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GRADUAÇÃO EM NUTRIÇÃO

Bruna Luiza Holand

# EFEITOS DO GENGIBRE SOBRE NÁUSEA E ÊMESE NA GESTAÇÃO: UMA REVISÃO SISTEMÁTICA

Porto Alegre
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Trabalho de Conclusão de Curso apresentado como requisito parcial para obtenção do grau de Bacharel em Nutrição, à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Departamento de Nutrição.

Orientadora: Prof[a]. Dr[a] Ionara Rodrigues Siqueira.
Coorientadora: M.Sc. Kamila Castro Grokoski.

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Porto Alegre, _____ de _____ de 2017

A Comissão Examinadora, abaixo assinada, aprova o Trabalho de Conclusão de Curso, intitulado "Efeitos do gengibre sobre náusea e êmese na gestação: uma revisão sistemática", elaborado por Bruna Luiza Holand, como requisito parcial para obtenção do grau de Bacharel em Nutrição.

Comissão Examinadora:

_____
Profª Drª Simone Morelo Dal Bosco - UFCSPA

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Profª Drª Martine Elisabeth Kienzle Hagen - UFRGS

_____
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## RESUMO

Introdução: Náuseas e vômitos durante a gestação são sintomas que afetam aproximadamente 80% das mulheres. Os fármacos antieméticos convencionais são potenciais teratógenos durante o período embrionário crítico da gravidez. O gengibre (*Zingiber officinale*) tem sido utilizado como agente terapêutico há séculos, embora ainda não haja consenso sobre o uso nas náuseas e vômitos gestacionais. Esta revisão sistemática foi realizada para avaliar a evidência da eficácia e segurança do gengibre para o tratamento de náuseas e vômitos durante a gestação.

Métodos: Para a realização desta revisão sistemática foram seguidas as diretrizes estabelecidas pelo PRISMA. Foi utilizada a base de dados MEDLINE (PubMed), para a seleção de ensaios clínicos randomizados (ECRs) de gengibre e náuseas e vômitos durante a gestação. A qualidade dos estudos foi avaliada.

Resultados: Um total de 92 estudos foi encontrado na primeira pesquisa. O índice Kappa de concordância foi k = 0,617. Finalmente, após todas as etapas da seleção, foram incluídos 15 estudos. Os estudos abordaram a eficácia do gengibre em comparação com placebo, vitamina B6 e outras drogas. A dose média de gengibre foi de 1000 mg/d.

Discussão: Todos os ECRs que compararam a eficácia do gengibre com o placebo relataram resultados positivos nas náuseas e vômitos gestacionais. Quando comparado com a vitamina B6, dois estudos mostraram que o gengibre é mais eficaz na redução da náusea. Além disso, não houve efeitos colaterais significativos ou efeitos adversos nos resultados da gestação, como teratogênese. Apesar dos estudos apresentarem dados concordantes, este trabalho evidencia a necessidade de estudos com tamanho de amostra e duração maiores e comparação a tratamentos reconhecidos, com randomização e cegamento adequados para aumentar a credibilidade dos dados obtidos.



Palavras chave: gestantes, vômitos, náuseas, gengibre, antiemético.

**SUMÁRIO**

# 1 INTRODUÇÃO

## 1.1 GESTAÇÃO

### 1.1.1 Ajustes fisiológicos na gestação

O período gestacional possui em média 40 semanas. Durante a gestação, ocorrem no corpo da mulher, uma série de ajustes fisiológicos, anatômicos e psicológicos, que são necessários para regular o metabolismo materno, promover o crescimento fetal e preparar a mãe para o parto e lactação (GRANGER, 2002; SAUNDERS, 2009). Estes ajustes estão associados a uma acentuada alteração hemodinâmica na circulação sanguínea materna, onde há um aumento do débito cardíaco e volume plasmático, e redução na resistência vascular e pressão arterial (GRANGER, 2002).

Durante toda a gestação, a mulher passa por constantes reformulações hormonais (KING, 2000). No início desta, cerca de 10 dias após a fecundação, as células trofoblásticas sinciciais produzem uma glicoproteína, a Gonadotrofina Coriônica Humana (hCG) (SAUNDERS, 2009), esta mantém o corpo lúteo – estrutura endócrina temporária – no princípio da gestação (KING, 2000). A subunidade β-hCG, que pode ser detectada na urina ou no sangue apenas alguns dias após a concepção, tem sua concentração drasticamente aumentada durante o início da gestação e possui um pico em até 60 dias, posteriormente, volta a baixar. A presença desta subunidade é um bom indicador de gestação (KING, 2000).

O corpo lúteo e a placenta são os principais responsáveis pela secreção de hormônios que mantêm a gravidez (KING, 2000). Enquanto que a placenta ainda não está bem formada, a principal fonte de secreção do hormônio progesterona é o corpo lúteo (KING, 2000; DAVIS E RUEDA, 2002). O hCG estimula o corpo lúteo a produzir progesterona, que é responsável por relaxar a musculatura lisa uterina e induzir a fase secretória no endométrio uterino (GUYTON E HALL, 2011), além de favorecer a deposição de gordura e estimular o apetite na gestação (SAUNDERS, 2009). A partir da oitava e nona semana de gestação, a síntese dos hormônios esteróides, progesterona e estrógenos, são de origem placentária. O estrogênio é responsável por reduzir as proteínas séricas, pela hiperpigmentação cutânea, aumento mamário, redução do apetite na segunda parte da gestação (SAUNDERS, 2009).

## 1.2 FISIOPATOLOGIA DAS NÁUSEAS E VÔMITOS

A fisiopatologia das náuseas e vômitos é bastante complexa, envolve vários neurotransmissores e seus receptores tanto do sistema nervoso central quanto do sistema nervoso periférico. Apesar de as náuseas e vômitos serem sintomas independentes, na grande parte das vezes a náusea antecede o vômito (QUIGLEY *et al.*, 2001). Náuseas são descritas como uma sensação desagradável na região epigástrica, que costumeiramente são acompanhadas de calafrios, produção excessiva de saliva, sudorese fria, entre outros (QUIGLEY *et al.*, 2001), e ocorrem como consequência da perda do tônus e da peristalse gástricos, juntamente com a contração duodenal. Após ocorrem as "arcadas", que são os movimentos espasmódicos do diafragma, da musculatura torácica e abdominal, o que aumenta a pressão intra-abdominal e assim há a expulsão do conteúdo gástrico, a êmese ou vômito. (GUYTON E HALL, 2011).

O controle deste processo se dá no Bulbo Raquidiano, mais precisamente no denominado centro do vômito, este recebe aferências de várias regiões encefálicas: (1) zona do gatilho – localizada na área postrema do IV ventrículo, (2) núcleo do trato solitário, (3) aparato vestibular - responsável pelo enjoo do movimento ou cinetose, (4) aferências sensoriais do trato gastrointestinal (TGI), (5) córtex cerebral relacionado à êmese induzida por dor, odores, visão e estado de ansiedade (QUIGLEY *et al.*, 2001; GONDIM *et al.*, 2009). Vários neurotransmissores e seus receptores estão envolvidos no controle do centro do vômito, como os histamínicos H1, dopaminérgicos D2, muscarínicos M1, neurocinina NK1 e receptores serotoninérgicos 5-HT3 (Figura 1) (GONDIM *et al.*, 2009).

### 1.2.1 Fármacos antieméticos

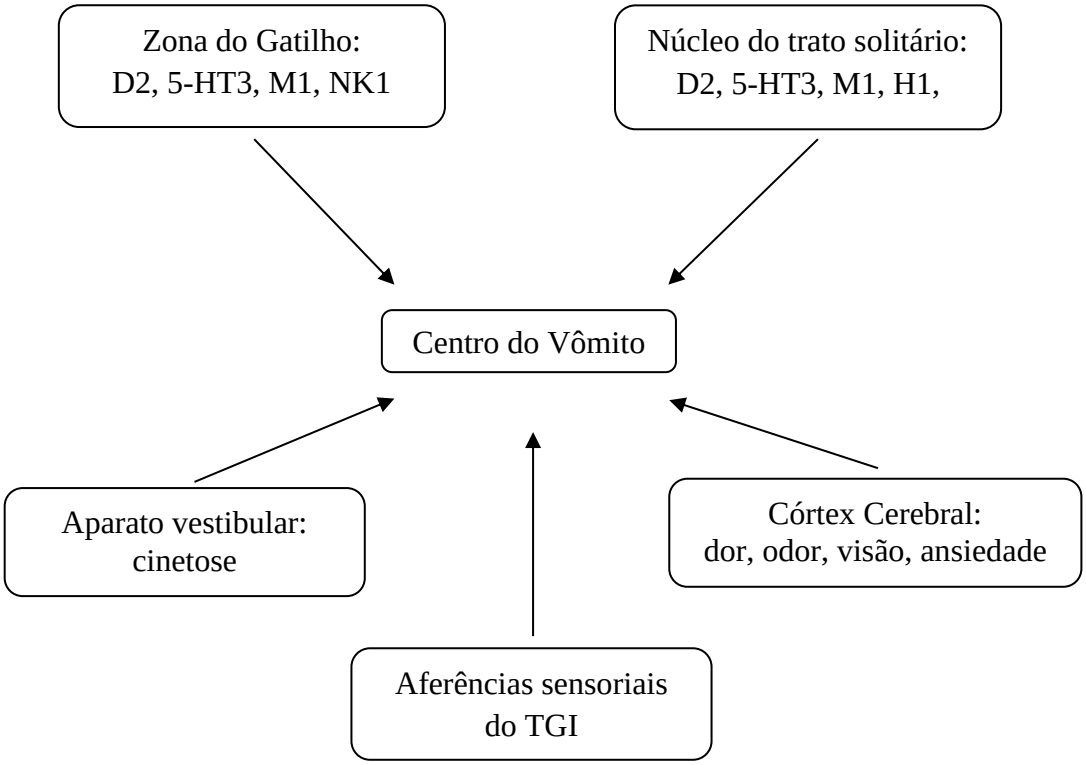
Os medicamentos antieméticos normalmente são classificados conforme o receptor nos quais atuam. Neste contexto, o conhecimento da fisiologia e de causas das náuseas e vômitos é importante para um adequado tratamento.

*Antagonistas do receptor 5-HT3*

Os antagonistas do receptor 5-HT3 atuam bloqueando os receptores 5-HT3 da serotonina (ASSOCIAÇÃO BRASILEIRA DE CUIDADOS PALIATIVOS, 2011; FERNANDES, 2013). Os efeitos deste fármaco prosseguem por um longo período de tempo,

mesmo após a metabolização do próprio. Fazem parte desta classe fármacos como a ondansetrona, granisetrona, dolasetrona. As principais diferenças entre estes fármacos estão nas suas estruturas químicas, farmacocinética e na forma com que se relacionam com o receptor (BRUNTON E PARKER, 2010).

**Figura 1 - Estímulos ao Centro do Vômito. Uma série de vias aferentes transporta estímulos da periferia ao Centro do Vômito.**




Legenda: D2 – Receptores dopaminérgicos; 5-HT3 – Receptores serotoninérgicos; M1 – Receptores muscarínicos; NK1 – Receptores de neurocinina; TGI – Trato Gastrointestinal.

