# Early postpartum oral metoclopramide augments lactogenesis II in insulin-dependent mothers with gestational diabetes: a randomized placebo-controlled trial

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**Research**

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# Abstract

Background Mothers with gestational diabetes are at risk of lactogenesis II delayed beyond the third postnatal day and early breastfeeding cessation, which may be overcome by prophylactic intervention. Research aim To evaluate the effect of oral metoclopramide commenced within twelve hours of delivery on lactogenesis II in mothers with insulin-dependent (iGDM) or diet-controlled (dGDM) gestational diabetes.

Methods Between July 2006 and January 2009, 73 mothers of term neonates (iGDM, n=20 and dGDM, n=53) were randomized to the metoclopramide (n=37) or placebo groups (n=36). Mothers with gestational diabetes in the intervention group received 30mg of oral metoclopramide daily for the first postnatal week in a randomized double-blinded placebo-controlled study. Primary outcome was lactogenesis II onset by postnatal day 3, while secondary outcomes included expressed human milk volumes (EHM) and exclusive breastfeeding rates and infant weight change.

Results 40% more iGDM metoclopramide users achieved lactogenesis II by postnatal day 3 (p=0.01), with 4.8-fold EHM increase over controls (p=0.04); 50% of iGDM mothers perceived lactogenesis II onset by day 2 and more rapid EHM accumulation was observed in all metoclopramide users. Despite this, metoclopramide-users demonstrated less exclusive breastfeeding, earlier cessation and more frequent formula-feeding.

Conclusions Short-term metoclopramide uses within the first 12 postnatal hours significantly improved daily EHM production and maternal perception of lactogenesis II onset in iGDM mothers. Treated iGDM mothers did not experience the natural EHM decrease of iGDM placebo-users. The low breastfeeding rate suggested that physiological breastfeeding barriers may not modifiable by metoclopramide or traditional lactation support.

# Clinical Trial Registration.

The trial was registered at ClinicalTrials.gov, study number NCT00477776 (https://clinicaltrials.gov/ct2/show/record/NCT00477776?term=Metoclopramide&cond=Breastfeeding&cntry=SG&rank=2&view=record)


# Introduction

Complete or predominant breastfeeding is the goal of breastfeeding-friendly hospitals and maternity units. This presents special challenges when managing high-risk pregnancies in which there are potential barriers to successful breastfeeding. Perinatal risk factors for lactation failure and discontinued breastfeeding include maternal gestational diabetes (GDM) or pre-gestational diabetes (1, 2). Infants of diabetic mothers are susceptible to hypoglycemia and often require early feeding after birth. Lactogenesis II (LCII) initiation is triggered by progesterone withdrawal and the rise and maintenance of prolactin and cortisol (1). Using breast-milk concentrations of lactose and citrate as LCII markers, it was

observed that women with insulin-dependent diabetes mellitus (iGDM) experience a 15–28 hour delay in LCII onset (3, 4); in these studies no differences were found in daily breast milk volume between diabetic and non-diabetic women by one week postpartum. Women with iGDM commence breastfeeding 24 hours later than non-diabetic women and demonstrate biochemical markers of delayed LCII associated with reduced milk expression in the first 3 days postpartum (3, 5). A higher frequency of early breastfeeds initiated within 12 hours postpartum stimulated LCII more efficiently in diabetic women (7). Diabetic mothers are physiologically predisposed to delayed LCII (4), resulting in increased pressure to feed formula to prevent neonatal hypoglycemia. Thus, mothers with diabetes represent a group at particularly high-risk for breastfeeding failure (2, 3). There is a small window of opportunity during which to assist women at risk of lactogenesis failure within the first few days of delivery (6, 7). Maternal perception of LCII provides positive reinforcement and feedback to mothers who may otherwise stop breastfeeding early in the absence of these observations. Interventions that prevent the anticipated lactogenesis delay will be useful reinforcements in lactation support.

While optimization of breastfeeding technique is still the first-line intervention to prevent lactation insufficiency, galactagogues may benefit women requiring additional enhancement of milk production. There are two medications which could be used as galactogogues. Domperidone is commonly used off-label as a galactagogue in Singapore but it is not approved by the US FDA for any application and is not available in the U.S.A. which significantly limits its utility (8). Domperidone may increase milk production acutely but does not appear to improve lactation insufficiency (9). Adverse effects of sudden cardiac death, cardiac arrhythmias and rebound symptoms have been reported with tapering dosages, though the risk of cardiac events may be less prominent in breastfeeding mothers due to their younger age (10, 11). Metoclopramide, a commonly-used anti-emetic which also promotes lactation by antagonizing dopamine release in the brain (12), does not carry cardiac side-effects and is FDA-approved which increases its availability. Metoclopramide use at daily doses of 15 mg-45 mg increases in milk production in a dose-dependent manner; treated mothers with lactational insufficiency reported significantly increased lactation, increased prolactin concentration and reduced supplementary feeding (12, 13). Commonly used for the purpose of relactation (14), its utility in establishing LCII has not been studied in mothers with the risk factors of diabetes or preterm delivery in controlled trials. Concerns arise regarding its association with depression, vertigo, headache and tardive dyskinesia, a potentially irreversible neurological disorder associated with prolonged treatment (12, 13, 15, 16).

A direct comparison of domperidone and metoclopramide demonstrated increased milk production following term deliveries with non-significant differences in efficacy and safety (15). Furthermore, in the majority of studies on low-and high-risk mothers, metoclopramide did not improve lactation insufficiency (12, 16). As these studies reported treatment initiated after lactation insufficiency was reported, knowledge gaps remain regarding prophylactic metoclopramide use in women at risk of lactation failure. We investigated the hypothesis that metoclopramide administered within 12 hours of delivery reduced delayed LCII in mothers with GDM following term deliveries in a placebo-controlled trial. In Singaporean women LCII occurs by 72 hours postpartum; delayed LCII onset is associated with unintended breastfeeding cessation and is defined as commencement after postnatal day 3 (6, 17).

# Materials And Methods

## Study design and recruitment numbers

We designed a prospective randomized placebo-controlled trial, conducted at the National University Hospital, Singapore, comparing early-use metoclopramide or placebo in GDM mothers on dietary restrictions only or using insulin. The primary outcome was augmentation of LCII onset by postnatal day 3 while secondary outcomes were expressed human milk (EHM) volumes, rates of exclusive breastfeeding, rate of infant weight change and adverse maternal and infant effects.

