Oral metoclopramide boosts lactogenesis II in mothers with preterm infants: a randomized placebo-controlled trial.

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Research

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Abstract

Background: Preterm mothers at risk of delayed lactogenesis II may benefit from early pharmcological intervention to initiate breastfeeding onset. Research aim. To evaluate the effect of oral metoclopramide on lactogenesis II in mothers of preterm infants commencing within twelve hours of delivery.

Methods: From April 2006 to May 2009,105 women were randomized to metoclopramide (term births, n=36;reterm n=20) or placebo (term,n=33;preterm,n=16). Mothers received 30 mg of oral metoclopramide daily for the first postnatal week in a randomized double-blinded placebo-controlled study. Primary outcome was augmentation of Lactogenesis II onset by postnatal day 3. Secondary outcomes were daily expression of breastmilk and maternal perception of lactogenesis II, breastfeeding practice and infant weight change over 6 months.

Results: Metoclopramide achieved 25% augmentation in lactogenesis II onset (p=0.09) with greater expressed human milk volumes in mothers of preterm infants. Daily expressed human milk volumes was higher among preterm mothers on metoclopramide compared to term placebo mothers who served as controls, significant on day 2 (19.9 vs 2.4ml, p=0.04) and day 3 (32.6 vs 8.8ml,p=0.04),and total expressed human milk volumes had increased by 8.2 fold by the end of week one. Most mothers reported first initiation of lactogenesis II by day 6, with 95-100% of term mothers confirmed by day 5 (not significant).

Conclusions: Short-term metoclopramide use starting within 12 postnatal hours boosted lactogenesisi II onset in preterm mothers, improving daily expressed human milk production and maternal perception of lactogenesis II onset.

Clinical Trial Registration.

The trial was registered at ClinicalTrials.gov, study number NCT00264719
https://clinicaltrials.gov/ct2/show/NCT00264719?
term=Metoclopramide&cond=Breastfeeding&cntry=SG&rank=1

Introduction

Complete or predominant breastfeeding is the preferred mode of feeding for the baby as recommended by World Health Organization and United Nations International Children's Emergency Fund. Tertiary maternity units managing high-risk pregnancies face especially challenging barriers to successful breastfeeding. Perinatal risk factors for lactation failure and discontinued breastfeeding include preterm delivery and low birth weight (1–3). Human milk is the ideal food for preterm infants as its composition is physiologically adapted to evolving biological needs (4). Yet most mothers of preterm infants face lactation difficulties resulting directly from physiological impediments to lactation, or indirectly due to separation from infants warded in the intensive care unit (4, 5). Lactogenesis II (LCII) is triggered by progesterone withdrawal and the rise and maintenance of prolactin and cortisol (2). Other physiological

hurdles delaying the lactogenesis trigger, including maternal obesity and diabetes, can compound the problem (2). There is a small window of opportunity to assist women at risk of lactogenesis failure within the first few days of delivery (6, 7). The key events are the production of copious milk that represents the onset of LCII and maternal perception of this event. This provides positive reinforcement and feedback to mothers who may otherwise stop breastfeeding early in the absence of these observations (8). Interventions that prevent the anticipated lactogenesis delay will be useful reinforcements in lactation support. While optimization of breastfeeding technique and frequency should still be the first-line intervention to prevent lactation insufficiency, galactagogues may benefit women requiring additional enhancement of milk production if first-line interventions are inadequate.

Although domperidone is commonly used off-label as a galactagogue, it is not approved by the US Food and Drug Administration (FDA) for any application and is not available in the U.S.A. (9). While domperidone may increase milk production acutely, it does not appear to improve long-term breastfeeding outcomes in women with lactation insufficiency (10, 11). Adverse effects of cardiac arrhythmias and sudden cardiac death, palpitations, syncope, seizures and loss of consciousness, anxiety and diarrhea, and the problems of rebound symptoms, have been reported with tapering dosages (12, 13). The risk of cardiac events may be less prominent in breastfeeding mothers due to their younger age and at the relatively low doses used; no adverse effects have been reported in breastfed infants of mothers taking domperidone (14). The FDA warning against domperidone use in lactating mothers significantly limits its utility (9). Metoclopramide is commonly used to enhance gastric emptying and promote lactation by antagonizing dopamine release in the brain, allowing serum prolactin levels on a dose-dependent basis to rise to augment milk production (15). The main advantages of this galactagogue over domperidone are its FDA-approved status which increases its availability, and the avoidance of cardiac side-effects. Dose-dependent increases in milk production have been demonstrated with metoclopramide at daily doses ranging from 15 mg-45 mg in treated mothers, who reported increased lactation and reduced use or complete elimination of supplementary feeding (15, 16). Mothers with term infants who reported lactational insufficiency received a daily dose of 30 mg of metoclopramide and demonstrated significantly increased milk production of 82.5–112.0%, with a 34% rise in prolactin concentration after one week of treatment, with minimal maternal and neonatal side effects reported (17). Commonly used for the purpose of relactation (18), its utility in establishing LCII has not been studied in mothers following preterm delivery in a controlled clinical trial. Concerns arise regarding its association with depression, vertigo, restless legs and headache among other adverse effects (15, 16, 19). Tardive dyskinesia is a potentially irreversible neurological disorder associated with treatment duration of more than 12 weeks, thus prolonged use should be avoided (20). When used as a galactagogue there is a possibility of related gastrointestinal symptoms in the infant, though significant paediatric side effects have not been reported in various trials (21).

A direct comparison of domperidone with metoclopramide concluded that both increased milk production in mothers with term infants in neonatal special care units with only non-significant differences in efficacy and safety; there was a non-significantly higher milk output with domperidone (19). While the majority of evidence appears to support domperidone as the first line galactagogue (10), treatment

effects are modest at best (17). Metoclopramide was less effective than domperidone in augmenting milk output for mothers of preterm infants (11). Clinical trials comparing metoclopramide with placebo have suggested shorter feeding times in women with preterm infants (22), but most have concluded that there were no significant differences in milk production volume, re-lactation time or infant weight gain (21, 23, 24). Furthermore, in the majority of studies on low and high risk mothers, metoclopramide did not appear to improve lactation insufficiency (15, 20, 24). As these studies mostly reported treatment initiated after lactation insufficiency was reported, knowledge gaps remain regarding prophylactic metoclopramide use in women who have delivered preterm at risk of lactation failure.