*Antagonistas do receptor de dopamina*

Os antidopaminérgicos têm como mecanismo de ação o antagonismo do receptor de dopamina D2 na zona do gatilho. Este grupo é composto por medicamentos com diferentes estruturas químicas, as três principais classes deste grupo são as fenotiazinas, que incluem a prometazina e a clorpromazina, as butirofenonas, onde se enquadra o droperidol, e as benzamidas, como a metoclopramida e a bromoprida (FERNANDES, 2013). A

metoclopramida também possui uma ação periférica nos receptores de serotonina 5-TH3 (BRUNTON E PARKER, 2010).

*Anti-histamínicos*

Os antagonistas da histamina, normalmente agem bloqueando os receptores H1 no núcleo do trato solitário e são eficazes no tratamento da cinetose. Esta classe tem como representantes antieméticos, os fármacos de primeira geração como o dimenidrinato, difenidramina e prometazina (BRUNTON E PARKER, 2010).

*Anticolinérgicos*

Os anticolinérgicos atuam antagonizando a acetilcolina através dos receptores muscarínicos M1, normalmente utilizados no tratamento da cinetose, possui como representantes a atropina e escopolamina (BRUNTON E PARKER, 2010).

*Dronabinol*

Um tratamento alternativo, especialmente no mercado europeu, é o THC sintético denominado dronabinol (Marinol®), um canabinóide que pode ser extraído da planta *Cannabis sativa*, popularmente conhecida como maconha. Sugere-se que seu efeito antiemético ocorra através de atividade anticolinérgica (BECKER E NARDIN, 2011) e pelos receptores canabinóides do subtipo CB1 presentes no centro do vômito (BRUNTON E PARKER, 2010).

## 1.3 NÁUSEAS E VÔMITOS NA GESTAÇÃO

Náuseas e vômitos são, provavelmente, os sintomas mais relatados durante o período gestacional. Estes sintomas são descritos por cerca de 60-80% das gestantes (GADSBY *et al.*, 1993; LACROIX *et al.*, 2000; JEWELL, 2003). Porém, em 0,3-1% dessas mulheres, estes sintomas se agravam, o que se denomina hiperêmese gravídica (GADSBY *et al.*, 1993; BASHIRI *et al.*, 1995; LACROIX *et al.*, 2000), esta condição pode levar, em muitos casos à desidratação, a perda de mais de 5% do peso corpóreo (NIEBYL, 2010), cetonúria, desequilíbrios hidroeletrolíticos, como hipocalemia (NIEBYL, 2010; TIAN *et al.*, 2016). Além destas possíveis complicações, a hiperêmese gravídica pode, devido ao desconforto, reduzir consideravelmente a qualidade de vida da gestante, afetando negativamente suas

relações sociais e, assim, o seu estado de humor (SHEEHAN, 2007; NIEBYL, 2010; PERLEN *et al.*, 2013; TIAN *et al.*, 2016).

Náuseas e vômitos gestacionais, comumente surgem entre a quarta e sexta semanas após o último período menstrual e possuem um pico entre a oitava e décima segunda semanas, momento em que se encerra o primeiro trimestre da gestação (LACROIX *et al.*, 2000; KOUZI, 2003). Sessenta por cento dos casos de náuseas e vômitos são resolvidos até o final do primeiro trimestre, e quando os sintomas se prolongam, cerca de 90% se resolve até a vigésima semana (NIEBYL, 2010).

O mecanismo exato que leva a estes sintomas na gestação ainda não foi totalmente elucidado. Uma teoria comumente aceita é a de que estes sintomas advêm devido às alterações hormonais que ocorrem durante a gravidez, onde há o aumento no nível sanguíneo de β-hCG, estradiol e progesterona (JARNFELT-SAMSIOE, 1987; SAPRA *et al.*, 2016). Uma evidência do envolvimento do β-hCG nas náuseas e vômitos na gestação é a doença trofoblástica gestacional. Nesta condição, ocorre um aumento característico de β-hCG, e ainda induz a náuseas e vômitos severos. Outra evidência é que gestantes com idade mais avançada, multíparas ou tabagistas, onde há menores níveis de β-hCG devido a um menor tamanho placentário, apresentam menores índices de náusea e vômito, enquanto que onde ocorre uma maior produção de β-hCG, por exemplo em gestações gemelares (onde a placenta possui um maior tamanho), as pacientes apresentam maiores níveis de náusea e vômito (WEIGEL E WEIGEL, 1989; DE ANDRADE, 2009; BRAGA *et al.*, 2014).

Ainda apoiando a hipótese sobre o envolvimento do estradiol e da progesterona, pode-se citar o fato de que algumas mulheres sentem náuseas ao tomar anticoncepcionais orais, os quais normalmente contêm uma combinação de estrogênio e progesterona (HUXLEY, 2000). Depue *et al.*(1987), demonstraram que mulheres com hiperêmese gravídica tendem a ter altos níveis de estradiol total, coincidindo com a hipótese de que o hormônio estradiol está relacionado com as náuseas e vômitos durante a gestação. Em outro estudo, a progesterona foi prescrita para mulheres não grávidas, onde houve uma redução na motilidade gástrica, e apresentaram como efeitos adversos, náuseas e vômitos, indicando que a progesterona pode ser envolvida nessa condição (WALSH *et al.*, 1996). Ainda, não se descarta o envolvimento de outros fatores, como psicológicos e nutricionais (KOUZI, 2003).

Devido aos diferentes graus de náuseas e vômitos, torna-se evidente a necessidade da utilização de ferramentas que auxiliem na determinação da gravidade dos sintomas e,

consequentemente, na definição do tratamento e obtenção da resposta desejada (BUSTOS *et al.*, 2016). Duas de várias ferramentas utilizadas hoje, para avaliação destes sintomas são o *Rhodes Index of Nausea and Vomiting* (RINV), e o *Pregnancy-Unique Quantification of Emesis* (PUQE) (MATTHEWS *et al.*, 2015). O RINV foi desenvolvido em 1984, originalmente para mensuração de náuseas e vômitos relacionados ao tratamento quimioterápico, foi validado em estudos de náuseas e vômitos gestacionais (RHODES *et al.*, 1984; MATTHEWS *et al.*, 2015). A ferramenta PUQE foi desenvolvida por pesquisadores do Programa Motherisk canadense baseada no RINV, porém analisa outros aspectos mais específicos da gestação (KOREN *et al.*, 2002; KOREN *et al.*, 2005; MATTHEWs *et al.*, 2015; BUSTOS *et al.*, 2016).

### 1.3.1 Antieméticos na gestação

No início da década de 60, a Talidomida, medicação inicialmente prescrita como sedativo-hipnótico e antiemético, desenvolvida na Alemanha, foi a causadora de uma série de nascimentos com más formações congênitas (LIMA *et al.*, 2001). A partir desta tragédia, a utilização de medicamentos por gestantes e seus efeitos sobre o feto, começaram a ser objeto de grande preocupação e pesquisa (CARMO E NITRINI, 2004). O *Food and Drug Administration* (FDA), é um órgão que controla os fármacos nos Estados Unidos da América, que classificou medicamentos em cinco categorias conforme o risco associado ao seu uso durante a gravidez (Quadro 1) (MENGUE *et al.*, 2001; CARMO E NITRINI, 2004; BODY E CHRISTIE, 2016).

O tratamento farmacológico durante a gravidez é contraindicado antes de 12 a 14 semanas, período em que ocorre o desenvolvimento embrionário, o que aumentaria o risco de teratogenicidade (WEGRZYNIAK *et al.*, 2012), porém seu uso deve ser analisado, pois ele se torna aceitável sempre que os benefícios superam os riscos.

O tratamento da êmese gravídica visa redução dos sintomas e correção de suas complicações, no entanto os efeitos prejudiciais sobre o feto devem ser considerados (FERNANDES, 2013). O tratamento inclui uma gama de opções, desde mudanças no estilo de vida e dieta até os tratamentos medicamentosos.

As modificações nos hábitos alimentares, tais como ingestão regular e em pequenas quantidades de líquidos, refeições com porções menores e mais frequentes, com alimentos

mais secos, ricos em carboidrato, que geralmente são mais toleráveis e a redução ou exclusão de alimentos ricos em gorduras, são medidas que podem auxiliar no alívio dos sintomas (ISMAIL E KENNY, 2007; WEGRZYNIAK *et al.*, 2012). Entretanto, quando as modificações alimentares não são suficientes, e a gestante começa a perder peso corporal, outras medidas terapêuticas devem ser tomadas.

**Quadro 1 - Classificação da *Food and Drug Administration* em categorias de risco para o uso de medicamentos na gravidez.**

| Classe | Risco gestacional |
|---|---|
| **A** | Estudos em humanos demonstraram que não existe risco fetal. |
| **B** | Os estudos em animais demonstraram que não existe risco, mas não há estudos em humanos, ou os estudos em animais demonstraram que existe risco, mas os estudos realizados no homem não. |
| **C** | Os estudos em animais demonstraram um efeito adverso sobre o feto, mas não existem estudos adequados e bem controlados em seres humanos, ou os estudos em animais demonstraram que não existe risco, mas não há informações sobre estudos realizados em humanos. |
| **D** | Os estudos no homem demonstraram que existe risco, mas o seu uso pode ser aceitável em casos, onde os benefícios superam os riscos. |
| **X** | O fármaco não deve ser consumido durante a gravidez. Os riscos experimentados superam qualquer vantagem. |

Fonte: Food and Drug Administration, 2008.

Uma interessante perspectiva é o uso de vitaminas no manejo de náuseas e vômitos. A suplementação de até 1,5 mg/dia com Tiamina (Vitamina B1) durante a gestação tem se mostrado uma conduta positiva para a redução das náuseas e vômitos gravídicas. Quando tolerada, a suplementação pode ser administrada por via oral, com doses de 25-50 mg três vezes ao dia, ou então, por via intravenosa, através de infusões semanais de 100 mg de

vitamina B1 em 100 ml de solução salina a 0,9% infundida durante 30-60 minutos (JARVIS E NELSON-PIERCY, 2011).

A Piridoxina (Vitamina B6) também está sendo comumente prescrita para o tratamento de náuseas e vômitos gestacionais (QUINLA E HILL, 2003; NIEBYL, 2010), apesar de seu mecanismo de ação ainda não estar bem definido, entende-se que não há uma relação direta entre a deficiência desta vitamina e a incidência de náuseas e vômitos durante a gestação (NIEBYL, 2010). Estudos estão sendo realizados para demonstrar os benefícios da vitamina B6 no controle da êmese gestacional, todavia a dose terapêutica diária utilizada em alguns destes estudos, que notaram a melhoria dos sintomas, variou entre 30 e 160 mg (SAHAKIAN *et al.*, 1991; VUTYAVANICH *et al.*, 1995; SRIPRAMOTE E LEKHYANANDA, 2003; SMITH *et al.*, 2004; CHITTUMMA *et al.*, 2007; JAMIGORN E PHUPONG, 2007; ENSIYEH E SAKINEH, 2009; FIROUZBAKHT *et al.*, 2014).

