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# The Effect of Metoclopramide on Prolactin Levels in Breastfeeding Mothers: A Systematic Review and Meta-Analysis

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***Abstract***

***Background***: Exclusive breastfeeding is beneficial to not only infants, but also mothers. Since prolactin stimulates milk production, increasing its levels through dopamine antagonists, such as metoclopramide, may enhance milk production. However, the efficacy of this method should be further studied. Therefore, this systematic review sought to determine the effects of metoclopramide on prolactin levels in breastfeeding mothers.

***Materials and Methods***: In this systematic review study, International and National data bases such as PubMed, Google Scholar, Cochrane Library, Scopus, Web of Sciences, SID, Magiran, and Iranmedex were searched for the keywords of lactation, breastfeeding, prolactin, metoclopramide and breast milk. Articles published during 1979 to 2016 in either English or Persian was selected. The review was limited to human clinical trials examining the effects of metoclopramide on mothers' serum prolactin levels. Two authors independently evaluated the eligibility the studies and cases of disagreement were resolved through consensus.

***Results*:** Five studies on the effects of metoclopramide on mothers' serum prolactin levels were included in this systematic review. Based on their results, compared to placebo, two weeks of metoclopramide administration did not have significant effects on mothers' serum prolactin levels (mean difference: 73.06; 95% confidence interval [CI]:-19.99 to 166.11) However, placebo-controlled studies showed significant changes in prolactin levels after using metoclopramide for three weeks (mean difference: 111.06; 95% CI: 1.93 to 220.20).

***Conclusion*:** The result of meta-analysis showed that the use of 10 mg of metoclopramide three times a day for three weeks increased mothers' serum prolactin levels after childbirth.

***Key Words***: Breastfeeding, Prolactin, Meta-analysis**,** Metoclopramide.

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## 1- INTRODUCTION

Exclusive breastfeeding for six months not only protects infants from gastrointestinal infections, but also provides several benefits for mothers even in developed countries (1-3). Based on global rates, most preterm births occur in the United States where 14.5 million preterm infants were born in 2010. Overall, preterm births comprise 11.1% of all births in the world and insufficient milk production in the mothers of these infants is a major problem (4, 5). A variety of physical, emotional, genetic, and environmental factors, along with hormonal balance, are involved in milk production. Two hormones, i.e. prolactin and oxytocin, are crucial in the initiation and continuation of lactation (6). Maternal diseases and various physical and emotional factors, including anxiety, fatigue, emotional stress, and separation of mothers from their infant, can reduce milk production (7). While prolactin secretion from the anterior pituitary stimulates milk production, the secretion of oxytocin from the posterior pituitary causes myoepithelial muscle contractions and lactation (8).

Serum prolactin levels can be increased through the use of chemical and natural dopamine antagonists, such as metoclopramide (9). Metoclopramide is a medication used to treat gastroesophageal reflux disease, gastroparesis, dyspepsia, and vomiting. It is also administered to stimulate lactation after childbirth (8, 10). However, metoclopramide is known to induce some central nervous system adverse effects, such as restlessness, drowsiness, insomnia, anxiety, and agitation, mostly in old people. Extrapyramidal symptoms caused by central dopamine receptor blockade are also seen in 25% of patients on high-dose metoclopramide and 5% of those receiving long-term treatments. Moreover, since long-term use of the drug causes tardive dyskinesia, it should not be used for long periods (11, 12). A review study on the prevention of diarrhea and vomiting during and after Cesarean section and on 14 studies about the side effects of metoclopramide reported no extrapyramidal reactions including sedation, headache, anxiety, and respiratory depression (13). Considering the significance of breastfeeding support, especially in mothers with preterm infants and mothers without enough lactation, a meta-analysis in this regard seemed essential. This systematic review study was performed to examine the available data about the effects of metoclopramide on mothers' serum prolactin and the side effects of the medicine in mothers and infants.

## 2- MATERIALS AND METHODS

### 2-1. Search strategy

First, Cochrane database was searched, but no review study about the effects of metoclopramide on prolactin levels in breastfeeding mothers was found. The following electronic databases were searched: Medline (via PubMed), EMBASE (via OvidSP), Scopus, Web of science, Cochrane library, Magiran, SID and Iranmedex. Our search strategy included the following national library of medical subject heading (Mesh) terms: "Metoclopramide" combined with "lactation" OR "breastfeeding" OR "breast milk" OR "prolactin". The search was limited to human clinical trials on the effects of metoclopramide on mothers' serum prolactin levels published in either English or Persian during Jan 1979 to Dec 2016. The researchers also searched for references in reviewed clinical trial articles.

