Chapter 11
Impact of Spontaneous Abortion of First-Trimester on Medical Management:
A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

Ananya Prabhu
Manipal College of Dental Sciences, India

Kavya Sharma
Panjab University, India

Anwesa Acharya
CMR University, Karnataka, India

Shivali Negi
Panjab University, India

Rinshu Dwivedi
National Institute Technology, Hamirpur, India

Pushpdant Jain
https://orcid.org/0000-0002-4933-4496
VIT Bhopal University, India

Ramesh Athe
https://orcid.org/0000-0002-2915-5095
Indian Institute of Information Technology, Dharwad, India

ABSTRACT

Medical management is a relatively safer option than the conventional surgical method in the first-trimester miscarriage. The chapter included studies which allocated women in the pharmacological intervention for spontaneous miscarriage in

DOI: 10.4018/979-8-3693-3711-0.ch011

the first trimester and determined the effectiveness, safety, and side-effect. Authors have included study trials of women with first-trimester miscarriage and conducted a review generating both direct and mixed evidence on the effectiveness and side effects of medical management. Out of 2246 studies found in the databases, 32 were included in the systematic review comprising of 56116 patients undergoing first-trimester miscarriage with 54,890 undergoing medical termination of pregnancy, and 7 studies were included in the meta-analysis. Results showed that the odds of success in medical intervention were low when compared with surgical intervention. Medical management of patients with symptoms of early miscarriage is safer and more effective compared to expectant and well tolerated compared to surgical management.

INTRODUCTION

A miscarriage is a common event that is defined as a nonviable gravidity with an empty/incomplete gestational sac, an embryo without cardiac movement or a gestational trophoblastic ailment with molar placental degeneration. It is estimated that 15%-20% of all pregnancies end in a miscarriage (Li et al., 2006). About 80% of this spontaneous miscarried pregnancy occurs in the 1st to 13th week of gestation and the risk decreases after 12 weeks' gestation (Li et al., 2011). Most patients are unaware of how frequent spontaneous miscarriage is in the first trimester affecting mental peace by causing anxiety (30%), post-traumatic stress (34%) depression (10%) (Shelley et al., 2005).

Therapeutic options such as surgical evacuation, expectant management, and medical management are carried out as a preventive strategy for the evacuation of the retained products of conception in missed miscarriage, blighted ovum, incomplete miscarriage and gestational trophoblastic disease to prevent any fatal morbidities (Joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985). For the past 50 years, surgical evacuation has been considered as the first line of treatment worldwide due to its 95% success rate for missed abortion (Joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985; Wijesinghe et al., 2011).

However, the expense and the complications of surgery and anesthesia are a major unresolved concern. Expectant care has reported a success rate ranging from 25–76% but the waiting period for spontaneous expulsion of remnant tissues may increase uncertainty and anxiety in some women (Lohr et al., 2018). Studies have shown pharmacological termination of pregnancy is a relatively safer and effective

option to surgery and offers a great potential for improving abortion access, as there is reduced requirement for infrastructure (Lin et al., 2006; Torky et al., 2018).

Treatment procedures include the usage of mifepristone, antiprogesterone, letrozole and a prostaglandin analogue, the most commonly used of which is misoprostol through oral, vaginal or sublingual routes alone or in combination (Page et al., 2021). Medical management using misoprostol or combined with mifepristone for spontaneous miscarriage in the first trimester had been widely researched. Studies have shown the employment of these drugs in various combinations, formulation, dosage for hospital use or in-home use (Athe et al., 2015; Page et al., 2021).

Medical treatment allows women undergoing intervention for miscarriage control over the timing, circumstances at the onset of bleeding, location and passage of pregnancy tissue. The most common side effects of using misoprostol are nausea, lower abdominal cramping, vaginal bleeding, vomiting, and fever (Ouzzani et al., 2016). The efficacy and safety of different medical treatment modalities in terms of composition, formulation and routes has been assessed by several studies, however it is important to examine the complete picture of the accumulated evidence.

In the present systematic review and meta-analysis, we aimed to determine the safety and efficacy of medical intervention on first-trimester spontaneous abortion.

METHODS:

This systematic review and meta-analysis were performed rendering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and was registered in Prospero CRD42020154395 (Athe et al., 2014; Porritt et al., 2014).

