Efficacy and safety of domperidone and metoclopramide in breastfeeding women: A systematic review and meta-analysis

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May 5, 2020

Abstract

ABSTRACT Background: Domperidone and metoclopramide are the most commonly prescribed galactogogues for enhancing milk production, but evidence supporting their efficacy and safety is contradictory. Objectives: To evaluate the efficacy and safety of domperidone and metoclopramide use by breastfeeding women. Search strategy: A systematic literature retrieval of Medline, Embase, Cochrane Library, PubMed, EBSCO, Web of Science, ClinicalTrials.gov and additional bibliography was conducted without time restriction. Selection criteria: Randomised controlled trials exploring the effects of domperidone and metoclopramide in breastfeeding women were included. The primary outcomes were the difference in human milk volume and maternal and neonatal side effects. Data collection and analysis: Two reviewers screened, extracted and assessed the eligible trials independently. Effect size with 95% confidence intervals were presented using random effect model. Main results: Fifteen studies were included. Pooled results demonstrated a low to moderate increase in daily human milk volume of 90.54 mL/day (95%CI 65.69, 115.39), 0.04 mL/day (95%CI 28.85, 28.93) with the use of domperidone and metoclopramide, respectively. No differences were noted in the incidence of maternal side effects with domperidone (RR1.20, 95%CI 0.74, 1.97) or metoclopramide (RR1.23, 95%CI 0.51, 2.94). Additionally, there were no significant differences in the volume of human milk and maternal side effects between the domperidone and metoclopramide group. Conclusions: Domperidone demonstrated a modest increase of 90.54 mL/day in milk production, and had a lower risk of side effects in mothers and infants, which could be considered as a suitable choice for breastfeeding women. Keywords: domperidone; metoclopramide; galactogogues; human milk; side effects

INTRODUCTION

Human milk is well-known to be the optimal source of enteral nutrition to support the growth and development of infants up to six months after birth [1]. However, a general decrease in the practice of breastfeeding has been noted in many countries. In the UK, the reported exclusive breastfeeding rate was 75% at birth and dropped to 14.8% at 6 months [2]. Similarly, it was reported that 74.4% of US infants were exclusively breastfeeding immediately after birth, but by six months this dropped to 34.7% [3]. The reason for the decreases is that women have been facing many challenges to maintain an adequate supply of human milk [4]. The Academy of Breastfeeding Medicine (ABM) claimed that insufficient supply was one of the most frequent causes cited by mothers to discontinue breastfeeding [5], with the reported prevalence ranging from 19.8% to 74.0% [6,7].

Multiple non-pharmacological interventions have been shown to be effective in promoting breastfeeding [8]. However, mothers may pursue therapy with galactogogues in response to insufficient milk supply since non-pharmacologic measures did not always work [9,10]. Galactogogues are pharmaceuticals or certain substances believed to assist in the initiation, maintenance or augmentation of maternal milk supply [5]. Previous studies suggested that mothers' demand for pharmaceutical galactogogues is increasing [11,12].

Currently, the ABM demonstrated that the most widely prescribed galactagogues are domperidone and metoclopramide [5]. Both are dopamine receptor antagonists that can promote milk production[13]. A survey

also reported the use of these pharmaceuticals to enhance milk production in Canada and Switzerland[14]. However, the ABM does not recommend any specific galactogogues for clinical practice due to insufficient supportive evidence [5], and domperidone and metoclopramide are not approved as galactogogues in the US due to cardiac-toxicity and neuro-toxicity concerns [15]. Therefore, available evidence on the efficacy and safety of domperidone and metoclopramide is controversial.

Previous systematic reviews have been published on the efficacy of domperidone in milk production [16-18]. However, there were some recent clinical trials (e.g., Rai 2016, Fazilla 2017) missing from these reviews. Additionally, no meta-analysis of metoclopramide was conducted on the outcomes of milk volume and side effects, and these results varied in original trials. Meanwhile, the comparative efficacy and safety between domperidone and metoclopramide warrant synthesis and verification. In light of this, the current review aims to systematically examine previous literature and to evaluate the efficacy and safety of domperidone and metoclopramide use by breastfeeding women.

METHODS

Design

This review was conducted complying with the Centre for Reviews and Dissemination guidelines [19], and reported following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [20]. This review was registered on PROSPERO on June 17, 2019, and the registration number is CRD42019139249. However, a modified version was submitted on December 26, 2019 due to some practical considerations in further implementation.

