Domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants – a systematic review and meta-analysis

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Running title: Domperidone and breast milk volume

ABSTRACT

Background

Mothers of preterm infants often struggle to produce enough breast milk to meet the nutritional needs of their infant. Galactagogues such as domperidone are often prescribed to increase breast milk supply, but evidence supporting their role in clinical practice is uncertain.

Objective

To evaluate the efficacy and safety of domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants

Search strategy

Medline, Embase, and Web of Science were searched without language restrictions, from first publication until January 2017. Bibliographies of articles and reviews were hand searched for additional reports.

Selection Criteria

Randomised controlled trials that compared domperidone with placebo in mothers of preterm infants (<37 weeks' gestation) experiencing insufficient milk supply.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, and evaluated study quality. Difference in breast milk volume, and adverse events, were combined using fixed effects meta-analysis.

Main Results

The pooled analysis of five trials consisting of 194 women demonstrated a moderate increase in daily breast milk volume of 88.3 mL/day (95% CI 56.8-119.8) with the use of domperidone compared with placebo. No difference was evident with respect to maternal adverse events (OR 1.05; 95%CI 0.65-1.71), with no reported cases of prolonged QTc

syndrome or sudden cardiac death. Sensitivity analyses showed no important differences in the estimates of effects.

Conclusions

Domperidone is well tolerated and results in a moderate short-term increase in expressed breast milk volume among mothers of preterm infants previously identified as having insufficient breast milk supply.

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Keywords: galactogogue; milk, human; domperidone; infant, premature; breast feeding; milk supply

Tweetable abstract: Domperidone leads to short-term improvements in breast milk volume in mothers of preterm infants

INTRODUCTION

The maternal and infant benefits of breastfeeding are well recognised, with breast milk considered the optimal form of nutrition to support the growth and development of term and preterm infants.[1, 2] For preterm infants in NICU (Neonatal Intensive Care Unit), the feeding of mothers' own breast milk reduces the incidence, severity, and risk of necrotizing enterocolitis (NEC), late onset sepsis, chronic lung disease, retinopathy of prematurity, rehospitalisation after NICU discharge, and neurodevelopmental problems in infancy and childhood.[3] Further, the ability for a mother to provide her own breast milk provides important psychological benefits, with breastfeeding mothers often reporting greater feelings of attachment, empowerment, and confidence.[4]

Mothers of preterm infants, however, face many challenges in initiating, establishing and maintaining an adequate supply of breast milk during their infant's prolonged hospitalisation. When insufficient milk supply persists despite the provision of appropriate lactation support, pharmacological treatment with a galactagogue (a medication that increases mother's milk supply) is often considered.[5] One of the best-studied and most commonly utilised galactagogues is domperidone, a dopamine receptor antagonist that is thought to increase breast milk supply by increasing serum prolactin levels.[6] Previous studies have demonstrated that use of domperidone is widespread[7, 8, 9] with a recent clinical practice survey from Australia and New Zealand identifying that domperidone is considered first-line in the treatment of low milk supply in the Neonatal Unit setting.[10]

Despite high frequency of use, controversy surrounds the use of domperidone, with key issues related to the regulatory status of domperidone.[11] Domperidone has been the subject of

regulatory warnings due to concerns regarding its QTc interval prolongation effects, but the relevance of these findings to younger, healthier lactating women has been questioned.[12-14] A recent commentary concluded that data is too limited in quality and quantity to provide evidence of effectiveness of domperidone for lactation enhancement.[11] This commentary did not undertake a systematic review or conduct a meta-analysis to determine currently available evidence on efficacy and safety, with the most recent Cochrane review published in 2012 and limited to the inclusion of just two studies.[15]

In light of this, we sought to undertake a systematic review and meta-analysis to evaluate the efficacy and safety of domperidone for treatment of low milk supply in mothers of preterm infants.

METHODS

Data sources and search strategy

This review was performed and reported in accordance with the preferred reporting items in systematic review and meta-analysis (PRISMA).[16] We searched three electronic databases from inception to January 2017: Ovid MEDLINE, Embase, and Web of Science. Medical subject headings (e.g. MeSH headings) and free word combinations using Boolean logic of the following search items were used: domperidone AND lactation, breastfeeding OR breast milk (**Appendix S1**). Previous reviews, bibliographies of published trials and cross references were also searched. Further, we searched the Australian New Zealand Clinical Trials Registry and the US ClinicalTrials.gov register for unpublished and ongoing trials. No language restrictions were applied to the search.

Study selection and data extraction

We included all randomized controlled trials (RCTs) that compared the effects of domperidone to placebo for the treatment of low milk supply in mothers of preterm infants. Eligible studies were those involving mothers of preterm infants (less than 37 weeks' gestation) who were not able to supply sufficient breastmilk for their infants' nutritional requirements and randomization occurred more than 72 hours following delivery. In addition, eligible studies were domperidone was prescribed for a minimum of five days following randomisation. The minimum duration of treatment was determined to be five days as this reflects the shortest duration of treatment identified in a recent clinical practice survey.[10] Studies published only as abstracts were eligible for inclusion providing there was sufficient information presented in the abstract to demonstrate that it met the inclusion criteria. In the case of a study published only in short format (i.e. conference abstract[17] or letter to the editor[18]), we contacted the study authors who provided us with additional required data.

