BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

DOI: 10.1111/1471-0528.16389
www.bjog.org

Systematic Review

Misoprostol for open myomectomy: a systematic review and meta-analysis of randomised control trials

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Accepted 19 June 2020. Published Online 28 July 2020.

Background Excessive blood loss is a significant risk of myomectomy with the potential need for hysterectomy.

Objective To study the effectiveness of preoperative misoprostol compared with placebo at open myomectomy on intra- and postoperative outcomes.

Search strategy PubMed, Cochrane, Scopus, MEDLINE and EMBASE.

Selection criteria Randomised control studies of women undergoing open myomectomy for symptomatic fibroids who were given either misoprostol or placebo preoperatively.

Data collection and analysis The revised Cochrane risk-of-bias tool for randomised trials was used to assess the risk of bias. Primary outcomes were blood loss, drop in haemoglobin and need for blood transfusion. Secondary outcomes were operative time, postoperative pyrexia and length of postoperative stay. Pooled effect sizes with corresponding 95% CI were calculated using random effects models. Data were analysed using two statistical models for statistical reliability.

Results Eight studies were included with a total of 385 patients, of which 192 received misoprostol. Preoperative misoprostol was significantly associated with lower blood loss by −170.32 ml (95% CI −201.53 to −139.10), lower drop in haemoglobin by −0.48 g/dl (95% CI −0.65 to −0.31), reduced need for blood transfusion (odds ratio [OR] −0.48, 95% CI −0.65 to −0.31), and a reduction in operative time by −11.64 minutes (95% CI −15.73 to −7.54). There was no difference in postoperative pyrexia or length of postoperative stay.

Conclusion Moderate- to high-quality studies have established that misoprostol minimises blood loss and need for blood transfusion at open myomectomy. This low-cost and readily available drug should be routinely administered prior to open myomectomy to improve clinical outcomes.

Keywords Blood transfusion, clinical practice, haemostasis, meta-analysis, misoprostol, myomectomy.

Tweetable abstract Use of misoprostol at open myomectomy reduces blood loss and need for blood transfusion with no impact on postoperative pyrexia.

Linked article This article is commented on by PC Jeppson, p. 484 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16426.

Please cite this paper as: Wali S, Balfoussia D, Touqmatchi D, Quinn S. Misoprostol for open myomectomy: a systematic review and meta-analysis of randomised control trials. BJOG 2021;128:476–483.

Introduction

Myomectomy is a common gynaecological procedure that can be approached, depending on fibroid location, hysteroscopically or abdominally either laparoscopically or through a laparotomy (open). Contributions to blood loss are multifactorial and are summarised in Figure 1. The impact of excessive blood loss can range from anaemia and blood transfusion, to hysterectomy, prolonged hospital stay and potentially death. In addition to preoperative patient optimization, it is crucial to be proactive to minimise intraoperative blood loss.

Misoprostol, a prostaglandin E1 analogue, acts as a uterotonic and vasoconstrictor and is commonly used in the management of postpartum haemorrhage.[1] It is relatively inexpensive with a long shelf life and has been classified by the World Health Organization as an essential medicine.[2] The use of misoprostol in the non gravid uterus has been established with evidence of uterine contractility,[3,4] although at varying doses and routes of administration.[5] As such, misoprostol has the potential to reduce blood loss at myomectomy and reduce the need for blood transfusion and hysterectomy.[6] Misoprostol has a mild self-

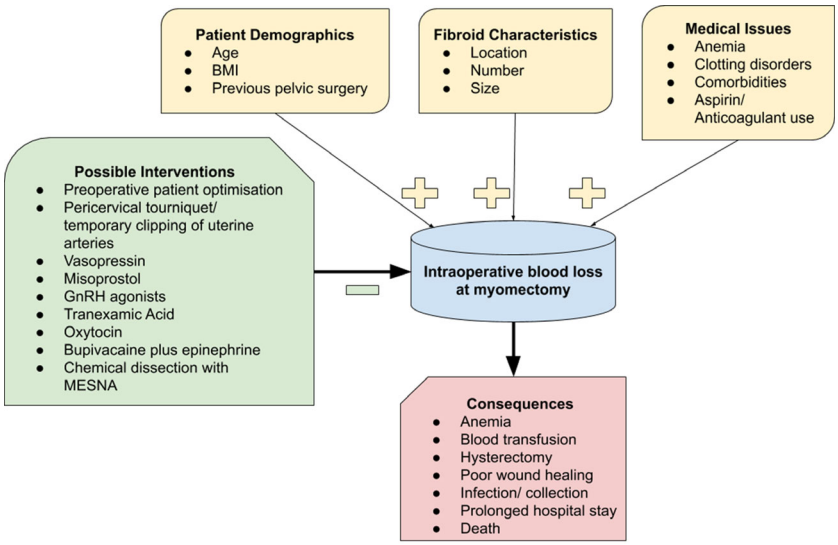


Figure 1. Multifactorial contributions to blood loss at myomectomy and consequences of excessive blood loss.