## Patient recruitment

Women with GDM were screened for eligibility at the antenatal clinics after 28 weeks' gestation, presented with study information and invited to participate if they intended to breastfeed. Participants gave their informed written consent and were enrolled into the trial. Inclusion criteria were: GDM diagnosed according to international criteria (18) and treated with diet control or insulin, singleton pregnancy, term delivery (≥37 weeks gestation) and agreement to randomization, to follow milk expression protocols and to consume trial drugs. Exclusion criteria included: multiple pregnancies, medical contraindications to breastfeeding, 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 were collected using standard proforma.

## Study design and rationale

Sample size was calculated using a-priori power analysis ($\alpha$=0.05, power 80%) based on 40-80% breastfeeding initiation among insulin and non-insulin dependent diabetics (2, 4). We required 40 women in each subgroup (diet-controlled GDM, insulin-dependent GDM, assigned metoclopramide or assigned placebo) to show a 25% reduction in delayed LCII. Thus, a total of 160 participants were required, allowing for 25% attrition rate.

## Randomization and study intervention

While consent was taken antenatally, block randomization was only performed at delivery within the group into which the patient was categorized, i.e. GDM on insulin (iGDM) or GDM on diet control (dGDM), 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 breastmilk. Participants, investigators and data analysts were blinded to the drug taken as unblinding of trial medications occurred only during final data analysis. The investigators were blinded to the preparation of the placebo made by the pharmacists.

### Sample collection and follow-up

Participants were provided standardized lactation counseling at each encounter by one of the trial investigators (DF, also an International Board-Certified Lactation Consultant) (6, 7). Mothers were instructed to express milk at approximately 3-hourly intervals using an electrical double-breast pump prior to each breastfeed for 15 minutes, measuring volumes in calibrated collection bottles. Direct breastfeeding for any duration was encouraged after expression. Total expressed EHM 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 (BF), mixed breast and formula feeding (MF) or 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 and 3 and 6 months by telephone**.** Data were verified and entered into the database by investigators (DF and VH), and verified for accuracy by an independent statistician (not part of the study team).

### 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 July 2006 and January 2009, 208 women were screened and 73 (iGDM, n=20 and dGDM, n=53) randomized to the metoclopramide (MET, n=37) or placebo groups (PLA, n=36). All participants received the allocated intervention (Figure 1). Eleven and 18 women from the MET and PLA groups respectively were eventually lost to follow-up as they declined continued surveillance. Data from 33 participants in MET (iGDM n=10, dGDM n=23) and 23 participants in PLA (iGDM n=9, dGDM n=14) were analysed; 17 mothers failed to be compliant to study drugs or record EHM volumes. Intention-to-treat analysis was performed on the participants. Mothers without GDM who had term deliveries and who were randomized to placebo in a parallel RCT (NCT00264719, using the same drug administration protocol) were used as non-diabetic controls.

**Figure 1. Randomization Flowchart**. It demonstrates the recruitment, eligibility screening and randomization of study participants, follow-up and data analysis.

## Demographics

Stratified randomization resulted in similar ethnic representation, parity, previous breastfeeding experience, body mass index (BMI) and gestational age at delivery between treatment and placebo GDM groups and controls. Even distribution of iGDM and dGDM participants between metoclopramide and placebo arms was achieved, although recruited numbers fell short of target particularly for iGDM (Table 1, Figure 2). There were trends towards higher overall BMI (24.5-26.0) and a higher proportion of BMI≥ 25 kg/m$^2$ in diabetic (35.0-39.6%) compared to non-diabetic mothers (6.1%); there were no differences in breastfeeding experience between diabetics and controls (Table 2).

**Table 1. Characteristics of Participants Receiving Treatment or Placebo (N=106)**

| | | Metoclopramide *n*=37 | Placebo *n*=36 | Non-diabetic controls *n*=33 | *P*- value |
|---|---|---|---|---|---|
| groups (% of group) | GDM-diet (dGDM) | 27 (73.0) | 26 (72.2) | - | |
| | GDM-insulin (iGDM) | 10 (27.0) | 10 (27.8) | - | NA |
| nicity (%) | Chinese | 13 (35.1) | 14 (38.9) | 18 (54.5) | |
| | Malay | 12 (32.4) | 12 (33.3) | 8 (24.2) | |
| | Indian | 10 (27.0) | 7 (19.4) | 6 (18.2) | |
| | Other | 2 (5.4) | 3 (8.3) | 1 (3.0) | 0.861 |
| le of delivery (%) | Spontaneous vaginal | 27 (81.8) | 21 (65.6) | 26 (78.8) | |
| | Assisted vaginal | 2 (6.1) | 1 (3.1) | 0 (0.0) | |
| | Caesarean section | 4 (12.1) | 10 (31.3) | 7 (21.2) | 0.162 |
| vious breastfeeding experience (%) | Yes | 23 (62.2) | 21 (58.3) | 18 (54.5) | |
| | No | 14 (37.8) | 15 (41.7) | 15 (45.5) | 0.738 |
| lical history (%) | Yes | 37 (100) | 36 (100) | 7 (21.2) | NA |
| (kg/m$^2$) | | 24.7±5.3 | 25.1±5.9 | 21.4±3.9 | 0.794 |
| n±s.d. | | | | | |
| >=25 kg/m$^2$ (%) | Yes | 13 (35.1) | 15 (41.7) | 2 (6.1) | |
| | No | 24 (64.9) | 21 (58.3) | 31 (93.9) | 0.566 |
| tational age (weeks) | | 37.7±2.3 | 38.3±1.3 | 38.6±1.2 | 0.195 |
| n±s.d. | | | | | |

