregnancy and lactation. <i>JNMA J Nepal Med Assoc</i> 2006;45(163):1.
<b>Anon.</b> Nausea and vomiting during pregnancy. <i>J Midwifery Women's Health</i> 2006; 51(6):303-4.
<b>Anon.</b> Zingiber officinale (ginger). <i>Monograph. Altern Med Rev</i> 2003;8(3):331-5.
<b>Bayles BP.</b> Herbal and other complementary medicine use by midwives. <i>Journal of midwifery and women's health</i> 2007;52: 473-478.
<b>Badell, ML, Ramin SM, Smith JA.</b> Treatment options for nausea and vomiting during pregnancy <i>Pharmacotherapy</i> , 2006; 26 (9 D): 1273-1287.
<b>Baggley A, Navioz Y, Maltepe C, et al.</b> Determinants of women's decision making on whether to treat nausea and vomiting of pregnancy pharmacologically. <i>Journal of midwifery and women's health</i> 2004;49(4):350-354.
<b>Blumenthal M .</b> Ginger as an antiemetic during pregnancy. <i>Alternative Therapies in Health and Medicine</i> , 2003; 9 (1):19-21.
<b>Boone SA, Shields KM.</b> Treating pregnancy-related nausea and vomiting with ginger. <i>Annals of Pharmacotherapy</i> , 2005; 39 (10): 1710-3.
<b>Borrelli F, Capasso R, Aviello G, et al.</b> Effectiveness and Safety of Ginger in the Treatment of Pregnancy-Induced Nausea and Vomiting. <i>Obstetrics &amp; Gynecology</i> , 2005; 105 (4.):849-856
<b>Bottomley C, Boume T.</b> Management and strategies for hyperemesis gravidarum. <i>Best practice and research in clinical obstetrics and gynecology</i> 2009; 23 (4):549-564.
<b>Buckner KD, Chavez ML, Raney EC, et al.</b> Health food store's recommendations for nausea and migraines during pregnancy. <i>Annals of Pharmacotherapy</i> 2005; 39(2):274-279.
<b>Bryer E.</b> A literature review of the effectiveness of ginger in alleviating mild-to-moderate nausea and vomiting of pregnancy. <i>J Midwifery Women's Health</i> 2005; 50(1):1-3.

- Cassileth B.** Complementary therapies, herbs, and other OTC agents. *Oncology* 2009; 23(10):904.
- Castleman, M.** The 55 best herbal remedies (cover story). *Natural Health*, 2004; 35 (8):168-11
- Challem J.** Medical journal watch: context and applications. *Alternative & Complementary Therapies*, 2009; 15 (5): 267-72.
- Chandra K, Einarson A, Koren G.** Taking ginger for nausea and vomiting during pregnancy. *Canadian Family Physician* 2002; 48: 1441-2.
- Chrubasik S, Pittler MH, Roufogalis BD, Zingiberis rhizome:** A comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005 (12): 684-701.
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**Reason for exclusion: Intervention other than ginger (n=2)**

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**APPENDIX 6.8: Risk of biased judgments in included studies****Basirat 2009**

ITEM	Author's judgments	Description
Adequate sequence generation?	Yes	A table of random numbers was used.
Adequate allocation concealment?	Yes	Treatment codes were kept in sequence in a sealed black envelope that could not be read through.
Adequate blinding?	No	Neither the physicians nor the subjects knew the composition of the biscuits. BUT 3 subjects in the ginger group did not want to continue eating the biscuits due to the hot spicy taste, so they could identify the treatment.
Incomplete outcome data addressed?	Yes	Reasons for all missing participants described
Free of selective reporting	Yes	Primary and secondary outcomes clearly stated and discussed.
Free of other bias?	Yes	

**Chittumma 2007**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	"Table of random numbers with block of four"
Adequate allocation concealment?	Yes	"treatment code was concealed... in sequence in sealed opaque envelope... drawn in ascending consecutive order" Codes broken only at end of the study.
Adequate blinding?	No	Codes were kept strictly confidential and broken only at end of the study, BUT 4 pts in ginger group could correctly identify what they were taking.
Incomplete outcome data addressed?	Unclear	3 subjects did not return for follow-up, no reasons provided. They were excluded from the analysis.
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	No	Some participants used cold medications, headache medications, and other ginger products. (confounder) Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting. This could be a confounder, as some may have followed this advice and may have a symptom relief due to dietary changes

**Ensiyeh 2009**

ITEM	Author's judgments	Description
Adequate sequence generation?	Yes	"Randomised into 2 groups, using a table of random numbers"
Adequate allocation concealment?	Unclear	Capsules were packed in an envelope. No additional information
Adequate blinding?	Unclear	Mentioned "double-blind". No further information.
Incomplete outcome data addressed?	Unclear	1 woman did not return for follow-up, no reasons provided, she was simply excluded due to no data collected.
Free of selective reporting?	Yes	Outcomes clearly stated and discussed
Free of other bias?	No	Verbal informed consent only, no written consent. Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting.

		This could be a confounder, as some may have followed this advice and may have symptom relief due to dietary changes.
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**Fischer-Rasmussen 1991**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	Cross-over design. Each patient became her own control. The hospital's dispensary randomized the packages.
Adequate allocation concealment?	Unclear	No information given
Adequate blinding?	Yes	Hospital's dispensary randomized the packages. "the code remained sealed until the study had been completed"
Incomplete outcome data addressed?	Yes	All missing participants well described and reported on
Free of selective reporting	Yes	Outcomes clearly stated and reported
Free of other bias?	Unclear	Ethics approval on reported. IV medication were continued to prevent dehydration.

