International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2020 Vol.10 (1) January-June, pp. 6-15/Deepa and Premlata
Research Article

A RANDOMIZED CONTROL TRIAL TO STUDY THE EFFICACY OF DOMPERIDONE AS A GALACTOGOGUE VERSUS PLACEBO

Deepa K.* and Premalatha R.
Department of Pediatrics, MVJ Medical College and Research Hospital, Bangaluru
**Author for Correspondence: deepakandgal123456@gmail.com*

ABSTRACT

Background: Lactation is beneficial to mother's health as well as provides specific nourishment, growth and development to the baby. Hence, it is a nature's precious gift for the infant; however, lactation insufficiency is one of the explanations mentioned most often by women throughout the world for the early discontinuation of breastfeeding and/or for the introduction of supplementary feeds by bottles. Globally, lactation insufficiency is a public health concern, as the use of breast milk substitutes increases the risk of morbidity and mortality among infants in developing countries and breast milk substitutes are the most common cause of malnutrition. Hence the present study is conducted so that it helps the mothers to continue breastfeeding and reduces infant mortality.

Objectives: To study the efficacy of domperidone in augmenting breast milk production compared with placebo effect, which will be evaluated in the form of weight gain and improved urine output in newborns, side effects and Safety of domperidone for mothers.

Materials and Methods: A total of 66 mothers of term and late preterms with lactation insufficiency fulfilling inclusion criteria were included. All mothers received breastfeeding counseling for 2 days before intervention. They were randomized to Domperidone (10 mg tid for 7 days) and placebo (5 mg tid for 7 days) groups. The neonates were weighed on daily basis and frequency of urine output was documented from D3 to D10.

Results: Among 66 mothers of late preterm and term neonate's demographic data were comparable among both the groups. The efficacy of the domperidone was estimated by mean weight gain in the newborns.The domperidone group neonates noticed to have weight gain from D5 compared to placebo from D7 and Domperidone group regained their birth weight by D7 compared to D10 in placebo group, which was statistically significant. The mean weight gain in domperidone group was 26.5+/-6.25g/day which is indirect evidence of increased milk output in mother compared to the 13.93 +/-7.66 g/day mean weight gain the placebo group. (p value <0.05) which was statistically significant. The increase in the urine output in the domperidone group was 6-8 times compared to 4 times in placebo group value <0.05, which was statistically significant. There were no adverse effects with domperidone in mothers.

Conclusion: If non pharmacological interventions like education about breastfeeding counseling fail to improve breast milk supply, domperidone can be used to increase the milk output in mothers with lactation insufficiency. Domperidone is well tolerated with no adverse effects.

Keywords*: Lactation Insufficiency, Galactogogues, Domperidone*

INTRODUCTION

Breast milk is very important for neonates. According to a WHO/UNICEF, more than one million infants worldwide die every year because they are not breastfed or given other foods too early. Babies who are not breastfed or who are fed other foods too early may have an increased risk of obesity, diarrhea, GI problems, respiratory and ear infections, urinary tract infection, bacterial meningitis botulism, necrotizing enterocolitis and allergic skin disorders. India is facing a grave challenge of having very high rates of child under nutrition and a high infant and child mortality, which demands an urgent need for comprehensive multi-pronged evidence based strategy to tackle the situation. Because of its nutritional superiority over animal milk makes it more advantageous, especially in a developing country like India. However, at the slightest problem encountered, mothers switch readily over to top/supplementary feeding.

Mother often feels that they have insufficient milk and faces numerous physical, emotional and logistical obstacles to breastfeeding and even small anxieties about milk supply can lead to lactation failure (Mathur *et al.,* 2009). Failing to receive the crucial breastfeeding support will also leads to lactation failure. Moreover, it is an established fact that poor nutrition of the mother can lead to poor growth and development of the fetus and to an insufficient quantity of milk.Perceived insufficient milk (PIM) is one of the reasons mentioned most often by women throughout the world for the early discontinuation of breast feeding and/or the introduction of supplementary bottles (Segaoera-*Millan et al.,* 1994).