Here we study the utility of metoclopramide administered within 12 hours of delivery on LCII establishment in mothers after preterm deliveries in a placebo-controlled trial. In Singaporean women LCII normally occurs by 72 hours postpartum, defined by maternal perception and objective evidence of copious breastmilk flow; delayed onset (> 72 h) is associated with unintended breastfeeding cessation (6, 25, 26). Here delayed LCII onset was defined as commencement after day 3.

Methods

Study design and recruitment numbers

We designed a prospective randomized placebo-controlled trial. It compared early-use metoclopramide with placebo in mothers with preterm deliveries to mothers of term infants. The primary outcome in this trial was augmentation of LCII onset by postnatal day 3 while secondary outcomes included breastfeeding practice, infant weight change and adverse maternal and infant effects.

Patient recruitment

Women with low-risk pregnancies and those with risk factors for preterm delivery were screened for eligibility at the antenatal clinics after 28 weeks' gestation. Women were given written study information and invited to consider participation. The participants gave their informed written consent and were enrolled into the trial at their next doctor's visit. Inclusion criteria were singleton pregnancy, term (≥37 weeks' gestation) or preterm (28 to <37 weeks) deliveries, agreement to randomization, willingness to follow milk-expression protocols and to consume trial drugs. Exclusion criteria were multiple pregnancies, medical contraindications to feeding human milk, maternal hyperprolactinemia, pre-gestational diabetes, use of medications contraindicated in breastfeeding, recorded adverse reactions to metoclopramide, refusal to be randomized or follow milk-expression protocols. Biometric data was collected using standard proforma.

Study design and rationale

Sample sizes were calculated for each trial independently, aiming for a 40% augmentation in LCII onset at a significance level of 0.05 and power of 80%. We targeted the same number of participants in each arm and allowed for a 25% attrition rate. Calculations based on compromised lactogenesis in 80% of women

with preterm infants (5) indicated that 40 women were required in each subgroup (preterm and term, metoclopramide and placebo).

Randomization and study intervention

While consent was taken antenatally, block randomization of participants was only performed at delivery and within the group into which the patients were categorized, utilizing a computer-generated randomization chart. Once assigned a trial number, participants received a plain envelope corresponding to that number containing the unidentified study drug packed by an independent pharmacist. Participants commenced the study drug within 12 hours of birth as follows: 30mg daily in divided doses for the first 7 days, 20mg daily for 3 days, then 10 mg daily for 2 days to avoid an abrupt decrease in milk production. Participants, investigators and data analysts were blinded to the drug taken as unblinding of trial medications occurred only during final data analysis.

Sample collection and follow-up

Participants were provided standardized lactation counseling at each encounter by trial investigator and International Board-Certified Lactation Consultant (6, 7). Mothers were instructed to express milk at approximately 3-hourly intervals using an electrical double-breast pump (Ameda Egnell, Buffalo Grove, IL) prior to each breastfeed for 15 minutes, measuring volumes in calibrated collection bottles. Direct breastfeeding was encouraged after expression for any duration. Total expressed human milk (EHM) volume was recorded daily for the first week in standardized breastfeeding diaries, along with frequency and duration of direct breastfeeds and other fluids fed to their babies for the first two weeks. Diaries were collected at the end of week 2 and participants completed an investigator-administered questionnaire detailing perinatal conditions, infant weight, feeding patterns (exclusive breastfeeding (EBF), mixed breastmilk and formula feeds (MF) and exclusive formula feeding (FF)), maternal and infant adverse effects and maternal perception of LCII. Self-recorded infant weights and breastfeeding status were reported to investigators at 6 weeks, 3 months and 6 months by telephone. Data were verified and entered into the database by the research co-ordinators (DF and JHH) and verified for accuracy by an independent statistician (not part of the study team). The initial study protocol included analysis of lactogenesis markers in human milk samples; due to administrative and technical delays these experiments were eventually removed.

Statistical analyses

Statistical analyses were conducted with SPSS 24.0 (Armonk, NY) and GraphPad Prism v6.07 (La Jolla, CA). Differences between groups in LCII onset, determined by EHM and maternal perception, were assessed by Chi-square or Fisher Exact tests. Two-sample t-tests or Mann Whitney U tests were performed to determine differences in EHM and infant weight change depending on normality assumptions being satisfied. Multiple regression analysis was performed to account for relevant covariates. Statistical significance was set at $p<0.05$.

Results

Recruitment and randomization

Between April 2006 and May 2009, 329 women with term and preterm deliveries were screened for eligibility and 224 women were excluded (Figure 1). Eventually 105 preterm and term subjects were randomized to metoclopramide (n=56) and placebo (n=49). Of mothers assigned metoclopramide, 20 had preterm births and 36 had term births; among placebo recipients, 16 had preterm births and 33 had term births (Table 1). All subjects received the allocated intervention. Attrition rates were 43% among participants (45/105) due to non-compliance to study drugs, failure to record EHM volumes and withdrawal of consent. Intention-to-treat analysis was performed on 105/105 preterm and term subjects.

Figure 1. Randomization of Subjects. Participants were screened for eligibility, randomized into treatment and placebo groups and followed-up over 6 months.

Demographics

Stratified randomization resulted in similar ethnic representation, parity, previous breastfeeding experience, body mass index (BMI) and gestational aged at delivery between treatment and placebo groups (Table 2). Even distribution of preterm and term subjects between metoclopramide and placebo arms was achieved. Gestational age among preterm births was 34.4±1.7 weeks. Mean birthweights were 3112±368.1g among term infants and 2418.7±578.4g among preterm infants (data not shown). Primiparity ranged from 33.3% for preterm mothers and 42.0% in term mothers. Caesarean delivery rates were 19.6% among metoclopramide and 22.9% among placebo recipients (Table 2).