Entre as medidas farmacológicas mais adotadas durante a gestação, a primeira linha terapêutica para o tratamento de náuseas e vômitos gestacionais inclui anti-histamínicos como a doxilamina, considerada categoria A (NIEBYL, 2010) e o dimenidrinato (ASSOCIAÇÃO BRASILEIRA DE CUIDADOS PALIATIVOS, 2011; FERNANDES, 2013; CASTILLO E PHILLIPPI, 2015), como categoria B.

Dentre os antidopaminérgicos, a metoclopramida, categoria B, é usualmente prescrita para os sintomas de náuseas e vômitos gestacionais, e apesar de estar relacionada com o desenvolvimento de discinesia tardia, e de haver indicações para que seu tratamento seja evitado por mais de 12 semanas, não está associada a malformações ou desfechos fetais desfavoráveis (EBRAHIMI *et al.*, 2010; NIEBYL, 2010); as fenotiazinas, devido aos seus efeitos adversos como sonolência e sedação, são utilizadas em menor escala (NIEBYL, 2010), apesar de não haver, até agora, dados que confirmem um aumento de efeitos adversos no feto, as fenotiazinas são classificadas como categoria C, entretanto elas podem ser implementadas no manejo de náuseas e vômitos quando outros antieméticos não estão disponíveis ou não foram eficazes (NIEBYL, 2010).

A ondansetrona é o antagonista dos receptores 5-HT3 amplamente utilizado para o tratamento de náuseas e vômitos induzidos por agentes quimioterápicos, devido a isso, acaba por ser utilizado no tratamento da êmese gravídica. Todavia, devido à escassez de dados que assegurem seu uso durante a gestação (EBRAHIMI *et al.*, 2010), é alocado na categoria B (KULAY JUNIOR *et al.*, 2003; FERNANDES, 2013), porém, só deve ser utilizado quando

outros fármacos não foram efetivos no tratamento da hiperêmese gravídica de intensidade grave (MYLONAS *et al.*, 2007; EBRAHIMI *et al.*, 2010; JARVIS E NELSON-PIERCY, 2011).

O interesse pelo uso de terapias da medicina complementar e alternativa, incluindo acupuntura (WEGRZYNIAK *et al.*, 2012), quiropraxia e fitoterápicos (KOUZI, 2003; ABED EL-HADY E WAFIK, 2009) aumentou consideravelmente nos últimos anos. Entretanto estudos de eficácia e segurança também devem ser desenvolvidos.

## 1.4 GENGIBRE

Originário da China e Índia, o gengibre (*Zingiber officinale*) é uma planta herbácea perene da família das *Zingiberaceae*. Cultivada devido ao seu rizoma comestível, para que seu desenvolvimento seja satisfatório, o seu cultivo deve ocorrer em climas predominantemente tropicais, pois é preciso períodos bem definidos de calor e umidade, onde a temperatura média fique em torno dos 25-30ºC (ELPO E NEGRELLE, 2004; BODE E DONG, 2011). Mencionado em textos antigos indianos, budistas, árabes, gregos e na literatura romana (GOVINDARAJAN, 1982A), o rizoma do gengibre hoje, é utilizado e comercializado em todo o mundo. Devido ao seu sabor picante e aroma característicos, é utilizado como condimento no preparo de pratos doces e salgados, bebidas como chás, sucos e cervejas, pães, bolos e biscoitos, geléias, e pode ser utilizado em diversas formas: fresco, seco, em conserva ou cristalizado (BODE E DONG, 2011; HEITMANN *et al.*, 2013), assim como comercializado em cápsulas, comprimidos, chás e extratos líquidos (LETE E ALLUÉ, 2016).

Os constituintes do rizoma de gengibre são numerosos e variam de acordo com o local de origem e frescor, porém as duas principais classes de fitoquímicos são a de óleos voláteis, como os sesquiterpenos e álcoois de sesquiterpeno que são responsáveis pelo aroma (GOVINDARAJAN, 1982A; CHRUBASIK *et al.*, 2005; MISHRA *et al.*, 2012), e a dos compostos fenólicos não voláteis, que respondem ao sabor picante, como os gingerois – [6]–gingerol, em maiores concentrações e, [8]– e [10]–gingerol, que ocorrem em menores concentrações – presentes no rizoma fresco, e os shogaols, que estão presentes no rizoma seco e são formados a partir dos gingerois, quando submetidos a processamentos térmicos, estes dois compostos parecem fornecer também, atribuições farmacológicas ao gengibre (GOVINDARAJAN, 1982B; WOHLMUTH *et al.*, 2005).

### 1.4.1 Efeitos farmacológicos do gengibre

O gengibre possui uma longa história de uso na medicina chinesa e Ayurveda devido a suas propriedades medicinais (GHOSH, 2011; MISHRA *et al.*, 2012), e por outras várias culturas para uma variedade de condições, entre elas enxaquecas, dores musculares e reumáticas, constipações, problemas digestivos, estimulante do apetite, náuseas e vômitos (WHITE, 2007).

No que diz respeito ao seu mecanismo de ação antiemético, ele ainda não foi bem definido. Acredita-se que este mecanismo envolva uma atividade inibitória sobre os receptores colinérgicos muscarínicos M3 e receptores serotoninérgicos 5-HT3 (WHITE, 2007; PERTZ *et al.*, 2011). Porém, seu efeito parece estar mais associado ao sistema gastrointestinal promovendo um aumento nos movimentos peristálticos e tônus gástrico, do que a nível central (WILKINSON, 2000a).

Poucos trabalhos estudaram o metabolismo de seus compostos. A meia-vida do [6]–gingerol, no plasma, quando administrado via intravenosa, aumentou significativamente quando os animais foram submetidos à insuficiência hepática induzida por tetracloreto de carbono. Quando foram induzidos à insuficiência renal, no entanto, a eliminação de [6]–gingerol não foi afetada. Estes resultados sugerem que o fígado está envolvido na metabolização do [6]–gingerol (NAORA *et al.*, 1992).

## 1.5 GENGIBRE E GESTAÇÃO

Durante centenas de anos, o gengibre é utilizado, como antiemético (GIACOSA *et al.*, 2015). E ao longo das últimas décadas, vem sendo investigado, clínica e cientificamente, sua eficácia como um fitoterápico no combate às náuseas e vômitos gestacionais (WILKINSON, 2000B), bem como sua segurança. Estudos demonstraram que o uso de gengibre, administrado oralmente, foi significativamente mais eficaz que placebos, na redução da frequência de vômitos e na intensidade de náuseas (FISCHER-RASMUSSEN *et al.*, 1991; VUTYAVANICH *et al.*, 2001; OZGOLI *et al.*, 2009; SABERI *et al.*, 2014), bem como não impacta os riscos de anomalias congênitas, mortalidade pré-natal, óbitos fetais, baixo peso ao nascer e baixo índice de APGAR (WILLETTS *et al.*, 2003; HEITMANN *et al.*, 2013). No entanto, ainda há incerteza quanto à dosagem segura de gengibre, assim como as consequências de uma superdose, a adequada duração do tratamento e potenciais interações

com fármacos. Alguns conselhos e instituições, como o "*American College of Obstetricians and Gynecologists*" considera o gengibre como um tratamento alternativo, porém, sabe-se que é preciso mais estudos que comprovem sua segurança, pois as evidências científicas até o presente momento são inconsistentes e limitadas.

## 2 JUSTIFICATIVA

Devido à alta prevalência de náuseas e vômitos durante a gestação e aos potenciais efeitos teratogênicos dos fármacos antieméticos, torna-se pertinente realizar uma revisão dos estudos, que sintetize sobre a eficácia e segurança do gengibre como antiemético durante a gestação. Apesar da literatura existente, os resultados encontrados até o presente momento não são conclusivos quanto ao uso e segurança do gengibre como antiemético durante a gestação. Portanto, o gengibre é uma planta medicinal segura e eficaz no tratamento de náuseas e vômitos ocasionados pela gestação?

## 3 HIPÓTESE

Hipótese Nula (#$H_0$): O tratamento com gengibre não altera náusea e êmese induzidas pela gestação

Hipótese Alternativa (#$H_1$): O gengibre é um eficiente antiemético e uma planta medicinal segura que pode ser utilizada por mulheres em período gestacional.

## 4 OBJETIVO

O objetivo deste trabalho foi elaborar uma revisão sistemática para avaliar a eficácia e segurança do uso de rizomas do gengibre (*Zingiber officinale*) no controle de náuseas e vômitos gestacionais.

# 5 MÉTODOS

Para a realização do presente estudo, foram seguidas as diretrizes estabelecidas pelo PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) (MOHER *et al.*, 2009).

## 5.1 CRITÉRIOS DE ELEGIBILIDADE

Foram considerados elegíveis estudos com delineamento de ensaios clínicos randomizados (ECR) realizados em gestantes (entre a 6ª e 20ª semana de gestação), publicados até maio de 2017, que relacionaram a eficácia do gengibre, quanto antiemético, quando administrado por via oral, em forma de cápsulas, em comparação com placebo ou algum outro ingrediente ativo. Foram excluídos estudos não originais (revisões, editoriais e cartas ao editor), estudos realizados com animais, em células *in vitro* e estudos não relacionados ao tema.

## 5.2 ESTRATÉGIA DE BUSCA NA LITERATURA

A busca foi realizada na base de dados eletrônico MEDLINE, via PubMed, com os termos MeSH e combinações ("*Ginger*" OR "*Zingiber Officinale*") AND "*Nausea*" AND "*Vomiting*" AND "*Pregnancy*". Além disto, para completar a busca, uma pesquisa manual na lista de referências dos artigos e revisões.

## 5.3 SELEÇÃO DOS ESTUDOS E COLETA DE DADOS

Na primeira etapa, os artigos encontrados na estratégia de busca foram analisados por títulos e resumos, de forma independente por dois revisores (BLH e KCG), e um terceiro revisor (IRS) resolveu as discordâncias quanto à inclusão/exclusão dos estudos. Aqueles artigos que preencheram os critérios de inclusão foram submetidos à análise de texto completo. A taxa de concordância entre os revisores foi avaliada através do coeficiente Kappa.

A extração de dados foi realizada de forma independente pelos autores para cada artigo, por meio da compilação em uma tabela, das principais características dos estudos (autores e filiação, ano de publicação, amostra, idade gestacional, critérios de inclusão/exclusão, métodos/questionários para avaliar vômitos e náuseas, intervenções, resultados e informações sobre a criança).

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# 6 ARTIGO DE REVISÃO A SER SUBMETIDO AO AUSTRALIAN AND NEW ZEALAND JOURNAL OF OBSTETRICS AND GYNAECOLOGY

## Effects of ginger (*Zingiber officinale*) on pregnancy-induced nausea and vomiting: a systematic review

Bruna Luiza HOLAND[1], Kamila Castro GROKOSKI[2], Ionara Rodrigues SIQUEIRA[3]

1 Departamento de Nutrição, Graduação em Nutrição, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Brazil.

2 Programa de Pós-Graduação em Saúde da Criança e do Adolescente (PPGSCA), Universidade Federal do Rio Grande do Sul, Brazil; Centro de Estudos em Alimentação e Nutrição – Hospital de Clínicas de Porto Alegre/Universidade Federal do Rio Grande do Sul (CESAN-HCPA/UFRGS), Brazil.

