Efficacy and safety of misoprostol for intrauterine device insertion in women with no previous vaginal delivery: a systematic review and meta-analysis of randomized controlled trials

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Keywords: Intrauterine device; misoprostol; vaginal delivery; contraception; efficacy

Abstract

Introduction: *The efficacy of misoprostol use for cervical priming before intrauterine device insertion (IUD) is controversial. This review aims to evaluate the evidence from published randomized controlled trials about the efficacy and safety of misoprostol before IUD insertion for pain relief in women with no previous vaginal delivery.*

Materials and methods: *We searched the following electronic databases: Web of Science, Cochrane CENTRAL, SCOPUS, and PubMed for relevant studies using the following Mesh terms: (misoprostol) AND (intrauterine device OR IUD). The primary outcome was the mean pain score during insertion. Secondary outcomes included the ease of insertion score, the rate of successful IUD insertion, the rate of IUD insertion failure, and the adverse effects.*

Results: *Ten randomized controlled trials (RCTs) (misoprostol: n=698 and placebo: n=689) were pooled in the analysis. The overall Standardized Mean Difference (SMD) of pain score did not favor either of the two groups (SMD= -0.09, 95%CI [-0.50, 0.33], p=0.007). Pooled results were highly heterogeneous (I2=93%, P<0.001). The total MD of the ease of insertion score favored the misoprostol group (MD= -1.36, 95% CI [-2.20, -0.52], p =0.002). The overall risk ratio (RR) of the number of failed insertions showed that misoprostol is associated with less IUD insertion failures compared to placebo (RR=0.55, 95% CI [0.38, 0.81], p=0.002). Finally, the overall risk showed that misoprostol is associated with more shivering, diarrhea and pelvic pain.*

Conclusions: *Misoprostol facilitates IUD insertion in women with no previous vaginal delivery, and is associated with 50% less chance for IUD insertion failure despite inducing mild adverse effects*

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Introduction

The intrauterine device (IUD) is one of the best contraceptive methods currently used worldwide. The World Health Organization (WHO) estimates that the IUD is used by over 160 million women (15.5%) of childbearing age worldwide.[1] It is a cheap, reversible, long-acting and highly effective method of contraception.[2]

Nulliparous women and those who have never delivered vaginally before are suspected of having more difficulty and pain during IUD insertion.[3] Such difficulty could be attributed to the tight cervical os in those women.[4]Several researchers have studied the impact of various medications to facilitate and relieve pain during IUD insertion such as lidocaine, misoprostol, and nitroprusside.[5]

Misoprostol is a synthetic prostaglandin E1 (PGE1) analog.[6] It can be administrated vaginally, rectally, orally, buccally and sublingually.[7] Its low price, easy administration, and easy storage make it more popular than other forms of PGs. It is widely used in obstetrics and gynecology mainly to induce cervical ripening and dilatation.[6] Therefore, it is mainly used for early termination of pregnancy and induction of labor.[8] It is also used to prevent postpartum hemorrhage.[9,10]

Due to the effect of misoprostol on the cervix, there is a growing hypothesis that misoprostol can reduce the pain perception in women during IUD insertion and increase the ease of insertion. Several studies have evaluated this hypothesis with contradictory results regarding the pain perception and ease of IUD insertion.[11-13]

Therefore, in this review; we aim to systematically evaluate the available evidence from randomized controlled trials (RCTs) regarding the efficacy and safety of misoprostol before IUD insertion for pain relief in women with no previous vaginal delivery.

Materials and Methods

We carried out this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[14] and was registered in PROSPERO (CRD42018109811). Because this study was a systematic review and meta-analysis, formal ethical approval was not required.

Search strategy

Three authors conducted an electronic search using several databases including Web of Science, Cochrane CENTRAL, SCOPUS, and PubMed for relevant studies from inception to October 2019. Combinations of the following MeSH terms were used: (misoprostol) AND (intrauterine device OR IUD OR intrauterine system OR IUS OR intrauterine contraception). We

examined the reference lists of all retrieved primary and review articles to identify cited articles not captured by electronic searches.

Eligibility criteria

We considered all published studies that satisfied the following criteria:

1. Population: women requesting IUD insertion who had never delivered vaginally, either nulliparous or delivered only by elective cesarean section.

2. Intervention: misoprostol administration before insertion

3. Comparator: placebo

4. Outcomes: the primary outcome was the pain score during insertion. Secondary outcomes included the ease of insertion score, number of failed insertions, number of successful insertions, and rate of adverse effects related to misoprostol use (abdominal discomfort, vaginal bleeding, diarrhea, and shivering).

5. Study design: randomized clinical trials (RCTs).

We excluded studies for the following reasons:

1. Non-randomized trials

2. In vitro and animal studies

3. Non-English studies

4. Studies whose data were unreliable for extraction and analysis

5. Studies on misoprostol use after previous insertion failure.

Duplicates were removed,and retrieved references were screened in two steps: the first step was to screen titles and abstracts for matching our inclusion criteria and the second step was to screen the full-text articles of eligible abstracts for eligibility to meta-analysis.

Study selection

The title and abstract of all identified articles were screened independently by three reviewers to assess relevance to this meta-analysis. In case of disagreement, the full text of such studies was retrieved and reviewed independently by a senior author (AMA) for a final decision.

All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two reviewers scored the studies and collected the information independently. In case of discrepancies in scoring, a consensus was reached after consultation of the study mentor (AS).

Data extraction and analysis

From each study, we extracted the study characteristics such as participants' baseline characteristics, study outcomes, and adverse effects of the drug or the placebo. Additionally, details for risk of bias were extracted, such asthe method of randomization,

allocation concealment, blinding, intention-to-treat analysis, and follow-up rates. One study (Dijkhuizen et al.[15]) reported both nulliparous and multiparous (delivering vaginally) women, only data of nulliparous women were extracted.