Two independent reviewers (LG and RG) screened the titles and abstracts of all studies initially identified, according to the selection criteria. Any disagreement was resolved through consensus or consultation with a third independent reviewer. Full-texts were retrieved from studies that satisfied all selection criteria. Two reviewers (LG and LS) utilized a standardized data extraction sheet to independently extract the following data: study characteristics (authors, years of publication, country), patient characteristics (eligibility criteria), and treatment outcome measures. Any disagreement in extracted data was resolved through consensus or consultation with a third independent reviewer.

The primary maternal outcome for which data was extracted was breast milk volume of EBM (in mL/day), which was either reported as change from baseline (mean difference, MD) or final value only. Where median breast milk volume was reported, as was the case for Rai et al.[18], this was converted to an estimated mean value using a previously validated approach.[19] [20] Where the standard deviation for change in breast milk volume was missing, as was the case for Campbell Yeo et al.[21], the standard deviation was imputed using the approach outlined by the Cochrane Handbook for Systematic Reviews of Interventions.[22] The secondary outcomes for which data were extracted included longer-term breastfeeding outcomes after completion of the RCT as well as maternal and neonatal adverse events reported during the RCT.

Study Quality Assessment

Two independent investigators (LG and LS) evaluated the methodological quality of included studies by assessing the risk of bias in accordance with the Cochrane collaboration's tool.[23] In summary, risk of bias was assessed by answering questions related to the following aspects of studies with 'Yes' (low risk of bias), 'No' (high risk of bias), or 'Unclear' (lack of information or uncertainty over potential bias): random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any disagreement was resolved by consensus.

Data Synthesis

We used Cochrane review manager software (REVMAN version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) for quantitative analysis. The mean differences (MD) in breast milk volume and associated 95% confidence intervals (CIs) were calculated using a

fixed-effects model. The relative risk (RRs) of adverse events and associated 95% confidence intervals (CIs) were calculated using a fixed-effects model.

We planned to use a random effects model if significant clinical heterogeneity was evident. Statistical heterogeneity was assessed in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if $T^2 > 0$ and either I^2 was >30% or a Chi-squared test for heterogeneity resulted in $p<0.10$. Heterogeneity was also visually explored using Forest plots to demonstrate MDs, RRs, and relative 95% CIs for individual studies. We planned to investigate potential for reporting bias using funnel plots if more than ten studies were identified as eligible for inclusion in the meta-analysis. Data permitting, we planned to conduct additional analyses according to gestational age at birth (very preterm <32 weeks versus moderate to late preterm 32 - <37 weeks), postnatal age, duration of treatment, and study quality. We performed subgroup analyses to investigate the potential sources of heterogeneity. With respect to study quality, based on the risk of bias evaluation within each of the seven domains as outlined in the Cochrane collaboration's tool, we determined a study to be of high quality if it received a low risk score on at least four domains, with three mandatory domains being sequence generation, allocation concealment, and incomplete outcome data.[22] Incomplete outcome data was considered critical to methodological quality given its potential to be related to the primary study outcome of breast milk volume. That is, women who withdrew from the study may be more likely to have had insufficient response to the assigned treatment. Additionally, sensitivity analyses were conducted to assess the influence of each individual study on the pooled estimates and to evaluate whether the overall estimates were dominated by one single study.

RESULTS

Study Characteristics

Figure 1 summarises the identification and selection process. Of the 232 studies identified after removal of duplicates, 10 full-text articles were screened for eligibility. Five of these were deemed ineligible owing to inclusion of mothers of term infants,[24, 25] or lack of placebo comparison group[26-28] (**Appendix S2**). This left a total of five studies included in the systematic review and meta-analysis.[17, 18, 21, 29, 30] Details of the characteristics of the studies are outlined in **Table S1**. A total of 210 women were enrolled in these trials and randomized to either domperidone or placebo groups. Outcome data were reported on 192 women, including 95 randomised to domperidone and 97 to placebo.

Inclusion criteria varied across studies. Gestational age ranged from <30 to <37 weeks. Low milk supply was variably defined as inability to attain a fixed volume of expressed breast milk (e.g. < 250 mL/day), or inability to attain a volume of expressed breast milk relative to their infants weight (e.g. < 150 mL/kg/day) or total feed requirements (e.g. < 100% of total daily requirements). All studies utilized a dose of 10 mg three times daily (30 mg/day), with a variable duration of treatment ranging from 5 to 14 days. In the study by Asztalos et al. following an initial 14-day treatment with either domperidone or placebo, all women then received domperidone for another 14-days.[29] Only data at the end of the initial 14-day treatment was included in this meta-analysis.

Quality Assessment

Risk of bias assessments for individual studies is summarized in **Table S2**, with a detailed description and justification of bias allocation outlined in **Appendix S3**. Overall the methodological assessment of included studies was of good quality. The main area of

possible bias related to incomplete outcome data, with attrition of greater than 10% of participants occurring within the domperidone treatment arm of three studies [45%[30], 18%[17], and 12%[18]], and the placebo arm of three studies [18%[17], 11%[29, 30]]. Overall, three studies were identified as having high risk of bias related to missing data due to the potential for missing data to significantly influence the primary outcome.[17, 29, 30]

Comparison Results

All five studies provided data on the primary efficacy outcome of daily breast milk volume, reported as either change from baseline,[17, 18, 21, 30] or final value only.[29]. Our meta-analysis identified that domperidone use leads to a modest increase in daily expressed breast milk volume compared with placebo (MD 88.3 mL/day; 95% CI 56.8-119.8 mL/day; **Figure 2**).