3 Programa de Pós-Graduação em Ciências Biológicas: Fisiologia (PPGFISIO), Universidade Federal do Rio Grande do Sul, Brazil.

Corresponding author: Ionara Rodrigues Siqueira, Programa de Pós-Graduação em Ciências Biológicas: Fisiologia, Universidade Federal do Rio Grande do Sul, Avenida Sarmento Leite, 500, 90040-060, Porto Alegre, RS, Brazil. [ionara@ufrgs.br].

**Effects of ginger (*Zingiber officinale*) on pregnancy-induced nausea and vomiting: a systematic review**

Short Title: Antiemetic Effect and Ginger

Abstract: 227 Main text: 1.817

4 tables and 1 figure

Keywords

Pregnant, vomiting, nausea, ginger, antiemetic

**Abstract**

**Introduction:** Pregnancy-induced nausea and vomiting (PINV) affects 60-80% of women. Considering that drug use, such as antiemetic drugs, during pregnancy and lactation requires concern, alternative approaches have been exploited. In this context, rhizome of the ginger (*Zingiber officinale*) has been used as a therapeutic agent for centuries although there is still no consensus regarding its use for PINV. This systematic review was performed in order to evaluate the evidence of the effectiveness and safety of ginger for PINV.

**Methods:** Randomized controlled trials (RCTs) of ginger and PINV were searched from MEDLINE (PubMed). The quality of studies was evaluated.

**Results:** A total of 92 studies were found in the first search. The measure of agreement of the Kappa was k=0.617. Finally 15 studies were eligible for further analysis. The studies addressed the efficacy of ginger compared with placebo, vitamin B6 and other drugs. The mean dose of ginger was 1000mg/d.

**Discussion:** The efficacy of ginger was higher than placebo in PINV in all RCTs. However, a few works showed that ginger is more effective than vitamin B6 reducing nausea. In addition, there were no significant adverse effects on pregnancy outcomes. Although this review indicates concordant data, further studies with a larger sample size as well as longer duration and comparison to recognized treatments with adequate randomization and blinding are need to increase the credibility of the outcomes.

## INTRODUCTION

Gestational nausea and vomiting usually has a peak between the 8th and 12th week of gestation[1; 2] and can be reduced until the 20th week.[1; 3] Pregnancy-induced nausea and vomiting (PINV) are commonly described complications, since it has been estimated that 60-80% of pregnant women suffer with these symptoms.[1; 3; 4] The most severe and persistent form is denominated hyperemesis gravidarum[5] affecting 0.3%-1.0% of pregnancies.[1; 3; 5]

Pathophysiology for these symptoms is still unclear and the etiology seems to be multifactorial, involving combinations of physiological, biological, psychological and sociocultural factors.[6; 7] Pharmacological treatment with antiemetics or other classes of drugs, for instance, chlorpromazine, prochlorperazine,[8; 9] atenolol,[10; 11] phenytoin[12; 13] is contraindicated before the 12th-14th gestational week, because these drugs show potential teratogenic effects when administered during the embryonic period.[14; 15] However, the treatment with vitamins (B6 and B1) and other drugs (such as metoclopramide, dimenhydrinate, ondansetron)[16] has been accepted.[17] In addition, the use of alternative therapies, such as medicinal plants, has been considered in order to treat PINV[18] improving the quality of life.

The rhizome of the ginger (*Zingiber officinale*) is a medicinal plant widely used due its antiemetic properties.[19] Several studies has suggested ginger to treat different conditions, such as chemotherapy-induced nausea,[20; 21; 22] dyspepsia,[23; 24] *Helicobacter pylori* infection,[25; 26] post-operative nausea and vomiting.[27] This species is widely recognized, although there still have not consensus regarding the use in the treatment to PINV.[7; 28; 29] The present systematic review was performed in order to evaluate the evidence of the effectiveness and safety of ginger for PINV.

## METHODS

For the accomplishment of the present study, the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) was followed. The search strategy was independently conducted from the MEDLINE (PubMed) database by two reviewers (BH and KCG). The MeSH terms used in the search were: ('Ginger' OR '*Zingiber officinale*' AND 'Nausea' AND 'Vomiting' AND 'Pregnancy'). In the first step, articles were analyzed by titles and abstracts, a third author (IRS) evaluated any disagreements. Those articles who met inclusion criteria underwent full-text analysis, and during this step the articles that were outside the scope of the review were excluded. In addition, the authors performed a snow-bailing (a hand-search in the articles from reference lists) and also checked review articles, aiming to find other studies suitable for the present review.

Randomized controlled trials (RCTs) with pregnant women between 6-20 weeks of gestational age (GA) with the use of ginger for the treatment of nausea and vomiting during the gestational period compared with placebo, B6 vitamin or other drugs. Studies that used ginger administered through oral intervention (fresh root, dried root, powder, tablets, capsules) was considered eligible for the present review, while the ones that considered ginger intervention via liquid extract or tea were excluded in order to avoid heterogeneity. All the, editorials, comments, and publications written in languages other than English were excluded.

The authors performed the data extraction independently for each article. The principal table of results was built using the main characteristics of the studies (authors and filiations, publication year, sample, gestational age, inclusion/exclusion criteria, methods/questionnaires to evaluate vomiting and nausea, interventions, outcomes and children's information).

The quality of the studies was evaluated according with the Jinks *et al* (2011)[30] criteria. This tool includes items such as sample size, study design, data analysis, outcomes and ethical

issues – points to evaluated in each study included in our review. The quality scores (0-8) was determined independently by two authors (BH and KCG) and the mean between both scores was considered.

Kappa coefficients were calculated to assess the agreement rate between the reviewers. For classification of the results, the agreement of the kappa value, according to Landis and Koch (1977)[31] was ranked as follows: 0–0.2 slight, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6– 0.8 substantial and 0.8–1.0 excellent or almost perfect.

## RESULTS

Selection and characterization of the studies included

Firstly, ninety two studies were found. After the first step, 10 studies were included. The flowchart describes the complete details concerning the search and selection strategy (Figure 1). The Kappa value was k=0.617 that correspond to substantial agreement score.[31; 32; 33] Some articles were included from snow bailing, finally 15 were completed all the requirements for this review. The extracted information was described separately for studies that used ginger and placebo (Table 1), B6 vitamin (Table 2) or drugs (Table 3). In addition, Table 4 showed the quality scores pointing to each study included.

Study characteristics

Articles included in the present study addressed the efficacy of ginger compared with placebo;[34; 35; 36; 37; 38; 39; 40; 41] ginger and vitamin B6;[37; 42; 43; 44; 45; 46] or ginger and drugs (metoclopramide,[40] dimenhydrinate,[47] doxalamine plus pyridoxine[48]). Nine of fifteen studies were double-blind, randomized, controlled trials.[35; 36; 37; 40; 41; 42; 43; 45; 47] A double-blind cross-over design was applied in one study.[39] The remaining studies were performed by single blind clinical trial,[34; 48] randomized controlled equivalent trial[44] and randomized clinical trial.[38; 46] Compliance, in order to verify the drug adherence, was shown in seven studies.[36; 40; 41; 42; 45; 47;

[48] The daily doses of ginger range between 450[48] and 2500 mg[41], but most studies adopted 1000 mg[34; 36; 37; 39; 42; 46; 47] of ginger per day. Treatment duration varied from three[45] to twenty one days.[44; 48] Five studies defined 20 weeks as the maximum gestational age for inclusion in the RCT.[34; 35; 37; 39; 40] The mean age of pregnant women among all the studies was 25.53±4.77 years.

Different questionnaires were used to evaluate nausea and vomiting symptoms in the studies (Supplementary material - Describe more details concern each tool used in the studies included). The most of part the studies used Visual Analogue Scale VAS, along with recording the number of episodes of vomiting daily in their analyses.[36; 37; 41; 42; 45; 47; 48] Seven studies advised the participants about diet changes,[34; 36; 37; 38; 42; 43; 45] and just a part of the articles provided outcomes about the children's information.[35; 36; 39; 41; 42; 44; 48]

## DISCUSSION

Nausea and vomiting are common problems during pregnancy. Taken that, the use of drugs must be avoided specially in early pregnancy; alternative therapies have been considered. It is important to note that traditional use of medicinal plants, such as ginger, peppermint, cranberry and raspberry, has been widely described.[49; 50; 51]

The primary objective of our study was to analyze the effectiveness of ginger for PINV. All RCTs comparing the efficacy of ginger versus placebo reported improvements in symptoms regardless of ginger dosage or form. Mohammadbeigi*et al*. (2011),[40] found a significant difference comparing the ginger effects to placebo for the Rhodes Index for Nausea and Vomiting (RINV) ($p = 0.004$). In addition, ginger showed similar effects to metoclopramide since there were no statistically differences ($p = 0.509$). Some works have compared ginger and vitamin B6, two of them showed that ginger is more effective at reducing nausea than vitamin B6;[42; 43] however the remaining ones found no differences between these

interventions.[44; 45; 46] The studies that comparing ginger versus drugs demonstrated that ginger is as effective as dimenhydrinate[47] and pyridoxine plus doxylamine[48] in the treatment of PINV, besides having fewer side effects.[47] Taken together, this review might indicate rhizomes of ginger as potential approach for PINV.

It is interesting to note that ginger has been widely used[19] to stomach ache, stomach ulcers, bacterial dysentery and dyspepsia,[51] and its antibacterial action, including an *in vitro* effect against *Helicobacter pylori* infection were described.[25; 26]

These properties can be involved at least in part with anti-nausea and antiemetic effects of ginger. A recent systematic review reported an association between *Helicobacter pylori* and hyperemesis gravidarum.[16] This study found the presence of hyperemesis gravidarum in 95% of patients that were positive for this microorganism when compared to a lower percentage in negative patients (50% with hyperemesis gravidarum).[52] Accordantly, patients suffering hyperemesis gravidarum treated with ginger[39] demonstrated positive results, reducing the symptoms, when compared to placebo. Although this study suggests that the ginger effects can be inherent from alterations in gastrointestinal motility, it is important to mention that these effects can be an overlap between the antiemetic effect and the inhibition effects from the microorganism growth. McParlin *et al*. (2016)[53] suggested ginger as an option for the treatment of mild symptoms in pregnancy, including the hyperemesis gravidarum and, furthermore, The American College of Obstetrics and Gynecology proposed as a treatment for PINV.[28]

The mechanism of action and/or active compounds have not been entirely understood, however the ability to inhibit serotonin (5-HT3) receptors in the gastrointestinal tract has been attributed to gingerols and shogaols, promoting an increase in gastrointestinal motility and prokinetic effects.[54; 55] It is important to mention that the metoclopramide and ginger can share these mechanisms of action[54; 55; 56] ameliorating the PINV symptoms.

In addition, our review can indicate that ginger seems to be safe, without major side effects or adverse events during pregnancy. A few studies reported some side effects.[36; 43; 44; 45; 47] Only one study reported that 4 women did not complete the treatment due to ginger intolerance.[35] Mild adverse effects were described (headache, drowsiness and mostly heartburn), but without significance between groups [45; 47] A cohort study with 1,200 women that reported using ginger during pregnancy found no association with any increased risk of congenital malformations and adverse pregnancy outcomes.[57] Unfortunately, this does not allow any conclusions to be made about the long-term safety of ginger in PINV, and knowledge on dosage and administration of ginger was not available.