### 2-2. Study selection

Randomized clinical trials, quasi-experimental clinical trials or cross-over trials on the effects of metoclopramide on mothers' serum prolactin levels were

evaluated in this study. The PICO (population, intervention, control, outcomes) of this study were as follows: The participants were breastfeeding women with term or preterm infants admitted in a neonatal intensive care unit (NICU) who administered metoclopramide for insufficient milk or for improving breastfeeding. The intervention involved the administration of 10 mg of metoclopramide two or three times a day for two-three weeks or without intervention. A comparison group was also included in which placebo was used in the same way as of metoclopramide. The outcomes were mothers' serum prolactin levels and side effects. Studies without a comparison group and those evaluating the effects of metoclopramide on other parameters, such as milk volume and infants' weight, were excluded.

### 2-3. Assessment quality of articles

The researchers searched all the studies available in this regard and evaluated their eligibility. Two authors independently evaluated the eligibility and quality of the studies and cases of disagreement were resolved through consensus. The searches yielded 15 studies. Two studies on the effect of metoclopramide on mothers' prolactin levels were excluded due to their incompliance with the determined PICO. Two other studies were excluded as they evaluated the volume of milk. Two studies were excluded since they focused on infants' weight. Two other studies comparing metoclopramide with domperidone were also excluded. One study was in German and prolactin was not measured in another one. Eventually, five studies were included in the study.

**Table.1** provides the study type, number of participants in each group, term and preterm infants, dosage and duration of metoclopramide administration, and outcomes (effects of metoclopramide on mothers' serum prolactin).

Two researchers independently examined the risk of bias based on Cochrane handbook and the criteria of selection bias (considering how to generate allocation sequence and concealment of allocation), performance bias (blindness of participant, personal and outcome assessors), attrition bias (incomplete outcome data) and reporting bias (selective reporting) (**Table.1 and Figure.1**).

### 2-4. Statistical Analysis

The information on mothers' serum prolactin levels was collected from five studies and combined using RevMan software version 5.3. Due to high heterogeneity of the studies ($I^2$ = 94% and 90%), the Random Effect was reported instead of Fixed Effect (14). There were insufficient studies per comparison and outcome to permit the use of funnel plots to assess publication bias. The number of studies required to test publication bias by funnel plot is ten or larger (14).

## 3-RESULTS

The five randomized controlled trials (RCTs) which compared the effects of metoclopramide and placebo on mothers' serum prolactin levels were:

The study of Gezelle et al. (1983) was double-blind RCT that was performed on thirteen randomly selected healthy breastfeeding women. Seven women received 10 mg of metoclopramide three times a day for eight days. None of the women and personnel were aware of the grouping. The women's prolactin levels were measured during the third to 28th days. According to the results, the mean serum prolactin levels on the 14th day were 67.9 (standard deviation [SD]=88.7) in the metoclopramide group and 68.5 (SD=84.1) in the control group. The corresponding values were 57.6 (67.5) and 47.8 (48.6) on the 21st day. The two groups had no significant differences in this regard.

The study of Kauppila and et al. (1985) was double-blind RCT that was performed on 33 women aged 25-34 years who had given birth 4-20 weeks before the study. All the women wanted to improve their breast milk. Insufficient milk production (less than 500 ml of milk) was detected in 13 women. Since the study aimed to determine the effects of metoclopramide on prolactin levels, 20 women without lactation problems were also included. Women's milk volume was carefully measured over 24 hours and the women were then randomly assigned to either the intervention group (receiving 10 mg of metoclopramide three times a day) and or the placebo group (receiving a placebo pill three times a day). After three weeks of medication, the mean serum prolactin levels were 210.7 (SD=131.4) and 68.5 (SD=58.3) in the intervention and placebo groups, respectively. There was a significant difference between the two groups.

Kauppila et al. (1981) in a RCT administered difference doses (5, 10, and 15 mg/day) of metoclopramide among 15 mothers and a placebo pill in an equal number of mothers. After two weeks of intervention, the group receiving 10 mg of metoclopramide and the placebo group had a significant difference in terms of serum prolactin level. The mean serum prolactin levels in the group receiving metoclopramide and the placebo group were 175.8 (SD=112.4) and 34.2 (SD=23.1), respectively.