It is not clear how many women genuinely have an inadequate supply of milk however; it would be an advantage if some means exist to increase milk production temporarily. There have been many identified and studied non pharmacological measures such as emotional support, kangaroo care, skin- skin contact, expressing breast milk, increasing pumping frequency and duration and types of mechanical expression that have been found to contribute to success in augmenting the breast milk production in mothers of preterm infants (Lewis *et al.,* 1980). For those mothers who are not responding to non –pharmacological measures, the use of galactogogues is often considered. Galactagogues (or lactogogues) are medications or substances believed to assist initiation, maintenance or augmentation of maternal milk production. Common indications for galactagogues are adoptive nursing (induction of lactation in a woman who was not pregnant with the current child), Relactation (reestablishing milk supply after weaning), and increasing a faltering milk supply because of maternal or infant's illness or separation (Montgomery *et al.,* 2004; Gabay *et al.,* 2002). Although certain medicines like Metoclopramide and domperidone are being used for augmenting lactation but are seldom recommended in view of their limited efficacy prospects and major safety concern.

MATERIALS AND METHODS

This study was conducted at the post natal ward in the department of pediatrics of MVJ Medical College & Research Hospital over a period two years from November 2017 to August 2019.It was a hospital based randomized controlled study. The study was approved by the Ethical committee of M.V.J. Medical College and Research Hospital. Mothers of late preterm and term neonates who have experienced insufficient milk production [Indirect evidence of poor milk production are: excessive weight loss (>6% on D3) or poor weight gain, decreased urine output in newborns on two consecutive days and subjective assumption of decreased milk production] were included in the study. Exclusion criteria were mothers with other co-morbid conditions ,who are intolerant to medication, who are on other medications influencing lactation or receiving medication known to alter the metabolism and pharmacokinetics of domperidone (oral azoles antifungals ,erythromycin antibiotics and MAO inhibitors) and mothers on other traditional galactogogues.

Sample size was calculated using formula

$N=2(Z_{\alpha/2}+Z_{\beta})^2P(1-P)/(p_1-p_2)$

Where $Z_{\alpha/2=}Z_{0.05/2=}Z_{0.025}=2.58$ *at type 1 error of 1%*$Z_{\beta=}Z_{0.025=}0.842=90\%$ *power,* p_1-p_2*=Difference in proportion in 2 different group= 50% P= Pooled prevalence=[proportion in Domperidone group(*p_1*)+proportion in placebo group(*p_2*)]/2=47*

$N= 2\times47\times53(2.58+1.28)^2/50\times50=74229/2500=30$ *in each group.*

Considering non response rate of 10% 30+3=33 patients in each group. Total of 66 mothers and neonates, 33 in each group**.** Minimum of 66 Puerperal mothers of late preterm and term infants experiencing insufficient breast milk production satisfying inclusion criteria were enrolled. Oral and written consent is taken from all those participating in the study. Before intervention during initial 2 days all mothers received breastfeeding counseling, according to WHO breastfeeding guidelines. They were randomized into 2 groups, included in study from Day 3 of life, when the babies have weight loss >6%

GROUP A: On domperidone 10mg orally 3 times daily for one week.

GROUP B: Identical placebo (folate 5 mg) orally 3 times daily for one week.

Neonates were weighed on daily basis and frequency of urine output was documented from day 1 to day 10 after giving domperidone or placebo. Lactation augmenting effect of domperidone is analyzed everyday in the form of daily weight gain, % weight gain from admission to discharge and improved urine output in newborns. The mothers were instructed to record any side effects during treatment, particularly dry mouth, headache, insomnia, abdominal cramps, diarrhea, nausea and urinary retention. Maternal variables like age, parity, mode of delivery and neonatal variables like birth weight, gestation age, and gender were assessed. Primary outcome was to assess increase in the milk volume with Domperidone in mothers of lactation insufficiency which was indirectly assessed by mean weight gain in the newborn and increase in the urine output and to study side effects associated with Domperidone.