It is important that the interpretation of these findings takes into account the limitations of the review. Exclusion of RCTs that were not in the English language was a limiting factor. Analyzing all the studies included in this review, we noticed some heterogeneity in the methods used that could produce some bias in the comparison of all the studies considered. In most cases, about 90%[1; 3] nausea and vomiting is resolved by the 20$^{th}$ week of gestation, however, most part of the studies selected pregnant women at GA<20[34; 35; 37; 39; 40] or ≤17[36; 41; 42; 46] weeks. The criteria of inclusion could create a bias to analyze the results related to ginger *per se*. In addition, some studies provided dietary recommendations and this management could be confounding the ginger antiemetic effect, because combined appointments (antiemetic substance + dietary recommendations) can better contribute for PINV decrease. It is important to recognize just one study evaluated placebo effect.[38]

In conclusion, this review showed studies that compare ginger to other possible solutions to PINV. The studies can indicate ginger use as effective for mitigating the severity of PINV symptoms, as well as for safely improving the quality of life during this period. However, further studies with a large number of participants, with a long follow-up period should be

performed in order to better understand both effect and safety of ginger for women suffering from PINV.

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**Figure 1. Flowchart concerning the search and selection strategy**

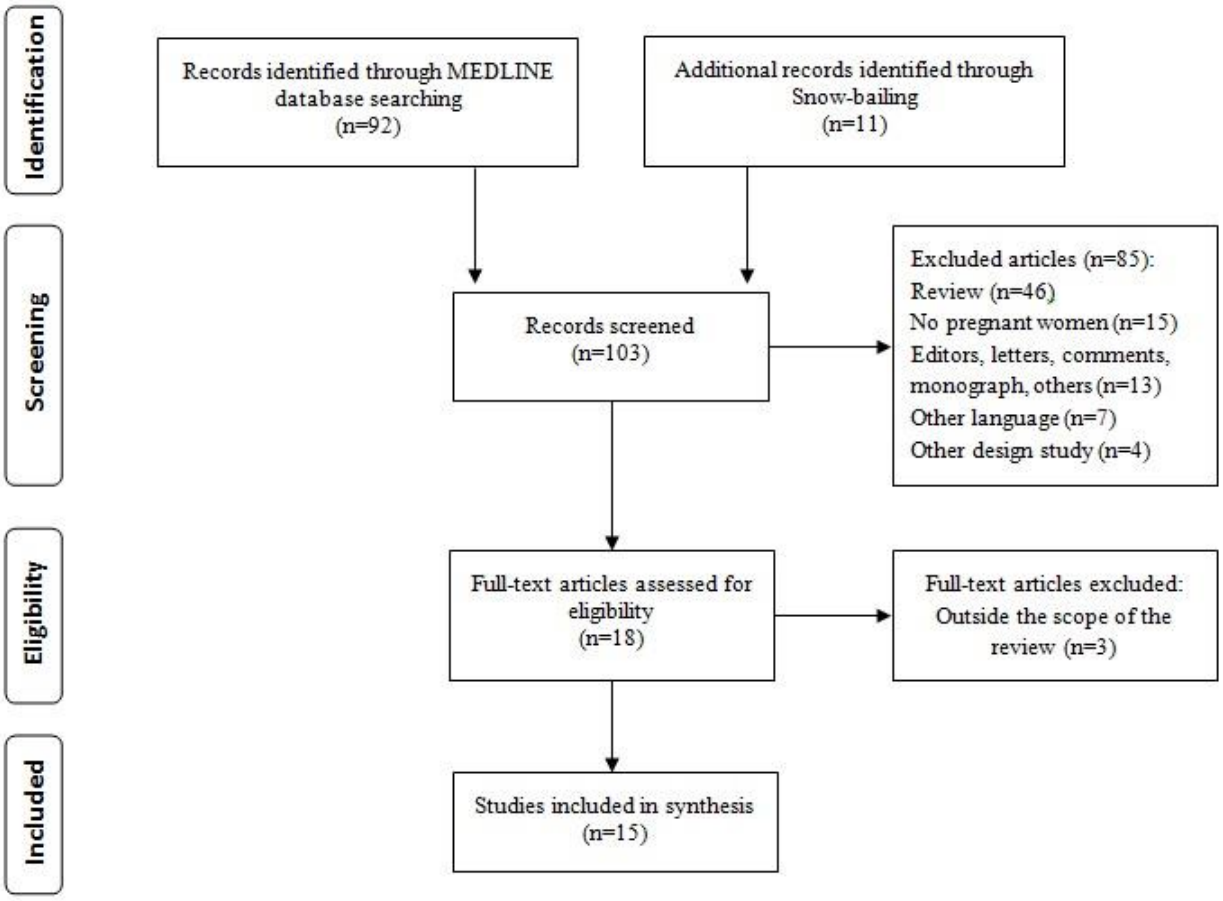

**Table 1. Studies included in the review with the use of placebo vs. ginger**

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
|---|---|---|---|---|---|---|
| **Mohammadbeigi *et al.*, 2011.** | Randomized Double-blind controlled trial | Recruited=120<br><br>Randomized=102 pregnant woman (27.26 ± 3.79 years) from B'esat Hospital<br><br>GA < 20weeks<br><br>Inclusion criteria: with nausea and vomiting, simple pregnancy and inefficacy of food regimens in controlling vomiting and nausea<br><br>Exclusion criteria: suffering from other diseases that need drugs for treatment, side effects caused by ginger intolerance, metoclopramide side effects (extra pyramidal side effects) and pregnancy side effects like abortion risk, bleeding and pyelonephritis | Sample calculated= 28 per group<br><br>For data collection (24h before treatment):<br>- Demographic and background data questionnaire<br>- RINV<br><br>During treatment:<br>- RINV: 10 questionnaires were given to the women in order to be filled up twice a day | Capsules were similar in appearance<br><br>- MET group (n=34): each capsule contained 10 mg of metoclopramide<br><br>- Ginger group (n=34): each capsule contained 200 mg of ginger essence<br><br>- Placebo group (n=34): each capsule contained 200 mg of flour<br><br>3 capsules were prescribed daily for 5 days<br><br>Total mg/d:<br>MET 30 mg<br>Ginger 600 mg | Nobody were excluded from analysis during study<br><br>- No differences about demographic characteristic between groups<br><br>- MET group showed a lesser number of vomiting, nausea, RINV when compared to placebo group (p = 0.018; p = 0.011; p = 0.025; respectively);<br><br>- Ginger had a lesser median of vomiting, nausea, RINV compared to placebo (p = 0.046; p = 0.003; p = 0.004; respectively);<br><br>- The results for vomiting, nausea, RINV showed a non-significance between MET and ginger groups (p = 0.718; p = 0.683; p = 0.509; respectively). | NI |
| **Ozgoli et al., 2009** | Single Blind Clinical Trial Study | Recruited=NI<br><br>Randomized=70 pregnant woman (23.7±4.9 years) recruited from Isfaham City | Sample calculated=NI<br><br>For data collection (24h before | Capsules were similar in appearance | A total of 3 (4%) patients didn't complete the study | NI |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | Multicentric | Hospitals<br><br>GA < 20weeks<br><br>Inclusion criteria: with mild and moderate nausea, with or without vomiting<br><br>Exclusion criteria: medical or surgical history, history of smoking or drug use | treatment):<br><br>- Demographic questionnaire<br>- Scale 0-10 (Fischer-Rasmussen et al.): severity of nausea and vomiting episodes were twice a day<br><br>During treatment:<br>- A 4-page questionnaire was given to each subject to be completed one page a day for four days<br><br>- After the first four days of treatment, a researcher interviewed the participant and completed the questionnaire based on the participant's responses to questions about general changes in nausea and vomiting, method of capsule use, and adherence to the | - Ginger group (n=32): each capsule contained 250mg of ginger root powder (Zintoma)<br><br>- Placebo group (n=35): each capsule contained lactose<br><br>4 capsules were prescribed daily for 4 days<br><br>Total mg/d:<br>Ginger 1000 mg | No participant used any other non-prescription item during the four intervention days<br><br><u>After treatment:</u><br><br>- 26% of ginger sample and 10% of placebo sample, had no nausea intensity<br><br>- 9% of ginger sample and 17% of placebo sample, reported nausea intensity severe ($p<0.05$)<br><br>- Nausea intensity improved significantly in 84% of ginger group versus 56% of the placebo group ($p < 0.05$)<br><br>- 21.5% of the women in the placebo group and 9% of the ginger group had no change in the intensity of nausea<br><br>- 9% of the placebo group had a reduction in the incidence of vomiting, which was not significantly different, but the incidence of reduction in the ginger group was 50%, significantly different. | |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | | dietary recommendations<br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications outside the trial | | | |
| **Willetts *et al.*, 2003** | Randomized Double-blind controlled trial | Recruited = 264<br><br>Randomized = 120 pregnant woman (19-44 years) recruited from the antenatal clinic at the Royal Hospital for Women<br><br>GA < 20weeks<br><br>Inclusion criteria: morning sickness daily for at least a week and inefficacy of food regimens in controlling vomiting and nausea<br><br>Exclusion criteria: hospitalization for dehydration during the current pregnancy, significant medical problems | Sample calculated= 48 per group<br><br>For data collection (the day after the first visit):<br>- RINV<br><br>During treatment:<br>- RINV: record their symptoms an hour after each capsule was swallowed | Capsules were identical in appearance<br><br>- Ginger group (n=48): each capsule contained 125 mg of ginger extract – EV.EXT35 (equivalent to 1.5g of dried ginger)<br><br>- Placebo group (n=51): each capsule contained soya bean oil<br><br>4 capsules were prescribed daily for 4 consecutive days<br><br>Total mg/d:<br>Ginger 500 mg | A total of 21 (17.5%) patients didn't complete the study<br><br>- No differences about demographic characteristic between groups, except from age<br><br>- 58% had nausea throughout the day with only 11% who had symptoms only in the morning<br><br>39% who participated had constant nausea and 58% reported vomiting episodes<br><br>- For both groups, there was a noticeable reduction in overall nausea experience score from baseline to day 1, which then appears to remain consistent through day 4 | - The birthweights, gestational ages and Apgar scores seen for the babies whose mothers participated were similar to those seen in the rest of the hospital population over the same period of time<br><br>- The rates of birth defects were similar to the general |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | (hypertension, epilepsy or diabetes) and known allergy to ginger<br><br>Women who had used ginger or prescription drug therapies for nausea were required to have a 3-day wash-out period prior to entering the study | | | - For nausea experience there was no significant difference between the ginger extract and placebo groups at baseline (p = 0.515 for treat)<br><br>- There was no significant difference between ginger extract and placebo groups for any of the vomiting symptoms<br><br>- For retching symptoms, the ginger extract group was shown to have significantly lower symptom scores than the placebo group for the first 2 days only (p<0.05)<br><br>- The main adverse event in this was reflux and heartburn | population and were all minor. |
| **Vutyavanich *et al.*, 2001** | Randomized Double-blind controlled trial | Recruited=88<br><br>Randomized=70 pregnant woman (28.48±5.6 years) recruited from the antenatal clinic at Maharaj Nakorn Chiang Mai University Hospital<br><br>GA<17weeks<br><br>Inclusion criteria: nausea with or without vomiting | Sample calculated=31 per group<br><br>For data collection (24h before treatment):<br>- VAS<br>- Record the number of vomiting episodes in the last 24h<br><br>During treatment:<br>- VAS: severity of | Capsules were similar in appearance<br><br>Both Ginger and placebo capsules were packed in an envelope<br><br>- Ginger group (n=32): each capsule contained 250 mg of ginger powder.<br><br>- Placebo group (n=35) | A total of 3 (4%) patients didn't complete the study<br><br>- No differences about demographic characteristic between groups<br><br>- In the ginger group (2.1±1.9) the median change in nausea scores was significantly greater than that in the placebo group (0.9±2.2) (p=0.014) compare day 1 to 4<br><br>- Intent-to-treat analysis showed a significantly greater reduction in | |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | Exclusion criteria: medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea and vomiting, mental health problems, used other medication in the past week that might aggravate or alleviate nausea or vomiting such as iron tablets or antiemetics, language or geographic barriers, unable to take the medication as prescribed, refused to participate in the trial; or were unable to return for a follow-up visit 1 week later | nausea was recorded twice daily at noon and at bedtime<br>- Record the number of vomiting episodes<br><br>- At 1-week follow-up, a Likert scale was used to assess treatment response<br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications outside the trial | 4 capsules were prescribed during 4 consecutive days after meals and before a bedtime<br><br>Total mg/d:<br>Ginger 1000 mg | nausea scores in the ginger group(3.5±2.5) than in the placebo group (2.0±3.4) only on day 4 of treatment (p=0.0348)<br><br>- 12/32 (37.5%) women in the ginger group had vomiting after 4 days of treatment and was significantly less (p=0.021) than that women in the placebo group 23/35 (65.7%)<br><br>Likert scale:<br><br>- 28/32 (87.5%) ginger-treated women reported that their symptoms improved, compared with only 10/35 (28.6%) in the placebo group (p<0.001)<br><br>- Headache occurred in five women (14.3%) in the placebo group and six (18.8%) in the ginger group. One patient in the ginger group had abdominal discomfort, one had heartburn, and another had diarrhea for 1 day. These side effects were reported as minor and did not preclude them from taking their prescribed medication | |