The PICO strategy (population, intervention, comparison, outcome) was used to build the research question. The population involved women undergoing early spontaneous miscarriage/ abortion in the first trimester; the intervention was the medical treatment to induce abortion; and complete miscarriage success, hemorrhage, blood transfusion, fever, incomplete uterine evacuation, repeat uterine evacuation procedure, re-infection, post-operative complications and re-hospitalization was the outcome result.

Thus, this systematic review sought to clarify the safety, efficacy and side effects of medical management on first trimester spontaneous miscarriage. The authors affirms that the article is an accurate and transparent review of the study being included with no important finding from the study omitted or manipulated.

a. Eligibility:

The review included original articles that evaluated the safety, efficacy and side effects of pharmacological management on first trimester spontaneous miscarriage.

Studies that included patients who do not receive medical intervention, review articles, letters to the editor, in vitro studies conference articles and case reports or series were excluded from this systematic review.

b. Search Strategy:

We searched the databases for studies that mentioned medical intervention for the abortion of first-trimester miscarriage from 2000 until 2022 in PubMed, MEDLINE, Embase, and Cochrane Library using key terms mentioned in **Supplementary Table 1**. We developed a search strategy which was adjusted for the respective database. Only free full text and English language filters were applied. The bibliographies were manually screened for additional relevant trials.

Table 1. Supplementary Table S1

Population	((((((((((((Miscarriage) OR (Recurrent spontaneous abortion)) OR (abortion)) OR (Recurrent pregnancy loss)) OR (Recurrent miscarriage)) OR (Spontaneous miscarriage)) OR (Spontaneous abortion)) OR (Pregnancy loss)) OR (Pregnancy)) OR (Pregnant)) OR (Gestation)) OR (1st trimester)) OR ("First-trimester"))
Intervention	(((((((((((("Medical management")) OR (Abortifacient Agents, Nonsteroidal)) OR (Abortifacient Agents)) OR (Misoprostol)) OR (Abortifacient agents, steroidal)) OR (Mifepristone)) OR (chorionic gonadotropin)) OR (oxytocics)) OR ("Medical")) OR (prostaglandin analogue)) OR (mifepristone)) OR (antiprogesterone))) AND ((((((((("Expectant management")) OR (Monitoring)) OR (Active monitoring)) OR (Waiting, watchful)) OR (Management, expectant)) OR (Active surveillance)) OR (Surveillance, active)) OR (Follow ups)))) AND ((((((((((("Vacuum Curettage") OR ("Vacuum Extraction, Obstetrical")) OR ("Operative hysteroscopy")) OR ("Ambulatory Surgical Procedures")) OR ("Dilatation and Curettage")) OR ("Electric vacuum aspiration")) OR ("Manual vacuum aspiration")) OR ("Suction aspiration")) OR (Surgery*)) OR ("Surgical management")) OR ("Surgical treatment")) OR (Curettage*)))
Outcome	((((((((((((((((((((((((((((((Haemorrhage) OR (Blood loss)) OR (Excessive blood loss)) OR (Excessive bleeding)) OR (Bleeding)) OR (Uterine haemorrhage)) OR (Uterine hemorrhage)) OR (hemorrhage)) OR (Blood transfusion)) OR (Febrile morbidity)) OR (Post-operative Febrile morbidity)) OR (Post-operative fever)) OR (Fever)) OR (High fever)) OR (Repeated uterine evacuation)) OR (Uterine evacuation)) OR (Repeated surgical evacuation)) OR (Second uterine evacuation)) OR (Incomplete uterine evacuation)) OR (Reinfection)) OR (Gynaecological infection)) OR (Rehabilitation)) OR (Rehospitalisation)) OR (Rehospitalization)) OR (Post operative pain)) OR (Abdominal pain)) OR (Post operative abdominal pain)) OR (Antibiotic medication)) OR (Antibiotic therapy)) OR (Antibiotic drugs)) OR (Chemotherapy)

The selected articles through these databases were de-duplicated and the titles and abstracts of the articles were read independently by two of the authors using the software Rayyan (Trinder et al., 2006). The studies which meet the inclusion criteria for the systematic review were identified at this stage. Cases of disagreement were resolved by discussing. Thus, eligible studies were included for qualitative and quantitative analyses, according to data availability.

c. Data Extraction:

Randomized trials, quasi-randomized studies, cohort study and case-control studies that evaluated medical treatment management of first-trimester miscarriage that was defined as a spontaneous loss of a non-viable intrauterine pregnancy between 0 and 13th weeks gestation were included. Studies that evaluated a combination of two treatment options (e.g. medical, surgical and expectant) were included. Studies with multiple comparison arms were also included. We manually extracted data, using a excel sheet on: year and author, country of study, sample size, age, confounding factors, type of intervention, pre-outcomes and outcomes: success rate, surgical treatment required, HB level, bleeding, abdominal pain, gestational sac or deciduae tissue, fever, nausea, blood transfusion, readmission, antibiotic requirement.

d. Assessment of risk of bias in included studies

The risk of bias for the chosen studies was evaluated with Joanna Briggs Institute (JBI) criteria (Ngai et al., 2001; Prasad et al., 2009). Two reviewers independently will decide whether there is "High risk", "Low risk" or "unclear risk" of bias. The risk of bias will be ranked high when the study reaches up to 49% of yes, moderate when it is 50-69% and low when it is above or equal to 70.

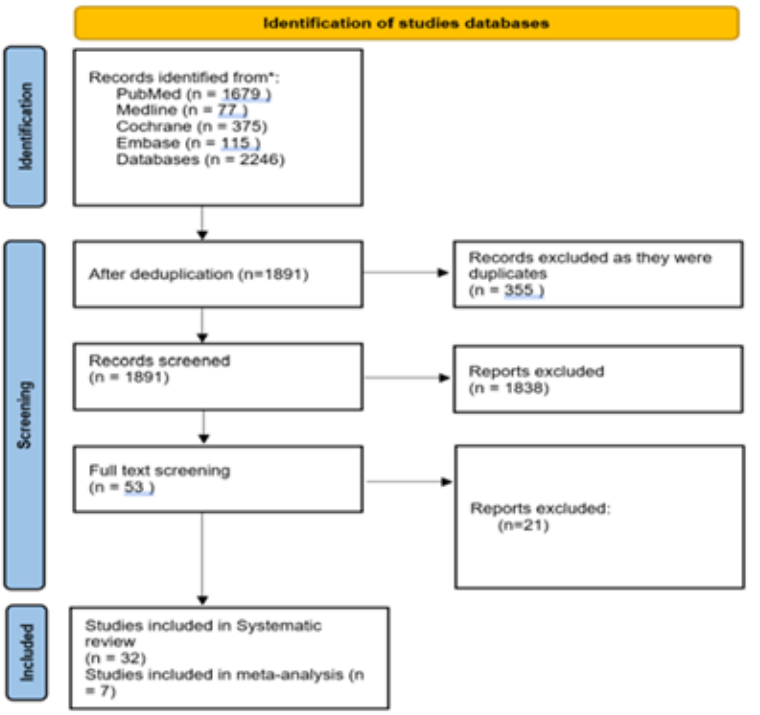
e. Statistical analysis

The meta-analyses were performed for suitable outcomes using Review Manager Software 5.4.1. Odds Ratio (OR) was used as effect measure for dichotomous variable outcome in the study such as success rate, surgery required, abdominal pain, infection rate, nausea and vaginal bleeding. Weighted mean difference was used for vaginal bleeding in days. The heterogeneity between the studies was verified by the inconsistency test (I-square). I-square values lower than 25% were considered low heterogeneity among the studies; values between 25 and 49% were considered moderate heterogeneity and values greater than 50% were considered high heterogeneity. When Tau square was equal to 0 the fixed effects model was used, and the random effects model was used. The dependent variable was success rate, need for secondary evacuation, vaginal bleeding and abdominal pain. The independent variables were medical vs surgical intervention or medical vs expectant management. If heterogeneity existed (I-square >50%), a meta-regression was used to test the study heterogeneity by relating study characteristics (Prasad et al., 2009).

RESULTS

Total 2246 articles indexed with the selected terms were identified from the literature i.e. 1679 in PubMed, 77 in Medline, 115 in Embase and 375 in Cochrane. The search in the gray literature resulted in seven eligible studies. 355 studies were duplicate studies in the databases and were excluded from the study. After full screening of articles based on inclusion and exclusion criteria there were 32 eligible articles in the studies, 32 articles were included in this systematic review, comprising of 56116 patients undergoing first trimester miscarriage with 54,890 undergoing medical termination of pregnancy. 7 studies were included in the meta-analysis as shown in **Figure 1** (Basu et al., 2003; Fernlund et al., 2018; Ibiyemi et al., 2019; Jain et al., 2002; Niinimäki et al., 2006; Shuaib & Alharazi, 2013; Zikopoulos et al., 2002).