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

Table 2. Baseline Characteristics within Subgroups (N=106)

| | | GDM-insulin (iGDM) *n*=20 | GDM-diet (dGDM) *n*=53 | Non-diabetic controls *n*=33 | *P*-value |
|---|---|---|---|---|---|
| ge (years) | *M(SD)* | 33.7 (4.7) | 32.0 (4.9) | 30.3 (5.5) | 0.200 |
| MI (kg/m$^2$) | *M(SD)* | 26.0 (6.5) | 24.5 (5.2) | 21.4 (3.9) | 0.300 |
| MI ≥ 25 kg/m$^2$ (%) | Yes | 7 (35.0) | 21 (39.6) | 2 (6.1) | |
| | No | 13 (65.0) | 32 (60.4) | 31 (93.0) | 0.717 |
| arity (%) | Primiparous | 5 (25.0) | 25 (47.2) | 13 (39.4) | |
| | Multiparous | 15 (75.0) | 28 (52.8) | 20 (60.6) | 0.086 |
| thnicity (%) | Chinese | 5 (25.0) | 22 (41.5) | 18 (54.5) | |
| | Malay | 8 (40.0) | 16 (30.2) | 8 (24.2) | |
| | Indian | 5 (25.0) | 12 (22.6) | 6 (18.2) | |
| | Other | 2 (10.0) | 3 (5.7) | 1 (3.0) | 0.587 |
| bove Secondary education (%) | Yes | 9 (45.0) | 24 (45.3) | 17 (51.5) | |
| | No | 11 (55.0) | 29 (54.7) | 16 (48.5) | 0.983 |
| mployment (%) | Yes | 17 (85.0) | 34 (54.2) | 21 (63.6) | |
| | No | 3 (15.0) | 19 (35.8) | 12 (36.4) | 0.083 |
| ntitled to >3 months maternity leave for | Yes | 13 (65.0) | 29 (54.7) | 13 (39.4) | |
| mployed subjects (%) | No | 3 (15.0) | 5 (9.4) | 7 (21.2) | |
| | Not applicable | 4 (20.0) | 19 (35.8) | 13 (39.4) | 0.400 |
| ousehold monthly income (%) | <SGD 5000 | 11 (55.0) | 32 (60.4) | 27 (81.8) | |
| | ≥SGD 5000 | 9 (45.0) | 21 (39.6) | 6 (18.2) | 0.677 |
| reastfeeding history (%) | Yes | 15 (75.0) | 29 (54.7) | 18 (54.5) | |
| | No | 5 (25.0) | 24 (45.3) | 15 (45.5) | 0.114 |
| ttended antenatal classes (%) | Yes | 2 (10.0) | 5 (9.4) | 4 (12.1) | |
| | No | 18 (90.0) | 48 (90.6) | 29 (87.9) | 0.942 |

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

**Figure 2. Demographics of Study Participants.** The participants are stratified in ethnicity (A), parity, breastfeeding history and mode of delivery (B). There were no differences between women with GDM randomized to treatment or placebo groups, and non-diabetic controls.

### Effects of metoclopramide on EHM volume and lactogenesis II onset

Rates of EHM increase were calculated after adjusting for ethnicity, parity and breastfeeding history. Daily mean EHM were similar between metoclopramide and placebo users, trending towards higher EHM in the metoclopramide group from day 4 onwards (Figure 3A). Higher EHM volumes were observed in all diabetic groups compared to non-diabetic controls, except for iGDM-placebo mothers in whom EHM fell below control levels after day 4 (Figure 3B, not significant). The daily gain in EHM over baseline (day 1) volumes was higher in iGDM-metoclopramide mothers on all days compared to controls, significant on day 3 (40.0mL vs. 6.1mL, $P$=0.04) while daily EHM gain fell after day 5 in iGDM-placebo mothers (Figure 3C). Though mean daily gain in EHM was higher in iGDM or dGDM mothers on metoclopramide (49.7mL and 51.4mL respectively) compared with placebo users, there were no statistical differences in daily EHM gain (Figure 3C, 3D). iGDM mothers benefitted the most from treatment, with 50% of iGDM-metoclopramide mothers reporting positive perception of LCII by day 2, at least one day ahead of the other GDM subgroups and controls, and 100% of mothers reporting LCII by day 7 (Figure 3E). In contrast, 50% of iGDM-placebo mothers reported LCII only by day 4-5 (Figure 3E).

**Figure 3. Expressed Breast Milk Volume (EBM) over the First Postnatal Week and Maternal Perception of Lactogenesis II Onset.** There were trends towards greater EBM among metoclopramide users compared to placebo (A) and all diabetic groups compared to controls, except for iGDM-placebo mothers after day 4 (B). iGDM-placebo mothers showed similar or lower EBM increase over day 1 compared to controls, while iGDM-metoclopramide mothers produced a higher EBM increase over day 1, significant on day 3 (C). EBM increase over day 1 among dGDM groups was similar to controls (D). 50% of iGDM-metoclopramide mothers reported perception of LCII by day 2, at least one day ahead of the other subgroups (E).

Based on the rise in daily EHM and maternal perception of milk coming in, the successful iGDM-metoclopramide mothers experienced an augmentation of 26.7% in LCII onset compared with iGDM-placebo mothers (adjusted RR 5.6; 95% CI, 1.4 – 20.0) (Table 3). There was no statistically significant difference in LCII onset between metoclopramide (60.9%) and placebo users (43.4%) among dGDM mothers (adjusted RR 1.7; 95% CI, 0.96-1.9), though RRR was 40.3% and NNTb was 5.7.

| | Treatment | n | Successful LCII ≤Day 3 (%) | Delayed LCII >Day 3 (%) | Adjusted p-value+ | RR+ 95% CI | RRI % NNT |
|---|---|---|---|---|---|---|---|
| iGDM | Metoclopramide | 10 | 60 | 40.0 | 0.014 | 5.6 | 80.2 |
| | Placebo | 9 | 33.3 | 66.7 | | 1.4 – 20.0 | 3.7 |
| dGDM | Metoclopramide | 23 | 60.9 | 39.1 | 0.072 | 1.7 | 40.3 |
| | Placebo | 14 | 43.4 | 56.6 | | 0.96 – 1.9 | 5.7 |

Note. +Adjusted for maternal age, BMI, parity, previously breastfed, ethnicity. LCII : lactogenesis II; RR: relative risk; CI: confidence interval; RRI: relative risk increase; NNT: number needed to treat; dGDM: diet-controlled gestational diabetes; iGDM: insulin-dependent gestational diabetes.