Information sources and search strategy

A systematic literature search was conducted in seven academic databases (PubMed, Embase, The Cochrane Library, Medline, ESBCO, Web of Science and ClinicalTrials.gov) to identify publications originating from inception to 17 October, 2019. The following terms from the National Library of Medical Subject Headings (MeSH) including galactogogues, domperidone, metoclopramide and breast feeding were combined to identify relevant citations. Other MeSH terms and free text terms in the PubMed database are presented in Appendix S1. Reference lists of relevant studies were checked in order to find any missing studies. Earlier reviews that addressed the topic of the current study were also inspected. Additionally, email alerts from four databases (Embase, PubMed, EBSCO and Web of Science) were requested to discover any new study published prior to this review being conducted. The remaining three databases were reviewed once a month. No time and language restrictions were applied in the search stage. The searching strategy saved in the platform of these databases was re-run before final analysis (in February 2020).

Eligibility criteria

The PICOS principle (population, intervention, comparison, outcomes and design) was used to construct the clinical question and evaluate the eligibility of potentially relevant studies. The population of interest was breastfeeding mothers with term or preterm infants experiencing normal lactation, inadequate milk production or lactation failure. Breastfeeding is defined as feeding infants with milk directly from the mother's breast [21]. All definitions of inadequate milk production and lactation failure were included, and the most common definition was human milk production failing to meet the needs of infants' daily oral feeding requirements. The intervention group received domperidone or metoclopramide. The control group received placebos or other compounds being considered as galactogogues. The primary outcome was the change in daily human milk volume, and reported maternal and infant side effects after domperidone and metoclopramide treatment. Secondary outcomes were the comparative effects between domperidone and metoclopramide on milk output and side effects of breastfeeding women. Human milk volume was measured in different ways with the most frequent measurement being a change in the weight of the infant after each breastfeeding session.

Only RCTs were included in the study design. However, research published in other formats was also eligible for inclusion if sufficient information was provided. If research was published as a conference abstract or

letter, the corresponding author of the research was contacted to request additional information that would meet inclusion criteria. Animal trials and articles not being able to find full-text after contacting the author were excluded.

Study selection and data extraction

All selected articles were exported into Endnote (Version X9, 2018). Two independent reviewers filtered the selected articles by reviewing titles and abstracts after identifying duplications. Subsequently, full-texts were retrieved from studies that met all selection criteria. Disagreements in selection were resolved through consensus or consultation with the third author.

Reviewers utilized a standardized data extraction sheet to independently extracted the following data: first author, publication year, country, participant characteristics, experimental and control methods and outcomes. Meta-analysis was conducted based on daily human milk volume and maternal side effects. The outcome of human milk volume was considered as the changes between the final value and baseline value, or the final value. Events of side effects were considered as reported incidences of side effects in mothers and infants. In addition, some minor transformation of data was conducted after referring to previous researches [17,22,23] and counselling with a statistician. Disagreements in extracted data were resolved through consensus or consultation with the third author.

Assessment of risk of bias

Two reviewers independently evaluated the risk of bias for each included study using the Cochrane Collaboration bias risk assessment tool and each item was assessed as "low risk", "unclear risk" or "high risk" [24]. The GRADE (grading of recommendations, assessment, development, and evaluation) system was applied to assess the strength of the evidence based on the meta-analysis[25]. Disagreements between two reviewers were resolved by involving the third author.

Data synthesis

Review Manager software (version 5.3; the Cochrane Collaboration, Copenhagen, 2014) was employed to conduct data analysis, with a significance level of 0.05. Risk ratio (RR) was utilized for dichotomous variables, and mean difference (MD) for continuous variables. Formulas used to calculate the changes in human milk volume were adopted from the previous review evaluating the efficacy of domperidone on milk production [18]. Summary measures were presented using effect size with 95% confidence intervals (CI). The inverse variance/Mantel-Haenszel method was used to integrate effect size with a random effects model. The random effects model was employed due to data not being similar (e.g., women with different delivery mode). Heterogeneity was quantified using Chi-square combined with $\mathbf{I^2}$ statistics in each pooled analysis. Heterogeneity was not regarded as important if $\mathbf{I^2}$ was less than 40% or the p -value of Chi-square test was greater than 0.1 [26].