Figure 1. PRISMA flow diagram for inclusion in the present meta-analysis of trials assessing the effect of medical-management on first trimester



a. Study characteristic

Five studies compared medical intervention with surgical and three compared with expectant management. The primary demographic characteristics of all the included 32 studies are tabulated in **Table 2.** Interventions varied in relation to intervention comparison, doses, routes and timing of medication. In most studies, complete abortion was defined as complete expulsion of the products of conception without surgical intervention. Not all trials reported the same outcomes, especially for the follow-up time. A complete abortion rate within about 7 – 14 days was mostly mentioned. We could compare the success rate of the intervention, and for the reported side effects, we could only compare the incidence of surgical evacuation required, abdominal pain and vaginal bleeding. For secondary outcomes nausea, vaginal bleeding in days, residual gestation sac and infection were used.

b. Risk of bias assessment

Out of the 32 articles included, 20 had randomized controlled trial design, 10 had quasi controlled design and two were cohort studies. The risk of bias was estimated using the JBI scale; most studies showed moderate to low risk of bias. The results of the quality assessment of the studies are shown in the **Table 3.**

c. Meta-analysis and meta-regression

7 studies were included in the meta-analysis and the details are mentioned in **Table 3andTable 4.** The results of meta-analysis for the outcomes are presented as forest plots in **Figure 2a-f**. The forest plot indicated that the odds of success in medical intervention was low when compared with surgical intervention (N= 1323, OR: 0.59; 95%CI[0.45, 0.77], Heterogeneity: $Chi^2 = 11.43$, df = 4 (P = 0.02); I^2 = 65%) whereas was high when compared with expectant management (N=1025, OR: 2.12; 95%CI [1.64, 2.74], Heterogeneity: $Chi^2 = 6.33$, df = 2 (P = 0.04); I^2 = 68%). The need for surgical evacuation was significantly higher (OR: 0.59; 95%CI [0.44, 0.79]). The effect size of vaginal bleeding was significant (OR: 1 1.08; 95%CI [0.74, 1.58]). The secondary outcomes evaluated were nausea (OR: 1.77; 95%CI [1.14, 2.75]), abdominal pain 1.71; 95%CI [0.99, 2.97] and infection (OR: 0.75; 95%CI [0.43, 1.29]).

Figure 2a. Forest plot for the outcome: Success rate of medical management vs surgical/expectant management

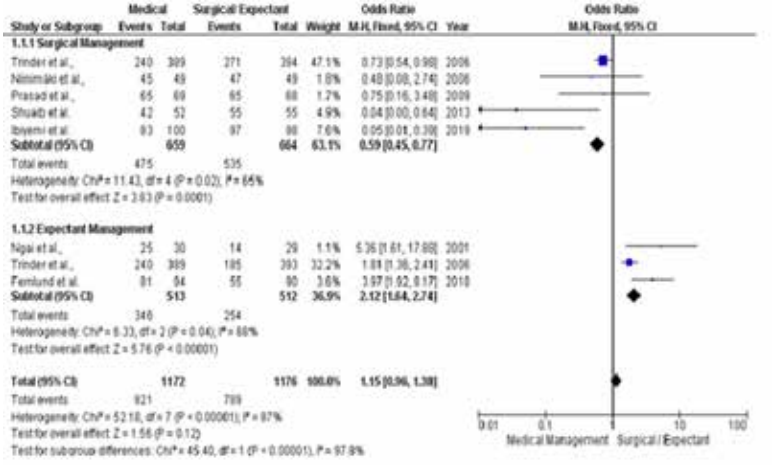


Figure 2b. Forest plot for the outcome: Surgery required in medical management vs surgical/expectant management