Augmentation in lactogenesis II onset

LCII commenced by postnatal day 3 in 59.6% of metoclopramide-users compared to 45.0% of placebo-users (RR 1.32, p=0.069). There was no evidence for statistically significant difference in LCII onset between treatment and control arms within term or preterm subgroups, though the relative risk reduction (RRR) for delayed LCII was greater in the preterm group (25.0%) than in term subjects (19.0%).

Daily expression of human milk and maternal perception of Lactogenesis II onset (Figure 2).

Rates of EHM increase were calculated after adjusting for ethnicity, parity and breastfeeding history. EHM increased more rapidly after day 3 in both metoclopramide and placebo users with a trend towards higher EHM with metoclopramide from day 2. Daily EHM volumes trended higher among metoclopramide users, particularly among preterm-metoclopramide users compared to controls (term-placebo users), significant on day 2 (19.9 vs 2.4mL, p =0.04) and day 3 (32.6 vs 8.8mL, p = 0.04); EHM volumes were similar among preterm and term metoclopramide users. Daily increments in EHM were higher in preterm-metoclopramide users, particularly on days 2 (19.0 vs 0.3mL, p = 0.02) and day 3 (31.6 vs 6.1ml, p = 0.03) compared to

controls(term-placebo users), and trended higher than other subgroups until the end of the first week. LCII was first reported by most around day 3 and confirmed in 95-100% of preterm mothers by day 6, and in 95-100% of term mothers by day 5.

Figure 2. Daily Expression of Breast milk and Maternal Perception of Lactogenesis II. (A) Mean daily EHM from metoclopramide users trended higher than EHM from placebo users. (B) Daily EHM was higher among PT-metoclopramide mothers compared to T-placebo mothers who served as controls, significant on day 2 (19.9 vs. 2.4 mL, p=0.04) and day 3 (32.6 vs. 8.8mL, p=0.04); EHM volumes in the PT-metoclopramide and T-metoclopramide groups were similar. (C) The daily increase in EHM over the day 1 volumes was significantly higher on days 2 (19.0 vs. 0.3mL, p=0.02) and 3 (31.6 vs. 6.1mL, p=0.03) in PT-metoclopramide than in T-placebo mothers and trended higher than other subgroups until the end of the week. (D) Most mothers reported first initiation of LCII around day 3. (E) Lactogenesis II was confirmed in 95-100% of PT mothers by day 6, and in 95-100% of T mothers by day 5 (not significant).

Effect of metoclopramide on breastfeeding practice (Figure 3)

Participants on metoclopramide and placebo showed similar frequencies of EBF, MF and FF over the first postnatal week. Subgroups showed similar breastfeeding practices during the first week. Breastfeeding was practiced by more preterm-placebo mothers than other subgroups from day 4, at a significantly higher rate than term-metoclopramide from days 4-7. Of mothers still breastfeeding at day 7, most practiced MF at 6 months with small numbers continuing to fully breastfeed across subgroups.

Figure 3. Breastfeeding Practices. *(*A) Subjects on metoclopramide and placebo showed similar frequencies of exclusive breastfeeding (BF), mixed feeding (BF+FF) and formula feeding (FF) over the first postnatal week. (B) Subgroups showed similar breastfeeding practices during the first week. (C) BF was practiced by more PT-placebo mothers than other subgroups from day 4, at a significantly higher rate than T-metoclopramide from days 4-7. (D) Of mothers practicing BF at day 7, most practiced mixed feeding at 6 months with small numbers continuing to fully breastfeed across subgroups.

Infant weight change over 6 months (Figure 4).

Infants of women in both treatment and placebo groups showed similar weight gain over 6 months; infants in the metoclopramide group weighed less at 2 weeks than placebo group infants (2.9kg vs 3.2kg, p=0.04). Infants of preterm-metoclopramide mothers were of lower weight than term placebo infants at all time-points, significant at 1, 2, 6 and 24 postnatal weeks.

Figure 4. Infant Weight Pattern over 6 Months. (A) Infants of women in both treatment and placebo groups showed similar weight gain over 6 months; infants in the metoclopramide group weighed less at 2 weeks than placebo group infants (2.9 vs. 3.2kg, p=0.04). (B) Infants of PT-metoclopramide mothers were

of lower weight than T-placebo infants at all time-points, significant 1, 2, 6 and 24 postnatal weeks (indicated by *).

Adverse effects

No adverse maternal effects were reported, while neonatal jaundice and hypoglycaemia were reported in two infants, unrelated to the use of study drugs.

Discussion

Prophylactic early metoclopramide use allowed the majority of mothers to experience LCII on time before postnatal day 3. However, this boosting effect was not statistically significant and did not achieve our target of 40% augmentation in LCII onset (5). It might be attributable to the small sample size. EHM increased significantly from d5 to d7 in preterm-metoclopramide users compared to controls. EHM volume increases in preterm-metoclopramide users were similar to term-metoclopramide users, suggesting that the intervention had, in the short-term, corrected lactation deficiencies in this vulnerable group and “normalised” milk output to the levels of term mothers not using galactagogues. The most substantial improvement was observed in preterm-metoclopramide users on day 2 to 3. Despite this EHM increase, fewer metoclopramide users practiced exclusive BF than MF, and slightly less exclusive BF in the first week than placebo-users, with the highest rate reported in preterm-metoclopramide users (42–50%). These poor breastfeeding rates among at-risk women were unexpected from the positive effects on EHM volumes. Barriers may arise from underlying pathophysiology or psycho-physical conditions associated with preterm delivery. Prenatal or postnatal anxiety increases breastfeeding-cessation risk and limits efficacy of peer support from lactation counsellors (27). Though we did not specifically study maternal anxiety, it is expected that psychosocial stress associated with preterm delivery in addition to separation and disorganized feeding will adversely affect breastfeeding (28), although mothers of preterm infants are often motivated to express milk (29, 30). Maternal anxiety should be actively managed in at-risk mothers, particularly as failed breastfeeding can perpetuate depressive symptoms (31). We did not periodically assess maternal perception of breastmilk sufficiency; metoclopramide-users may have developed low self-efficiency leading to early cessation despite successful initiation (32). The common first-line interventions of optimizing breastfeeding technique and feeding frequency may not effectively address low milk supply in this context, while social support may only have limited success in mitigating these effects (33), and are less likely to succeed in communities with low breastfeeding prevalence like Singapore (34–36). These findings reiterate the need for wholistic support in identified at-risk mothers who will benefit from specific interventions initiated within an hour of birth, as recommended by the American College of Obstetrics and Gynaecology (37). There may be some value in starting metoclopramide within a few hours of delivery in at-risk mothers, in anticipation of their physiological predisposition to lactation failure, along with early human milk expression with the understanding that residual lactation deficiencies may persist (1, 3).