All data were entered into RevMan software (Review Manager, version 5.1, The Cochrane Collaboration, 2011; The Nordic Cochrane Centre, Copenhagen, Denmark) for meta-analysis. The mean difference (MD)and 95% confidence interval (CI) were calculated for continuous data, while the relative risk (RR) and 95% CI were calculated for dichotomous data.

Statistical heterogeneity between studies was evaluated graphically using forest plots and statistically using I-squared (I^2) test. Values of ≥50% were indicative of high heterogeneity. When heterogeneity was significant, a random-effects model was used for meta-analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity. Pooled analyses of data from all studies were performed for various outcomes.

Risk of bias assessment

We assessed the risk of bias according to the Cochrane risk of bias tool, which is described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[16] We used the quality assessment table provided (part 2, Chapter 8.5). Assessment included the following domains: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment is categorized as low, unclear or high risk of bias.

Publication bias

Although the number of included studies in the current analysis was ten studies, we could not assess the publication bias using the Egger test as each outcome includes less than ten studies.

Results

Characteristics of included studies

Our search retrieved 231 unique citations from searching electronic databases. We excluded 191 studies that did not meet our inclusion criteria and removed the duplicates using Endnote software. After reading the full text of forty studies, we excluded thirty studies which were ineligible. We searched the references of the included RCTs manually, but we did not find any more relevant records. Ten RCTs recruited 1387 women (misoprostol: n=698 and placebo: n=689) who underwent IUD insertion were finally included in this meta-analysis (Figure 1). The characteristics of the included studies are summarized in Supplemental Table.

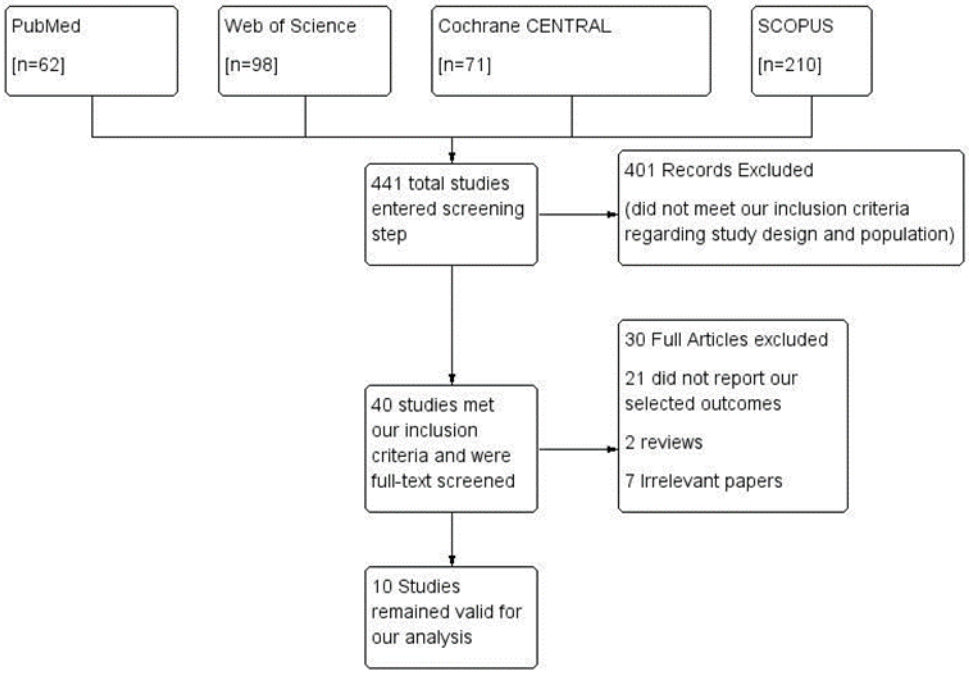

Figure 1: PRISMA Flow Chart of the study selection process, using RevMan software for windows.

Potential source of bias

According to the Cochrane risk of bias assessment tool, the risk of bias assessment was low. Ten studies specified their methods of randomization of patients, nine of them reported allocation concealment, and nine of them also reported proper blinding of participants and personnel. Two studies, Saav et al.[7] and Ibrahim et al.,[17] reported no blinding of participants; therefore, they were categorized as high risk. Eight studies reported proper blinding of outcome assessment, and six studies had a low risk of reporting bias. No other bias was found and no missing data as well. The quality of the included studies ranged from moderate to high quality. A summary of quality assessment domains is shown in Figure 2.