**Table 3. Lactogenesis II Onset by Postnatal Day 3**

### Effect of metoclopramide on breastfeeding practice

The majority of the study population practiced mixed feeding (MF) and there were no differences in rates of exclusive breastfeeding (BF), MF or formula-only feeding (FF) between MET and PLA groups (Figure 4A); BF was practiced by 34.2±3.8% of MET and 33.1±2.4% of PLA participants. iGDM-metoclopramide mothers showed a daily BF rate of 20%, while FF rate was 10% on days 1-3 and 30% from day 4 onwards, higher than other subgroups (Pearson $X^2$ $p<0.02$). dGDM-metoclopramide mothers showed a daily BF rate of 30-48% with the remainder practicing MF (Figure 4B). BF for at least 5 consecutive days was lower in iGDM-metoclopramide compared to other subgroups (10% vs. 33.3-36.4%, $p<0.05$, Figure 4C). Of mothers across all groups exclusively breastfeeding at day 7, the number still breastfeeding (any type) and practicing BF at 6 months was highest in term controls and lowest in iGDM subgroups (Figure 4D).

**Figure 4. Breastfeeding Practices**. Similar rates of exclusive breastfeeding (BF), mixed (BF+FF) and formula-only feeding (FF) were observed among metoclopramide and placebo users (A). Subgroups showed similar breastfeeding practices but 30% of iGDM-metoclopramide mothers practiced FF on days 4-7 (B), higher compared to other subgroups (Pearson $X^2$ $p<0.02$). Only 10% of iGDM-metoclopramide mothers practiced BF for at least 5 postnatal days compared to 30-40% of mothers in the other subgroups including controls ($p<0.05$, C).Of mothers practicing BF at day 7, a higher number of control mothers practiced BF at 6 months compared to the GDM subgroups (D).

### Infant weight change

While there was no difference in the overall infant weight gain between MET and PLA over 6 months (Figure 5A), the increase over birth weight was 5-24% lower in MET compared to PLA at all timepoints,

significant at week 2 (3.1% vs. 8.0%, *P*=0.04, Figure 5B). Infant weight gain was similar between subgroups. Increase over birth weight was significantly lower among infants of iGDM-metoclopramide mothers compared to all subgroups at week 2 (Figure 5C), significantly lower than non-diabetic controls (0.3% vs. 8.0%, *P*=0.04, Figure 5D).

**Figure 5. Infant Weight Gain.** There were no differences in infant weights between treatment and placebo groups (A) but there was greater gain over birth weight in week 2 among placebo-group compared to treatment-group infants (8.0 vs. 3.1%, *p*=0.04). Otherwise the rate of interval weight gain was similar (B). Similarly, infant weights among GDM subgroups and controls were similar at the various time-points (C). Gain over birthweight in infants of iGDM-metoclopramide mothers was lower at 0.3% in week 2 compared to 8.0% in controls (*p*=0.04), whereas the rate of weight gain was similar across all groups at the later time-points (D).

### Adverse effects

All adverse outcomes reported in neonates were neonatal jaundice (n=1) and hypoglycemia (n=1). The latter was documented in an infant of a GDM mother prior to initiating study medication. Four maternal adverse events were reported; these were mastitis and post-natal blues (dGDM-metoclopramide, n=2), increased postnatal bleeding not amounting to hemorrhage (iGDM-metoclopramide) and periorbital swelling (iGDM-placebo).

# Discussion

Prophylactic early metoclopramide augmented LCII onset in all GDM users. The iGDM mothers achieved an augmentation of 26.7% in LCII onset, which exceeded our target of 25% augmentation. The augmentation in dGDM group was not significant probably due to the small sample size. The number needed to treat to benefit (NNTb) was small, between 3 and 6 women, suggesting that this may be an effective therapy to boost lactogenesis in these at-risk mothers. EHM increases in iGDM and dGDM mothers on metoclopramide exceeded EHM observed in non-diabetic controls on placebo, suggesting that the intervention had, in the short-term, corrected lactation deficiencies in these groups. iGDM-metoclopramide mothers did not show the natural day 5 EHM decrease of iGDM-placebo mothers. Despite the early EHM increase however, metoclopramide-users practiced less exclusive breastfeeding than mixed feeding, less exclusive breastfeeding in the first week than placebo-users, and had the highest frequency of formula-feeding (iGDM-metoclopramide). The low breastfeeding rates were unexpected from the positive effects on EHM. Together with the natural EHM decline from day 5 observed in iGDM-placebo mothers, these suggest the presence of physiological barriers not modifiable with lactation support or pharmacological interventions as used in this study.

These barriers may arise from underlying pathophysiology or psycho-physical conditions associated with GDM, such as maternal overweight or obesity (19, 20); in our cohort 35–40% of GDM mothers had BMI over 25 kg/m$^2$ (compared to 6% of non-diabetic controls). High maternal BMI is a contributive factor to

breastfeeding failure independent of other obstetric complications, with obese women showing a higher rate of breastfeeding cessation than non-obese women despite a similar initiation frequency (21, 22). Though our study did not stratify participants by BMI nor was it powered to examine this variable, we expect that this may have contributed to early breastfeeding cessation in GDM mothers despite objective evidence of initial success. Insulin resistance, encountered in GDM and obesity, may directly contribute to poor lactogenesis (23). Insulin-signaling pathway imbalances affect LCII-onset via reduced milk-synthesis potential (24). Other metabolic disturbances including altered maternal leptin:adiponectin ratio, reduced prolactin response to suckling or overexpression of protein tyrosine phosphatase receptor type F in mammary tissue can negatively affect sustained lactogenesis via disordered milk duct development, delayed LCII onset or suboptimal milk let-down (24–28). Adipose tissue concentrates progesterone and may result in consistently higher progesterone levels among obese women as compared to normal-weight women, which consequently delays the lactogenesis trigger and results in a diminished prolactin response to breastfeeding (1). GDM thus increases the physiological risk of lactation failure even before delivery (29). Supportive measures, including galactagogues, may only have limited impact on breastfeeding (30). This is a concern considering the high local prevalence of GDM (31). Common first-line interventions of optimizing breastfeeding technique and feeding frequency will not effectively address low milk supply, a problem more common in GDM mothers than latch or nipple problems (5, 24).