Strengths And Limitations

This was a prospective randomized placebo-controlled trial using metoclopramide, a drug commonly prescribed to pregnant women for hyperemesis, readily available and inexpensive, and well-tolerated in pregnancy (FDA category B). The treatment regimen was easy to implement within 12 hours of delivery, acceptable to mothers and can be easily replicated in well-selected at-risk women who express a desire to breastfeed and accept early pharmacological treatment. We did not achieve the planned number of participants in the at-risk subgroups as recruitment was challenging and the loss to follow-up substantial owing to labor-intensive EHM monitoring. This limits our ability to interpret the true effects of metoclopramide. We did not study the effect of maternal obesity, anxiety or self-efficiency nor factor in changing expectations during the breastfeeding journey.

Conclusion

These findings reiterate the need for wholistic support in identified at-risk mothers who will benefit from specific interventions initiated within an hour of birth, as recommended by the American College of Obstetrics and Gynaecology (37). There may be some value in starting metoclopramide within a few hours of delivery in at-risk mothers, in anticipation of their physiological predisposition to lactation failure, along with early human milk expression with the understanding that residual lactation deficiencies may persist (2).

Abbreviations

LCII
lactogenesis II; EHM:expressed human milk; EBF:exclusive breastfeeding; MF:mixed breastmilk and formula feeds; FF:exclusive formula feeding; BMI:body mass index. RR:relative risk; RRR:relative risk reduction.

Declarations

Ethics approval and consent to participate

Ethical approval was granted under the National Healthcare Group, Singapore (NHG) Domain-Specific Review Board (DSRB Domain D) DSRB-D/05/183, approved in 2006.

Consent for publication: Not applicable

Availability of data and materials

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors confirm no competing financial or other conflict of interest. The authors confirm that this manuscript is not under consideration elsewhere and has not been published before.

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Authors' contributions

YS Chong, CNZM and YS Chan obtained funding for the grants. DF recruited and collected and entered the data. YHC did blocked randomization of the participants. Data analysis was conducted by YHC, CNZM, DF. JHH reviewed and monitored data, MR helped with recruitment referrals whilst YS Chong oversee the operations of the study and CNZM, DF and JHH did the literature review and edited the paper. All authors read and approved the final manuscript.

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References

1.
Zanardo V, Pigozzo A, Wainer G, Marchesoni D, Gasparoni A, Di Fabio S, et al. Early lactation failure and formula adoption after elective caesarean delivery: cohort study. Arch Dis Child Fetal Neonatal Ed. 2013 Jan;98(1):F37–41.
2.
Neville MC, Morton J. Physiology and endocrine changes underlying human lactogenesis II. J Nutr. 2001 Nov;131(11):3005S-8S.
3.
Cordero L, Oza-Frank R, Moore-Clingenpeel M, Landon MB, Nankervis CA. Failure to initiate breastfeeding among high risk obstetrical patients who intended to breastfeed. Journal of neonatal-perinatal medicine. 2016;9(4):401–9.
4.
Geddes D, Hartmann P, Jones E. Preterm birth: Strategies for establishing adequate milk production and successful lactation. Semin Fetal Neonatal Med. 2013 Apr;18(3):155–9.
5.
Cregan MD, De Mello TR, Kershaw D, McDougall K, Hartmann PE. Initiation of lactation in women after preterm delivery. Acta Obstet Gynecol Scand. 2002 Sep;81(9):870–7.
6.

Fok D, Aris IM, Ho J, Chan YH, Rauff M, Lui JK, et al. Early initiation and regular breast milk expression reduces risk of lactogenesis II delay in at-risk Singaporean mothers in a randomised trial. Singapore Med J. 2018 Jun;60(2):80–8.
7.
Mattar CN, Chong YS, Chan YS, Chew A, Tan P, Chan YH, et al. Simple antenatal preparation to improve breastfeeding practice: a randomized controlled trial. Obstet Gynecol. 2007 Jan;109(1):73–80.
8.
Tan DJA, Lew JP, Jumhasan MB, Pang C, Sultana R, Sng BL. Investigating factors associated with success of breastfeeding in first-time mothers undergoing epidural analgesia: a prospective cohort study. Int Breastfeed J. 2018;13:42.
9.
U.S. Food & Drug Administration. [Internet]. FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production. 2004. [Cited on March 10, 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm.
10.
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: an international journal of obstetrics gynaecology. 2018 Oct;125(11):1371–8.
11.
Asztalos EV, Campbell-Yeo M, da Silva OP, Ito S, Kiss A, Knoppert D, et al. Enhancing Human Milk Production With Domperidone in Mothers of Preterm Infants. Journal of human lactation: official journal of International Lactation Consultant Association. 2017 Feb;33(1):181–7.
12.
Drugs and Lactation Database (LactMed). [Internet]. Bethesda(MD): National Library of Medicine(US); 2006. Domperidone; [cited 2018 Mar 10]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK501371/.
13.
Doggrell SA, Hancox JC. Cardiac safety concerns for domperidone, an antiemetic and prokinetic, and galactogogue medicine. Expert Opin Drug Saf. 2014 Jan;13(1):131–8.
14.
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. Journal of human lactation: official journal of International Lactation Consultant Association. 2013 Feb;29(1):38–44.
15.
Kauppila A, Anunti P, Kivinen S, Koivisto M, Ruokonen A. Metoclopramide and breast feeding: efficacy and anterior pituitary responses of the mother and the child. Eur J Obstet Gynecol Reprod Biol. 1985 Jan;19(1):19–22.
16.
Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. Lancet. 1981 May;1(8231):1175–7.