RESULTS

Study selection

Totally, fifteen studies met inclusion criteria after 2137 articles were identified from PubMed (n=250), Embase (n=615), Cochrane Library (n=145), Medline (n=300), EBSCO (n=580), Web of Science (n=231), ClinicalTrials.gov (n=13) and other sources (hand searching of references) (n=3). After several screenings, 2122 articles were excluded and 15 articles on domperidone and metoclopramide were retained for qualitative synthesis. Furthermore, literature retrieval was re-run before the final analysis (in February 2020) and no eligible trial was found. Therefore, fifteen studies were ultimately retained for qualitative synthesis [27-41], and twelve trials were entered into the meta-analysis (see Figure 1).

Study characteristics

Fifteen RCTs involving 710 mothers were included in the current review. Ten trials were conducted in high-income countries: three in Canada[28,29,34], two in the US [39,40], two in Finland [36,38], one in Australia[27], one in

England [30] and one in Belgium [37]. The remaining five trials were conducted in the low- and middle- income countries, with one in Thailand[31], Pakistan [32], India[33], Indonesia [35] and Iran[41]. The detailed characteristics of the included studies are summarized in Table S1.

Risk of bias of included studies

The risk of bias assessment of included studies is summarized in Table S2, and a detailed description and justification are outlined in Appendix S2. Overall, the main area of possible bias in the original studies was related to the three aspects. An inadequate introduction of protocol resulting in 'unclear risk of reporting biases' in most of studies [27,28,30-33,36-41]. The 'unclear risk of selection biases' was observed in seven studies, with lacking the clear demonstration of allocation concealment or randomisation process[27,28,32,35-38]. Five studies were related to the 'unclear risk of attrition biases' due to unclear reasons for participants' withdrawal [27,36,38-40].

Results of Individual Studies

Human milk volume

All studies of domperidone showed significantly higher human milk volume in the domperidone group than in the placebo group[27-29,31-35]. However, the outcome of human milk volume varied in the metoclopramide compared with the placebo group. Two studies reported that milk volume was significantly increased in breastfeeding mothers who received metoclopramide treatments[37,38]. The other three studies showed that metoclopramide was not associated with human milk production[39-41]. The remaining study stated that both 30 mg and 45 mg of metoclopramide significantly increased the daily milk volume, whereas 15 mg did not differ significantly from the placebo group[36]. Additionally, two studies reported that mothers using domperidone had a slighter higher milk output than the metoclopramide group, although there were no significant differences[27,30].

Side effects

Four studies of domperidone [27,30,31,34] and six studies of metoclopramide [27,30,36,38,40,41] reported maternal or neonatal side effects, or both. The details are listed in Table S3. No maternal side effects were reported in four trials of domperidone [28,29,33,35] and one trial of metoclopramide [37]. Neonatal side effects were reported in three trials of domperidone [28,29,34] and two trials of metoclopramide [36,37]. However, two trials of domperidone [28,29] and one trial of metoclopramide[36] found no side effects in infants. The remaining studies did not mention side effects as outcome measurements[32,39].

Synthesis of Results

Human milk volume

Six RCTs of domperidone involving 247 mothers of preterm infants[27-29,33-35] provided data on the daily human milk volume. The random effects model showed that domperidone increased daily human milk volume by 90.54mL/day (95%CI [65.69, 115.39],$p<0.001$), with an acceptable statistical heterogeneity (I^2 =8%, $p<0.001$).

Metoclopramide was evaluated in three RCTs involving 99 mothers of preterm infants [27,39,40]. There was no statistically significant difference in daily human milk volume between the metoclopramide group and the placebo group (MD=0.04mL/day, 95%CI [-28.85, 28.93], p =1.00). No evidence of heterogeneity was observed in metoclopramide (I^2 =0%,p =0.64). Additionally, the meta-analysis on women with term infants was not performed due to original data limitations. The details are listed in Figure 2.

Maternal side effects

Side effects of domperidone were assessed in six RCTs[27-29,33-35] involving 249 mothers with preterm infants. No statistically significant in the incidence of side effects was observed between the domperidone group and the placebo group (RR=1.20, 95%CI [0.74, 1.97], p =0.46). No heterogeneity was found in domperidone (I^2 =0%, p =0.53). No pooled results on term infants were available due to the insufficient data provision.

Regarding metoclopramide, three RCTs including 188 women of term infants[36,37,41] reported the incidences of side effects. There were no significant differences in women of term infants (RR=1.09, 95%CI [0.31, 3.84], p =0.90) between the two groups. A higher heterogeneity was observed in women of term infants, with the value of 68% (I^2 =68%,p =0.08). A different dosage may be the reason for the heterogeneity. Women in Tabrizi's study took 30mg of metoclopramide daily [41], and the events of maternal side effects in Kauppila's study were due to three different dosages[36]. No pooled results on preterm infants were available due to the insufficient data provision. The details are listed in Figure 3.