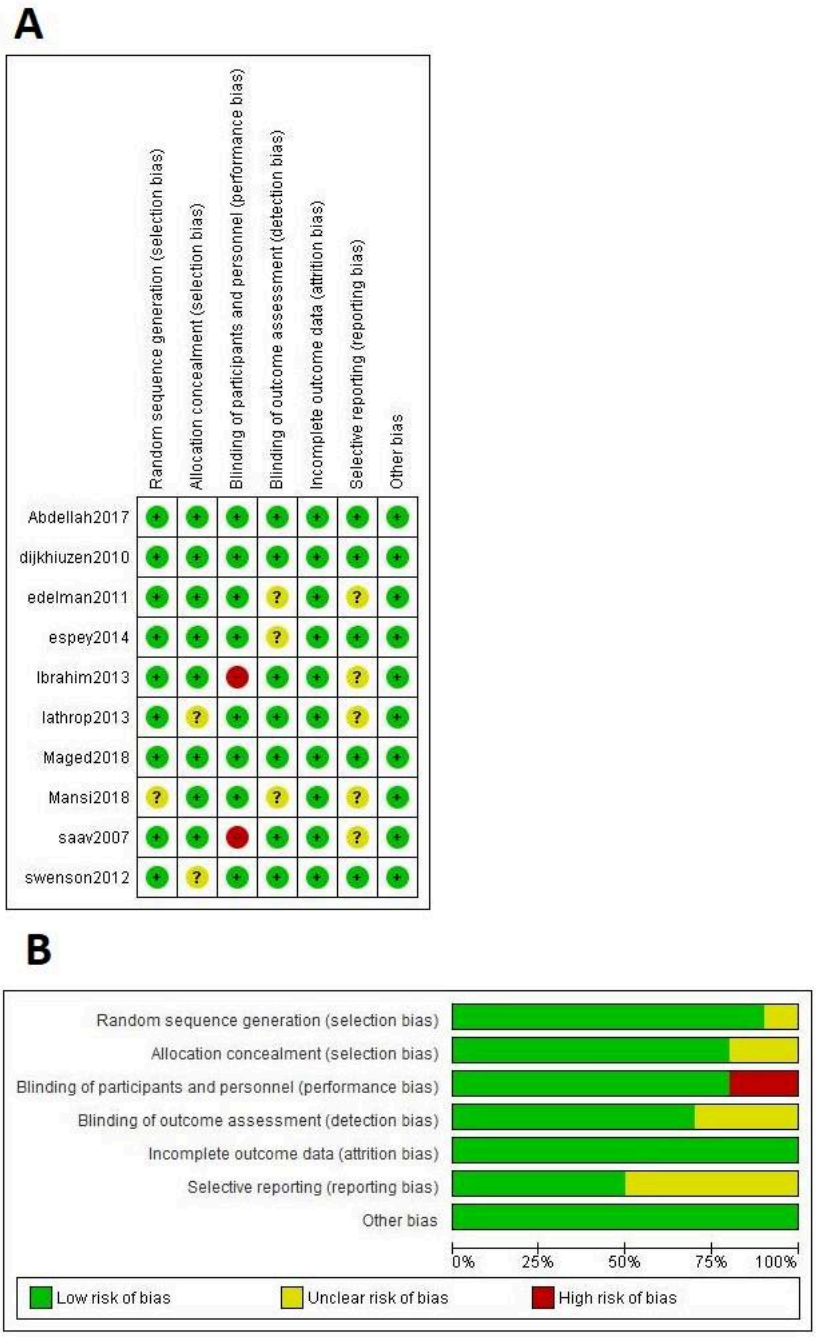

Figure 2: Diagram of quality assessment of included studies (A) and Risk of bias summary graph (B) according to Cochrane's risk of bias assessment tool.

Outcomes

Pain Score during insertion

The overall Standardized Mean Difference of pain score did not favor either of the two groups (SMD= -0.09, 95%CI [-0.50, 0.33], p=0.007). Pooled results were highly heterogeneous (I^2=93%, P<0.001) due to the diversity of drug doses (200, 400, and 600 mcg) and different routes of administration (oral, vaginal, and sublingual). Therefore, subgroup analysis was performed to investigate the effect of different doses and routes of administration on pain outcome.

First: According to the route of administration, we found that misoprostol was not effective whether given orally, vaginally, or sublingually.

1. *Oral route*: the SMD did not favor either of the two groups (SMD= 0.24, 95%CI [-0.16, 0.63], p=0.24). Pooled results were heterogeneous (I^2=61%, P=0.05). (Figure 3a). Heterogeneity was best resolved by excluding Espey et al.[12] Results favored the placebo over misoprostol after exclusion (SMD= 0.43, 95% CI [0.14, 0.72], p=0.003, I^2=0%, P=0.9) (Figure 3b)