17.
Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. Pediatrics. 1986 Oct;78(4):614–20.
18.
Seema, Patwari AK, Satyanarayana L. Relactation: an effective intervention to promote exclusive breastfeeding. J Trop Pediatr. 1997 Aug;43(4):213–6.
19.
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 Neonatal Ed. 2012 Jul;97(4):F241-5.
20.
Drugs and Lactation Database (LactMed). Bethesda(MD): National Library of Medicine(US); 2006. Metoclopramide; [cited 2018 Mar 10]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK501352/.
21.
Bazzano AN, Cenac L, Brandt AJ, Barnett J, Thibeau S, Theall KP. Maternal experiences with and sources of information on galactagogues to support lactation: a cross-sectional study. International journal of women's health. 2017;9:105–13.
22.
Mussavi M, Asadollahi K, Abangah G. Effects of Metoclopramide on Feeding Intolerance among Preterm Neonates; A Randomized Controlled Trial. Iranian journal of pediatrics. 2014 Oct;24(5):630–6.
23.
Brodribb W. ABM Clinical Protocol #9: Use of Galactogogues in Initiating or Augmenting Maternal Milk Production, Second Revision 2018. Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine. 2018 Jun;13(5):307–14.
24.
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.
25.
Demirci J, Schmella M, Glasser M, Bodnar L, Himes KP. Delayed Lactogenesis II and potential utility of antenatal milk expression in women developing late-onset preeclampsia: a case series. BMC Pregnancy Childbirth. 2018 Mar;18(1):68.
26.
Brownell E, Howard CR, Lawrence RA, Dozier AM. Delayed onset lactogenesis II predicts the cessation of any or exclusive breastfeeding. J Pediatr. 2012 Oct;161(4):608–14.
27.
Sharifi F, Nouraei S, Shahverdi E. The Relation of Pre and Postnatal Depression and Anxiety with Exclusive Breastfeeding. Electronic physician. 2016 Nov;8(11):3234–9.
28.
Hobbs AJ, Mannion CA, McDonald SW, Brockway M, Tough SC. The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. BMC Pregnancy

Childbirth. 2016 Apr;16:90.
29.
Fleurant E, Schoeny M, Hoban R, Asiodu IV, Riley B, Meier PP, et al. Barriers to Human Milk Feeding at Discharge of Very-Low-Birth-Weight Infants: Maternal Goal Setting as a Key Social Factor. Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine. 2017;12:20–7.
30.
Lewis ED, Richard C, Larsen BM, Field CJ. The Importance of Human Milk for Immunity in Preterm Infants. Clinics in perinatology. 2017 Mar;44(1):23–47.
31.
Ystrom E. Breastfeeding cessation and symptoms of anxiety and depression: a longitudinal cohort study. BMC Pregnancy Childbirth. 2012 May;23:12:36.
32.
Meedya S, Fahy K, Kable A. Factors that positively influence breastfeeding duration to 6 months: a literature review. Women birth: journal of the Australian College of Midwives. 2010 Dec;23(4):135–45.
33.
Chapman DJ, Morel K, Bermudez-Millan A, Young S, Damio G, Perez-Escamilla R. Breastfeeding education and support trial for overweight and obese women: a randomized trial. Pediatrics. 2013 Jan;131(1):e162-70.
34.
Leow TYQ, Ung A, Qian S, Nguyen JT, An Y, Mudgil P, et al. Exploring infant feeding practices: cross-sectional surveys of South Western Sydney, Singapore, and Ho Chi Minh City. BMC Pediatr. 2017 Jun;17(1):145.
35.
Kronborg H, Vaeth M. The influence of psychosocial factors on the duration of breastfeeding. Scandinavian journal of public health. 2004;32(3):210–6.
36.
Pang WW, Aris IM, Fok D, Soh SE, Chua MC, Lim SB, et al. Determinants of Breastfeeding Practices and Success in a Multi-Ethnic Asian Population. Birth. 2016 Mar;43(1):68–77.
37.
The American College of Obstetrics and Gynecology. ACOG Committee Opinion No. 756: Optimizing support for breastfeeding as part of obstetric practice. Obstet Gynecol. 2018;132(4):e187-96.

Tables

Table 1 Baseline Characteristics of the Participants (N=105)

		Term non-diabetic (>37w gestation) (*n*=69)	Preterm delivery (<37w gestation) (*n*=36)	*p*-value
ge (years)	*M(SD)*	29.0 (6.1)	29.0 (5.8)	0.869
MI (kg/m^2)	*M(SD)*	21.4 (4.1)	22.2 (4.1)	0.348
MI >=25 kg/m^2 (%)	Yes	8 (11.6)	5 (13.9)	
	No	60 (87.0)	30 (82.3)	0.715
	Unknown	1 (1.4)	1 (3.8)	
rity (%)	Primiparous	29 (42.0)	12 (33.3)	
	Multiparous	40 (58.0)	24 (66.7)	0.386
hnicity (%)	Chinese	35 (50.7)	11 (30.6)	
	Malay	24 (34.8)	19 (52.8)	
	Indian	7 (10.1)	3 (8.3)	
	Other	3 (4.3)	3 (8.3)	0.187
ove Secondary education (%)	Yes	34 (49.3)	16 (44.4)	
	No	35 (50.7)	19 (52.8)	0.731
	unknown	0 (0.0)	1 (3.8)	
nployment (%)	Student/housewife	24 (34.8)	16 (44.4)	
	Employed	45 (65.2)	19 (52.8)	0.279
	unknown	0 (0.0)	1 (3.8)	
titled to >3 months maternity leave for employed subjects	Yes	31 (44.9)	17 (47.2)	
)	No	12 (17.4)	11 (30.6)	
	Not applicable	26 (37.7)	7 (19.4)	0.035
	unknown	0 (0.0)	1 (3.8)	
ousehold monthly income (%)	<SGD 5000	56 (81.2)	30 (83.3)	
	≥SGD 5000	13 (18.8)	5 (13.9)	0.562
	unknown	0 (0.0)	1 (3.8)	
eastfeeding history (%)	Yes	38 (55.1)	23 (63.9)	
	No	31 (44.9)	13 (36.1)	0.385
tended antenatal classes (%)	Yes	13 (18.8)	4 (11.1)	
	No	56 (81.2)	31 (86.10	
	unknown	0 (0.0)	1 (3.8)	0.334