limiting side effect profile at the 400-μg dose, with fever being associated with higher doses.[4]

A previous systematic review on the use of misoprostol to reduce blood loss at myomectomy[7] included three randomised control trials (RCT)[8–10] comprising 169 patients, of whom 83 were in the study group. The use of misoprostol resulted in a significantly lower blood loss but no difference in operative time, fall in haemoglobin, need for blood transfusion or postoperative fever. The systematic review was limited by the small number of studies and small number of experimental group patients. Most importantly, it was limited by the inclusion of both open and laparoscopic myomectomy in their primary analysis of the effect of misoprostol on blood loss. A meta-analysis involving six RCTs (576 patients, 288 laparoscopic versus 288 open myomectomies) concluded that the laparoscopic approach to myomectomy has significantly less blood loss, drop in haemoglobin and longer operative time.[11] Therefore, any analyses comparing the effect of an intervention on blood loss or operative time between open and laparoscopic myomectomies cannot be interpreted with reliability.

Our systematic review aims to update the work done by Iavazzo in 2015[7] to include more recent RCTs, and to analyse studies describing only open myomectomies in order to produce a meaningful analysis that can be used by clinicians to make evidence-based decisions.

Methods

Data sources and search

We systematically searched five medical electronic databases for trials investigating the effect of preoperative misoprostol at open myomectomy on surgical outcomes. These included PubMed, Cochrane Central Register of Controlled Trials, Scopus, MEDLINE and EMBASE. All databases were assessed from inception to 20 February 2020. We used the following key search terms: 'myomectomy', 'fibroid', 'myoma', 'misoprostol', 'prostaglandin' and 'cytotec' to identify potential articles. The search was repeated by two authors (SW and DB) as well as an experienced medical librarian. We used MESH terms where possible and searched for additional trials in the reference lists of relevant articles identified via the above searches. As our study was a review, there was no direct patient or public involvement. No funding was received.

Study selection

Two authors (SW and DB) performed the study selection and data collection. All English language full-text articles that described randomised control trials were screened. Inclusion criteria for studies were women of reproductive age with symptomatic fibroids undergoing open myomectomy and given either misoprostol (rectal/vaginal/sublingual) or placebo preoperatively. Outcome measures were determined by the researchers, as there is no published core outcome set for myomectomy. Primary outcomes were blood loss, drop in haemoglobin and need for blood transfusion. Secondary outcomes were operative time, postoperative pyrexia and length of postoperative stay. We excluded studies that used any additional blood loss-minimising strategies in the methodology (oxytocin, vasopressin, artery ligation, tourniquet, tranexamic acid and preoperative GnRH analogues) and any prostaglandin other than misoprostol in the experimental group. We also excluded studies that used a laparoscopic, robotic or hysteroscopic approach to myomectomy.

Articles were initially screened based on the title and abstract. For those identified as meeting the inclusion criteria, the full text was then retrieved and screened. Abstracts from conferences or abstracts where the main text was not available were excluded, although corresponding authors were contacted to provide data and methodology and their studies included if these were provided.

Data collection

We extracted data using the Cochrane Public Health Group Data Extraction and Assessment Template.[12] This included study information, participant characteristics, intervention information (timing of preoperative misoprostol, dose and route of myomectomy), outcomes and risk of bias assessment. The outcomes assessed in this study were estimated intraoperative blood loss measured in millilitres (ml), drop in haemoglobin (g/dl), need for blood transfusion, operative time (minutes), postoperative fever (defined as a temperature of ≥38°C within 24 hours of the operation) and duration of postoperative hospital stay (days).

Risk of bias assessment

Two reviewers (SW and DB) used the Cochrane Collaboration's tool (RoB 2) for assessing risk of bias and classified studies as having high, low or unclear risk of bias.[13] This tool assesses five domains for bias: selection, performance, detection, attrition and reporting. Disagreement was resolved by discussion; no third party adjudication proved necessary.