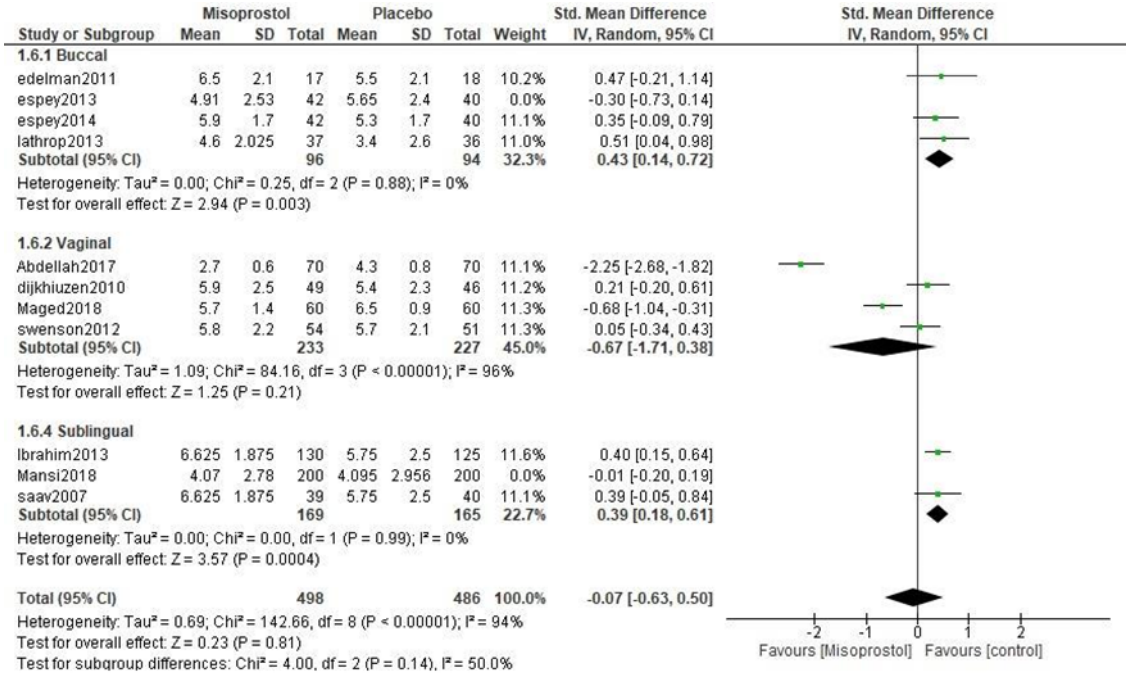

Figure 3a: Forest plot for subgroup analysis of the Pain Score outcome by route, before leave-one-out analysis

2. *Vaginal route*: the SMD did not favor either of the two groups (SMD= -0.67, 95%CI [-1.71, 0.38], p=0.21). Pooled results were highly heterogeneous (I^2=96%, P<0.001; Figure 3a). Heterogeneity could not be solved by the leave-one-out method.

3. *Sublingual route*: the SMD did not favor either of the two groups (SMD= 0.23, 95%CI [-0.07, 0.54], p=0.14). Pooled results were heterogeneous (I^2=73%, P=0.03; Figure 3a). Heterogeneity was best resolved by excluding Mansi, 2018 study.[18] Results favored the placebo over misoprostol after exclusion (SMD= 0.39, 95% CI [0.18, 0.61], p=0.0004, I2=0%, P=0.9; Figure 3b)

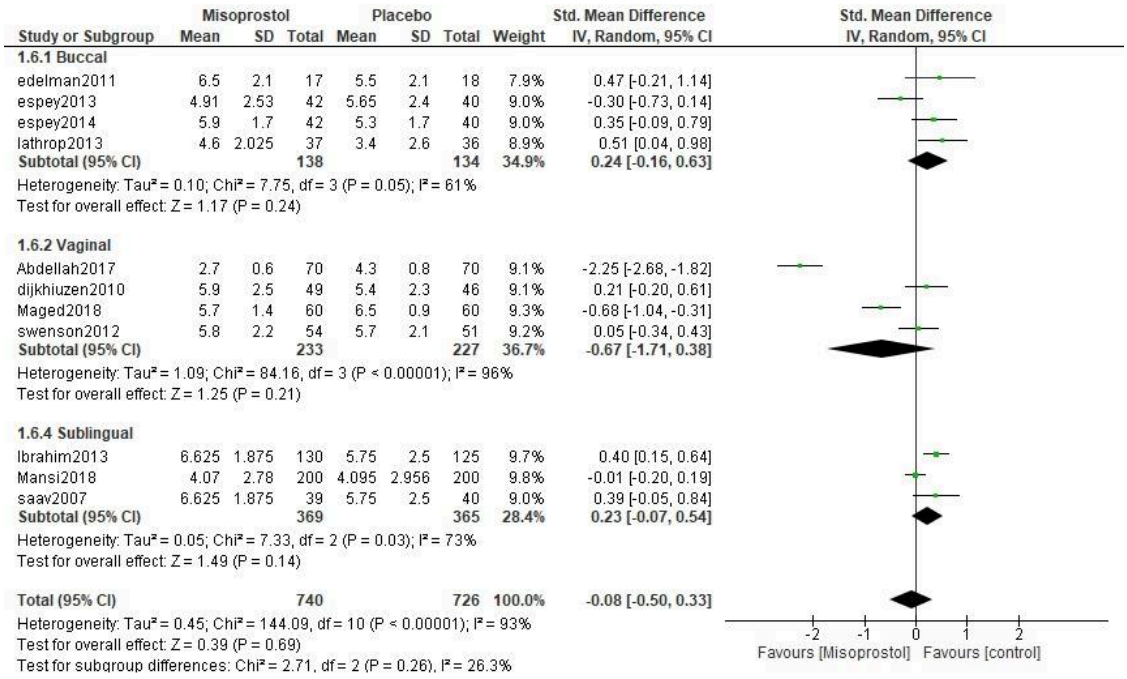

Figure 3b: Forest plot for subgroup analysis of the Pain Score outcome by route, after leave-one-out analysis

Second: depending on the misoprostol dose, we found that misoprostol reduces IUD insertion pain when given at a high dose (600mcg) and is not effective when given at low doses (200 & 400mcg). Nine studies used a dose of 400mcg misoprostol, the analysis of the nine studies did not favor either of the two groups (SMD= 0.02, 95% CI [-0.58, 0.53], p=0.9). Pooled results were heterogeneous (I^2=94%, p<0.0001; Figure 4a).