Longer-term breastfeeding outcomes were investigated in three studies, with none suitable for meta-analysis due to heterogeneity in evaluation timing or lack of sufficientdata.[21, 29, 30] Further, following completion of each clinical trial, women were able to obtain and use domperidone in an unrestricted manner. With that in mind, da Silva et al. reported no difference in the proportion of infants discharged home who were breastfeeding between the two groups, but the proportions were not stated.[30] Campbell-Yeo et al. reported on the proportion of women continuing to breastfeed in the domperidone and placebo groups at 2 weeks after the end of the study period (86.4% vs. 62.5%; p=0.13) and at infant discharge from hospital (54.6% vs. 52.2%; p=0.87).[21] Asztalos et al. also reported on the proportion of women breastfeeding in the domperidone and placebo groups, this time at term corrected age (57.8% vs. 60.0%; p=0.83) and at 6 weeks corrected age (42.2% vs. 44.4%; p=0.83).[29]

Maternal adverse events were assessed in all included studies, although reporting of these differed amongst the studies. Three studies reported no significant maternal adverse events at all in either treatment group.[18, 21, 30] Adverse events were reported in two studies,[17, 29] with the pooled estimate identifying no difference in prevalence between women receiving domperidone compared with placebo (RR 1.05; 0.65-1.71; **Figure 3**). Adverse events reported included headache, gastrointestinal symptoms, respiratory symptoms, and neuro-behavioural symptoms (e.g. sleep disturbance, dizziness, drowsiness or restlessness). No serious adverse effects were reported in any study and no women withdrew from any study directly due to adverse effects. Potential cardiac adverse events were only specifically evaluated in one study.[29] Asztalos et al. investigated for potential prolonged QTc syndrome before and after intervention.[4] No women were identified as having a prolonged QTc interval.

Neonatal adverse events were only specifically reported in three studies.[21, 29, 30]
No neonatal adverse events in either treatment group were reported in two studies.[21, 30]
Asztalos et al. reported 14 adverse events in each treatment group, but did not report on prevalence.[29] Further, they investigated for potential prolonged QTc syndrome in 91 infants at the start of the study and 76 infants at the end. A total of 5 infants were found to have a QTc interval > 500 ms, two were identified at the start of the study and three at the end. All of these infants were clinically asymptomatic and no intervention was required.

Heterogeneity and Sensitivity Analyses

While some degree of heterogeneity was noted between studies, this was not considered to be important. A similar treatment effect was observed when studies were stratified according to duration of treatment of 5-7 days (MD 87.4 mL/day; 95% CI 25.4-149.5 mL/day) or 14 days

(MD 88.6 mL/day; 95% CI 52.1-125.2 mL/day; **Figure S1**). A formal subgroup analysis identified no statistically significant difference according to duration of treatment (P=0.97). When stratified according to study quality, difference in breast milk volume was greater among studies identified at low risk of bias (MD 121.7 mL/day; 95% CI 74.6-168.9 mL/day) compared to those identified at high risk of bias (MD 61.5 mL/day; 95% CI 19.2-103.8 mL/day; Pinteraction=0.06, **Figure S2**). Additional sensitivity analyses were performed according to sequential omission of individual studies and evaluation of the overall impact on the pooled results. The omission of any individual study did not substantially alter the overall mean difference in maternal breast milk volume (**Table S3**).

DISCUSSION

Main Findings

Our systematic review and meta-analysis demonstrates that in situations where mothers of preterm infants continue to experience low milk supply despite the use of non-pharmacological strategies, short-term domperidone use results in a moderate 86 mL/day increase in expressed breast milk volume. This increase represents almost 40% of total daily milk intake for a typical preterm infant weighing 1.5 kg and receiving enteral feeds of 150 mL/kg/day. Although the total sample included in the meta-analysis was <200 women, no maternal or neonatal adverse events from any RCT was attributed to domperidone.

Strengths and Limitations

We made considerable effort to include all relevant RCTs, which included contacting authors to obtain additional information. The validity of the results are further supported by the

comprehensive literature search, independent study selection and data extraction processes, methodological quality assessment, and use of sensitivity analyses. Despite differences in duration of domperidone treatment across studies, there was limited heterogeneity in the effectiveness measure. The observed benefit of domperidone remained following a range of sensitivity analyses, adding some robustness to the findings and suggesting that the results are not unduly influenced by extreme findings from one or two RCTs.

The most important limitation is the small number of included trials and small number of participants in each of these trials. By comparison, past meta-analyses included only 2 or 3 RCTs,[15, 31] and the recent publication of new RCTs on this topic indicate that this systematic review is both timely, with the most up-to-date data and the greatest number of RCTs. For the primary outcome of expressed breast milk volume these studies are reasonably well powered, but with only 105 women in total exposed to domperidone remain underpowered for identifying less common maternal or infant adverse outcomes.

Further, due to identifying fewer than ten studies for inclusion we were unable to explore publication bias. Nonetheless, the potential for publication bias appears somewhat mitigated by the fact that we did not identify any registered clinical trials involving domperidone that remain unpublished.