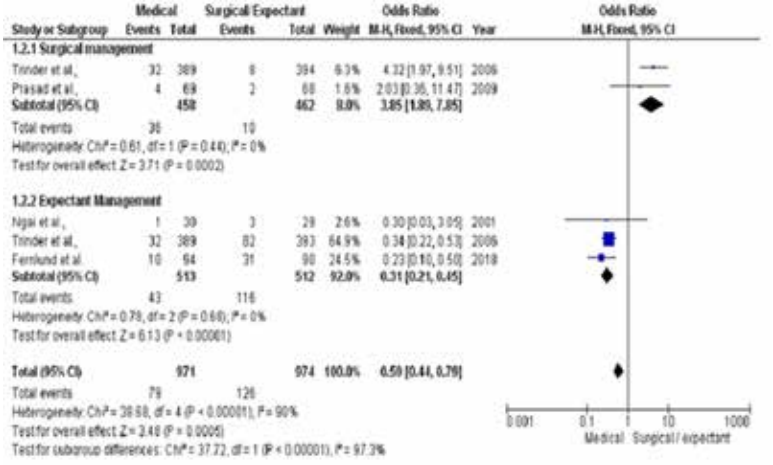


Figure 2c. Forest plot for the outcome: Vaginal bleeding in medical management vs surgical/expectant management

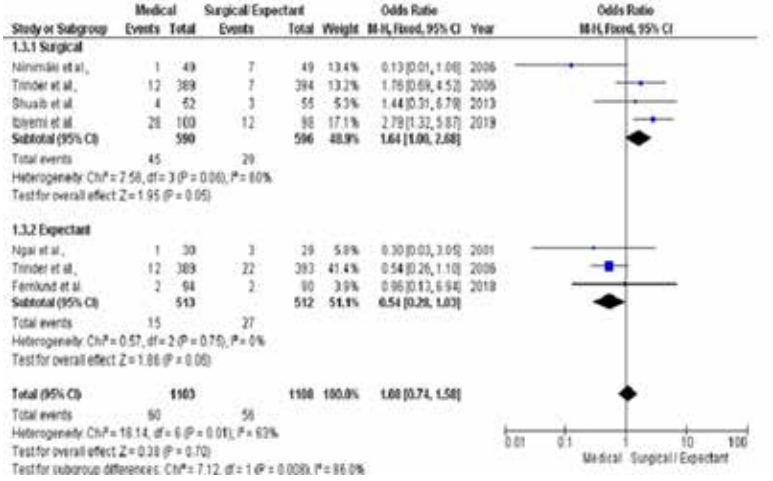


Figure 2d. Forest plot for the outcome: Abdominal pain in medical management vs surgical/expectant management

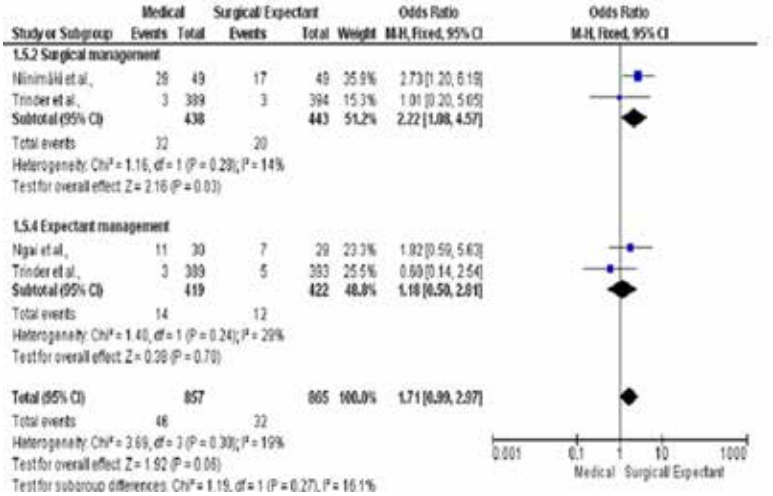


Figure 2e. Forest plot for the outcome: Nausea in medical management vs surgical/ expectant management