Statistical analysis

Categorical data was represented in the form of Frequencies and proportions. *Chi- square test* was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. *Independent t test* was used as test of significance to identify the mean difference between two quantitative variables. *Graphical representation of data***:** MS Excel and MS word was used to obtain various types of graphs such as bar diagram. *P value* (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. **.**

RESULTS

Total 66 term and late preterm neonates and their mothers were studied, 33 in each group. Demographic data are as follows**:**

Table 1: Mean Gestational Age Comparison between two groups

	Group						P Value
	DOMPERIDONE		FOLATE		Total		
	Mean	SD	Mean	SD	Mean	SD	
Gestational age (in weeks)	37.49	1.53	37.90	1.82	37.76	1.73	0.177

There was no significant difference in mean Gestational age between two groups.

Table 2: Sex Distribution between two groups

		GROUP					
		DOMPERIDONE		FOLATE		TOTAL	
		Count	%	Count	%	Count	%
Sex	Female	17	51.02%	15	46.46%	32	47.97%
	Male	16	48.98%	18	53.54%	34	52.03%
	Total	33	100.00%	33	100.00%	66	100.00%

χ 2 = 0.273, df = 1, p = 0.602

There was no significant difference in Sex distribution between two groups.

Table 3: Mean Birth Weight (in kgs) Comparison between two groups

	GROUP						P Value
	DOMPERIDONE		FOLATE		TOTAL		
	Mean	SD	Mean	SD	Mean	SD	
Birth Weight (in kgs)	2.6	0.52	2.68	0.29	2.62	.39	0.12

There was no significant difference in mean birth weight between two groups.

Table 4: Mode of Delivery Comparison Between Groups

MOD	DOMPERIDONE		FOLATE		TOTAL	
	Number	%	Number	%	Number	%
LSCS	18	53	18	56	36	54.6
NVD	15	46	15	44	30	45.3
TOTAL	33		33		66	

*χ 2 = 4.150, df = 1, p = 0.062**
There was no significant difference in mode of delivery between two groups

Table 5: Mean Mothers Age Comparison between two groups

	GROUP						P Value
	DOMPERIDONE		FOLATE		TOTAL		
	Mean	SD	Mean	SD	Mean	SD	
Mothers Age (in yrs)	24.39	2.41	24.72	2.62	24.61	2.55	0.461

There was no significant difference in mother's age distribution between two groups.

Table 6: Parity Distribution between two groups

Parity	Domperidone		Folate		Total	
	Number	%	Number	%	Number	%
PRIMI	47	62	44	58	91	60
MULTI	28	37	31	41	59	40

There was no significant difference in parity distribution in both groups.

Table 7: Mean Percentage Weight Loss on Day 3 Comparison between 2 groups

	Group						P Value
	Domperidpone		Folate		Total		
	Mean	SD	Mean	SD	Mean	SD	
Percentage Weight loss on Day 3	9.00	1.87	8.68	2.00	8.78	1.96	0.346

Mean Percentage Weight loss on Day 3 in Domperidone group was 9.00 ± 1.87% and in folate group was 8.68 ± 2.00%. There was no significant difference in Percentage Weight loss on Day 3 between two groups**.**

Table: 8 Risk factors for lactation insufficiency (>6% wt loss on d3 in newborns)

Risk Factors	Domperidone %	Placebo %	P value	OR(CI)
Mat. Age				
<20	**3.6**	**1.5**		
20-30	**94**	**97.5**		
>30	**2.4**	**1**	**0.6**	**O.8(0.2-1)**
Parity				
Primi	**62**	**58**		
Multi	**37**	**42**	**0.4**	**1.86(1.2-2.4)**
Mod				
LSCS	**53.6**	**56**		
NVD	**46.4**	**44**	**0.08**	**1.96(1.8-2.94)**
Nipple prob.				
YES	**58**	**51**		
NO	**42**	**49**	**0.4**	**1.17(0.74-1.86)**
GA				
Preterm	42.24%	44.44%		
Term	4.06%	4.86%	0.3	1.57(1.4-2.34)
SEX	\			
FEMALE MALE	51.02	46.46		
	48.98	53.54	0.1	0.96(0.8-1.04)
BWT				
<2.5	30.33	33.56		
>2.5	69.67	66.44	0.5	0.6(0.5-1.2)

In our study Primi mothers have 1.86 times more risk of lactation insufficiency .Mothers that have undergone LSCS had 1.96 times more risk of lactation insufficiency. Mothers with nipple issues had 1.17 times more risk of lactation insufficiency. Late preterm neonates have 1.57 times more risk of lactation insufficiency. There was no correlation between maternal age and gender, birth weight of neonates.