Lastly, this meta-analysis only studied the effect of domperidone in mothers of preterm infants, and therefore cannot be used to determine its role in mothers of term infants.

Interpretation

The benefits of enhancing breast milk supply to maternal and infant wellbeing are established. Every 10 mL/kg/day increase in mothers own milk fed to preterm infants was associated with ~1-point higher scores on Bayley's Scale of Infant Development and a 5% reduction in odds of rehospitalisation by 2.5 years of age.[32] Thus, the additional 86 mL of mother's own milk supply following domperidone treatment may have a clinically meaningful impact on preterm health and development. Further, higher milk supply in postpartum period is associated with improved long-term breastfeeding outcomes.[33] A recent randomised study by O'Connor et al. demonstrated no difference in neurodevelopmental outcomes of very preterm infants fed supplemental donor human milk compared with preterm formula, highlighting the critical importance of strategies for enhancing mother's own milk production.[34]

Given the myriad of factors contributing towards insufficient milk supply, domperidone use should not be considered a panacea for improving breastfeeding outcomes for all women. Non-pharmacological strategies such as breastfeeding education, early initiation of breastfeeding, promotion of kangaroo mother care, supply and appropriate use of breast pumps, and regular breast milk expression, remain paramount for supporting optimal breastfeeding outcomes.[35]

Based on this meta-analysis, there is insufficient evidence to determine whether treatment effects differ according to dose or duration of treatment. Placebo controlled studies identified in this review are limited to those investigating a daily dose of 30 mg. Two studies have investigated the effects of a higher dose of domperidone (60 mg/day) on treatment response but were excluded from this review as they did not include a placebo group.[26, 27] Both these

RCTs failed to demonstrate a statistically significant difference between treatment groups.[26, 27] While Asztalos et al. observed an increase in breast milk volume from baseline to day 14, no further increase was observed over the subsequent 14 days.[29] Given no study has continued to observe women after cessation of treatment, it is uncertain whether continued use is required to sustain the observed increase in breast milk volume or whether supply remains unaffected. Further, the optimal approach towards treatment cessation remains unclear. Common practice recommendations for tapering treatment, rather than abrupt cessation, appear unsupported by any direct clinical evidence.[36] Given the benefits of domperidone observed in this review, areas relating to dose and duration of treatment that may further improve treatment efficacy represent key areas of future research. Collectively, the evidence supports the use of domperidone at a dose of 10 mg three times daily for two weeks in mothers of preterm infants experiencing low milk supply.

Recently, concerns have arisen regarding the increased risk of adverse cardiac effects associated with the use of domperidone in general adult populations,[37] but the relevance of these findings to younger, healthier lactating women is uncertain and has been questioned.[12-14] Such concerns have led international regulatory agencies such as the European Medicines Agency and Health Canada to recommend caution regarding the use of domperidone.[38, 39] The largest body of evidence regarding the potential cardiac safety of domperidone in lactation comes from a recent Canadian study.[40] Smolina et al. identified 45,518 women who were dispensed domperidone in the postnatal period, of which 21 cases of ventricular arrhythmia were identified with no deaths.[40] Although the authors concluded that they found a possible association between domperidone exposure and hospitalization for ventricular arrhythmia (aHR 1.69; 95% CI 0.48-5.96), all cases occurred among women who had a previous history of ventricular arrhythmia. That is, among 43,683 with no previous history of

cardiac arrhythmia who were prescribed domperidone, there was not a single case of ventricular arrhythmia.[40] Notably, according to a previous drug utilization study undertaken by the same authors, approximately 90% of women included in the study were exposed to doses greater than 30mg daily.[9] This finding suggest domperidone is associated with a very small risk of cardiac arrhythmia when used in accordance with established prescribing guidelines that contraindicate use in women with a previous history of cardiac arrhythmia.[41] Further supporting evidence can be taken from the study by Asztalos et al. included in this review in which 90 women had an ECG at study entry and at the end of the 4-week study period, with no women having any evidence of QTc prolongation.[29] Lastly, a recent review of two studies using the regulatory agency gold standard for assessment of QT prolongation concluded that domperidone (tested up to 80 mg/day) is not associated with QT prolongation in healthy female volunteers.[42] Based on this evidence, any future RCTs attempting to evaluate the impact of domperidone on cardiac arrhythmias or sudden cardiac death would require a sample size of >100,000 women, which is clearly impractical.

Conclusion

In situations where mothers of preterm infants continue to experience low milk supply despite the use of non-pharmacological strategies, short-term domperidone use results in a modest 86 mL/day increase in expressed breast milk volume. Initiation of domperidone should only occur after careful assessment of the women and implementation of non-pharmacological supports such as lactation consultation, increasing frequency of expressing and the use of appropriate mechanical expression devices. Despite concerns regarding the potential of prolonged QTc syndrome and sudden cardiac death, the risks associated with

domperidone use among healthy lactating women with no history of cardiac arrhythmia appear small.

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Author Contribution: LEG, conceived the review, selected and reviewed studies identified by the scientific literature search, did the Cochrane risk of bias evaluation, carried out data extraction and analysis, drafted the article, and was responsible for the integrity of the paper. RMG was involved in selecting and review of studies identified by the scientific literature search, and critical review and editing of the final paper. LGS was involved in completing the Cochrane risk of bias evaluation, data extraction and analysis, interpretation of data, drafting of the manuscript, and critical review and editing of the final paper. LAH was involved in interpreting the data, and critical review and editing of the final paper. All authors approved the final version for submission.