Statistical considerations/data synthesis

For each included study, we calculated the mean difference between the post-intervention outcome values of the intervention arm and the control arm. Where a study reported more than one outcome, we included the measure that was most homogeneous to the other included studies. Data were analysed using REVMAN 5.4 according to standard Cochrane guidelines[14] analysing trial participants in groups to which they were randomised regardless of whether they actually received the treatment assigned. For dichotomous data we expressed study results as odds ratios (OR) with 95% confidence intervals (CI). For continuous data we recorded the means and their standard deviations for each arm of the trial and expressed study results as weighted mean differences (WMD) with 95% CI. Where only the median was reported, we assumed that the mean was equal to the median (after checking for skewness) and estimated the standard deviation from the range (range × 0.95/4). After review by the scientific editor, the data was reanalysed in R using a more conservative restricted maximum likelihood (REML) model (with Hartung-Knapp-Sidik-Jonkman [HKSJ] confidence interval method) to adjust for the small difference in outcomes, especially in the blood loss analysis, which might become non-significant with more rigorous within-study adjustment.

We assessed heterogeneity using I^2 statistic, χ^2 test for homogeneity and visual inspection of the Forest plots. We did not use funnel plots to examine for publication bias given that standard mean differences are naturally correlated with their standard errors and can produce spurious asymmetry. Furthermore, when there are fewer than 10 studies included in the meta-analysis, the power of the tests is too low to distinguish chance from real asymmetry.

Results

Search results and study selection

From the database search, 269 potentially relevant articles were identified using our search strategy (Appendix S1). After the duplicates and non-relevant articles were removed, 14 RCTs were retrieved for comprehensive evaluation. Finally, eight RCTs fulfilling all the inclusion criteria were included in the present systematic review and meta-analysis (Figure S1).

Quality assessment

RoB analyses found the evidence in the studies to be of moderate- to high-quality (Figure S2).

Study characteristics

The included studies were published between May 2003 and June 2019. The number of participants in each study ranged from 25 to 80, with a total of 385, of which 192 were in the misoprostol experimental group. Studies were conducted in Egypt,[15–17] Turkey,[8] Thailand,[18] Uganda[19] and Iran.[9,20] The studies had similar inclusion and exclusion criteria (Table S1). Further details about the study participants' baseline demographics, fibroid details, intervention dose, route of administration and timing are presented in Table S2. There were no baseline differences between intervention groups in any of the included studies in terms of patient age, BMI, number of fibroids or preoperative uterine size.

The studies varied in their misoprostol regimen in terms of dose, timing and route of administration. Six studies used 400 μg[8,15–19] and two used 200 μg[9,20] of misoprostol. The drug was administered vaginally 60–180 minutes preoperatively,[8,9,19] rectally 30–60 minutes preoperatively[15–18] or sublingually 30 minutes preoperatively.[9]

Three studies removed a maximum of five fibroids[16,17,20] and two studies removed a mean of 5.5 ± 1[8] and 6.43 ± 4.98[19] fibroids in the misoprostol group. Two studies do not comment on the number of fibroids removed[9,15] and Maneerat and Tongmai[18] do not describe their open myomectomy data on fibroid number and size separately from their laparoscopic cases. The largest fibroid diameter

removed was documented in five studies[8,9,16,17,20] with a pooled mean largest diameter of 106.81 ± 35.32 mm.

Primary outcomes

Estimated blood loss

Data on blood loss was available from seven studies.[8,9,15–19] The pooled standardised mean difference (SMD) was −169.56 ml (95% CI −200.70 to −138.41), $P < 0.00001$ (Figure 2).

Drop in haemoglobin

Three studies[9,16,17] reported on change in haemoglobin with a statistically significant SMD of −0.48 g/dl (95% CI −0.65 to −0.31), $P < 0.00001$ (Figure S3).

Blood transfusion

All eight studies[8,9,15–20] reported on need for blood transfusion; however, Maneerat and Tongmai's data were not included in the analysis as they do not separate their data for open and laparoscopic myomectomy for this outcome. Use of misoprostol resulted in a lower need for blood transfusion with an odds ratio of 0.29 (95% CI 0.16–0.52), $P < 0.00001$ (Figure 3).

Secondary outcomes

Operative time

Data on operative time was available from seven studies[8,9,16–20] and demonstrated a lower SMD operative time in the misoprostol group of −11.64 (95% CI −15.73 to −7.54) minutes, $P < 0.00001$ (Figure 4).