Note. Data represented as n (%) unless otherwise stated

Table 2 Characteristics of Subjects Receiving Treatment and Placebo (N=105)

		Metoclopramide (*n*=56)	Placebo (*n*=49)	p-value
Subgroups (%)	Term	36 (64.3)	33 (67.3)	
	Preterm	20 (35.7)	16 (32.7)	NA
Ethnicity (%)	Chinese	26 (46.4)	20 (40.8)	
	Malay	24 (42.9)	19 (38.9)	
	Indian	2 (3.6)	8 (16.3)	
	Other	4 (7.1)	2 (4.1)	0.159
Mode of delivery (%)	Spontaneous vaginal	43 (76.8)	37 (77.1)	
	Assisted vaginal	2 (3.6)	0 (0.0)	
	Caesarean section	11 (19.6)	11 (22.9)	0.397
Previous breastfeeding experience (%)	Yes	33 (58.9)	28 (57.1)	
	No	23 (41.1)	21 (42.9)	0.853
Medical history (%)	Yes	14 (25.0)	11 (22.4)	
	No	42 (75.0)	38 (77.6)	0.759
BMI (kg/m^2)	*M(SD)*	21.8 (4.0)	21.6 (4.3)	0.838
BMI >=25 kg/m^2 (%)	Yes	9 (16.1)	4 (8.5)	
	No	47 (83.9)	43 (91.5)	0.250
Gestational age (weeks)	*M(SD)*	37.1 (2.7)	37.4 (2.2)	0.607

Note. Data represented as n (%) unless otherwise stated

Figures

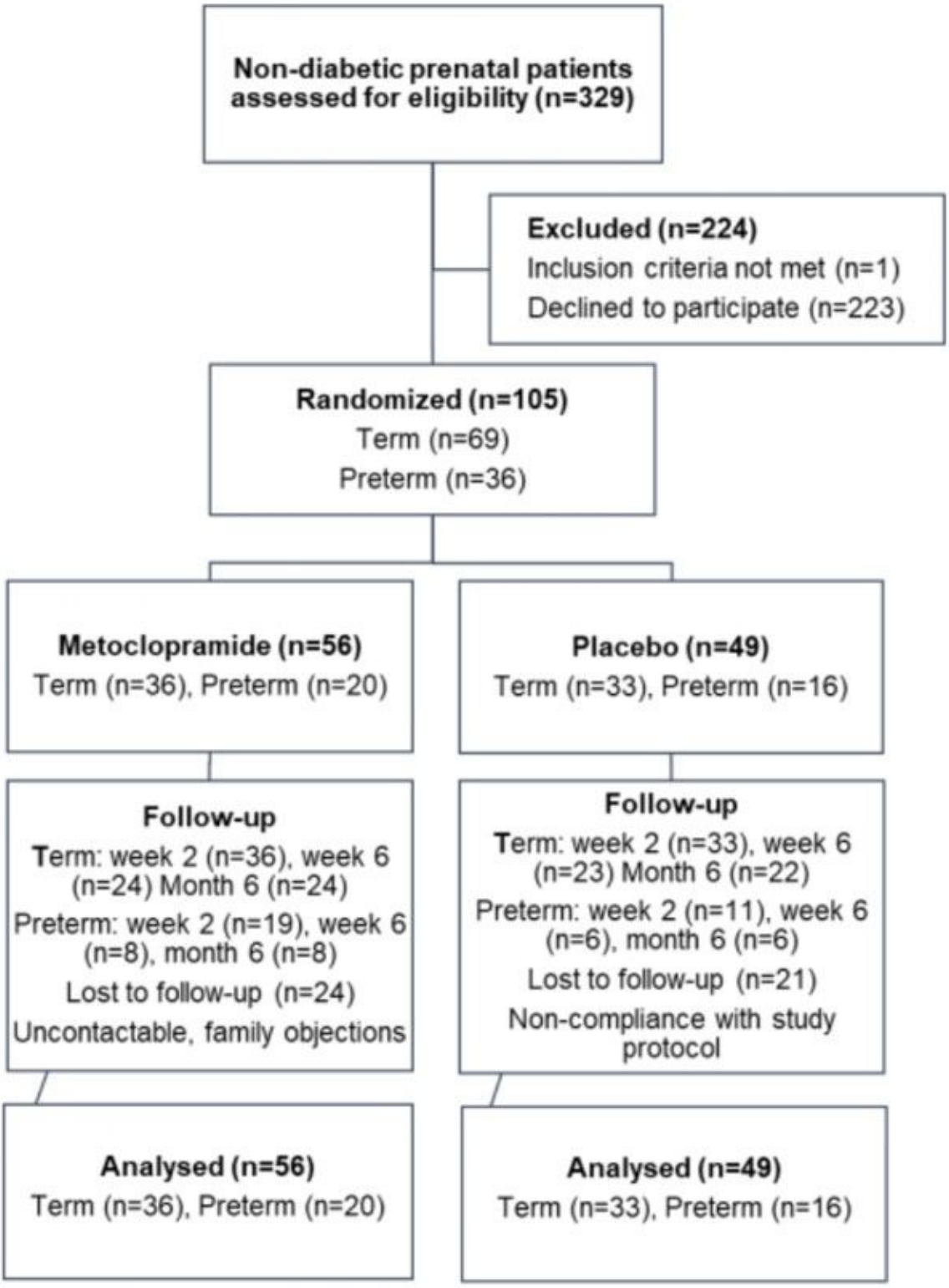

Figure 1

Randomization of Subjects. Participants were screened for eligibility, randomized into treatment and placebo groups and followed-up over 6 months.