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Table/Figure Caption List:

Figure 1. Flow diagram of included studies

Figure 2. Forest plot showing the use of domperidone versus placebo on mean daily expressed breast milk volume

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Figure S1. Forest plot showing the use of domperidone versus placebo on mean daily expressed breast milk volume according to duration of treatment

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573 **Figure S2. Forest plot showing the use of domperidone versus placebo on mean daily**

574 **expressed breast milk volume according to study quality assessment**

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576 **Figure 1. Flow diagram of included studies**
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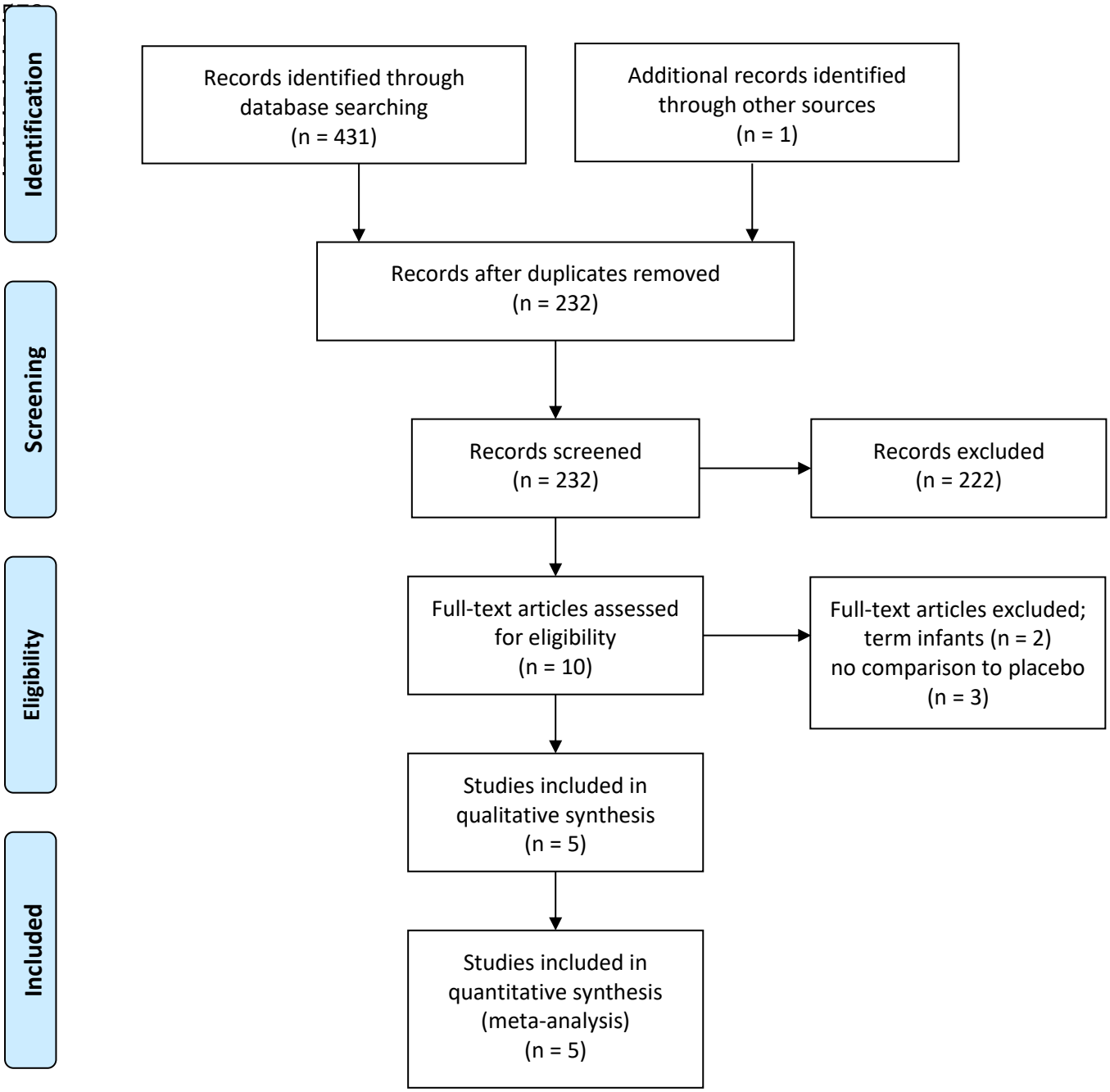