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). 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, 35). Increasing awareness of the benefits of breastfeeding for mother and infant, especially of the reduced long-term risk of metabolic conditions in breast-fed infants creates a stronger incentive to improve lactation through a multidisciplinary approach (35, 36). Offspring of diabetic mothers are at an increased risk of developing impaired glucose tolerance themselves; there is evidence that the first week of life appears to be the critical window period for nutritional programming in offspring of diabetic mothers (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 h 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 could not be predicted as there were no prior studies to help with the estimates. Reluctance to consume the drug led to refusal as we approached 208 mothers and only 25% agreed to participate. Besides the reluctance to take the drug, the medications compliance was equally challenging leading to the substantial loss to follow-up despite the labor-intensive EHM monitoring. This was coupled by lower than expected delivery numbers resulting in lacking ability to reach the sample size target. To stretch the recruitment period in order to achieve the target numbers was

not attainable. The culture of participating in research was still in its infancy stage as the rates of exclusive breastfeeding in Singapore were not high at the time of the study. Hence, the observed not statistically significant results might be due to type II error, it warrants further study with larger sample size. This limits our ability to interpret the true effects of metoclopramide. We did not study the effects 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 ACOG (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; GDM:gestational diabetes; iGDM:insulin-dependent gestational diabetes; dGDM:diet-controlled gestational diabetes; EBF:exclusive breastfeeding; MF:mixed breastmilk and formula feeds; FF:exclusive formula feeding; MET:metoclopramide group; PLA:placebo group. RR:relative risk; CI:confidence interval; RRI:relative risk increase; NNT:number needed to treat. NNTb:number needed to treat to benefit; BMI:body mass index.

# 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/06/024, 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. Neville MC, Morton J. Physiology and endocrine changes underlying human lactogenesis II. J Nutr. 2001;131:3005S-8S.
2. 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;9:401-9.
3. Neubauer SH, Ferris AM, Chase CG, Fanelli J, Thompson CA, Lammi-Keefe CJ, et al. Delayed lactogenesis in women with insulin-dependent diabetes mellitus. Am J Clin Nutr. 1993;58:54-60.
4. Cordero L, Gabbe SG, Landon MB, Nankervis CA. Breastfeeding initiation in women with gestational diabetes mellitus. Journal of neonatal-perinatal medicine. 2013;6:303-10.
5. Matias SL, Dewey KG, Quesenberry CP, Jr., Gunderson EP. Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus. Am J Clin Nutr. 2014;99:115-21.
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;
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;109:73-80.

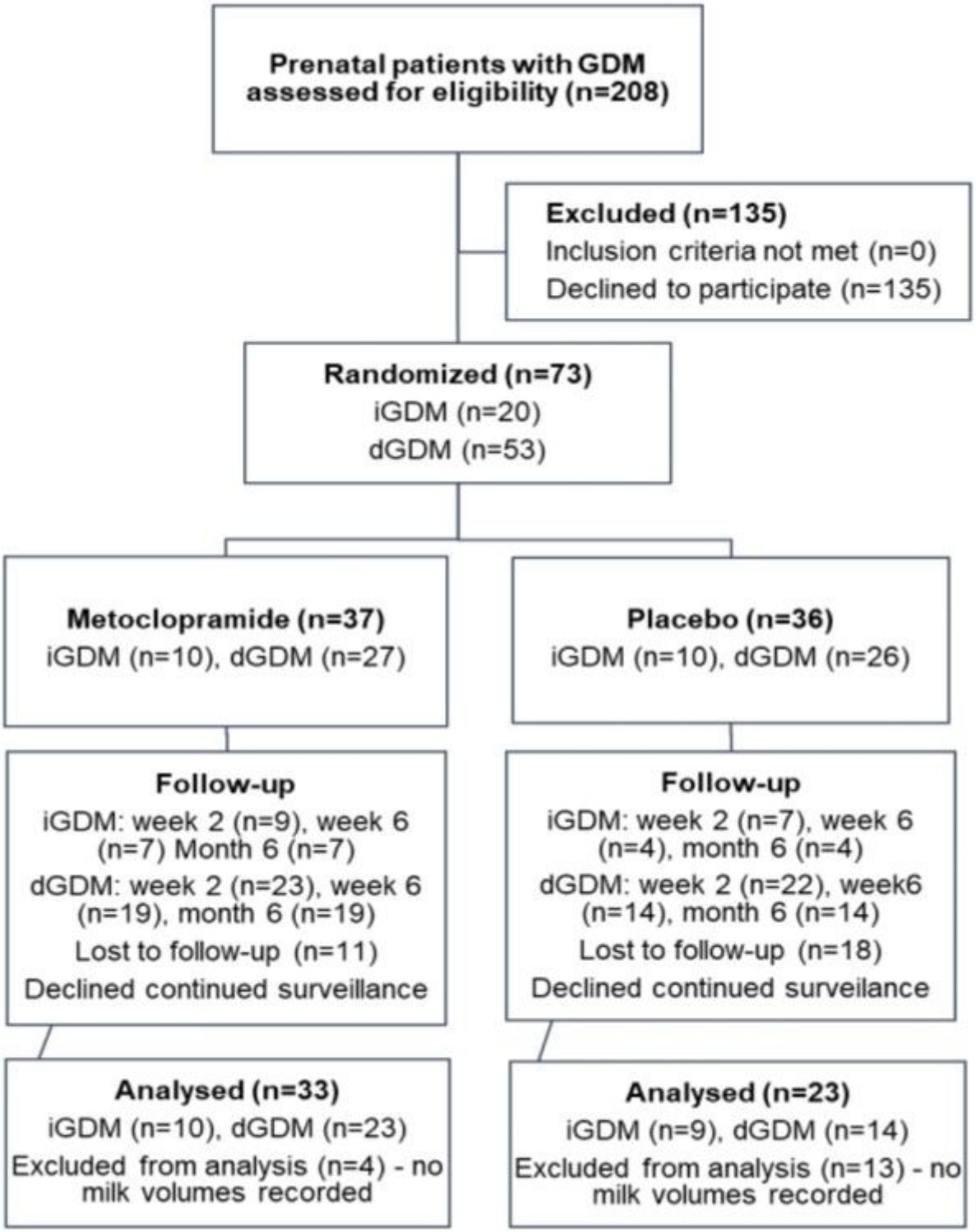
8. U.S. Food & Drug Administration. [Internet]. FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production. 2004. [Cited on March 10, 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm
9. Asztalos EV, Campbell-Yeo 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;33:181-7.
10. 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/.
11. Doggrell SA, Hancox JC. Cardiac safety concerns for domperidone, an antiemetic and prokinetic, and galactogogue medicine. Expert Opin Drug Saf. 2014;13:131-8.
12. 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;19:19-22.
13. Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. Lancet. 1981;1:1175-7.
14. Seema, Patwari AK, Satyanarayana L. Relactation: an effective intervention to promote exclusive breastfeeding. J Trop Pediatr. 1997;43:213-6.
15. 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;97:F241-5.
16. 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/.
17. Brownell E, Howard CR, Lawrence RA, Dozier AM. Delayed onset lactogenesis II predicts the cessation of any or exclusive breastfeeding. J Pediatr. 2012;161:608-14.
18. Kachikis A, Eckert LO, Walker C, Oteng-Ntim E, Guggilla R, Gupta M, et al. Gestational diabetes mellitus: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017;35:6555-62.
19. Pinheiro TV, Goldani MZ, group I. Maternal pre-pregnancy overweight/obesity and gestational diabetes interaction on delayed breastfeeding initiation. PloS one. 2018;13:e0194879.
20. Blickstein I, Doyev R, Trojner Bregar A, Brzan Simenc G, Verdenik I, Tul N. The effect of gestational diabetes, pre-gravid maternal obesity, and their combination ('diabesity') on outcomes of singleton gestations. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018;31:640-3.
21. Kitsantas P, Pawloski LR. Maternal obesity, health status during pregnancy, and breastfeeding initiation and duration. The journal of maternal-fetal & neonatal medicine : the official journal of the