Table 9: Mean Percentage Weight Gain (g/d) Comparison between two groups after starting domoperidone or placebo

	Group						P Value
	Domperidone		Folate		Total		
	Mean	SD	Mean	SD	Mean	SD	
Percentage Weight Gain (g/d)	26.59	6.25	13.93	7.66	18.12	9.36	< 0.001*

Mean Percentage Weight Gain in domperidone group was 26.59 ± 6.25 g/d and in folate group was 13.93 ± 7.66 g/d. There was significant difference in Percentage Weight Gain between two group Table: 10 Percentage weight change on daily basis in both groups

Table: 10 Percentage weight change on daily basis in both groups

Day of life	Mean change in wt Domperidone		Mean change in wt Placebo		P value
	In gms	%	In gms	%	
BWT	2600		2620		0.26
3	2380	-9.2	2400	-8.34	0.34
4	2378	-9.32	2360	-9.9	0.01
5	2450	-6.12	2320	-10.4	0.003
6	2540	-5	2300	-10.9	0.001
7	2624	0.9	2460	-6.1	0.002
8	2660	2.3	2500	-4.4	0.001
9	2620	2.0	2560	-3.5	0.003
10	2660	3.04	2640	1	0.001

In our study neonates in Domperidone group started to gain weight gain from D5 of life, compared D7 in placebo group ,which was statistically significant (p value<0.005) .Neonates in Domperidone group

noticed to regain their birth weight by D7,compared to D10 in Placebo group, which was statistically significant (p value< 0.005).
Percentage weight change from D3 to D10 was 2-3% in Domperidone group compared to in placebo it was 1-2% which was statistically significant (P value< 0.005).

Table 11: Urinary frequency distribution in both groups

Day of life	Mean of Number of voids/Day		p value
	Domperidone	Placebo	
	MEAN	MEAN	
Day 3	2.18	2.08	0.2
Day4	6.64	4.30	0.44
Day5	7.00	5.45	0.003
Day6	8.28	4.17	0.02
Day7	6.71	6.30	0.15
Day8	7.05	4.56	0.001
Day9	8.65	6.92	0.01
Day10	6.28	4.97	0.002

In our study urine frequency increased from D4 of life in most of the neonates(66.4%) in Domperidone group, compared to placebo 2-4 times/d on D4 and increased to 6 -8 times/day from D7, which was statically significant (p value< 0.005)

Comparison of Adverse Effects of Domperidone:

Adverse Effects	Domperidone (In Counts)
YES	0(0%)
NO	75(100%)

In our study there were no adverse effects with Domperidone in mothers

DISCUSSION

Total 66 mothers who had lactation insufficiency (>6% weight loss and decreased urine output) on D3 of life were allotted into two groups (Domperidone and placebo). All mothers received counseling regarding breastfeeding as per WHO guidelines on 1st 2 days of life before intervention. From D3 of life domperidone or placebo was given. After that on daily basis newborns weights and urine output were monitored from D3 to D10 of life. And effect of domperidone vs. placebo on milk output was studied. In the present study total of 66 neonates were enrolled, 33 in each group. There was no significant difference in the demographic data between the two groups with regards to maternal age (mean-24 yrs), parity (61% primi), gestational age (mean-37 wks), and sex (female 47.97%, male 52.03%) and mean birth weight (2.6 kg)of the newborn, mode of delivery (LSCS 54.6%, vaginal 45.4%) .
The present study included neonates with mean GA of 37wks and (Paul *et al.,* 2015) also included term neonates, Hill PD et al included both term and preterm mothers. Empower trial included preterms (<29wks), (Mathur *et al.,* 2009) included late preterms (36.7wks), (Orlando P. Silva *et al.,* 2001) included preterms (29.1wks) in the study.