Guzman et al. (1979) in a RCT recruited 21 women with full-term infants, normal pregnancy, and a history of reduced lactation. They were divided into two groups. The intervention group received 10 mg of metoclopramide twice a day. The placebo group included 10 women who received a placebo with a regimen similar to that of metoclopramide. Women who complained of insufficient lactation in the second week after childbirth received metoclopramide. Thirty women with normal lactation were assigned to the comparison group (without intervention). There were significant differences in the mean serum prolactin levels between the group receiving metoclopramide 338.1 (SD=59.2) and the comparison group 160 (SD=27.3) in the second and third weeks.

In Toppare et al.'s (1994) clinical trial, mothers with confirmed insufficiency in lactation received 10 mg of metoclopramide three times a day for two weeks. Mothers with sufficient lactation were assigned to a comparison group. There was no significant difference between the two groups in terms of serum prolactin levels. The mean serum prolactin levels in the case group after receiving metoclopramide 93.3 (SD=65.6) did not significantly differ from that in the comparison group 96.2 (SD=59.5) (**Table.2**).

The results of meta-analysis showed that two weeks of metoclopramide administration did not affect mothers' serum prolactin levels (mean difference: 73.06; 95% CI:-19.99 to 166.11) (**Figure.2**). However, three weeks of medication had significant effects on mothers' serum prolactin levels (mean difference: 11.06; 95% CI: 1.93 to 220.20) (**Figure.3**). Infants' weight was examined in two studies and daily lactation was evaluated in two other studies. These studies were not included in this meta-analysis (*Please see the tables and figures at the end of paper*).

## 4- DISCUSSION

According to this study, metoclopramide increased mothers' serum prolactin against the group receiving placebo or no intervention. After three weeks of medication, three of the five studies indicated significantly higher serum prolactin levels in the intervention group than in the control group. A review study performed by Gabay reported that

metoclopramide had several applications. For instance, 10 mg of metoclopramide three times a day was used for increasing lactation in mothers of preterm infants and for the treatment of maternal and infant diseases. Similar to our findings, this was proven in most of the included studies (8). No specific side effect was mentioned in studies performed by Guzman et al. (1979) and Gezelle et al. (1983) (15, 16).

Kauppila et al. (1985) reported fatigue, headache, and diarrhea in the group receiving metoclopramide and fatigue and dizziness in the group receiving placebo (17). In another study by Kauppila et al. (1981), seven women reported fatigue, headache, hair loss, and intestinal problems. One woman who had received 45 mg of metoclopramide complained of intestinal problems in her infant. Three women in the placebo group reported side effects similar to those of metoclopramide (18). Toppare et al. (1994) reported insomnia, fatigue, and restlessness (19).

Guzman et al. (1979) examined the effects of metoclopramide on mothers' serum prolactin levels and found a significant difference between the metoclopramide and placebo groups in the second and third weeks. However, the paper did not include adequate explanation about allocation concealment, Random sequence generation and blinding (15). In Gezelle et al.'s (1983) study, the mean serum prolactin levels in the metoclopramide and placebo groups were not significantly different on the $14^{th}$ and $21^{st}$ days. However, the two groups had significant differences in daily lactation during the fifth to eighth days. This study did not use a blinding personal strategy (16). In a study by Kauppila et al. (1985), there was a significant difference between the metoclopramide and placebo groups in the third week. There was also a significant increase in daily milk flow in the metoclopramide group. However, the two groups were not significantly different in terms of serum thyroid stimulating hormone (TSH) and free thyroxin (FT4) levels. This study used no blinding personal strategy and did not provide any information about the allocation concealment of the participants (17). In a cross-over study performed by Kauppila et al. (1981), the intervention group received 10 mg metoclopramide pills three times a day for two weeks. The metoclopramide and placebo groups had a significant difference. Using 30 and 45 mg/day of metoclopramide increased daily lactation and reduced infants' need for supplementing with formula. No information about blinding and allocation concealment was provided (18).

In Toppare et al.' (1994) study, the intervention group received 10 mg of metoclopramide three times a day. The control group consisted of 23 mothers with enough lactation. However, no significant differences were found between the two groups. This study was not randomized and did not present complete information on blinding of participant, allocation concealment, blinding outcome assessment (19). The strengths of the studies examined in this review were their RCT design (in most cases), the use of 10 mg of metoclopramide three times a day for two or three weeks (again in most cases), serum prolactin measurement in all mothers, and having a control group. In two studies, due to ethical considerations, mothers with insufficient lactation did not receive placebo instead of metoclopramide. Therefore, the control group consisted of mothers with sufficient lactation. Other limitations of this study were that the selected studies were performed a long time ago and their sample was small. Therefore, further studies with larger sample size are required.