European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2010;23:135-41.

22. Bever Babendure J, Reifsnider E, Mendias E, Moramarco MW, Davila YR. Reduced breastfeeding rates among obese mothers: a review of contributing factors, clinical considerations and future directions. Int Breastfeed J. 2015;10:21.
23. Sandler V, Reisetter AC, Bain JR, Muehlbauer MJ, Nodzenski M, Stevens RD, et al. Associations of maternal BMI and insulin resistance with the maternal metabolome and newborn outcomes. Diabetologia. 2017;60:518-30.
24. Lemay DG, Ballard OA, Hughes MA, Morrow AL, Horseman ND, Nommsen-Rivers LA. RNA sequencing of the human milk fat layer transcriptome reveals distinct gene expression profiles at three stages of lactation. PloS one. 2013;8:e67531.
25. De Bortoli J, Amir LH. Is onset of lactation delayed in women with diabetes in pregnancy? A systematic review. Diabetic medicine : a journal of the British Diabetic Association. 2016;33:17-24.
26. Kratzsch J, Bae YJ, Kiess W. Adipokines in human breast milk. Best practice & research Clinical endocrinology & metabolism. 2018;32:27-38.
27. Ley SH, O'Connor DL, Retnakaran R, Hamilton JK, Sermer M, Zinman B, et al. Impact of maternal metabolic abnormalities in pregnancy on human milk and subsequent infant metabolic development: methodology and design. BMC public health. 2010;10:590.
28. Mihalopoulos NL, Urban BM, Metos JM, Balch AH, Young PC, Jordan KC. Breast-feeding, Leptin:Adiponectin Ratio, and Metabolic Dysfunction in Adolescents with Obesity. Southern medical journal. 2017;110:347-52.
29. Nommsen-Rivers LA, Dolan LM, Huang B. Timing of stage II lactogenesis is predicted by antenatal metabolic health in a cohort of primiparas. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2012;7:43-9.
30. Hauff LE, Leonard SA, Rasmussen KM. Associations of maternal obesity and psychosocial factors with breastfeeding intention, initiation, and duration. Am J Clin Nutr. 2014;99:524-34.
31. Padmapriya N, Bernard JY, Liang S, Loy SL, Cai S, Zhe IS, et al. Associations of physical activity and sedentary behavior during pregnancy with gestational diabetes mellitus among Asian women in Singapore. BMC Pregnancy Childbirth. 2017;17:364.
32. Meedya S, Fahy K, Kable A. Factors that positively influence breastfeeding duration to 6 months: a literature review. Women and birth : journal of the Australian College of Midwives. 2010;23:135-45.
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;131: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 pediatrics. 2017;17:145.

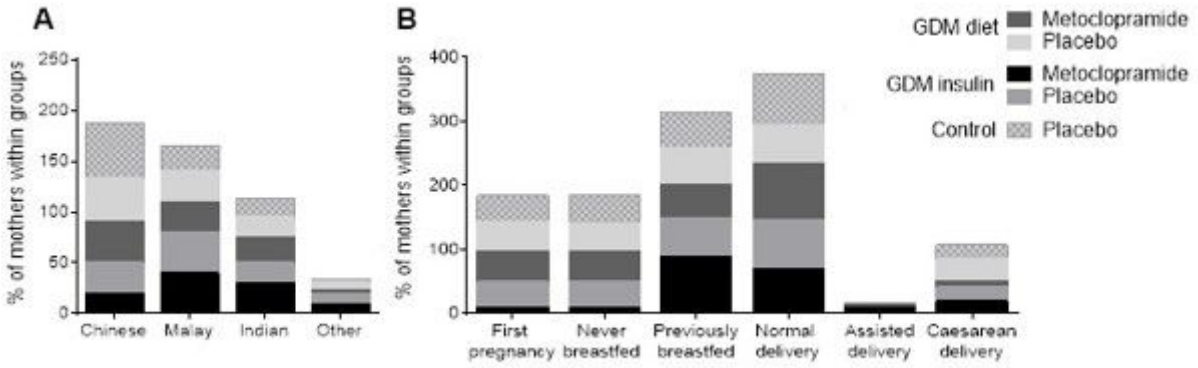
35. Pang WW, Aris IM, Fok D, Soh SE, Chua MC, Lim SB, et al. Determinants of Breastfeeding Practices and Success in a Multi-Ethnic Asian Population. Birth. 2016;43:68-77.
36. Aris IM, Soh SE, Tint MT, Saw SM, Rajadurai VS, Godfrey KM, et al. Associations of infant milk feed type on early postnatal growth of offspring exposed and unexposed to gestational diabetes in utero. European journal of nutrition. 2017;56:55-64.
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