| **Firouzbakht *et al.*, 2016** | Randomized Double-blind | Recruited=NI<br><br>Randomized=120 pregnant | Sample calculated=NI<br><br>For data collection | Capsules were coded and packet in similar | A total of 23 (19%) patients didn't complete the study | NI |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | controlled trial<br><br>Multicentric | woman (24.77±4.8 years) recruited from health centers in Amol/Iran.<br><br>GA < 20weeks<br><br>Inclusion criteria: nausea with or without vomiting and age between 18-35 years<br><br>Exclusion criteria: suffering from diseases or problems such as high blood pressure, epilepsy, diabetes, known sensitivity to ginger, hospitalization due to severe nausea and vomiting and also those with no possibility to be followed-up were excluded from the study | (24h before treatment):<br>- VAS<br>- Recording the frequency of nausea and vomiting in the last 24h with a plus sign (+)<br><br>During treatment:<br>- VAS<br>- Recording the frequency of nausea and vomiting in daily with a plus sign (+)<br><br>One week after the drug administration, a Likert scale, was used to assess treatment response.<br><br>- All women given information regarding proper diet and avoiding of high-fat food intake | appearance.<br><br>- Ginger group (n=24): each capsule contained 250mg of ginger root powder (Zintoma)<br><br>- B6 group (n=35): each capsule contained 40mg of vitamin B6<br><br>- Placebo group (n=28): each capsule contained 40mg of sugar.<br><br>1 capsule each 6h were prescribed daily for 4 consecutive days.<br><br>Total mg/d:<br>Ginger 1000 mg<br>Vitamin B6 160 mg<br>Placebo 160 mg | - No differences about demographic characteristic between groups<br><br>- No difference showed before treatment for severity of nausea [ginger (6±3.3), B6 (5.8±3.7) and placebo (5.21±3.15)] and frequency of vomiting [ginger (4.16±2.14), B6 (1.49±1.17) and placebo (5.02±1.17)]; however all groups reduced the values after the treatment for severity of nausea [ginger (0.8±0.4, p<0.001), B6 (0.88±0.54, p<0.001) and placebo (3.01±2.07, p<0.001)] and frequency of vomiting [ginger (0.89±0.47, p<0.001), B6 (0.88±0.5, p=0.022) and placebo (0.49±0.13, p=0.13)]<br><br>Likert scale:<br><br>- The most part of patients for ginger (60.6%) and B6 (61%) reduced the severity of symptoms and 18.3%, 8.8% the patients worsened for respective groups. Although for placebo group 42.7% reduced and the values for patients worsened and continuous with the symptoms were similar (32.2%, 25.1%, respectively). | |
| **Saberi *et al.*, 2014** | Randomized controlled | Recruited=431 | Sample calculated=33per | Capsules were similar in | A total of 14 (12%) patients didn't | NI |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | trial | Randomized=120 pregnant woman (26.71±4.76) recruited from the Prenatal Care Unit of Naghavi Hospital Kashan<br><br>GA < 16 weeks<br><br>Inclusion criteria: nausea without or with mild to moderate vomiting, being a volunteer, gestational age less than 16 weeks, singleton pregnancy, reading and writing ability, no digestive disease, no history of treatment with other antiemetic medication within the last three weeks and residency in Kashan.<br><br>Exclusion criteria: not complete the forms, side effects from consuming ginger capsules, subjects who were advised that the treatment was not effective and that they needed further treatment, and subjects who vomited more than five times per day | group<br><br>For data collection:<br>- RINV<br><br>During treatment:<br>- RINV: questionnaires were given to the women in order to be filled up every 12h<br><br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications outside the trial.<br><br>- The researcher contacted every participant twice during the study: in the fourth day to answer the women's questions in the three groups and to ask them to start the recommended method | appearance.<br><br>- Ginger group (n=37): each capsule contained 250mg of ginger root powder (Zintoma)<br><br>- Placebo group (n=36): each capsule contained lactose<br><br>- Control group (n=33)<br><br>3 capsules were prescribed daily for 4 days.<br><br>Total mg/d:<br>Ginger 750 mg<br><br>- No intervention was made during the first three days and then both placebo and ginger groups received four days treatment | complete the study<br><br>- No differences about demographic characteristic between groups except from age of marriage and wanted or unwanted pregnancy<br><br>-The total RINV score was significantly greater in the ginger group (8.5±4.75) than in the placebo (1.96±4.02) and control (-1.34±3.88) groups, p=0.001. When stratified this scale the means of reduction for vomiting, nausea and retching in the ginger group was 2.52±2.41, 3.86±2.35 and 2.15±1.62 respectively; placebo group was 0.2±2.24, 1.26±1.57 and 0.45±1.60 respectively and control group was 0.97±2.24, -0,33±1.74 and -0.34±1.26 respectively. | |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | | and in the seventh day to request that they return the RINV forms for evaluation of their responses to the treatment | | | |
| **Basirat *et al.*, 2007** | Randomized Double-blind controlled trial | Recruited=NI<br><br>Randomized=65 pregnant woman (19-35 years) recruited from the antenatal clinic of Yahyanejad hospital<br><br>GA between 7-17 weeks<br><br>Inclusion criteria: nausea and vomiting, weight within 20% of normal weight at the beginning of pregnancy<br><br>Exclusion criteria: coexistence of other diseases that might manifest with vomiting such as thyroid disease, history of gastroenteritis, or gastrointestinal disease, infections, multiple pregnancy, hyperemesis gravidarum, trophoblastic | Sample calculated=NI<br><br>For data collection (24h before treatment):<br>- VAS<br>- Record the number of vomiting episodes<br><br>During the treatment:<br>- VAS: severity of nausea was recorded daily at bedtime.<br>- Record the number of vomiting<br><br>At 1-week follow-up, a Likert scale was used to assess treatment response | Biscuits were identical looking and both were packed in a similar envelope<br><br>- Ginger group (n=32): each biscuit 500mg of ginger powder was incorporated<br><br>- Placebo group (n=30)<br><br>5 biscuits daily for 4 days. Time of consumption was based on patient's demand, especially when they experienced nausea<br><br>Total mg/d:<br>Ginger 2500mg | A total of 3 (4.6%) patients didn't complete the study<br><br>- No differences about demographic characteristic between groups<br><br>- The ginger group showed a significantly greater values before and in the end of the treatment than placebo group (2.57±1.77 vs 1.39±1.62; p=0.01)<br><br>- For the baseline and the average until the end of the treatment ginger (5.88±1.83, 2.57±1.77) and placebo (4.67±1.97, 1.39±1.62) groups showed significant differences (p=0.008, p=0.010, respectively)<br><br>- The number of vomiting episodes before and in the end of the treatment in the ginger group (0.96 ± 0.21) and in the placebo group (0.62 ±0.19) was not significant (p=0.243) | - No abnormal pregnancy and delivery outcome ocurred and no infants had any congenital abnormalities recognized and all were discharged in good condition. |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | disease and psychological disorders, used other medication that might aggravate or alleviate nausea or vomiting such antiemetics, iron tablets during last week | | | - 11/32 (34%) women in the ginger group had no vomiting versus 6/30 (18%) in the placebo group<br><br>Likert scale<br><br>- 27/32 (84%) women in the ginger group reported felt "much better", compared with 17/30 (57%) women in the placebo group, and the difference between the groups was significant (p=0.043) | |
| **Fischer-Rasmussen *et al.*, 1990** | Randomized Double-blind cross-over trial | Recruited=6700<br><br>Randomized=30 pregnant woman (18-39 years) recruited from department of obstetrics and gynecology of Hvidore Hospital<br><br>GA<20 weeks<br><br>Inclusion criteria: hyperemesis and in whom the symptoms persisted after 2 days, the first severity score should mount up 10 points or more for including the patient, their condition should allow oral intake of capsules<br><br>Exclusion criteria: diseases | Sample calculated=NI<br><br>For data collection:<br>- Severity score<br><br>During the treatment:<br>- Relief score (day 5): for the evaluation of an effect of treatment<br>- Severity score (day 6)<br>- Relief score and preference to treatment period I or II (day 11)<br><br>- Other antiemetic medication was withdrawn, but parenteral fluids were | The woman who received ginger in the first treatment period in the second received placebo and vice versa. Each woman was her own control<br><br>- Capsules of ginger containing 250mg of ginger powder<br><br>- Capsules of placebo containing 250mg of lactose | A total of 3 (10%) patients didn't completed the study<br><br>- No differences about demographic characteristic between groups<br><br>Relief scores:<br><br>- Ginger to placebo period I and II: 4.1, -0.1<br><br>- Placebo to ginger period I and II: 0.9, 3.7<br><br>- The ginger treatment period had a significantly greater relief in the symptoms when compared to placebo treatment period (p=0.035), the difference obtained especially was by a reduced number of attacks of vomiting | - 1 woman had a spontaneous abortion in the 12th week of gestation<br><br>-The mean birth weight was 3585 g (range 2450-5150 g)<br><br>-The mean gestational age at delivery was 39.9 weeks (range 36-41 weeks)<br><br>-All infants were without |

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| | | that might manifest with gastrointestinal symptoms such gallbladder or liver disease, duodenal ulcer, pancreatitis, and not follow the study protocol | allowed to be continued | | and of decreased nausea<br><br>- 19 (70.4%) women related preferred the ginger period and 4 (14.8%) preferred the placebo treatment (p=0.003). In addition, 4 (14.8%) were unable to state any preference | deformities and discharged in good conditions<br><br>-All had Apgar scores of 9-10 after 5 min. |

GA – Gestational Age; MET – Metformine; NI – No Information; VAS - Visual analogue scale; RINV – Rhodes Index for Nausea and Vomiting.