### 4-1. Limitation

One of the limitations of this systematic review was heterogeneity of included

studies that reduce the generalizability of findings. Also, the poor quality of included studies was another limitation of this study that can be effective on the obtained results.

## 5- CONCLUSIONS

The result of this study showed that the use of 10 mg of metoclopramide three times a day for three weeks increased mothers' serum prolactin levels. Therefore, administration of metoclopramide to mothers with insufficient lactation may be effective. However, regarding the small sample size of the included studies, further studies on larger samples are recommended.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENTS

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**Table-1:** Risk of bias in included studies

| Bias | Authors Judgment | Support for judgment |
|---|---|---|
| **Kauppila et al. (1985)** | | |
| Random sequence generation (selection bias) | Low risk | Women were randomized to receive metoclopramide (10 mg 3 times daily orally) or a placebo (1 tablet 3 times daily) for a period of 3 wk. |
| Allocation concealment (selection bias) | Unclear risk | No specific information regarding allocation concealment was given. |
| Blinding of personnel (performance bias) | High risk | There was no blinding of personnel. |
| Blinding of participant (performance bias) | Low risk | There was blinding of participant |
| Blinding of outcome assessment (detection bias) | Low risk | There was blinding of outcome assessor. |
| Incomplete outcome data (attrition bias) | High risk | Four women taking metoclopramide and 4 taking the placebo discontinued the trial for unknown reasons. |
| **Gezelle et al. (1983)** | | |
| Random sequence generation (selection bias) | High risk | This study is non randomized trial. |
| Allocation concealment (selection bias) | High risk | This study is non randomized trial. |
| Blinding of personnel (performance bias) | Low risk | Neither the medical/nursing staff were aware of the nature of the tablets. |
| Blinding of participant (performance bias) | Low risk | Neither the mothers were aware of the nature of the tablets. |
| Blinding of outcome assessment (detection bias) | Low risk | This study was a double blind controlled trial. |
| Incomplete outcome data (attrition bias) | Low risk | All participant completed the study. |
| **Kauppila et al. (1981)** | | |
| Random sequence generation (selection bias) | Low risk | Three different doses of metoclopramide 5,10, 15 mg were given 3 times daily to fifteen mothers for 2 weeks. The order of the active drug and the placebo was randomized within each dose group an there was a pause of 1 week without any medication between treatments. |
| Allocation concealment (selection bias) | Unclear | No specific information regarding allocation concealment was given. |
| Blinding of personnel (performance bias) | Unclear | No specific information regarding blinding of personnel was given. |
| Blinding of participant (performance bias) | Unclear | No specific information regarding blinding of participant |
| Blinding of outcome assessment (detection bias) | Unclear | No specific information regarding blinding of outcome assessment |
| Incomplete outcome data (attrition bias) | High risk | Five women in metoclopramide group discontinued the trial, three because they thought that the drug was having no effect, two women gave no reason for stopping. |

| | | |
|---|---|---|
| **Guzman et al. (1979)** | | |
| Random sequence generation (selection bias) | High risk | This study is a non-randomized trial. |
| Allocation concealment (selection bias) | High risk | This study is a non-randomized trial. |
| Blinding of personnel (performance bias) | Unclear | No specific information regarding blinding of personnel was given. |
| Blinding of participant (performance bias) | High risk | The control group didn't receive intervention. |
| Blinding of outcome assessment (detection bias) | Unclear | No specific information regarding blinding of outcome assessment was given. |
| Incomplete outcome data (attrition bias) | Low risk | All participant completed the study. |
| **Toppare et al. (1994)** | | |
| Random sequence generation (selection bias) | High risk | This study is a non-randomized trial. |
| Allocation concealment (selection bias) | High risk | This study is a non-randomized trial. |
| Blinding of personnel (performance bias) | Low risk | Participants were also examined by blinded physicians of internal medicine after using the drug. |
| Blinding of participant (performance bias) | High risk | The control group didn't receive intervention. |
| Blinding of outcome assessment (detection bias) | Unclear | No specific information regarding blinding of outcome assessment was given. |
| Incomplete outcome data (attrition bias) | Low risk | All participant completed the study |