# Figures



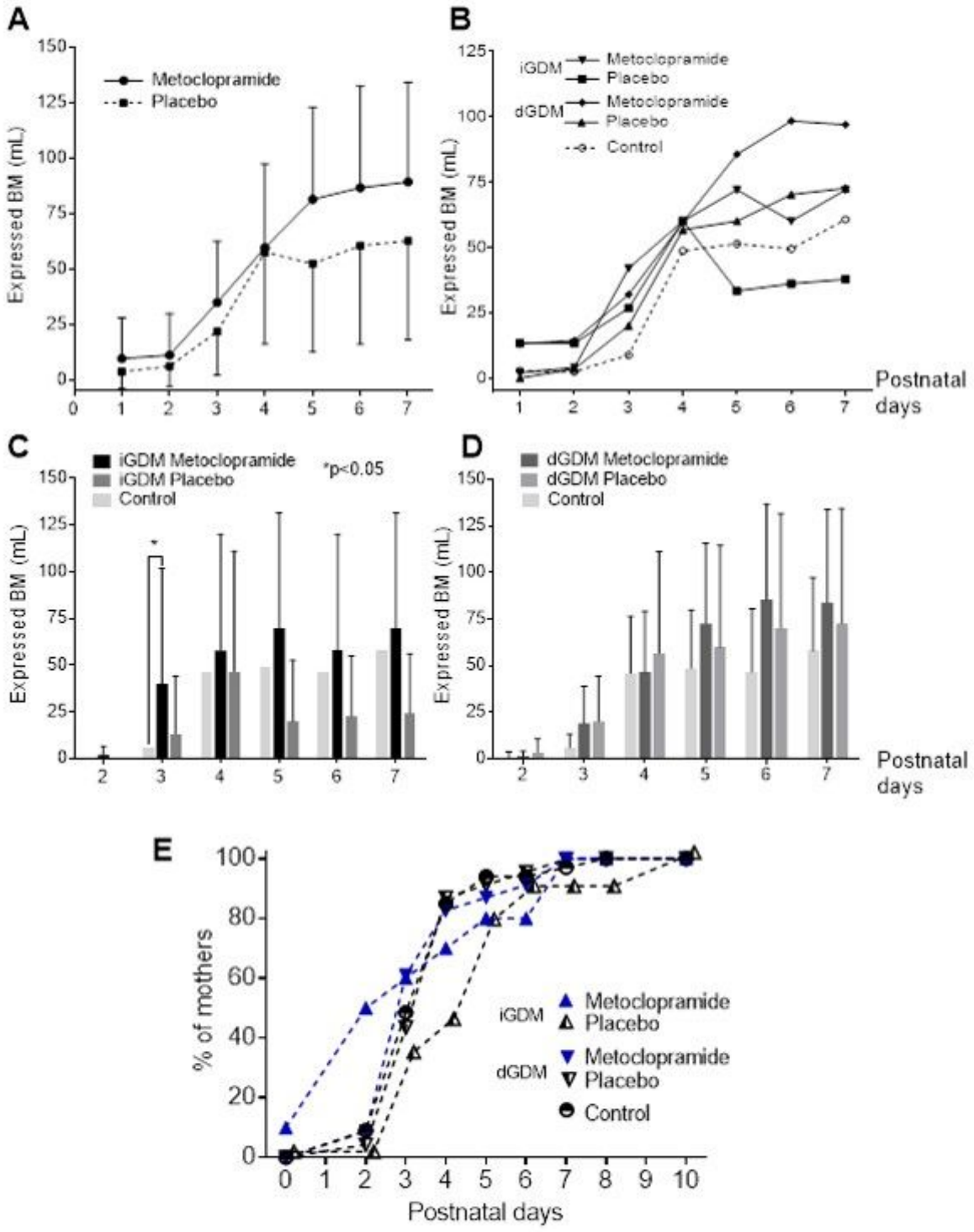

## Figure 1

Randomization Flowchart. It demonstrates the recruitment, eligibility screening and randomization of study participants, follow-up and data analysis.