Domperidone versus Metoclopramide

Outcomes on milk production

Data on milk production of domperidone versus metoclopramide were found in two RCTs involving 85 mothers [27,30]. The use of domperidone resulted in a slightly higher volume of expressed milk compared with a placebo, but no significant difference was observed (MD=33.36mL/day, 95%CI [-17.74, 84.47], p =0.20). No heterogeneity was observed in the two studies (I^2 =0%, p =0.96). The details are listed in Figure S1.

Outcomes on maternal side effects

Data on the incidence of maternal side effects of domperidone versus metoclopramide were found in two RCTs involving 85 mothers[27,30]. No significant difference was found between the incidence of maternal side effects between the domperidone group and the metoclopramide group (RR=0.65, 95%CI [0.23, 1.81], p =0.41). There was no heterogeneity in the two studies (I^2 =0%, p =0.38). No neonatal side effects were observed in the two studies [27,30]. The details are listed in Figure S2.

In summary, the current meta-analysis was identified in twelve RCTs involving 540 mothers. If there were three arms (two experimental groups and one control group) in included studies, arms matching the inclusion criteria were chosen [27]. All pooled analyses and the GRADE evidence profile of the current review are listed in Table S4.

DISCUSSION

Main findings

This current review suggested that domperidone and metoclopramide produced an increased milk supply in breastfeeding women, 90.54mL/day and 0.04mL/day. There were no significant differences in maternal side effects with the use of domperidone and metoclopramide, and no serious adverse effects were observed in these two pharmaceuticals. Additionally, no significant differences in human milk volume and maternal side effects were observed between the domperidone and metoclopramide group. Therefore, domperidone may be more suitable for promoting milk supply when compared with metoclopramide due to moderate increases in human milk volume and the lower risks of side effects among mothers and infants.

Strengths and Limitations

The comparisons between domperidone and metoclopramide on human milk volume and side effects in the current meta-analysis are the first reported comparisons. Meanwhile, the pooled results on the efficacy and safety of metoclopramide are also the first explored analysis. Additionally, the current meta-analysis of domperidone included all eligible trials, which may be helpful to provide more comprehensive and robust conclusions.

However, there are some limitations in this study. First, the homogeneity of the included studies varies in some aspects: participant characteristics (e.g., gestational weeks, delivery mode), intervention dosage and duration, and the definition of insufficient milk supply. These differences may lead to doubtful results, implying the need for more standard designed trials. Second, the outcome of human milk volume in domperidone and metoclopramide was found in women of preterm infants, so it cannot be generalized to mothers with term infants. Third, the small number of participants is an important limitation. But the researchers have systematically reviewed and synthesized all eligible trials compared with other reviews. Fourth, older and

low-to-moderate quality original studies were included to achieve a more systematic and comprehensive understanding of domperidone and metoclopramide. More high quality and multi-centre original studies to explore the efficacy and safety of domperidone and metoclopramide are recommended. Fifth, researchers of the current study intended to conduct meta-analysis for synthesizing other clinically relevant outcomes (e.g., milk components, infant weight gain), but were unable to do so due to inadequate and unavailable data of the original trials. More specific and follow-up indicators should be the focus of future studies. Finally, selection bias may exist in this research because only articles published in English were included.

Interpretation

The current findings are consistent with previous meta-analysis using domperidone to significantly increase human milk volume[17,18]. This consistence could be owing to the mechanism of domperidone, which is a dopamine antagonist that can enhance milk volume through stimulating prolactin release[5]. Metoclopramide is another dopamine antagonist, but previous studies reported conflicting results of metoclopramide on human milk volume. A recent trial of metoclopramide involving 112 women of term infants supported the current results [41]. The shorter intervention duration might be the similarity in considering the insignificant results. However, an older study showed an increased milk yield after metoclopramide therapy [42], which was inconsistent with the current study. The intervention duration should be taken into consideration to explain this difference. The mean intervention duration in the current review was about eight days and four weeks in the trial. Another consideration might be the participants' characteristics. This trial included women of term infants, whereas women with preterm infants were included in the meta-analysis.