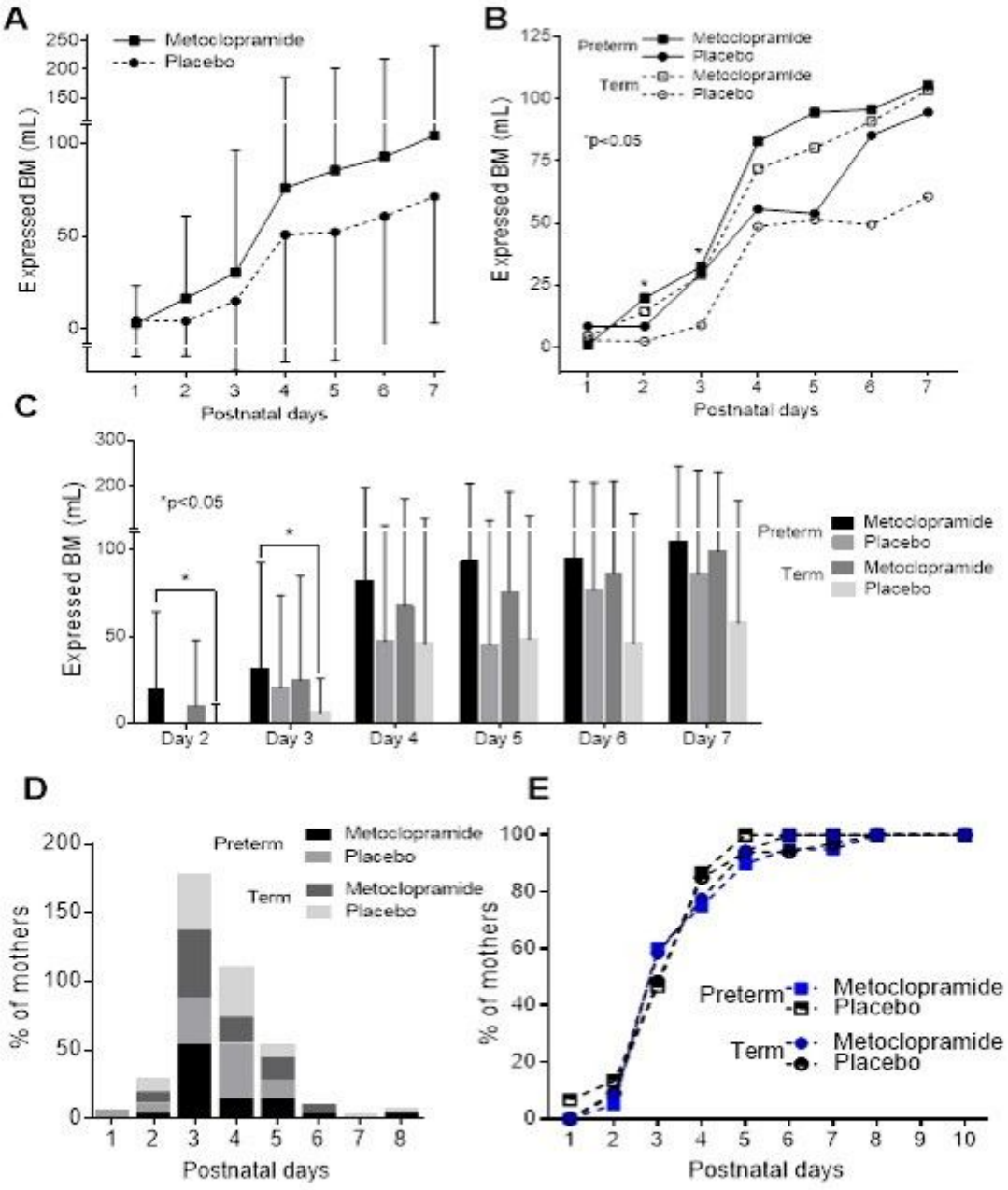

Figure 2

Daily Expression of Breast milk and Maternal Perception of Lactogenesis II. (A) Mean daily EHM from metoclopramide users trended higher than EHM from placebo users. (B) Daily EHM was higher among PT-metoclopramide mothers compared to T-placebo mothers who served as controls, significant on day 2 (19.9 vs. 2.4 mL, p=0.04) and day 3 (32.6 vs. 8.8mL, p=0.04); EHM volumes in the PT-metoclopramide and T-metoclopramide groups were similar. (C) The daily increase in EHM over the day 1 volumes was significantly higher on days 2 (19.0 vs. 0.3mL, p=0.02) and 3 (31.6 vs. 6.1mL, p=0.03) in PT-metoclopramide than in T-placebo mothers and trended higher than other subgroups until the end of the week. (D) Most mothers reported first initiation of LCII around day 3. (E) Lactogenesis II was confirmed in 95-100% of PT mothers by day 6, and in 95-100% of T mothers by day 5 (not significant).