The present study included mothers with mean age group of 24yrs (Mathur *et al.,* 2009), (Orlando *et al.,* 2001), (Elise W-x Wan *et al.,* 2008) conducted study in maternal age group 23yrs , 28.2 yrs, 29 yrs.
Our study group included total of female (42.97%), male (52.03%) neonates (Mathur *et al.,* 2009) included 70% male and 30% female neonates.
In our study most of the mothers (54.6%) underwent LSCS and 45.3% mothers underwent NVD. In (Jantarasaengam *et al.,* 2012) study mode of delivery was LSCS in 100% cases, (Campbel-Yeo et al 2010) 45.5%,50% was Lscs in domperidone and placebo group and in (Petraglia *et al.,* 1985) mode of delivery was normal vaginal.
In our study most of the mothers (6O %) with lactation insufficiency were primi, 40% were multigravida. In (Mathur NB *et al.,* 2009) study most of them were Primi mothers.
In our study Primi mothers had 1.86 times more risk of lactation insufficiency**.** In (Mathur *et al.,* 2009) study also primi mothers have 2 times high risk of lactation insufficiency. Cause may be due to inadequate knowledge about breastfeeding in primi mothers and stress factors may lead to lactation insufficiency.
Mothers who have undergone LSCS had 1.96 times more risk of lactation insufficiency.
Similarly in (Jantarasaengaram *et al.,* 2012) study Lscs mothers had 1.5 times more risk of lactation insufficiency. This could be due to delayed initiation of breastfeeding in Lscs mothers.
Late preterm neonates have 1.57 times more risk of lactation insufficiency.
Similarly Hill PD et al study showed that preterm mothers have 2.82 times more risk of not producing adequate milk compared to term mothers. This could be because of late preterms have attachment and sucking problems.
In our study 58%, 51%of mothers in domperidone and folate group had nipple issues like sore nipple, inverted nipple, short nipple. Mothers with nipple issues had 1.17 times more risk of lactation insufficiency.
There was no association between other demographic data like maternal age, weight and gender of the neonate with lactation insufficiency.
In our study domperidone or placebo were given after 2 days of breastfeeding counseling from D3 of life to D10 for 7 days. Breastfeeding counseling was advised in (Osadchy *et al.,* 2012) study also. Similar dosage (10 mg TID) of domperidone is used in majority of studies. (Ingram *et al.,* 2012) study group received domperidone for first 10 days, (Campbell *et al.,* 2010) study group received for first 2 weeks and (Knoppert *et al.,* 2001) study group received domperidone for 4 weeks.
In our study the quantity of milk produced was assessed by daily weighing the babies and measuring frequency of urine output after giving domperidone or placebo to the mother from D3 to D10 of life. Similar method was used to assess the milk output in the study of (Petralgia *et al.,* 1985) the mothers breastfed their infants and quantity of milk produced was estimated everyday by weighing the infants before and after breastfeeding. In the other three studies the mothers fed their babies with milk collected using a pump. In these studies, the quantities of produced milk were assessed after collection.
In our study mean weight gain in neonates per day is 26+/-6.25 g/day compared to the placebo group 13.93+/-7.66 g /day (P value< 0.001) which is indirect evidence of milk output.
There were no studies available to compare the daily weight gain.
In Other studies efficacy of Domperidone was studied by calculating expressed milk volume.
(Da Silva *et al.,* 2001) found that between the 1st and 7th day of treatment , the volume of milk produced increased by 49.5ml+/-29.4(44.5%) in the domperidone group compared to the 8+/-39.5 ml/day (16.6%) in the control group(P<0.05).(Petraglia *et al.,*1985) showed that after 10 days of treatment, the daily milk production increased for the domperidone treated mothers , with a mean increase of 326ml/day compared to 63 ml /day in control group (P value<0.05). Jantarasaengaram *et al.,* (2012) showed that volume of collected milk was approximately 191+/-136.1ml/day after 4 days of domperidone treatment compared to 91.4+/-60.3ml/day in the control group (P< 0.003). Campbell-Yeo *et al.,* (2010) demonstrated a increase in milk volume of 267% after 14 days of domperidone treatment compared to 18.5% in the control group