Postoperative fever

Four studies[8,16,17,19] reported on postoperative fever with no difference in pyrexia in the two groups: OR 1.27 (95% CI 0.58–2.78), $P = 0.56$ (Figure S4).

Duration of postoperative hospital stay

Three studies provided data on postoperative hospital stay.[8,16,17] The SMD in the misoprostol compared with the placebo group was −0.14 days (95% CI −0.31 to 0.04), $P = 0.12$ (Figure S5).

Re-analysis on R using the REML model with HKSJ method

All primary outcomes in the misoprostol group showed ongoing statistical significance, with all confidence intervals increasing with this conservative analysis. There was no change in the lack of statistical significance for the secondary outcomes (Appendix S2).

Discussion

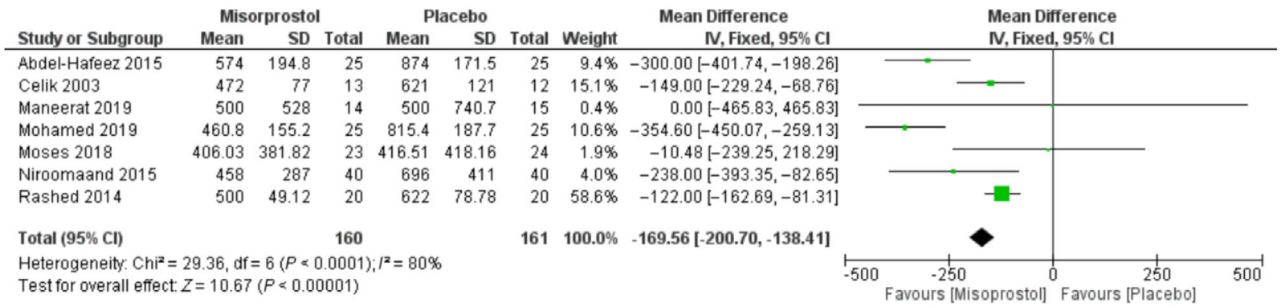
Main findings

Our meta-analysis involves moderate- to high-quality evidence and confirms the findings by Iavazzo et al.[7] that misoprostol significantly reduces blood loss at open myomectomy without increased febrile morbidity. In addition, our analysis found a reduction in blood transfusion and a reduction in operative time in the misoprostol group. Although the reduction in blood loss and fall in haemoglobin may appear modest at 170 ml and 0.48 g/dl, respectively, the clinical significance lies in the reduction in the need for blood transfusion in the misoprostol arm. The results of this analysis are applicable to all women of BMI <30 undergoing open myomectomy without comorbidities or a previous laparotomy.

Strengths and limitations

The main strength of this meta-analysis is the focused scope to limit clinical baseline heterogeneity and the comprehensive search strategy that has captured all the available eligible studies to provide the most up-to-date analysis. Although blood loss had high statistical heterogeneity ($I^2 = 80\%$) it remained statistically significant on repeat conservative analysis. The most clinically relevant outcome, the need for blood transfusion, has no statistical heterogeneity ($I^2 = 0\%$) and remained statistically significant on conservative re-analysis.

The main potential limitation is the applicability of the results to more complex operations involving larger



. . **Figure 2.** Mean difference in estimated blood loss (ml) in the misoprostol group compared with the placebo group.

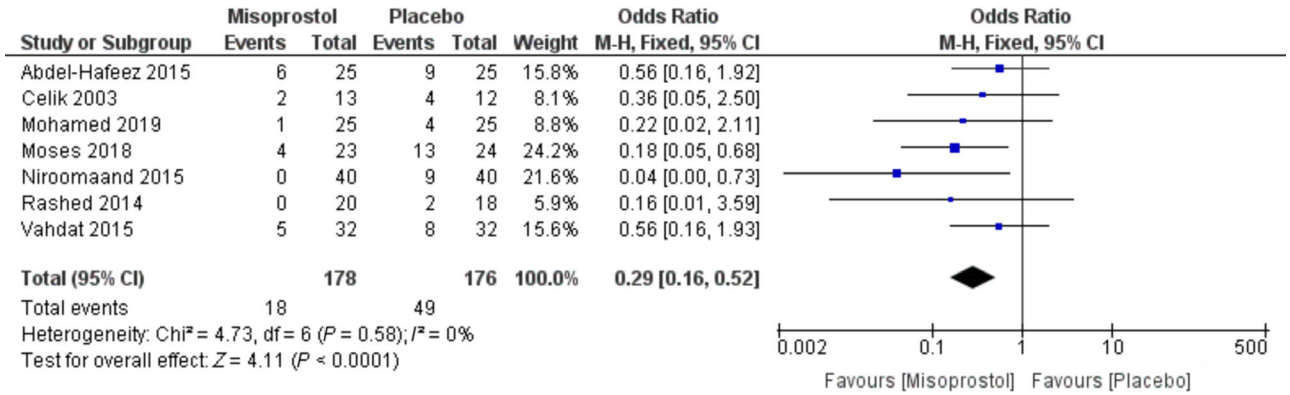


Figure 3. Pooled odds ratios for need for blood transfusion in the misoprostol group compared with the placebo group.