**Table 2. Studies included in the review with the use of vitamin B6 vs. ginger**

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
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| **Ensiyeh *et al.*, 2008** | Randomized Double-blind controlled trial | Recruited=80<br><br>Randomized=70 pregnant woman (24.6±4.05 years), recruited from the antenatal clinic at Fatemieh Hospital<br><br>GA ≤ 17 weeks<br><br>Inclusion criteria: first attendance at clinic and had experience with nausea with or without vomiting<br><br>Exclusion criteria: medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea and vomiting, mental health problems, used other medication that might aggravate or alleviate nausea or vomiting. Nausea or vomiting, such as iron tablets or antiemetics; refused to participate in the trial; or were unable to return for a follow-up visit 1 week later | Sample calculated= 31 per group<br><br>For data collection (24h before treatment):<br>- VAS<br>- Record the number of vomiting episodes in the last 24h<br><br>During treatment:<br>- VAS: severity of nausea was recorded three times daily<br>- Record the number of vomiting episodes<br><br>At 1-week follow-up, a Likert scale was used to assess treatment response<br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications | Both B6 and Ginger capsules were packed in an envelope containing eight capsules<br><br>- Ginger group (n=35): each capsule contained 500 mg of ginger powder<br><br>- B6 group (n=34): each capsule contained 20 mg of vitamin B6<br><br>Two capsules were prescribed daily, after breakfast and dinner for 4 days<br><br>Total mg/d:<br>Ginger 1000 mg<br>B6 40 mg | A total of 11 (14%) patients didn't complete the study<br><br>- No differences about baseline characteristics between groups<br><br>- The median change in nausea score (baseline minus average post-therapy nausea score) in the ginger group (2.2±1.9) was significantly greater (p= 0.024) than that in the vitamin B6 group (0.9±1.7)<br><br>- There was no significant difference in the overall change in the number of vomiting episodes between the groups<br><br>Likert scale:<br><br>- In the ginger group, 29/35 (82.8%) women reported an improvement in their symptoms, compared with 23/34 (67.6%) women in the vitamin B6 group (p = 0.52) | - Two spontaneous abortions in the ginger group and one in the B6 group (p<0.05)<br><br>- Term birth occurred in 29/35 (82.9%) subjects in the ginger group and 28/34 (82.4%) in the B6 group<br><br>- No babies had any congenital anomalies and all were discharged in good conditions. |

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| **Chittumma *et al.*, 2007** | Randomized Double-blind controlled trial<br><br>Multicentric | Recruited=NI<br><br>Randomized=126 pregnant woman (24.1±5.2 years), recruited from the antenatal clinic in Bangkok Metropolitan Administration Medical College and Vajira Hospital<br><br>GA ≤ 16 weeks<br><br>Inclusion criteria: with nausea with or without vomiting<br><br>Exclusion criteria: hyperemesis gravidarum used other medication that might aggravate or alleviate nausea or vomiting such as iron tablets or anti-emetics, unable to take oral capsules, medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea and vomiting, language or geographic barriers | Sample calculated=57 per group<br><br>For data collection (24h before treatment):<br>- RINV modified (Gideon, 2001)<br><br>During treatment:<br>- RINV modified: severity of the symptoms was recorded once daily<br>- Occurrence of the side effect (drowsiness, heartburn, palpitation, and mouth dryness)<br><br>- Patients were requested to return the day after completing their medication to assess their responses to treatment.<br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications | Capsules were identical in appearance<br><br>Both B6 and Ginger capsules were packed in an envelope containing 24 capsules<br><br>- Ginger group (n=61): each capsule contained 325 mg of ginger powder<br><br>- B6 group (n=62): each capsule contained 12.5 mg of vitamin B6<br><br>2 capsules were prescribed 3 times daily before meals for 4 days<br><br>Total mg/d:<br>Ginger 1950 mg<br>B6 75 mg | A total of 3 (2%) patients didn't complete the study<br><br>- No differences about baseline characteristics between groups<br><br>- Both ginger group (8.7±2.2 before treatment and 5.4±2.0 post treatment) and B6 group (8.3±2.5 before treatment and 5.7±2.3 post treatment) improved nausea and vomiting scores from the baseline<br><br>- The average score change of nausea and vomiting in the ginger group was more than in the B6 group (3.3±1.5 versus 2.6±1.3), and was statistically significant (p=0.042)<br><br>- 95.1% the patients in the ginger group and 96.8% in the B6 group had 100% compliance<br><br>- Four patients in the ginger group and eight patients in the B6 group took other medications or other ginger products during the treatment. | NI |

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| **Smith *et al.*, 2004** | Randomized controlled equivalence trial | Recruited=NI<br><br>Randomized=291 pregnant woman (29±5.3 years), recruited from The Women's and Children's Hospital<br><br>GA between 8-16 weeks<br><br>Inclusion criteria: with nausea or vomiting<br><br>Exclusion criteria: dehydration, if there were reasons to suspect their symptoms were not the result of pregnancy, allergy to ginger or vitamin B6. The previous use of antiemetics, ginger, or vitamin B6 did not exclude entry to the trial. Women could continue to use any existing medication or other measures other than ginger or vitamin B6 during the trial, and a record of use was made at the start and end of the trial | Sample calculated = 113 per group<br><br>For data collection:<br>- RINV: severity of the symptoms was recorded once daily for 3 days<br><br>During treatment:<br>- RINV: severity of the symptoms was recorded in the 7, 14 and 21 day of the treatment<br><br>- Occurrence of any side effects and adverse pregnancy outcome. The standard definitions of pregnancy outcome from the South Australian Health Commission Pregnancy Outcome<br><br>Unit were used to examine the incidence of pregnancy outcome between study groups | All capsules were contained in an opaque brown soft gel capsule<br><br>- Ginger group (n=120): each capsule contained 350 mg of ginger powder<br><br>- B6 group (n=115): each capsule contained 25 mg of vitamin B6<br><br>3 capsules were prescribed daily for 21 days<br>Total mg/d:<br>Ginger 1050 mg<br>B6 75 mg | A total of 56 (19%) patients didn't completed the study<br><br>- No differences about baseline characteristics between groups<br><br>- Ginger was therapeutically equivalent to vitamin B6 for improving nausea, dry retching, and vomiting ($p<0.001$)<br><br>- 66 (53%) women reported an improvement taking ginger, and 69 (55%) reported an improvement with vitamin B6 (relative risk 0.97; 95% CI 0.77, 1.21)<br><br>- At the end of the intervention, the use of antiemetics was reported by 51 women (20%) | - 12 (4.1%) spontaneous abortion in the first or second trimester, 3 (1%) women experienced a stillbirth, and there were no neonatal deaths<br><br>- In total, 9 babies (3%) were born with congenital abnormality. Among women receiving ginger, 3 babies were born with a congenital abnormality, and in the vitamin B6 group, 6 babies were born with a congenital abnormality. |

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| **Sripramote *et al.*, 2003** | Randomized Double-blind controlled trial<br><br>Multicentric | Recruited = NI<br><br>Randomized = 138 pregnant woman (22.1±5.53 years), recruited from the antenatal clinic in Bangkok Metropolitan Administration Medical College and Vajira Hospital<br><br>GA ≤ 16 weeks<br><br>Inclusion criteria: nausea with or without vomiting and requested antiemetics<br><br>Exclusion criteria: medical disorders such hepatitis or gastrointestinal diseases, taken other medication in the past week that might aggravate or alleviate nausea or vomiting, mental health problems, language or geographic barriers, hospitalizes for hyperemesis gravidarum or refused to participate in the trial | Sample calculated = 67 per group<br><br>For data collection:<br>- VAS<br>- Record the number of vomiting episodes<br><br>During treatment:<br>- VAS: record the severity of nausea and vomiting 3 times daily in the morning, at the noon and at bedtime.<br>- Record the number of vomiting episodes<br>- Occurrence of the side effect (drowsiness, heartburn, palpitation, and mouth dryness)<br><br>- All women were advised to divide their food intake into frequent small meals, rich in carbohydrates and low in fat, and not to take any other medications or other ginger preparation outside the trial<br><br>- They were asked to return in one week<br><br>- Compliance was assessed by monitoring the attendance at schedule | Capsules were similar in appearance<br><br>Both B6 and Ginger capsules were packed in an envelope<br><br>- Ginger group (n=64): each capsule contained 500 mg of ginger powder<br><br>- B6 group (n=64): each capsule contained 10 mg of vitamin B6<br><br>3 capsules were prescribed daily before meals for 3 days.<br>Total mg/d:<br>Ginger 1500 mg<br>B6 30 mg | A total of 10 (7%) patients didn't complete the study<br><br>- No differences about demographic characteristic between groups<br><br>- Both groups showed improvement of nausea symptom during the 3-day treatment<br><br>- The mean score change from baseline in the ginger group was 1.4±2.22, which was significantly different ($p<0.001$) and in the B6 group was 2.0± 2.19, which was significantly different ($p<0.001$)<br><br>- The difference of average score change on day 1-3 when comparing the two groups was 0.6 (95% CI -1.4, 0.2), a non-significant difference ($p=0.136$)<br><br>- Baseline compared to 3 day treatment both groups showed reduction in vomiting episodes<br><br>- The mean of vomiting episode change in the ginger group was 0.7± 2.18, was significantly different ($p=0.003$) and B6 group was 0.5±1.44, ($p=0.008$)<br><br>- After 3-day ginger treatment, the number of patients with vomiting was less than those in the B6 group:<br><br>28/64 (43.8%) *versus* 38/64 (59.4%) ($p=0.146$). | NI |

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| **Javadi *et al.*, 2013** | Randomized clinical trial<br><br>Multicentric | Recruited=NI<br><br>Randomized=102 pregnant woman (26.5±4.1 years) recruited from the health centers of University of Medical Sciences of Qazvin<br><br>GA < 17 weeks<br><br>Inclusion criteria: singleton pregnancy with nausea<br>Exclusion criteria: background disease such urinary tract infection, gastrointestinal, hepatic, biliary, bloodclotting, thyroid, diabetes or hypertension diseases, taking any kind of drugs, suffering from hyperemesis gravidarum, food intolerance and history of recent hospitalization due to pregnancy-induced nausea, allergenic to ginger, and with twin or molar pregnancies | Sample calculated=46 per group<br><br>For data collection:<br>- MPUQE<br><br>During the treatment:<br>- MPUQE: once a day | Ginger group (n=47): each capsules contained 250mg of ginger<br><br>B6 group (n=48): each capsules contained 40mg of vitamin B6<br><br>The ginger group would receive 4 capsules daily and B6 group would receive 2 capsules daily both groups for 4 days<br>Total mg/d:<br>Ginger 1000mg<br>B6 80mg | A total of 7 (6.8%) patients didn't completed the study<br><br>- No differences between demographic characteristic between groups<br><br>- MPUQE total scores was significant between ginger and B6 group before and in the end of the treatment (9.80±2.03, 6.28±1.63, p<0.001; 9.35±1.97, 5.98±1.45, p<0.001, respectively)<br><br>- The means was not significant changes between the groups for before and the fourth day the treatment (p=0.172 and p=0.290, respectively)<br><br>- Number of retching times in vitamin B6 group was more reduced; however, this reduction was not statistically significant (p=0.333)<br><br>- Comparing between the groups the number of occurrence of nausea (p=0.158) and its duration (p=0.148) no significant difference. | NI |

GA – Gestational Age; NI – No Information; B6 – Vitamin B6; VAS - Visual analogue scale; RINV – Rhodes Index for Nausea and Vomiting; CI – Confiance risk; MPUQE – Montherisk Pregnancy-Unique Quantification of Emesis and nausea.