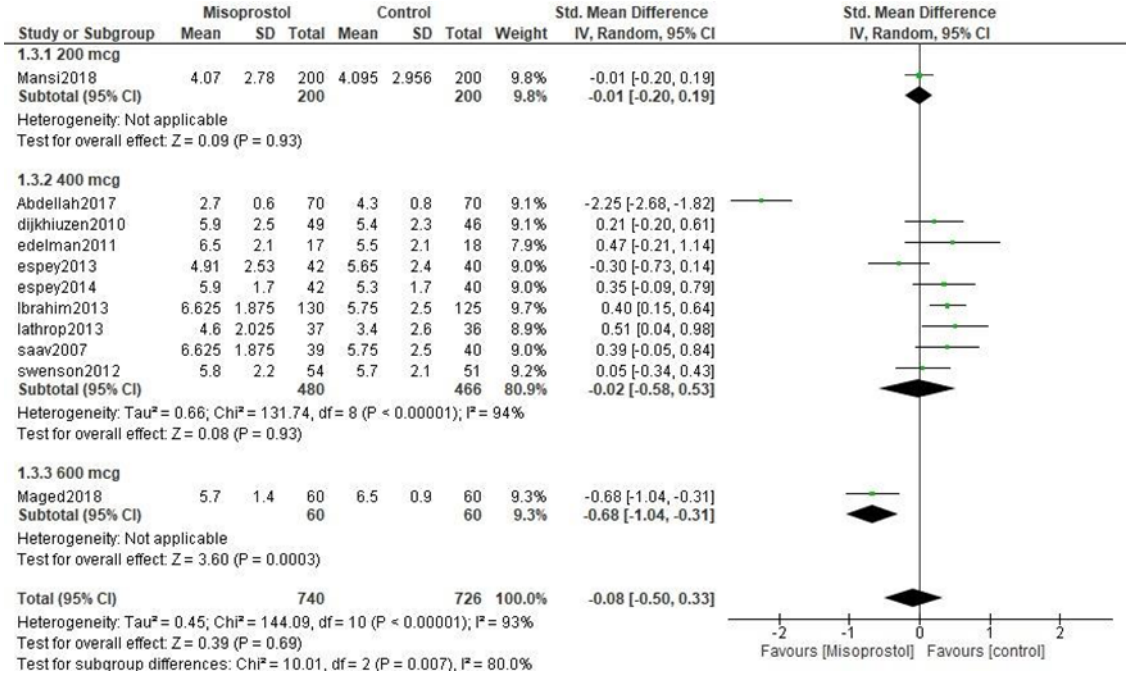

Figure 4a: Forest plot for subgroup analysis of the Pain Score outcome by dose, before leave-one-out analysis.

Heterogeneity was best resolved by excluding the Abdellah et al. study.[13] Results favored the placebo arm over misoprostol (SMD= 0.25, 95%CI [0.07, 0.43], p=0.006, I^2=34%, P=0.15; Figure 4b).

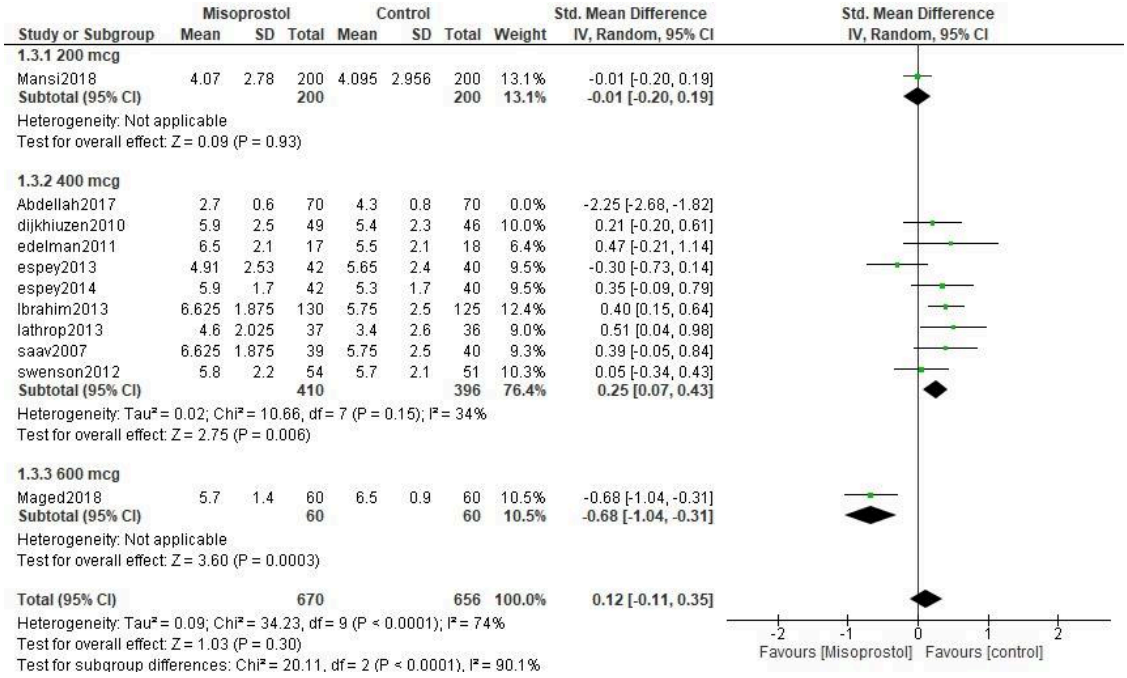

Figure 4b: Forest plot for subgroup analysis of the Pain Score outcome by dose, after leave-one-out analysis

Only one study, Mansi, 2018,[18] reported the use of 200 mcg dose and found no significant difference between groups (MD= -0.01, 95% CI [-0.20, 0.19], p=0.9). Similarly, only one study Maged et al.[19] reported the use of 600mcg dose and found a significant difference favoring the drug over the placebo group (MD= -0.68, 95% CI [-1.04, -0.31], p=0.003).

Ease of insertion score

The pooled mean difference (MD) of the ease of insertion score favored the misoprostol group over the placebo group (MD= -1.22, 95% CI [-1.72, -0.73], p<0.0001). Pooled results were homogeneous (P =0.15, I^2 = 48%; Figure 5).