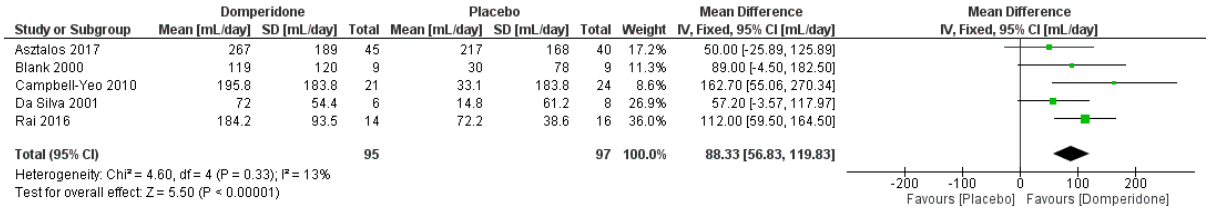
Domperidone
Placebo
Mean Difference
Mean Difference
Study or Subgroup
Mean [mL/day]
SD [mL/day]
Total
Mean [mL/day]
SD [mL/day]
Total
Weight
IV, Fixed, 95% CI [mL/day]
IV, Fixed, 95% CI [mL/day]
Asztalos 2017 267 189 45 217 168 40 17.2% 50.00 [-25.89, 125.89]
Blank 2000 119 120 9 30 78 9 11.3% 89.00 [-4.50, 182.50]
Campbell-Yeo 2010 195.8 183.8 21 33.1 183.8 24 8.6% 162.70 [55.06, 270.34]
Da Silva 2001 72 54.4 6 14.8 61.2 8 26.9% 57.20 [-3.57, 117.97]
Rai 2016 184.2 93.5 14 72.2 38.6 16 36.0% 112.00 [59.50, 164.50]
Total (95% CI) 95 97 100.0% 88.33 [56.83, 119.83]
Heterogeneity: Chi² = 4.60, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 5.50 (P < 0.00001)
-200
-100
0
100
200
Favours [Placebo]
Favours [Domperidone]

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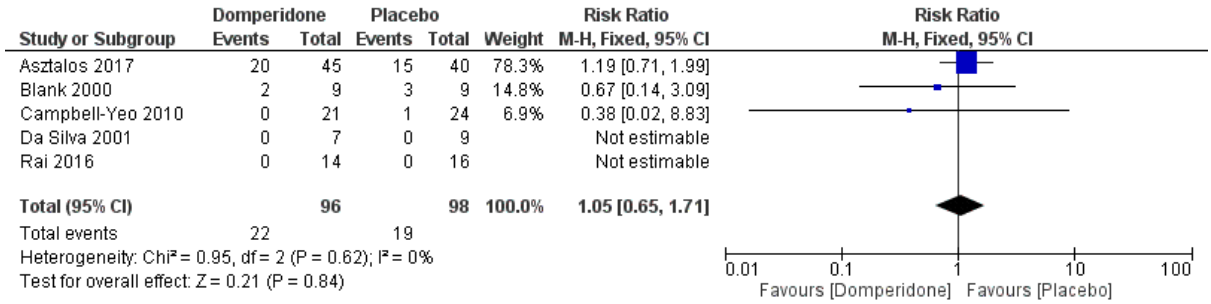
Domperidone
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Asztalos 2017 20 45 15 40 78.3% 1.19 [0.71, 1.99]
Blank 2000 2 9 3 9 14.8% 0.67 [0.14, 3.09]
Campbell-Yeo 2010 0 21 1 24 6.9% 0.38 [0.02, 8.83]
Da Silva 2001 0 7 0 9 Not estimable
Rai 2016 0 14 0 16 Not estimable
Total (95% CI) 96 98 100.0% 1.05 [0.65, 1.71]
Total events 22 19
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)
0.01
0.1
1
10
100
Favours [Domperidone]
Favours [Placebo]

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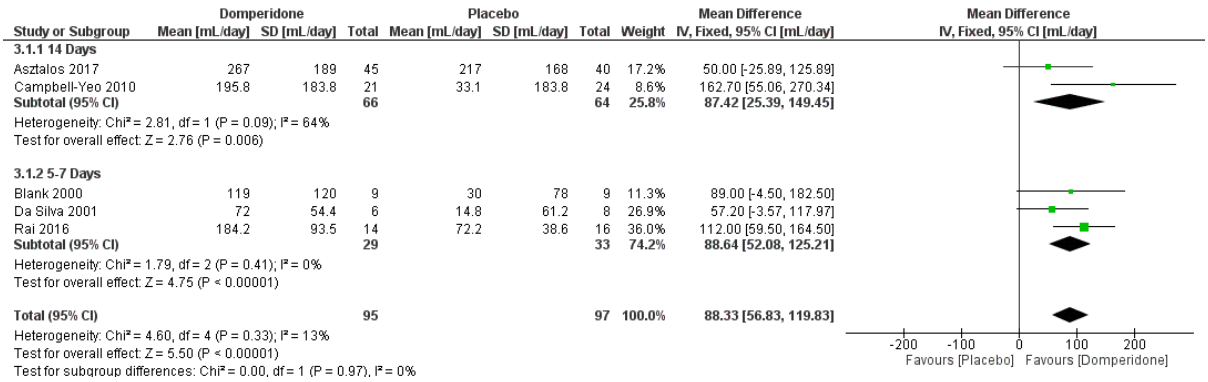