The current results supported a previous review showing no significant maternal adverse events among domperidone and placebo groups[17]. It can be explained that domperidone may be associated with a small risk of side effects. Moreover, no serious adverse events were found in the current review. A population-based cohort study involving 247,349 women reported no ventricular arrhythmias or sudden cardiac deaths among domperidone users [43]. A recent meta-analysis involving 390 patients ranging from infants to adults also suggested domperidone does not result in QT prolongation[44]. A previous study identified that the risks associated with domperidone among lactating women with no history of cardiac arrhythmia were less [45]. However, a recent systematic review concluded that oral domperidone usage was associated with a significantly increased risk of cardiac arrhythmia and sudden cardiac death, while most of the participants in the meta-analysis were male and elderly [46]. Similarly, no significant difference in maternal side effects was observed between the metoclopramide and placebo group, which reveals a decreased likelihood of side effects when taking metoclopramide. A cohort study involving 113,612 women also reported that there was no relationship between women who used metoclopramide and the increased risk of any several adverse effects [47]. However, metoclopramide has the potential to cross the blood-brain barrier, so it could be induced central nervous system side effects, while it was mostly reported in elder person[48,49]. Therefore, a benefit-risk analysis should be done of breastfeeding women who received domperidone and metoclopramide. Additionally, neonatal side effects were rarely reported in the review, but it should be of concern in further studies.

Most importantly, dose-effects of domperidone and metoclopramide on milk production and side effects were reported in previous studies. A randomised crossover trial illustrated that both 30mg and 60mg doses resulted in significant increases in milk production among mothers of preterm infants, but women who received 60mg doses had higher value in increased milk volume than 30mg (367% and 215%, respectively)[50]. Another RCT involving 15 women of preterm infants showed a dose of domperidone of 60mg was associated with a clinical increase in milk production when compared with 30mg[51]. But the trial also reported that women who received 60mg of domperidone reported more frequency of side effects comparing with 30mg of domperidone [51]. A case-control study revealed that high doses of domperidone were associated with sudden cardiac death [52]. Concerning metoclopramide, a placebo-controlled, cross-over trial including women with term infants demonstrated that doses of 30mg or 45mg significantly increased human milk volume, whereas 15mg of metoclopramide showed no significant effects [36]. Moreover, in respect to neonatal side effects, an infant of a mother who took 45mg/day showed some intestinal discomfort [36]. Therefore, dose-effects of domperidone and metoclopramide should be taken into consideration in the future.

Certainty, it should also be noticed that no significant difference in human milk volume and maternal side effects was found between the domperidone and metoclopramide group. Both domperidone and metoclopramide are dopamine D_2 receptor antagonists, thus having the similar mechanism to promote milk production[53]. Therefore, metoclopramide could be considered as an alternative treatment for domperidone on breastfeeding production. However, considerations should be taken seriously when prescribing these medicines because some adverse outcomes were also related to the two pharmaceuticals [13,54].

CONCLUSIONS

Considering the evidence of risk-benefit analysis described, the use of domperidone may be more suitable for breastfeeding women, with the modest increase of 90.54mL/day of human milk volume and lower risk of side effects in mothers and rare side effects in infants. Metoclopramide may be an alternative treatment when domperidone is unsuitable for mothers with history of cardiac disease. Moreover, dose-response of domperidone and metoclopramide in human milk volume and side effects should be addressed in further studies. However, the information in the current review could be insufficient to make definitive recommendations on intervention dosage and duration among domperidone and metoclopramide. More information from high-quality multi-centre RCTs is needed to determine appropriate dosages and duration of use during breastfeeding.

ACKNOWLEDGMENTS

The authors would like to thank my teacher Qiao Huang who major in statistics and epidemiology in Evidence-based medicine in Centre for Evidence-Based and Translational Medicine of Wuhan University for his guidance, support, and interpretation of data analysis. We also wish to thank my teacher Yun-yun Wang who major in Evidence-based medicine in Centre for Evidence-Based and Translational Medicine of Wuhan University for her assistance and guidance on the use of GRADE system. They report no conflict of interest and received no funding.

DISCLOSURE OF INTERESTS

The authors report no conflict of interest relevant to the subject of this article.

CONTRIBUTION TO AUTHORSHIP

Quan Shen conceived, designed and wrote the present study. Quan Shen, Mei-chen Du and Sharon R. Redding performed literature search. Quan Shen, Mei-chen Du and Wen-wen Du evaluated the included RCTs and extracted data. Quan Shen, Mei-chen Du and Sharon R. Redding conducted data analysis and interpretation. Yan-qiong Ouyang oversaw the conduct of the study, and provided critical feedback regarding study design. All authors critically reviewed and revised the manuscript. We certify that all authors are responsible for the content of the manuscript and have read and approved the final manuscript.

ETHICS

Ethics approval is not required for a systematic review.