(P,0.005). Donovan *et al.,* (2012) demonstrated a modest increase in expressed milk volume of 99.49ml/day. The mean volume of milk produced before the treatment in domperidone and control group was 3.9+/-4.6ml/day and 3.4+/-9.3 ml/day respectively.

Neonates who were enrolled had mean weight loss of 9% on D3 of life in both domperidone and placebo group and decreased urine output which is indirect evidence of decreased milk output in mothers. In both groups after giving domperidone or placebo from D3 of life weight change and urine output were monitored on daily basis. Neonates noticed to have weight gain (1-2%) from D5 in Domperidone group compared to D7 in placebo group which is statistically significant. This could be due to most of the mothers in the Domperidone group had let down reflex earlier compared to placebo group, due to domperidone being dopamine antagonist increases prolactin secretion.

Percentage of weight gain from D3 to D10 was 2-3 % in domperidone group compared to 1-2% in placebo group. In Domperidone group neonates noticed to regain birth weight on D7 (61%) and in Placebo group neonates regained their birth weight on D10 (64 %). 2% and 5 % in domperidone and placebo group did not regain birth weight at D10 which is not statistically significant.

On D3 they received Domperidone or Placebo and urine output was monitored daily (number of wet diapers per day).Urine frequency increased from D4 of life in most of the neonates (66.4%) in Domperidone group i.e. 6-8 times /day compared to placebo group 2-4 times/day on D4 and increased to 6-8 times /day from D7 of life, which is statically significant.(p value <0.05).

Whenever mother's milk output is adequate, babies will have 6-10 times urine output per day which is indirect evidence of milk output adequacy. After intervention with Domperidone in lactation insufficiency, we found in our study increase in the urine output 6-8 times which is an indirect evidence of increase in milk output in mothers. No other studies were available to compare increase in urine output as an indirect evidence of improve in milk output.

In our study there were no adverse effects like dry mouth, headache, insomnia, abdominal cramps,diarhoea, nausea and urine retention found in mothers .Similarly in (Campbel *et al.,* 2010 ;Petralgia et al.,1985 ; Da Silva et al.,2001) studies no significant maternal adverse effects in treatment groups. Adverse effects like dry mouth and abdominal cramp reported in (Jantarasaengam *et al.,* 2012) study. This could be because in our study Domperidone was used in minimal dosage of 30 mg per day for shorter duration of 7 days compared to above studies for 14 days, which might had lead to side effects. These GIT side effects (dry mouth, abdominal cramps)are common when Domperidone was used in increasing doses(60 mg/day). Domperidone should not be used for inadequate lactation where mother or infant has a cardiac disorder known to affect the QT interval these cardiac adverse effects are most common when Domperidone was used in a dose 90mg/day.

CONCLUSION

61% of primi mothers experienced lactation insufficiency. 68.2% of mothers who had undergone LSCS had lactation insufficiency, 44.44% late preterms have risk of lactation insufficiency. In Domperidone group weight gain in the neonates was noticed from D5 of life compared to placebo group on D7, which was statistically significant. There is significant increase in weight gain per day in Domperidone group (26.59+/-6.25) compared to placebo group (13.93+/-7.66) which is an indirect evidence of increased milk volume. In domperidone group neonates gained their birth weight by D7 of life compared to placebo group who gained birth weight by D10 of life, which was statistically significant. In Domperidone group percentage weight gain from D3 to D10 was 2-3% compared to placebo group which was 1%, which was statically significant.