**Table 3. Studies included in the review with medications vs. ginger**

| Reference | Design | Population | Methods | Intervention | Results | Childrens |
|---|---|---|---|---|---|---|
| **Pongrojpaw *et al.*, 2007** | Randomized Double-blind controlled trial | Recruited=NI<br><br>Randomized=170 pregnant woman (27.11±5.55 years), recruited from the antenatal clinic Thammasat University Hospital<br><br>GA < 16 weeks<br><br>Inclusion criteria: with nausea and vomiting<br><br>Exclusion criteria: clinical dehydration, gastrointestinal diseases, unable to take oral capsules, unable to return for one week follow up, had known allergy to ginger or dimenhydrinate, used other medication that might aggravate or alleviate nausea or vomiting, refused to participate in the trial | Sample calculated=NI<br><br>For data collection (24h before treatment):<br>- VAS<br>- Record the number of vomiting episodes in the last 24 hours<br><br>During treatment:<br>- VAS: severity of nausea was recorded twice daily<br>- Record the number of vomiting episodes | Capsules were identical in appearance<br><br>- Ginger group (n=77): each capsule contained 500 mg of ginger powder<br><br>- DIM group (n=74): each capsule contained 50 mg of dimenhydrinate<br><br>2 capsules were prescribed daily for 7 days<br>Total mg/d:<br>Ginger 1000 mg<br>DIM 100 mg | A total of 19 (11%) patients don't completed the study, and them were excluded from analysis final<br><br>- No differences about baseline characteristics between groups<br><br>- After adjusting the variation of the difference nausea score and vomiting times before the treatment in both groups, the mean of nausea score in day 1-7 of the treatment were decreased in both groups<br><br>- DIM group showed a lesser number of vomiting in the day 1-2 when compared to ginger group with statistical significance ($p<0.05$), but after day 3-7, the daily mean vomiting times in both groups were not statistically different ($p>0.05$). | NI |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Biswass *et al.*, 2011** | Randomized Single-blind controlled trial<br><br>Multicentric | Recruited=NI<br><br>Randomized=78 pregnant woman (22.2±3.76 years) recruited from.<br><br>GA between 6-16 weeks<br><br>Inclusion criteria: morning sickness without having received any treatment earlier for the same<br><br>Exclusion criteria: multiple gestation, gestational trophoblastic disease, hyperemesis gravidarum, ovarian cyst, gastroesophageal reflux disease or other forms of acid peptic disorders, chronic or serious diseases of major organs o if the containing food, spices, or beverages, or taking medication other than those permitted, not follow the study protocol | Sample calculated=NI<br><br>For data collection:<br>- VAS<br><br>During the treatment:<br>- VAS: severity of nausea and vomiting were record in the each visits and about the last week<br>- The subjective feeling of well-being was assessed as a binary (yes/no) variable at each visit<br>- Record the number of vomiting episodes<br><br>The follow-up visits happened at the end of first and second weeks | - Ginger group (n=34): each capsule contained 150mg of dried ginger (LHR-2445AE)<br><br>- DOX group (n=29): each capsule contained 10mg of doxalamine+10mg of pyridoxine (DOXANATE)<br><br>For the ginger group 3 capsules were prescribed daily, and fro DOX group were prescribed 2-3 capsules daily, both for 21<br>Total mg/d:<br>Ginger 450mg<br>DOX 40-60mg | A total of 15 (19.23%) patients didn't complete the study<br><br>- No differences about demographic characteristic between groups<br><br>- Both groups had the decrease in the severity of nausea and vomiting, this decrease was statistically significant when comparing the baseline with the time of the second follow-up visit<br><br>- Vomiting scores in particular showed a precipitous decline, with the median values tending towards 0 at study end in both groups<br><br>- Both groups had an considerably reduced in the nausea severity but the symptom persisted at study end<br><br>- In the baseline, 25 (73.53%) the women in the ginger group said feeling well-being and 17 (58.62%) in the DOX group. At the study end 27 (79.41%) the woman in the ginger group said feeling well-being and 29 (58.62%) in the DOX group. | NI |

GA – Gestational Age; NI – No Information; VAS - Visual analogue scale; DIM – Dimenhydrinate; DOX – Doxanate.

**Table 4. Quality score of studies included**

| Author & Year | Purpose, hypothesis clear & appropriate | Methods clear & appropriate measures | Sample size is given | Randomization used | Attrition rate recorded | Data analysis rigorous | Outcomes clearly described | Ethical issues addressed | Total Score (max 8) |
|---|---|---|---|---|---|---|---|---|---|
| **B6** | | | | | | | | | |
| Ensiyeh *et al.*, 2008 | 1 | 1 | 1 | 1 | 1 | 0.5 | 1 | 1 | 7.5 |
| Chittumma *et al.*, 2007 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 7.5 |
| Smith *et al.*, 2004 | 1 | 0.5 | 1 | 1 | 0.5 | 1 | 1 | 1 | 7 |
| Sripramote *et al.*, 2003 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 7.5 |
| Javadi *et al.*, 2013 | 1 | 0.5 | 1 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 5 |
| **PLACEBO** | | | | | | | | | |
| Mohammadbeigi *et al.*, 2011 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0.5 | 7.5 |
| Ozgoli et al., 2009 | 1 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | 1 | 5.5 |
| Willetts *et al.*, 2003 | 0.5 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 1 | 6.5 |
| Vutyavanich *et al.*, 2001 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Firouzbakht *et al.*, 2016 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | 1 | 1 | 5.5 |
| Saberi *et al.*, 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Basirat *et al.*, 2007 | 0.5 | 1 | 0.5 | 0.5 | 1 | 0.5 | 1 | 1 | 6 |
| Fischer-Rasmussen *et al.*, 1990 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | 0.5 | 1 | 6 |
| **OTHER** | | | | | | | | | |
| Pongrojpaw *et al.*, 2007 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 1 | 1 | 1 | 6 |
| Biswass *et al.*, 2011 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 1 | 0.5 | 1 | 5.5 |

**Supplementary Material.** Describe of the methods used by the articles included in the systematic review

| Method of evaluation of symptoms | Description | Author | Articles with methodology |
|---|---|---|---|
| Rhodes Index 5 items | The index include 5 items (duration of nausea, frequency of nausea, distress from nausea, frequency of vomiting, amount of vomiting), 5-point Likert scale. Assesses symptoms in the last 12 hours. | Rhodes, 1984 | Mohammadbeigi (2011) |
| Rhodes Index Form 2 | The index include 8 items that described the signs using a Likert scale ranging from mild (zero) to very severe (four) with a maximum total score of 32. Assesses symptoms in the last 12 hours | Rhodes, 1999 | Smith (2004)<br>Willetts (2003)<br>Saberi (2014) |
| Rhodes Index Modified | This method used the correlation with all components Rhodes index form 2 plus two simpler scoring systems, one with three (length of nausea, number of episodes of nausea and number of vomits) and one with five physical symptoms (length of nausea, number of episodes of nausea and number of vomits, number of retching and the volume of vomits) | Gideon, 2001 | Chittumma (2007) |
| Scoring system | This method was develop from authors and is contain scores to evaluate duration of vomiting and numbers of vomiting attacks per day | Self-made score | Fischer-Rasmussen (1991)<br>Ozgoli (2009) |

| | | | |
|---|---|---|---|
| VAS | This scale consist in to grade the severity of nausea over the past 24 hours (baseline score) by marking an asterisk corresponding to their perceived state on a 10-cm vertical line, ranging from 0 (no nausea) to 10 (nausea as bad as it could be). | | Ensiyeh (2008)<br>Pongrojpaw (2007)<br>Firouzbakht (2016)<br>Basirat (2007)<br>Biswass (2011)<br>Sripramote (2003)<br>Vutyavanich (2001) |
| MPUQE | The MPUQE scoring system include times of feeling of nausea during a day, number of occurrences of vomiting during a day, and number of retches during a day. The results are scored on a 1-5 scale, and the score 6 or lower was considered as mild, 7 to 12 as moderate, and 13 or higher as severe symptoms | Koren, 2002 | Javadi (2013) |

VAS - Visual analogue scale; MPUQE – Montherisk Pregnancy-Unique Quantification of Emesis and nausea.

## 7 CONSIDERAÇÕES FINAIS E PERSPECTIVAS

Esta revisão sistemática nos permitiu analisar criticamente os estudos incluídos. As atuais evidências sobre a segurança e o efeito antiemético do gengibre mostraram que este exerce uma atividade positiva na redução das náuseas e êmese gestacionais. Este composto mostrou-se efetivo sem grandes efeitos adversos e efeitos teratogênicos. Apesar da heterogeneidade entre estes estudos, o gengibre pode ser considerado um antiemético alternativo para o tratamento de náusea e vômitos em gestantes. Com base nestas considerações, fica a perspectiva da realização de ensaios clínicos randomizados que foquem a eficácia e segurança com diferentes doses do gengibre durante a gestação.

## ANEXO A – NORMAS DA REVISTA AUSTRALIAN AND NEW ZEALAND JOURNAL OF OBSTETRICS AND GYNAECOLOGY

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*Journal article*

1 Court, K.A., Dare, A.J., Weston-Webb, M., et al. Establishment of lipiodol as a fertility treatment – Prospective study of the complete innovative treatment data set. *Aust N Z J Obstet Gynaecol* 2014; **54**: 13–19.

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2 Williams K, Galerneau F. Maternal transcranial Doppler in pre-eclampsia and eclampsia. Ultrasound Obstet Gynecol 2003. DOI: 10.1002/uog.83.

*Book*

2 Kaufmann HE, Baron BA, McDonald MB, Waltman SR (eds). The Cornea. New York: Churchill Livingstone; 1988.

*Chapter in a Book*

3 McEwen WK, Goodner IK. Secretion of tears and blinking. In: Davson H (ed.). The Eye, Vol. 3, 2nd edn. New York: Academic Press; 1969; 34–78.

*Electronic material*

5 Cancer-Pain.org [homepage on the internet]. New York: Association of Cancer Online Resources, Inc.; c2000–01 [Cited 2015 May 11]. Available from: www.cancer-pain.org/.

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