FUNDING

The authors did not receive funding or other support for this publication.

REFERENCES

1. World Health Organization. 10 facts on breastfeeding [Internet]. Geneva: World Health Organization; 2017 [Cited 18 Dec 2019] Available from: https://www.who.int/features/factfiles/breastfeeding/en/.
2. Centers for Disease Control and Prevention. Breastfeeding report card-United States [Internet]. USA: Centers for Disease Control and Prevention; 2011 [Cited 10 Dec 2019] Available from: https://www.cdc.govlbreastfeedingldatalreporteard2.htrn.

3. United National International Children's Emergency. Infant and young child feeding [Internet]. USA: United National International Children's Emergency. [Cited 10 Dec 2019] 2019; Available from: https://data.unicef.org/topic/nutrition/infant-and-young-child-feeding/.
4. Grzeskowiak LE, Wlodek ME, Geddes DT. What evidence do we have for pharmaceutical galactagogues in the treatment of lactation insufficiency? – A narrative review. Nutrients. 2019 Apr; 11(5): E974. PubMed PMID: 31035376.
5. Brodribb W. ABM Clinical Protocol #9: Use of galactogogues in initiating or augmenting maternal milk production, second revision 2018. Breastfeed Med. 2018 Jun; 13(5): 307-14. PubMed PMID: 29902083.
6. Zhang K, Tang L, Wang H, Qiu L, Binns CW, Lee AH. Why do mothers of young infants choose to formula feed in China? Perceptions of mothers and hospital staff. Int J Environ Res Public Health. 2015 Apr; 12(5): 4520-32. PubMed PMID: 25918908.
7. Vila-Candel R, Duke K, Soriano-Vidal FJ. Effect of early skin-to-skin mother-infant contact in the maintenance of exclusive breastfeeding: Experience in a health department in Spain. J Hum Lact. 2018 May; 34(2): 304-12. PubMed PMID: 28099044.
8. Wouk K, Lara-Cinisomo S, Stuebe AM, Poole C, Petrick JL, McKenney KM. Clinical interventions to promote breastfeeding by Latinas: A meta-analysis. Pediatrics. 2016 Jan; 137(1): e20152423. PubMed PMID: 26668300.
9. Asztalos EV, Campbell-Yeo M, Da-Silva OP, Kiss A, Knoppert DC, Ito S. Enhancing breast milk production with domperidone in mothers of preterm neonates (EMPOWER trial). BMC Pregnancy Childbirth. 2012 Aug; 12: 87. PubMed PMID: 22935052.
10. Mannion C, Mansell D. Breastfeeding self-efficacy and the use of prescription medication: A pilot study. Int J Gynecol Obstet. 2012 Dec; 2012: 562704. PubMed PMID: 22220176.
11. Grzeskowiak LE, Dalton JA, Fielder AL. Factors associated with domperidone use as a galactogogue at an Australian tertiary teaching hospital. J Hum Lact. 2015 May; 31(2): 249-53. PubMed PMID: 25355785.
12. Bazzano AN, Hofer R, Thibeau S, Gillispie V, Jacobs M, Theall KP. A review of herbal and pharmaceutical galactagogues for breast-feeding. Ochsner J. 2017 Dec; 16(4): 511-24. PubMed PMID: 27999511.
13. Asztalos EV. Supporting mothers of very preterm infants and breast milk production: A review of the role of galactogogues. Nutrients. 2018 May; 10(5): E600. PubMed PMID: 29757199.
14. Winterfeld U, Meyer Y, Panchaud A, Einarson A. Management of deficient lactation in Switzerland and Canada: A survey of midwives' current practices. Breastfeed Med. 2012 Aug; 7: 317-8. PubMed PMID: 22224508.
15. Sewell CA, Chang CY, Chehab MM, Nguyen CP. Domperidone for lactation: What health care providers need to know. Obstet Gynecol. 2017 Jun; 129(6): 1054-8. PubMed PMID: 28486375.
16. Donovan TJ, Buchanan K. Medications for increasing milk supply in mothers expressing breastmilk for their preterm hospitalised infants. Cochrane Database Syst Rev. 2012 Mar; 3: CD005544. PubMed PMID: 22419310.
17. Grzeskowiak LE, Smithers LG, Amir LH, Grivell RM. Domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants: A systematic review and meta-analysis. BJOG. 2018 Oct; 125(11): 1371-8. PubMed PMID: 29469929.
18. Taylor A, Logan G, Twells L, Newhook LA. Human milk expression after domperidone treatment in postpartum women: A systematic review and meta-analysis of randomized controlled trials. J Hum Lact. 2019 Aug; 35(3): 501-9. PubMed PMID: 30481478.
19. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. Layerthorpe, UK: York Publishing Services Ltd; 2009.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009 Jul; 339: b2535. PubMed PMID: 19622551.
21. World Health Organization. Implementation of the baby-friendly hospital initiative [Internet]. Geneva: World Health Organization; 2013 [Cited 10 August 2019] Available from: https://www.who.int/elena/titles/bbc/implementation_bfhi/en/.
22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the