**Table-2:** Summary of studies carried out on effect of metoclopramide on prolactin in puerperal women.

| Reference | Number of participant | Design | MTC* does | MTC duration of treatment | Neonate | Main outcome | Side effect (Maternal and infant) |
|---|---|---|---|---|---|---|---|
| Guzman et al. (1979) | 11MTC/10P† | RCT | 10 mg twice daily | 4 weeks | Full term | Increase PRL‡ level | - |
| Gazelle et al. (1983) | 7MTC/6P | Placebo controlled trial | 10mg three times daily | 8 days | Full term | Increase PRL‡ level | - |
| Kuppila et al. (1985) | 11MTC/14P | RCT | 10 mg three times daily | 3 week | - | Increase PRL‡ level | MTC group: Tiredness, headache and nausea<br>Placebo: Tiredness and dizziness |
| Kauppila et al. (1981) | 15 MTC/14P | Cross-over | 5,10,15 mg 3 times day | 2 weeks | - | 30 mg and 45 mg MTC increased significantly PRL‡ level<br>15 mg MTC didn't increased significantly PRL‡ level | MTC group: tiredness, headache, hair loss anxiety intestinal disorders.one child of a mother receiving 45mg of MTC daily also had some intestinal discomfort. |
| Toppare et al. (1994) | 32 control /32 MTC | RCT | 10 mg three times daily | 15 days | 16 term infants-<br>16 premature infants | Significant increase in PRL‡ level | MTC group: Insomnia<br>Restlessness<br>vertigo |

MTC (metoclopramide); †P (placebo); ‡PRL (prolactin).