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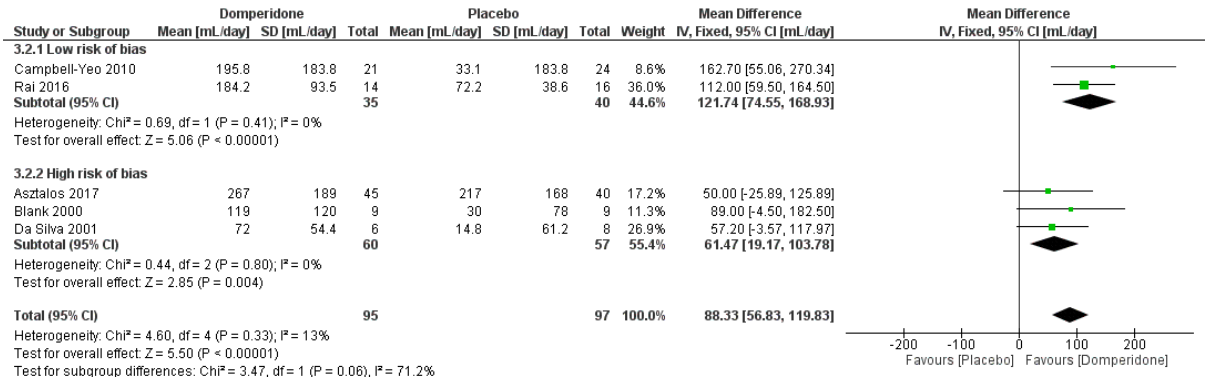
Domperidone
Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean [mL/day] SD [mL/day] Total Mean [mL/day] SD [mL/day] Total Weight IV, Fixed, 95% CI [mL/day]
IV, Fixed, 95% CI [mL/day]
3.2.1 Low risk of bias
Campbell-Yeo 2010 195.8 183.8 21 33.1 183.8 24 8.6% 162.70 [55.06, 270.34]
Rai 2016 184.2 93.5 14 72.2 38.6 16 36.0% 112.00 [59.50, 164.50]
Subtotal (95% CI) 35 40 44.6% 121.74 [74.55, 168.93]
Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 5.06 (P < 0.00001)
3.2.2 High risk of bias
Asztalos 2017 267 189 45 217 168 40 17.2% 50.00 [-25.89, 125.89]
Blank 2000 119 120 9 30 78 9 11.3% 89.00 [-4.50, 182.50]
Da Silva 2001 72 54.4 6 14.8 61.2 8 26.9% 57.20 [-3.57, 117.97]
Subtotal (95% CI) 60 57 55.4% 61.47 [19.17, 103.78]
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.85 (P = 0.004)
Total (95% CI) 95 97 100.0% 88.33 [56.83, 119.83]
Heterogeneity: Chi² = 4.60, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 5.50 (P < 0.00001)
Test for subgroup differences: Chi² = 3.47, df = 1 (P = 0.06), I² = 71.2%
-200
-100
0
100
200
Favours [Placebo]
Favours [Domperidone]

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Table S1. Characteristics of included studies comparing domperidone to placebo

Study (Country)	Publication Type	Domperidone [Randomised / Completed Study (%)]	Placebo [Randomised / Completed Study (%)]	Dose	Duration of Treatment (Days)	Gestational Age (Weeks)	Eligibility Criteria	Continued follow-up after study completion
Asztalos et al 2017 (Canada)	Full-text	45 / 45 (100)	45 / 40 (89)	10 mg TDS	14	<30	8-21 days postpartum and mechanically expressing breast milk with low milk supply (<150mL/kg/day, changed to <250 mL/kg/day during the study) or experiencing a reduction in milk supply by 1/3 or 20% from a peak volume during the previous 72 hour period	Yes; until 6 weeks post-term gestation
Blank et al 2000 (Australia)	Conference Abstract	11 / 9 (82)	11 / 9 (82)	10 mg TDS	5	<34	At least 7 days postpartum and mechanically expressing breast milk with insufficient milk supply (<250mL/day) despite non-pharmacological intervention	No
Campbell-Yeo et al. 2010 (Canada)	Full-text	22 / 21 (95)	24 / 24 (100)	10 mg TDS	14	<31	At least 3 weeks postpartum and mechanically expressing breast milk with lactation failure (decreasing milk supply by >30% from peak volume or inability to provide adequate breast milk to meet daily nutritional intake of their infant) despite non-pharmacological intervention	Yes; until infant discharge from hospital
da Silva et al. 2001 (Canada)	Full-text	11 / 6 (55)	9 / 8 (89)	10 mg TDS	7	<37	Mechanically expressing breast milk with low milk production (inability to meet daily nutritional intake of their	Yes; until infant discharge

							infant) despite non-pharmacological intervention.	from hospital
Rai et al 2016 (India)	Research Letter	16 /14 (88)	16 / 16 (100)	10 mg TDS	7	<37	7-14 days postpartum and mechanically expressing breast milk with low milk supply (not defined)	No

TDS, three times daily

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Table S2: Risk of Bias Assessments of Randomised Controlled Trials of Domperidone for Increasing Maternal Breast Milk Supply

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Asztalos et al. 2017	Low	Low	Low	Low	High	Low	Unclear
Blank et al. 2000	Unclear	Unclear	Low	Low	High	Low	Low
Campbell-Yeo et al. 2010	Low	Low	Low	Low	Low	Low	Low
Da Silva et al. 2001	Low	Low	Low	Low	High	Low	Low
Rai et al. 2016	Low	Low	Low	Low	Low	Low	Low

Table S3. Sensitivity analysis for effect of domperidone compared with placebo on maternal breast milk volume following exclusion of individual studies