**Keating 2002**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	"Computer generated numbers matching the numbers on identical appearing bottles of ginger or placebo syrup"
Adequate allocation concealment?	Yes	"identical appearing bottles of ginger or placebo syrup" Syrup prepared by independent company.
Adequate blinding?	No	One woman could not tolerate the taste of the ginger, stopped treatment.
Incomplete outcome data addressed?	Yes	Reasons for missing participants well described
Free of selective reporting	No	At beginning of article the authors state that the purpose of the study is to assess the acceptance and clinical value of the ginger syrup, but there is no reporting on the acceptance.
Free of other bias?	Unclear	Statistical analysis was not applied due to small nr of pts in each group. Treatment was for 14 days, but results given on values for 9days. Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting. This could be a confounder, as some may have followed this advice and may have symptom relief due to dietary changes

**Ozgoli 2009**

ITEM	Author's judgement	Description
Adequate sequence generation?	Unclear	"The participants were randomly assigned"
Adequate allocation concealment?	Unclear	No information given
Adequate blinding?	Yes	"Single blind" "The participants were blinded to the contents of the capsules"
Incomplete outcome data addressed?	Yes	Reasons for all missing participants described
Free of selective reporting	Yes	Primary and secondary outcomes clearly stated and discussed
Free of other bias?	Unclear	Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting. This could be a confounder, as some may have followed this advice and may have symptom relief due to dietary changes.

**Pongroj paw 2007**

ITEM	Author's judgments	Description
Adequate sequence generation?	Unclear	"were randomly allocated." No further information given.
Adequate allocation concealment?	Unclear	"Capsules were identical in size, color and odor." No further information
Adequate blinding?	Unclear	In abstract it is called a double-blind RCT, but no further info given on blinding of personnel.
Incomplete outcome data addressed?	Unclear	No reasons provided for the 19 subjects lost to follow-up
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	No	The researchers decided on a lower dose of Dimenhydrinate (the control) than was used in previous studies, and that is usually prescribed, because they wanted to improve compliance and avoid loss to follow-up. This lower dose could lead to lower scores.

**Smith 2004**

ITEM	Author's judgments	Description
Adequate sequence generation?	Yes	"Computer generated randomization schedule used balanced variable blocks, prepared by researcher not involved in the trial."
Adequate allocation concealment?	Unclear	"capsules were contained in an opaque brown soft gel capsule"
Adequate blinding?	No	Participants were blinded, and computer operator blinded. BUT some ginger users, and vit B6 users correctly identified what they were taking (unblinding)
Incomplete outcome data addressed?	Unclear	Not all clear reasons for lost to follow-up – "forms not returned, and other", also "Discontinued ginger" in both groups – unclear.
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	Unclear	Participants were allowed to continue with other meds. Documentation at start and end of study. No diff between 2 groups, and the analyses were adjusted for this variable. (bias?)

**Sripramote 2003**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	"... pharmacist no responsible for patient care used random numbers to prepare treatment assignments with block of four."
Adequate allocation concealment?	Unclear	".. assignment in sequence in sealed opaque envelopes that were drawn in ascending consecutive order." BUT the vit B6 capsules weighed less than the ginger capsule. (10mg vs 500mg, in identical capsules).
Adequate blinding?	Yes	"treatment codes were kept strictly confidential for blinding the physician and subjects, and were broken at the end of the study"
Incomplete outcome data addressed?	Unclear	No reasons given for the 10 subjects lost to follow-up.
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	No	Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting. This could be a confounder, as some may have followed this advice and may have symptom relief due to dietary changes

**Vutyavanich 2001**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	'a researcher who was not responsible for patient care, used a table of random numbers to prepare the treatment assignment'
Adequate allocation concealment?	Yes	"sealed black envelopes that could not be read through"
Adequate blinding?	Yes	"list that reveled drug codes given to patients were kept strictly confidential...not accessible to the physicians" Pre-trial testing showed that participants could not correctly identify what they took.
Incomplete outcome data addressed?	No	3 missing participants in placebo group did not return for follow-up. (Intent-to-treat analysis was done by assuming the 3 missing pts in placebo group values as high as the best pt in ginger group.)
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	No	Dietary advice was given to both groups to adjust food intake to help reduce nausea and vomiting. This could be a confounder, as some may have followed this advice and may have symptom relief due to dietary changes

**Willettts 2003**

ITEM	Author's judgment	Description
Adequate sequence generation?	Yes	" randomization was done by Eurovita Pty Ltd using randomization blocks of six"
Adequate allocation concealment?	Yes	"...sealed envelopes...posted to us." Both capsules were wax sealed and identical in appearance.
Adequate blinding?	Yes	Double blind – the participants, administrators ad those assessing the outcomes were all blinded.
Incomplete outcome data addressed?	Yes	All missing participants are described in detail. Lost participants were excluded from analysis.
Free of selective reporting	Yes	Outcomes clearly stated and discussed
Free of other bias?	Unclear	Eurovita Pty Ltd was responsible for the randomization, and they funded the study. (??)

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