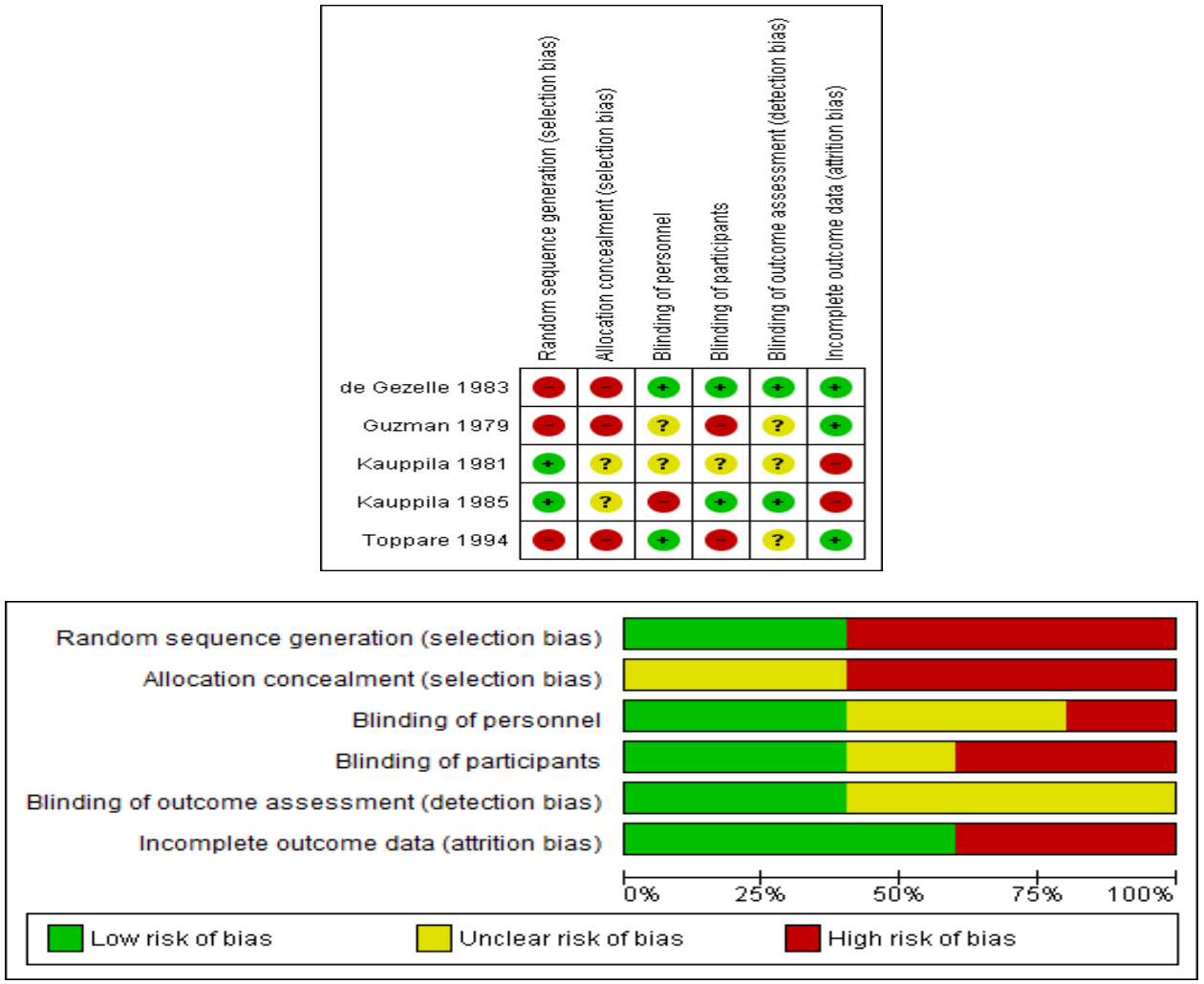


**Fig.1:** Diagram of bias in the included studies.

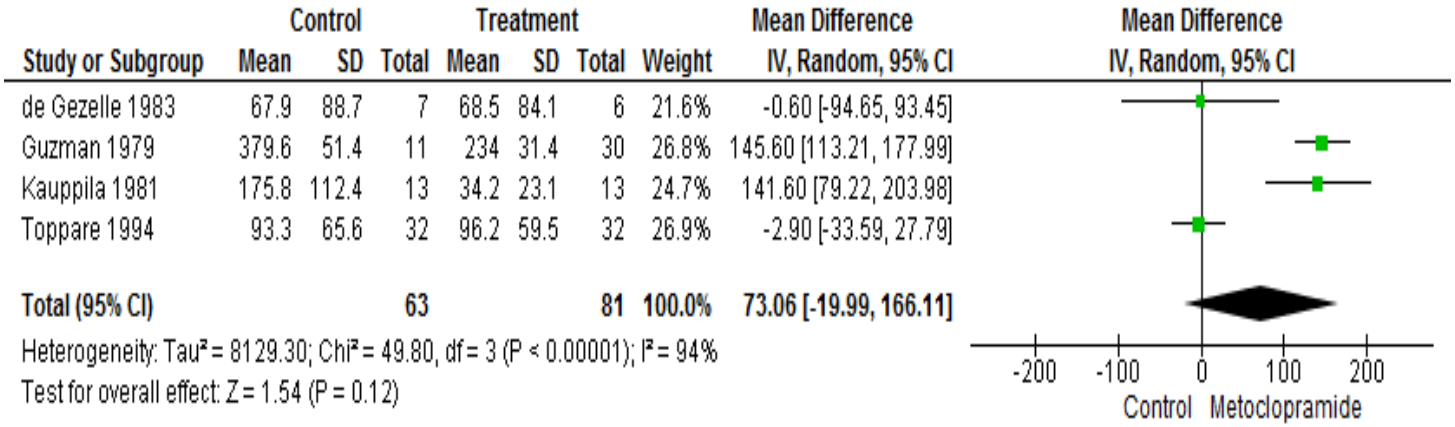


**Fig.2**: The effect of Metoclopramide on maternal prolactin in two weeks.

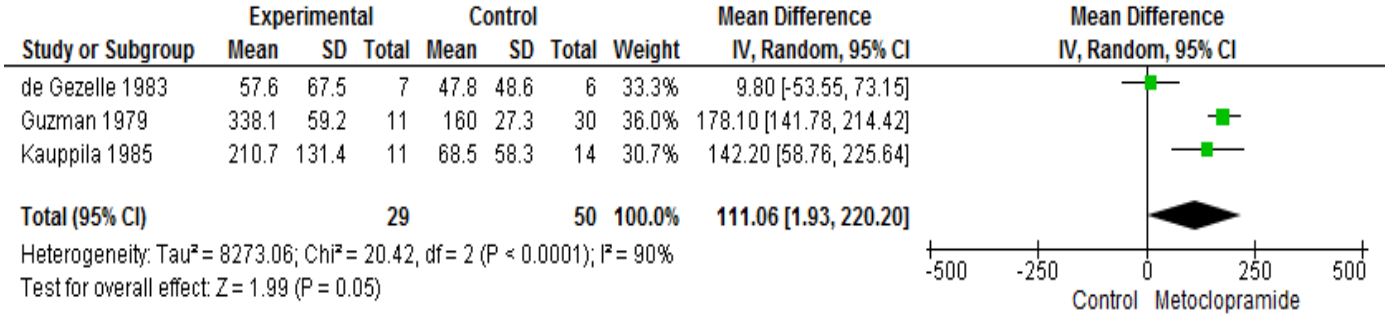


**Fig.3:** The effect of Metoclopramide on maternal prolactin in three weeks.