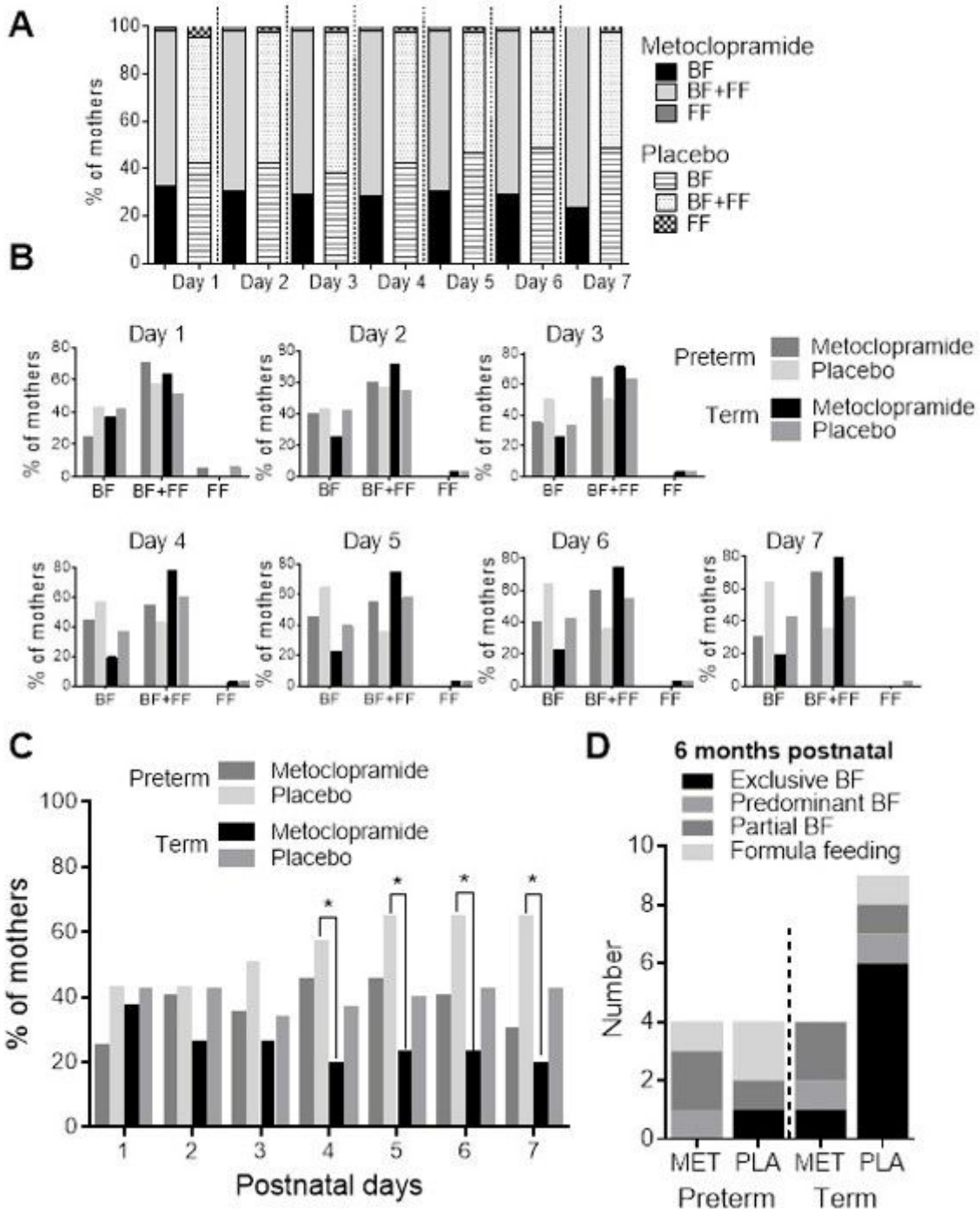

Figure 3

Breastfeeding Practices. (A) Subjects on metoclopramide and placebo showed similar frequencies of exclusive breastfeeding (BF), mixed feeding (BF+FF) and formula feeding (FF) over the first postnatal week. (B) Subgroups showed similar breastfeeding practices during the first week. (C) BF was practiced by more PT-placebo mothers than other subgroups from day 4, at a significantly higher rate than T-metoclopramide from days 4-7. (D) Of mothers practicing BF at day 7, most practiced mixed feeding at 6 months with small numbers continuing to fully breastfeed across subgroups.

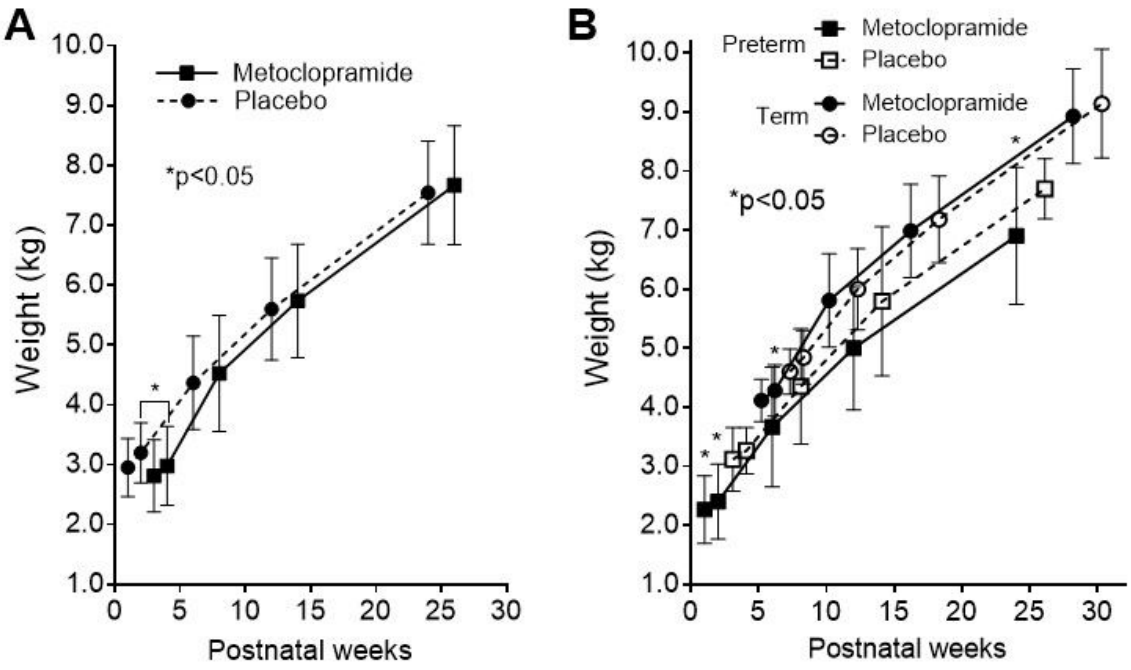

Figure 4

Infant Weight Pattern over 6 Months. (A) Infants of women in both treatment and placebo groups showed similar weight gain over 6 months; infants in the metoclopramide group weighed less at 2 weeks than placebo group infants (2.9 vs. 3.2kg, p=0.04). (B) Infants of PT-metoclopramide mothers were of lower weight than T-placebo infants at all time-points, significant 1, 2, 6 and 24 postnatal weeks (indicated by *).