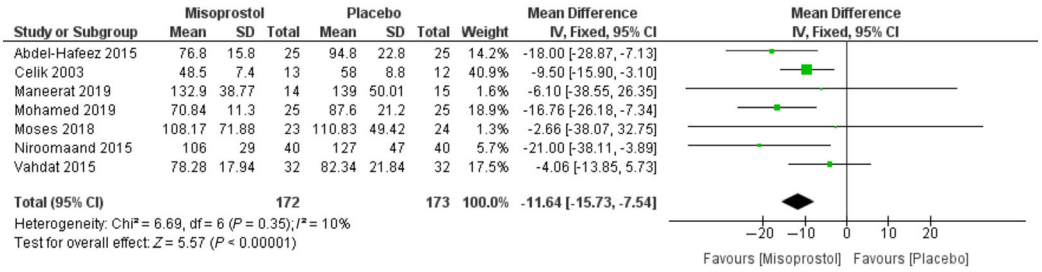


Figure 4. Mean difference in operative time (minutes) in the misoprostol group compared with the placebo group.

numbers and/or sizes of fibroids than those in the included studies, although the use of misoprostol in these cases would not be contraindicated. The variability in dose, timing and route of administration of misoprostol in the included studies is not necessarily a limitation, as discussed in the pharmacokinetics of misoprostol below.

Route, timing and dose of misoprostol

The route of misoprostol administration influences the onset and duration of action,[4] effects achieved and side effect intensity.[21] The oral and sublingual routes produce the fastest and strongest uterotonic effect compared with the vaginal and rectal routes (Table S3) but with more side effects.[3,4] The onset of action of the oral, sublingual and vaginal routes is within 30 minutes, whereas the rectal route takes longer at 100 minutes (Table S3).[4] The sublingual route has the highest peak plasma concentration and systemic bioavailability,[4] whereas the vaginal and rectal routes offer the most sustained plasma levels,[3] although this is dependent on the hydration of the mucosa.[4] All routes have a duration of action of at least 2 hours,[4] which suffices for an uncomplicated open myomectomy. The varying timing and route of administration of the included studies might potentially reduce the beneficial effects of misoprostol had the uterine incision been made before the onset of action or peak concentration.

The effect of the dose of misoprostol on blood loss at open myomectomy has been evaluated by two RCTs. Ragab compared 400 μg once 1 hour preoperatively, compared with twice, 3 hours and 1 hour preoperatively (n = 69).[22] Abbas compared 400 μg twice, 1 and 3 hours preoperatively with 200 μg once, 3 hours preoperatively (n = 80).[23] Both found significantly reduced blood loss and operative time with the higher dose misoprostol compared with the lower dose with no increase in postoperative pyrexia, concluding that the higher dose of 400 μg twice, 1 and 3 hours preoperatively was more effective. This dose is higher than that used in any of our included studies and may result in a more substantial reduction in blood loss.

Interpretation in light of other evidence

Other prostaglandins

Shokeir et al. conducted an RCT involving 108 women to explore the role of 20 mg vaginal dinoprostone (a prostaglandin E2) versus placebo at open myomectomy; they

found a significant reduction in blood loss and blood transfusion.[24] Dinoprostone is less affordable and less readily available than misoprostol. Importantly, unlike misoprostol, it should be used with caution in patients with asthma and its use in haemorrhage is not well established.

Misoprostol versus other haemorrhage-reducing techniques at open myomectomy

A recent network meta-analysis by Samy (2019) found that the use of vasopressin in combination with misoprostol ranked the highest in minimising blood loss at open myomectomy compared with oxytocin, tranexamic acid and misoprostol alone.[25] However, they did not include five of the RCTs included in our study,[15,17–20] which may have affected the results for the misoprostol-only arm of the network meta-analysis.