size of a sample. BMC Med Res Methodol. 2005 Apr; 5: 13. PubMed PMID: 15840177.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec; 14: 135. PubMed PMID: 25524443.
24. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Chichester, UK: John Wiley & Sons, Ltd; 2011.
25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr; 336(7650): 924-6. PubMed PMID: 18436948.
26. Du MC, Ouyang YQ, Nie XF, Huang Y, Redding SR. Effects of physical exercise during pregnancy on maternal and infant outcomes in overweight and obese pregnant women: A meta-analysis. Birth. 2019 Jun; 46(2): 211-21. PubMed PMID: 30240042.
27. Blank C, Eaton V, Bennett J, James SL. A double blind RCT of domperidone and metoclopramide as pro-lactational agents in mothers of preterm infants. p. 73. Perinatal Society of Australia and New Zealand 5th Annual Conference, Canberra, Australia. 2001.
28. Da-Silva OP, Knoppert DC, Angelini MM, Forret PA. Effect of domperidone on milk production in mothers of premature newborns: A randomized, double-blind, placebo-controlled trial. Can Med Assoc J. 2001 Jan; 164(1): 17-21. PubMed PMID: 11202662.
29. Campbell-Yeo ML, Allen AC, Joseph KS, Ledwidge JM, Caddell K, Allen VM, et al. Effect of domperidone on the composition of preterm human breast milk. Pediatrics. 2010 Jan; 125(1): 107-14. PubMed PMID: 20008425.
30. Ingram J, Taylor H, Churchill C, Pike A, Greenwood R. Metoclopramide or domperidone for increasing maternal breast milk output: A randomised controlled trial. Arch Dis Child-Fetal. 2012 Jul; 97(4): F241-5. PubMed PMID: 22147287.
31. Jantarasaengaram S, Sreewapa P. Effects of domperidone on augmentation of lactation following cesarean delivery at full term. Int J Gynecol Obstet. 2012 Mar; 116(3): 240-3. PubMed PMID: 22189066.
32. Inam I, Bashir-Hashmi A, Shahid A. A comparison of efficacy of domperidone and placebo among postnatal women with inadequate breast milk production. Pak J Med Health Sci. 2013 Jun; 7(2): 314-6.
33. Rai R, Mishra N, Singh D. Effect of domperidone in 2nd week postpartum on milk output in mothers of preterm infants. Indian J Pediatr. 2016 Aug; 83(8): 894-5. PubMed PMID: 27109392.
34. Asztalos EV, Campbell-Yeo M, Da-Silva OP, Ito S, Kiss A, Knoppert D. Enhancing human milk production with domperidone in mothers of preterm infants. J Hum Lact. 2017 Feb; 33(1): 181-7. PubMed PMID: 28107101.
35. Fazilla TE, Tjipta GD, Ali M. Domperidone and maternal milk volume in mothers of premature newborns. Paediatr Indones. 2017 Jan; 57(1): 17-22.
36. Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation on metoclopriade. Lancet. 1981 May; 317(8231): 1175-7.
37. De Gezelle H, Ooghe W, Thiery M, Dhont M. Metoclopramide and breast milk. Eur J Obstet Gynecol Reprod Biol. 1983 Apr; 15(1): 31-6. PubMed PMID: 6350073.
38. Kauppila A, Anunti P, Kivinen S. Metoclopramide and breast feeding: Efficacy and anterior pituitary responses of the mother and the child. Eur J Obstet Gynecol Reprod Biol. 1985; 19(1): 19-22.
39. Hansen WF, Mcandrew S, Harris K, Zimmerman MB. Metoclopramide effect on breastfeeding the preterm infant: A randomized trial. Obstet Gynecol. 2005 Feb; 105(2): 383-9. PubMed PMID: 15684169.
40. Fife S, Gill P, Hopkins M, Angello C, Boswell S, Nelson KM. Metoclopramide to augment lactation, does it work? A randomized trial. J Matern Fetal Neonatal Med. 2011 Nov; 24(11): 1317-20. PubMed PMID: 21410420.
41. Tabrizi SO, Mirghafourvand M, Dost AJ, Mohammad-Alizadeh-Charandabi S, Javadzadeh Y, Seyedi R. Effect of metoclopramide administration to mothers on neonatal bilirubin and maternal prolactin: A randomized, controlled, clinical trial. World J Pediatr. 2019 Apr; 15(2): 135-42. PubMed PMID: 30519818.