Number of successful insertions

The pooled risk ratio did not favor either of the two groups (RR= 1.04, 95% CI [1.00, 1.08], p=0.06). However, the data were heterogeneous (p=0.06, I^2= 50%; Figure 6a). Heterogeneity was best resolved by excluding Lathrop et al.[20] Pooled results favored the misoprostol group (RR= 1.05, 95% CI [1.01, 1.08], p=0.01; Figure 6b)

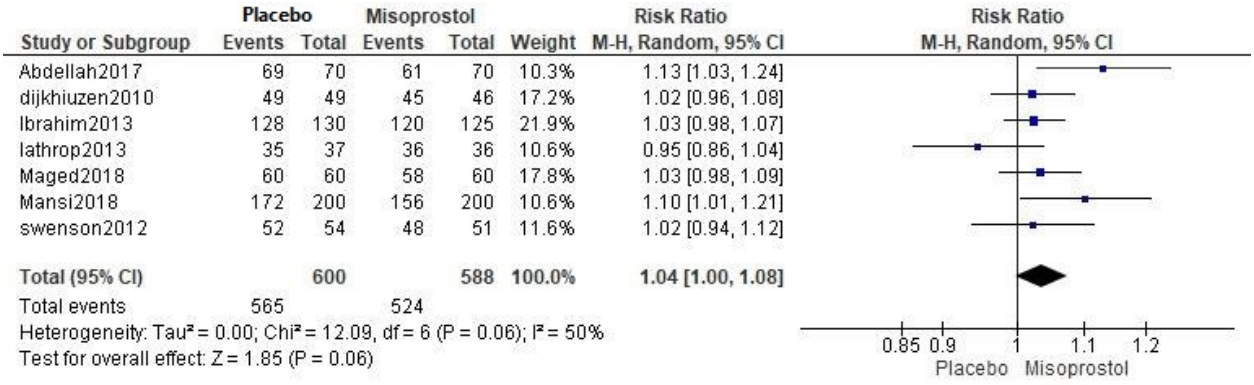

Figure 6a: Forest plot for successful IUD insertions outcome, before leave-one-out analysis.

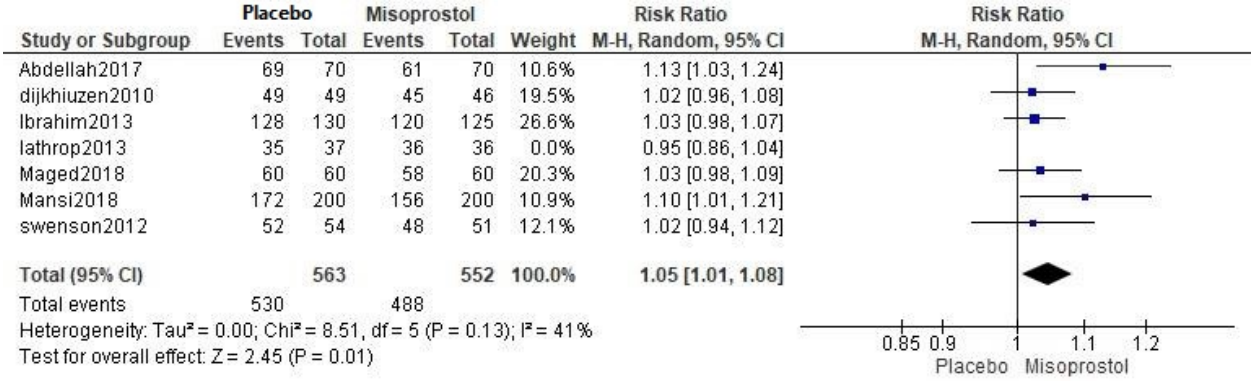

Figure 6b: Forest plot for successful IUD insertions outcome, after leave-one-out analysis.

Number of Failed Insertions

The overall risk ratio of failed insertions showed that misoprostol is associated with less IUD insertion failures compared to placebo (RR= 0.55, 95% CI [0.38, 0.81], p=0.002). Pooled results were homogenous (p=0.47, I^2 = 0%; Figure 7).

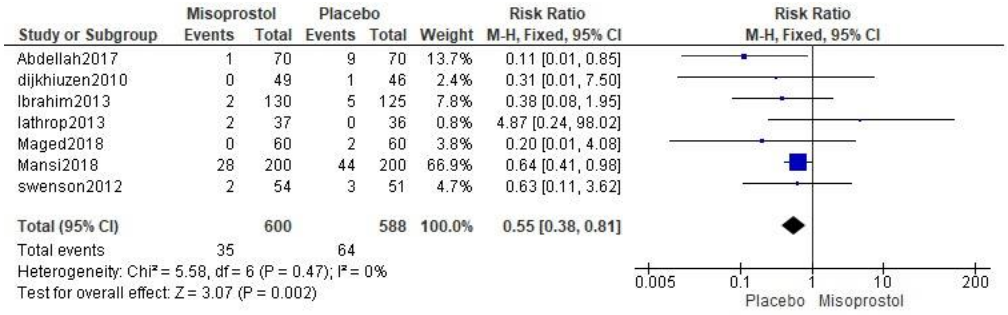

Figure 7: Forest plot for failed IUD insertions outcome.

Misoprostol adverse effects

1. Shivering: the overall risk showed that misoprostol is associated with more shivering (RR =5.22, 95% CI [2.16, 12.59], p= 0.0002). Pooled results were homogenous (p =0.77, I^2 =0%) (Figure 8a).

2. Diarrhea:the overall risk ratio showed that misoprostol is associated with more diarrhoea (RR =2.64 95% CI [1.24, 5.66], p= 0.01). Pooled results were homogenous (p =0.59, I^2 =0%) (Figure 8b).

3. Abdominal or pelvic pain: the overall risk ratio showed that patients in misoprostol group had more incidence of pelvic pain (RR= 8.00, 95% CI [4.07, 15.74]). Pooled results were homogenous (p= 0.13, I^2= 48%) (Figure 8c).