There is significant increase in urine output in the domperidone group (6-8 times)compared to placebo group.(4-6 times).No adverse effects like dry mouth, headache, insomnia, abdominal cramps, diarrhea, nausea and urine retention were found in mothers. Domperidone is well tolerated and results in increase in milk volume among mothers identified as having insufficient milk supply. If non pharmacological

interventions like education about breastfeeding counseling fail to improve breast milk supply, domperidone can be used to increase the milk output**.**

REFERENCES

Asztalos EV, Campbell-Yeo M, Da Silva OP, Kiss A, Knoppert DC, Ito S *et al.*, (2012). Enhancing breast milk production with Domperidone in mothers of preterm neonates (empower trial). *BMC Pregnancy and Childbirth* **12** 87.

Campbell-Yeo M, Allen AC, Joseph KS, Ledwidge J, Allen V, Dooley K (2010). Effect of Domperidone on the Composition of Preterm Human Breast Milk: Randomized, Double Blind, Placebo-Controlled Trial. *Pediatrics* **125**(1) e107–e114.

Da Silva OP, Knoppert DC, Angelini MM, Forret PA (2001). Effect of Domperidone on milk production in mothers of premature newborn: randomized, double-blind, placebo-controlled trial. *Canadian Medical Association Journal* **l4** 1721.

Donovan TJ and Buchanan K (2012). Medications for increasing milk supply in mothers expressing breast milk for their preterm hospitalized infants. *Cochrane Database Systemic Review* **3** CD005544.

E. W. X. Wan, K. Davey, M. Page-Sharp, P. E. Hartmann, K. Simmer and K. F. Ilett (2008). Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. *British Journal of Clinical Pharmacology* **66**(2) 283–335.

Gabay PG (2002). Galactogogues: medications that induce lactation. *Journal of Human Lactation* **18** 274–279

Ingram J, Taylor H, Churchill Pike A and Greenwood R (2012). Metoclopramide or domperidone for increasing maternal breast milk output: a randomized controlled trial. *Archives on Diseases in Child Fetal Neonatal Edition* **97** F241–F245.

Jantarasaengaram S, Sreewapa P (2012). Effects of domperidone on augmentation of lactation following cesarean delivery at full term. *International Journal of Gynaecology Obstetrics* **116**(3) 240-243.

Knoppert DC, Page A, Warren J, Seabrook JA, Carr M, Angelini M and Killick D DaSilva OP (2013). The effect of two different domperidone doses on maternal milk production. *Journal of Human Lactatio*n 29(1) 38-44. doi: 10.1177/0890334412438961

Lewis PJ, Devenish C, Kahn C (1980). Controlled Trial of Metoclopramide in the Initiation of Breast Feeding. *British Journal Clinical Pharmacology* **9** 217-9.

Mathur NB and Dhingra D (2009). Perceived Breast Milk Insufficiency Mothers of Neonates Hospitalized in Neonatal Intensive Care Unit. *Indian Journal Pediatrics* **76**(10) 10036.

Montgomery A and Wight N(2004) .Use of Galactagogues in Initiating or Augmenting Maternal Milk Supply. The Academy of Breastfeeding Medicine Protocol Committee. **80**(5) 147-154

Osadchy A, Moretti ME and Koren G (2012). Effect of domperidone on insufficient lactation in puerperal women : a systemic review and metaanalysis of randomized controlled trials. *Obstetrics and Gynaecology International* 642893.

Paul C, Zenut M, Dorut A, Coudore MA, Vein J and Cardot JM *et al.*, (2015). Use of domperidone as a galactagogue drug: a systematic review of the benefit- risk ratio**.** *Journal of Human Lactation* **31**(1) 57-63

Petraglia F, De Leo V, Sardelli S, Pieroni ML, D'Antona N and Genazzani AR (1985). Domperidone in defective and insufficient lactation. *European Journal of Obstetrics Gynecology Reproductive Biology* **19** 281-7.

Segãoera-Millãn S, Dewey KG and Perez-Escamilla R J (1994). Factors Associated with Perceived Insufficient Milk in a Low-Income urban Population in Mexico. *Nutrition* **124** 202-212.