Excluded Study	Number of Women Included in Analysis		Mean Difference (mL/day)	95% Confidence Interval (CI)
	Domperidone	Placebo		
Overall Estimate	95	97	88.3	56.8-119.8
Asztalos et al. 2017	50	57	96.3	61.7-130.9
Blank et al. 2000	86	88	88.2	54.8-121.7
Campbell-Yeo et al. 2010	74	73	81.4	48.4-114.3
Da Silva et al. 2001	89	89	99.8	62.9-136.6
Rai et al. 2016	81	81	75.0	35.6-114.4

Appendix S1. Search Strategy for Medline

1. Domperidone[MeSH] OR "domperidone"
2. Lactation[MeSH] OR "lactation"
3. Milk, Human [MeSH] OR "breastmilk" OR "breast milk"
4. Breast Feeding [MeSH] OR "breastfeeding" OR "breast feeding"
5. 2 OR 3 OR 4
6. 1 AND 5

Appendix S2. Summary of excluded studies

Study	Reason for exclusion
Petraglia 1985	RCT comparing domperidone with placebo in mothers of term infants. Excluded as studied mothers of term infants.
Wan 2008	Double-blind randomised crossover trial comparing dosage of domperidone in mothers of preterm infants less than 37 weeks. Excluded as no comparison to placebo.
Ingram 2011	Double-blinded RCT comparing metoclopramide and domperidone on breast milk output of mothers of preterm infants. Excluded as no comparison to placebo.
Jantarasaengaram 2012	RCT in mothers of term infants delivered by caesarean comparing domperidone and placebo. Excluded as studied mothers of term infants and commenced less than 24 hours postpartum
Knoppert 2012	RCT comparing dosage of domperidone in mothers of preterm infants less than 33 weeks gestation. Excluded as no comparison to placebo.

Appendix S3. Risk of Bias Evaluations for Individual Studies

Blank et al 2000 – Risk of Bias Table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential number generation envelopes. Unclear how this was generated
Allocation concealment (selection bias)	Unclear risk	Not stated in paper
Blinding of participants and personnel (performance bias)	Low risk	Domperidone and lactose placebo in identical capsules
Blinding of outcome assessment (detection bias)	Low risk	Double-blinded
Incomplete outcome data (attrition bias)	High risk	All randomized cases reported. 6 cases were excluded from the study due to failure to adhere to expression protocol or drug compliance. It is unclear which arm these participants were allocated to and whether loss to follow up differed by group.
Selective reporting (reporting bias)	Low risk	All randomized cases accounted for in published data. Pre-specified and expected outcomes reported in manuscript.
Other bias	Low risk	Nil other bias detected

Da Silva et al. 2001 - Risk of bias table

Bias	Authors' Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomization was achieved using a random numbers table
Allocation concealment	Low risk	Random allocation by pharmacy

(selection bias)		
Blinding of participants and personnel (performance bias)	Low risk	Domperidone and lactose placebo in identical capsules
Blinding of outcome assessment (detection bias)	Low risk	Double-blinded
Incomplete outcome data (attrition bias)	High risk	Domperidone arm – 4 withdrawals. Placebo arm – no withdrawals. Individual data published showing EBM volumes incomplete for further 2 cases, 1 domperidone and 1 placebo case
Selective reporting (reporting bias)	Low risk	All randomized cases accounted for in published data. Pre-specified and expected outcomes reported in manuscript.
Other bias	Low risk	Nil other bias evident

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626 ***Campbell-Yeo et al. 2010 - Risk of bias table***
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Bias	Authors' Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule by computer
Allocation concealment (selection bias)	Low risk	Computerised assignment to group by off-site pharmacy staff
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded
Blinding of outcome assessment (detection bias)	Low risk	Double-blinded
Incomplete outcome data (attrition bias)	Low risk	1 mother withdrawn after randomization but prior to receiving treatment (domperidone group).
Selective reporting (reporting bias)	Low risk	Published protocol available and pre-specified and expected outcomes reported in manuscript.
Other bias	Low risk	Nil other bias detected

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630 ***Rai et al. 2016 - Risk of bias table***
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Bias	Authors' Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization using computer based software
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk	Identical capsules for domperidone and sugar placebo

Blinding of outcome assessment (detection bias)	Low risk	Blinding of participants and research personnel
Incomplete outcome data (attrition bias)	Unclear risk	Two mothers in domperidone group requested early discharge from hospital and therefore withdrew from the study. Given strength of treatment effect, this loss to follow-up was not considered to significantly alter the study finding.
Selective reporting (reporting bias)	Low risk	Pre-specified and expected outcomes reported in manuscript.
Other bias	Low risk	No other bias detected

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634 ***Asztalos et al. 2017 - Risk of bias table***
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Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using 24hr/day web-based randomization service at the coordinating centre
Allocation concealment (selection bias)	Low risk	All study personnel, point of care personnel and mothers were masked to the allocation.
Blinding of participants and personnel (performance bias)	Low risk	For outcome of first 14 days, blinded, however, not blinded for days 15-28 (which is not relevant for the purpose of this review)
Blinding of outcome assessment (detection bias)	Low risk	Blinding of participants and research personnel
Incomplete outcome data (attrition bias)	High risk	N=5/45 (11%) missing milk volume data for day 14 in placebo group. Loss to follow-up could be related to treatment efficacy and was considered to have a potentially significant impact on measured primary outcome
Selective reporting (reporting bias)	Low risk	Reported all research questions outlined in the study protocol published in 2012
Other bias	Unclear risk	Eligibility criteria changed during study due to poor recruitment.

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