4. Vaginal bleeding during insertion: no significant difference was found between both groups regarding vaginal bleeding (RR =1.35, 95% CI [0.77, 2.38], p= 0.29). Pooled results were homogenous (p =0.13, I^2 =47%) (Figure 8d).

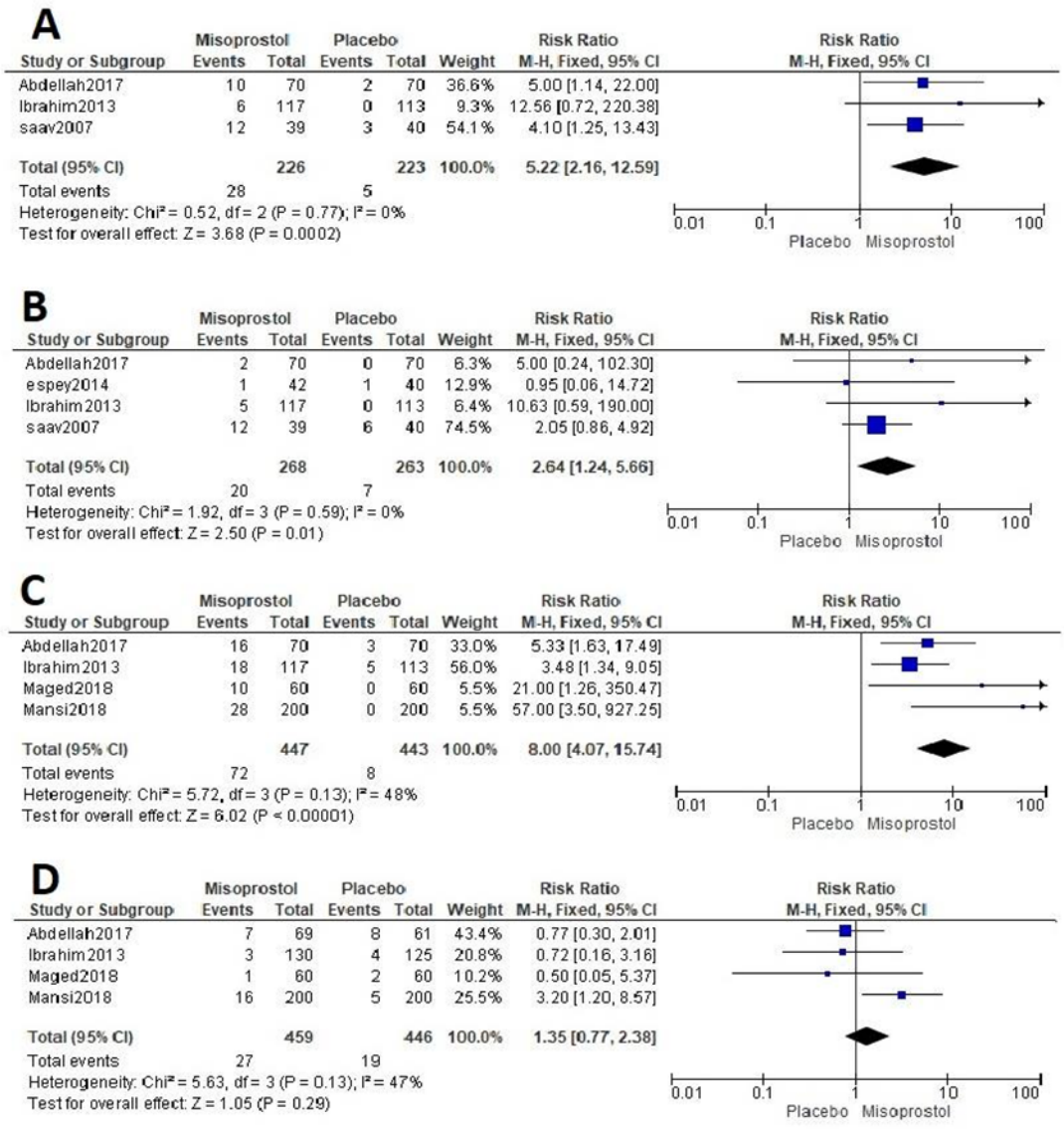

Figure 8: Forest plot for misoprostol adverse effects, A) shivering, B) Diarrhea, C) Abdominal pain, and D) Vaginal bleeding during insertion. As shown in the figures, misoprostol significantly causes slight adverse effects than placebo (except in vaginal bleeding)

Discussion

The present systematic review showed that the administration of misoprostol before IUD insertion significantly facilitates the process of insertion and is associated with less IUD insertion failures in women with no previous vaginal delivery. However, it does not decrease the associated pain with the

procedure.

The role of misoprostol in cervical priming in non-pregnant women before office gynecological procedures is not well established despite many previous publications in the literature. However, there are reports of its effectiveness in inducing cervical dilation and hence decreasing the incidence of procedural resistance and associated non-compliance.[21,22] Zhou et al. in their systematic review stated that misoprostol had a significant effect on cervical ripening before hysteroscopy.[23] Similarly, Hou et al. found that misoprostol is effective for cervical ripening and increasing the ease of IUD removal with less pain perception in postmenopausal women.[24] On the other hand, Zapata et al. and Matthews et al. in two systematic reviews evaluated the use of misoprostol before IUD insertion among patients of any parity found no evidence to support routine administration of misoprostol before IUD insertion.[25,26] There were no differences in success of insertion, difficulty of insertion and pain perception with prior administration of misoprostol.