42. Guzmán V, Toscano G, Canales ES, Zárate A. Improvement of defective lactation by using oral metoclopramide. Acta Obstet Gynecol Scand. 1979; 58(1): 53-5. PubMed PMID: 369279.
43. Mehrabadi A, Reynier P, Platt RW, Filion KB. Domperidone for insufficient lactation in England 2002-2015: A drug utilization study with interrupted time series analysis. Pharmacoepidemiol Drug Saf. 2018 Dec; 27(12): 1316-24. PubMed PMID: 30106193.
44. Bor S, Demir M, Ozdemir O, Yuksel K. A meta-analysis on the cardiac safety profile of domperidone compared to metoclopramide. United European Gastroenterol J. 2018 Nov; 6(9):1331-46. PubMed PMID: 30386606.
45. Lebedevs T, BPharm, PostGradDipPharm, Kendrick C, BPharm (Hons). Pharmacological management of common lactation problems. J Pharm Pract Res. 2019 Apr; 49: 192-8.
46. Leelakanok N, Holcombe A, Schweizer ML. Domperidone and risk of ventricular arrhythmia and cardiac death: A systematic review and meta-analysis. Clin Drug Invest. 2016 Feb; 36(2): 97-107. PubMed PMID: 26649742.
47. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med. 2009 Jun; 360(24): 2528-35. PubMed PMID: 19516033.
48. Hofmeyr GJ, van Iddekinge B. Domperidone and lactation. Lancet. 1983 Mar; 1(8325): 647. PubMed PMID: 6131323.
49. Tabrizi SO, Mirghafourvand M, Seyedi R. The effect of metoclopramide on prolactin levels in breastfeeding mothers: A systematic review and meta-analysis. Int J Pediatr. 2017 Dec; 5(9): 5827-38.
50. Wan EW, Davey K, Page-Sharp M, Hartmann PE, Simmer K, Ilett KF. Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. Brit J Clin Pharmaco. 2008 Aug; 66(2): 283-9. PubMed PMID: 18507654.
51. Knoppert DC, Page A, Warren J, Seabrook JA, Carr M, Angelini M, et al. The effect of two different domperidone doses on maternal milk production. J Hum Lact. 2013 Feb; 29(1): 38-44. PubMed PMID: 22554679.
52. Arana A, Johannes CB, McQuay LJ, Varas-Lorenzo C, Fife D, Rothman KJ. Risk of out-of-hospital sudden cardiac death in users of domperidone, proton pump inhibitors, or metoclopramide: A population-based nested case-control study. Drug Saf. 2015 Dec; 38(12): 1187-99. PubMed PMID: 26350642.
53. Gabay MP. Galactogogues: Medications that induce lactation. J Hum Lact. 2002 Aug; 18(3): 274-9. PubMed PMID:12192964.
54. Smolina K, Mintzes B, Hanley GE, Oberlander TF, Morgan SG. The association between domperidone and ventricular arrhythmia in the postpartum period. Pharmacoepidemiol Drug Saf. 2016 Oct; 25(10): 1210-4. PubMed PMID: 27296864.

Figure/Table legends

Figure 1. PRISMA flow diagram

Figure 2. Forest plot of domperidone/metoclopramide versus placebo of the changes in milk volume

Figure 3. Forest plot of domperidone/metoclopramide versus placebo regarding side effects. All meta-analysis was conducted in women of preterm infants except that the side effects between metoclopramide group and placebo group included mothers with term infants

Figure S1. Forest plot of domperidone versus metoclopramide regarding milk production

Figure S2. Forest plot of domperidone vs metoclopramide regarding side effects

Table S1. Characteristics of included studies

Table S2. Risk bias of included studies

Table S3. Side effects of domperidone and metoclopramide

Table S4. Effect estimates and GRADE evidence profile comparing galactogogues versus placebo. I-V,

Inverse-Variance; M-H, Mantel-Haenszel; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation

Appendix S1. The PubMed search terms

Appendix S2. Risk of bias evaluations for individual studies