Mostafa-Gharabaghi conducted an RCT ($n = 70$) comparing misoprostol 400 μg with 30 units oxytocin infusion at open myomectomy and found misoprostol to be superior at reducing blood loss, operative time and need for blood transfusion.[26]

In comparison with intraoperative mechanical artery occlusion, Ali found the tourniquet to be superior at reducing blood loss, need for blood transfusion and operative time when compared with 400 μg misoprostol ($n = 36$).[27] By contrast, two larger RCTs found no difference in blood loss with misoprostol versus mechanical artery compression ($n = 80$, 400 μg misoprostol versus peri-cervical tourniquet[28] and $n = 60$, 400 μg misoprostol versus bilateral uterine artery ligation).[29] Both studies concluded that misoprostol is comparable to mechanical artery occlusion at reducing blood loss without the potentially significant associated surgical complexity and risks of these techniques.

A prospective comparative study by Shafqat of 50 women undergoing open myomectomy for a single intramural fibroid found that 400 μg misoprostol 60 minutes preoperatively significantly reduced blood loss by 171 ml compared with intraoperative intravenous tranexamic acid, but there was no difference in the need for blood transfusion.[30]

Laparoscopic myomectomy

Whereas this meta-analysis specifically examined studies of misoprostol in open myomectomy, the evidence for the use of misoprostol as a sole haemostatic agent at laparoscopic myomectomy is also encouraging. One RCT ($n = 67$) found 400 μg preoperative misoprostol resulted in a significant reduction in blood loss (126 ± 41 ml) at laparoscopic myomectomy compared with placebo.[10]

Clinical practice

A survey of gynaecologists found that the most common intraoperative measures used to reduce blood loss at myomectomy (unspecified route) were: vasopressin (94.1%), vasopressin with epinephrine (26.6%), intravenous tranexamic acid (73.5%), mechanical tourniquet (66.2%), misoprostol (33.8%), uterine artery ligation (22.1%), topical sealant (17.6%) and intraoperative blood salvage (11.8%).[31] The survey concluded that most gynaecologists are uncertain of the optimal peri-/intraoperative approach for haemorrhage reduction. It is important to note that the evidence for vasopressin as a single agent is limited compared with that of misoprostol and is based on a single RCT of 20 patients conducted in 1994 which showed a reduction in blood loss of 450 ml but no reduction in the need for blood transfusion.[32] The serious side effects of vasopressin (bronchospasm, cardiac arrest, angina and fluid imbalance)[33] which must be balanced against any haemorrhage-reducing benefit, have resulted in its prohibition for use at myomectomy in some European countries.

Conclusions

The reduction in blood loss and need for blood transfusion in this meta-analysis of preoperative misoprostol versus placebo at open myomectomy are clinically and globally significant. Given that misoprostol has an acceptable side effect profile, is inexpensive and readily available, routine preoperative use should be encouraged in women with no contraindications. The evidence suggests a dose of 400 μg by any route of administration either once, 30–60 minutes preoperatively, or twice, 3 hours apart. In view of the potential superiority of the sublingual route, this can be adopted prior to anaesthesia and can be incorporated into surgical checklists to avoid omission. Clinical guidelines should be developed and updated in line with evolving evidence in order to streamline surgical practice, encourage evidence-based medicine and make open myomectomy as safe as possible.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

SW initiated and managed the project and contributed to literature search, ROB analysis, data collection, data analysis and write up including response to reviewers. DB initiated the project, checked the literature search, contributed to ROB analysis and write up including response to reviewers. DT provided feedback on the paper and contributed to write up. SQ provided feedback on the paper, contributed to write up, and approved the final paper and response to reviewers.

Details of ethics approval

No ethical approval was needed for this study.

Funding

No funding was received.

Acknowledgements

Miss Ramya Cooke, librarian at Hillingdon Hospital, helped with the literature search.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Selection of studies included in meta-analysis.

Figure S2 (A). Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S2 (B). Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure S3. Mean difference for drop in haemoglobin (g/dl) in the misoprostol group compared with the placebo group.

Figure S4. Pooled odds ratios (ORs) for febrile morbidity in the misoprostol group compared to the placebo group.

Figure S5. Mean difference in hospital stay (days) in the misoprostol group compared to the placebo group.

Table S1. Inclusion and exclusion criteria of included studies.

Table S2. Study characteristics and subject demographics.

Table S3. Route of misoprostol administration and onset and duration of action.

Appendix S1. Search strategy.

Appendix S2. Re-analysis in R using REML model with HKSJ method. ■

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