## Figure 2

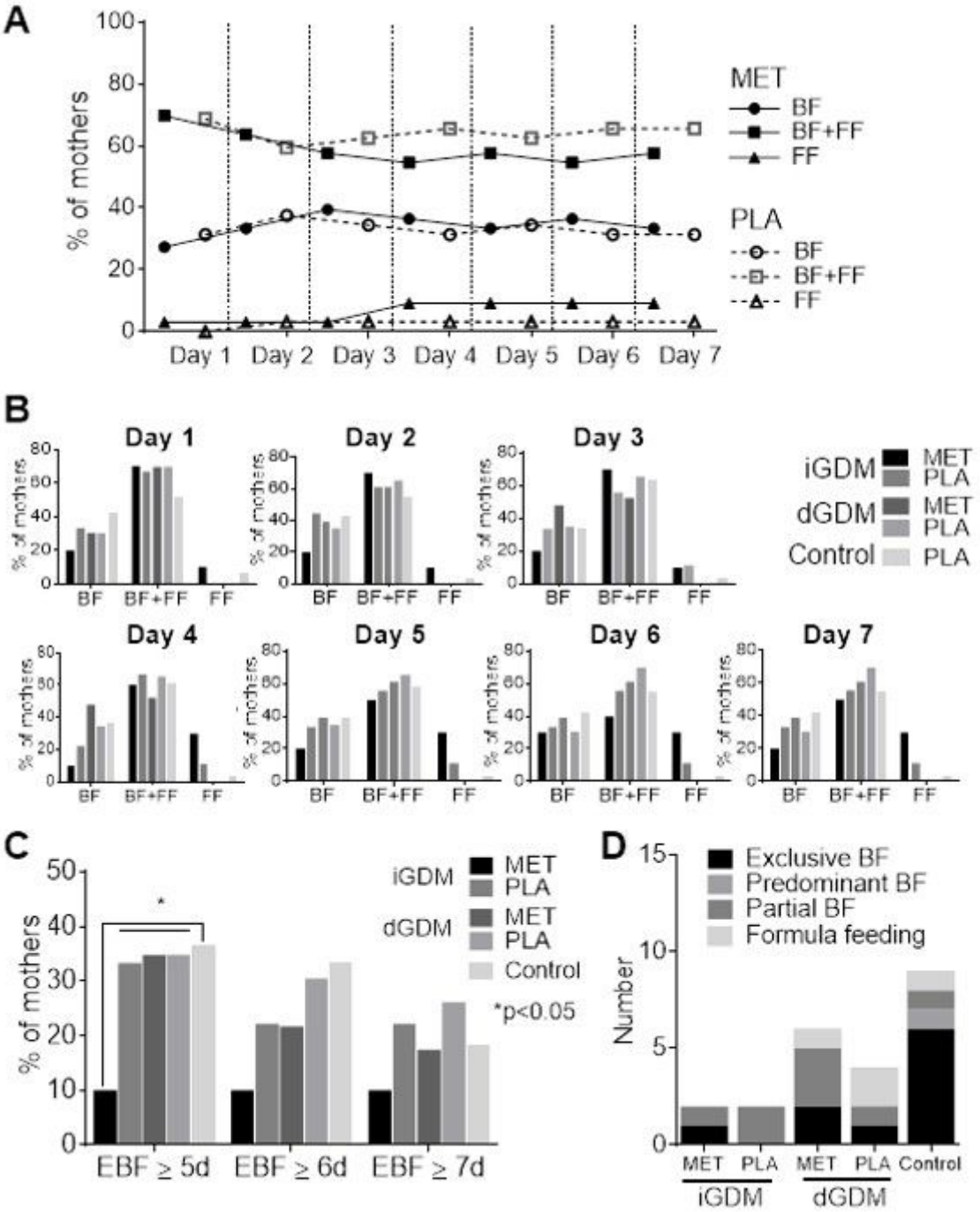
Demographics of Study Participants. The participants are stratified in ethnicity (A), parity, breastfeeding history and mode of delivery (B). There were no differences between women with GDM randomized to treatment or placebo groups, and non-diabetic controls.




## Figure 3

Expressed Breast Milk Volume (EBM) over the First Postnatal Week and Maternal Perception of Lactogenesis II Onset. There were trends towards greater EBM among metoclopramide users compared to placebo (A) and all diabetic groups compared to controls, except for iGDM-placebo mothers after day 4 (B). iGDM-placebo mothers showed similar or lower EBM increase over day 1 compared to controls, while iGDM-metoclopramide mothers produced a higher EBM increase over day 1, significant on day 3 (C). EBM

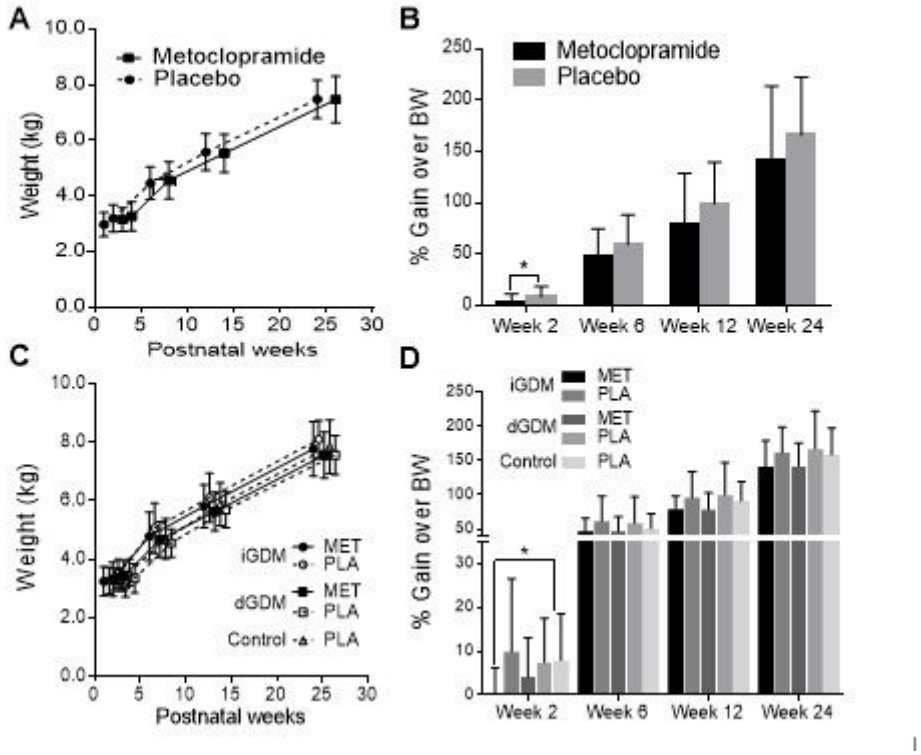
increase over day 1 among dGDM groups was similar to controls (D). 50% of iGDM-metoclopramide mothers reported perception of LCII by day 2, at least one day ahead of the other subgroups (E).




## Figure 4

Breastfeeding Practices. Similar rates of exclusive breastfeeding (BF), mixed (BF+FF) and formula-only feeding (FF) were observed among metoclopramide and placebo users (A). Subgroups showed similar breastfeeding practices but 30% of iGDM-metoclopramide mothers practiced FF on days 4-7 (B), higher compared to other subgroups (Pearson X2 p<0.02). Only 10% of iGDM-metoclopramide mothers practiced BF for at least 5 postnatal days compared to 30-40% of mothers in the other subgroups

including controls (p<0.05, C).Of mothers practicing BF at day 7, a higher number of control mothers practiced BF at 6 months compared to the GDM subgroups (D).




## Figure 5

Infant Weight Gain. There were no differences in infant weights between treatment and placebo groups (A) but there was greater gain over birth weight in week 2 among placebo-group compared to treatment-group infants (8.0 vs. 3.1%, p=0.04). Otherwise the rate of interval weight gain was similar (B). Similarly, infant weights among GDM subgroups and controls were similar at the various time-points (C). Gain over birthweight in infants of iGDM-metoclopramide mothers was lower at 0.3% in week 2 compared to 8.0% in controls (p=0.04), whereas the rate of weight gain was similar across all groups at the later time-points (D).