In the present review, three studies measured the ease of insertion score by a VAS scale and reported their results. Two of them showed that misoprostol facilitates IUD insertion significantly, while only one reported no difference. The net analysis favored the misoprostol group.

Regarding the pain associated with the procedure, many studies used different doses and routes of administration to investigate the effect of the drug on pain perception. We performed two subgroup analyses separately in an attempt to accurately describe the effect of the drug on pain and the role of different doses and routes of administration.

The analysis showed that misoprostol is not effective whether given orally, vaginally, or sublingually. Low doses (200 & 400 mcg) did not demonstrate any effect; however, high dose (600 mcg) was associated with a significant decrease in pain score.

Due to this variety of doses and routes of administration, we encountered high heterogeneity among our included studies, which may have masked and influenced the effect of the drug on different outcomes.

After using the leave-one-out method provided by Cochrane's handbook, we found that the misoprostol group had significantly higher pain scores than placebo when administered orally and sublingually, and similar pain scores when administered vaginally.

It is reported that pain tolerability is less in nulliparous,[22] and women who delivered only by cesarean section (CS) compared to women who delivered vaginally.[13] This may affect the outcomes of certain studies such as Edelman et al.,[27] Espey et al.,[12] Lathrop et al.,[20] Saav et al.[7]and Swenson et al.[28]

Some researchers reported that delivery by CS only might be associated with failure of IUD insertion, which can be explained by the presence of scar at the internal OS interfering with cervical ripening.[29] This could explain the high failure rate reported by Mansy.[18]

Our findings are supported by the fact that misoprostol has long been used to reduce pain in various gynecological procedures. Although many interventions had been compared to it, the results favored misoprostol. Esin et al. reported that misoprostol is more effective than lidocaine in reducing pain associated with hysteroscopy.[30] Issat et al. reported the same results, and additionally, it was found that the effect of misoprostol is not affected by patients' age, hormonal status, parity, or type of hysteroscopy.[31]Fouda et al. found that misoprostol is more effective than uterine straightening by bladder distension and that the insertion of the hysteroscope was easier in the misoprostol group.[32]

According to a review by Grimes et al. non-steroidal anti-inflammatory drugs (NSAIDs) have shown a great effect in reducing pain during IUD insertion.[33] There was a debate among previous studies comparing misoprostol to NSAIDs. During endometrial biopsies, Telli et al. did not find a significant difference between misoprostol and NSAIDs regarding pain relief.[34] Hassa et al. found that in hysterosalpingography (HSG), NSAIDs did not differ significantly compared to misoprostol regarding pain relief 30-min after the procedure. However, NSAIDs have a favorable outcome in relieving pain during the procedure.[35]

The known reported adverse effects of misoprostol include diarrhea, abdominal pain, shivering, and vaginal bleeding during IUD insertion. The distribution of adverse effects showed increased side effects in the misoprostol group compared to the control group *(except vaginal bleeding, which did not differ).*The adverse effects are affected by the dose and route of administration.[36] The included studies in our meta-analysis reported different routes of administration including (buccal, sublingual and vaginal). Vaginal and buccal misoprostol isassociated witha slow rate of absorption and clearance with a lower peak plasma level.[37,38]

Unlike both of them is the sublingual route of administration which has a rapid rate of absorption and higher peak plasma level,[38] hence associated with a higher rate of GIT side effects.Thisexplains the elevated rates of gastrointestinal side effects in Saavet et al.,[7] Mansy[18] and Ibrahimet et al.[17] studies in which they used the sublingual route for administration of misoprostol. The rate of abdominal and pelvic pain showed a consistent increase in the misoprostol group compared to the control group across the studies regardless ofthe route of administration. No evidence of a significant difference between the two groups in the incidence of bleeding. However, shivering was significantly more prevalent in the misoprostol group.

Regarding the number of failed insertions in each group, we found that the number of failed insertions in the misoprostol group is half that of the control (0.1% of the population in the control group had failed insertions compared to 0.05% in the misoprostol). As for the number of successful insertions, the analysis did not favor either of the two groups; however, this may be due to high heterogeneity among the studies. The analysis, when

done on a fixed-effects model favors misoprostol significantly (p =0.002).

Additionally, the results of failed insertion showed less failure in the misoprostol group. Therefore, the effect of misoprostol on successful insertions is clinically significant. The presence of heterogeneity among studies may have masked it.

Further trials reporting the ease of insertion score and pain scores with different doses are recommended. Additionally, more RCTs need to be done comparing misoprostol to NSAIDs.

Strengths

Our meta-analysis includes ten RCTs, which is a good number for providing a 'clinically significant' evidence for our findings. We excluded any studies other than RCTs, and to our knowledge, this is the first systematic review and meta-analysis that evaluated the efficacy and safety of misoprostol administration in women with no previous vaginal delivery.

Limitations

There are some limitations to our study: firstly, the use of different routes of administration of misoprostol across the studies (buccal, sublingual and vaginal) which affect the rate of absorption, peak plasma level and rate of clearance hence the efficacy and side effects of the drug.[34]Moreover, the administration of different doses and by different routes of administration resulted in significant heterogeneity among the studies. This heterogeneity may have masked and/or influenced the effect of misoprostol on our outcomes. Considering the high heterogeneity, one wonders if pooling of these studies is appropriate.The pooled sample size also may not be adequately powered to detect meaningful differences, as the insertion success rate was overall very high. Finally, the ease of insertion score outcome was reported in only three of ten studies.

Conclusion

Misoprostol significantly facilitates the process of IUD insertion and is associated with half the insertion failure rate compared to the control groups in women with no previous vaginal delivery. However, it does not decrease pain perception associated with IUD insertion.

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