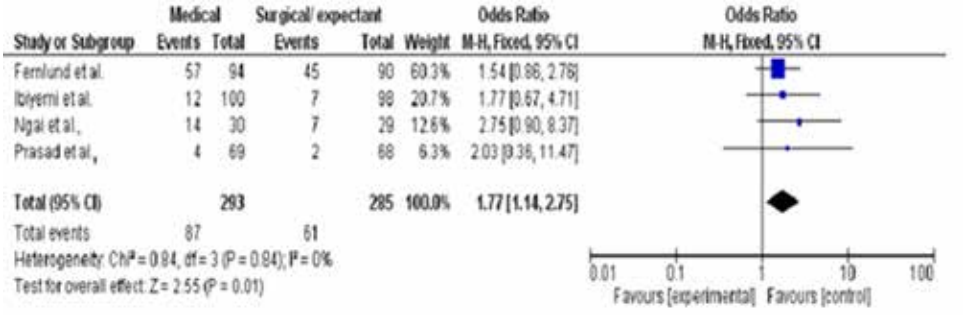
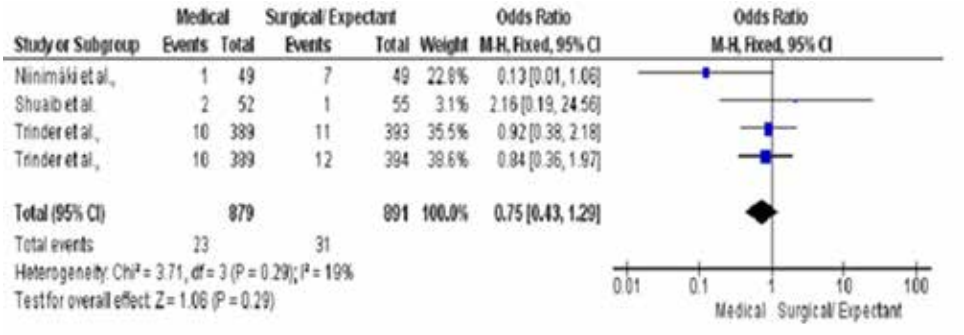


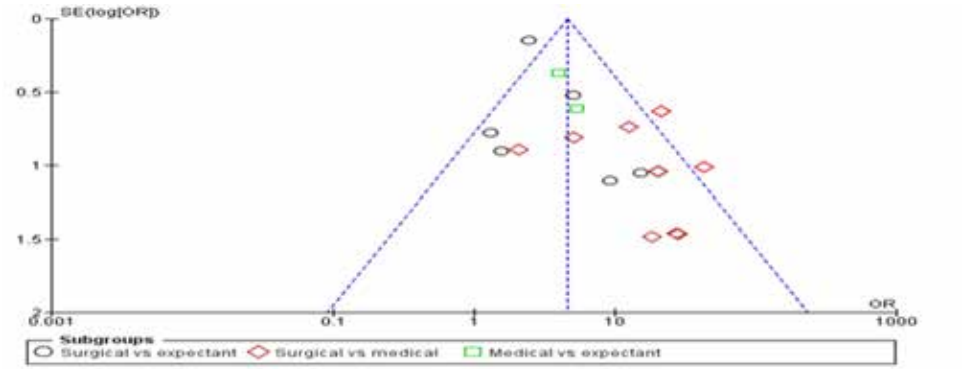
Figure 2f. Forest plot for the outcome: Infection in medical management vs surgical/ expectant management



Publication bias

The funnel plot was symmetrical, indicating there is no of publication bias as shown in **Figure 3a-c.** Which was confirmed using Egger's weighted regression analysis (Egger's test, p=0.621). This may be due to the fact that the publications with statistically significant results are more likely to be submitted and published than the studies with non-significant results.

Figure 3. Funnel plot showing symmetry for medical management verses surgical and expectant



DISCUSSION

New clinical approaches have evolved to try to minimize unnecessary surgical interventions whilst aiming to maintain low rates of morbidity and mortality from miscarriage. Medical approach is a frequently chosen option. Among the 32 selected studies, 5 studies compared the medical intervention with surgical (Basu et al., 2003; Fernlund et al., 2018; Ibiyemi et al., 2019; Jain et al., 2002; Zikopoulos et al., 2002) and three compared medical intervention with expectant management (Fernlund et al., 2018; Niinimäki et al., 2006; Shuaib & Alharazi, 2013) for the spontaneous miscarriage in the first trimester. Among the seven studies selected for the meta-analysis, it was observed that only one study utilized a combination of mifepristone and misoprostol while the other six used only misoprostol in various doses and possible routes of administration were vaginal, oral, vaginal plus oral, sublingual (Jain et al., 2002).

From the studies, it was observed that the success of complete abortion was higher in medical when compared to expectant whereas the medical treatment was inferior in comparison to surgical treatment. The reason for failure of abortion in medical vs surgical is due to the residual sac remaining which required surgical evacuation at the end of the follow-up.

In terms of study settings, the evidence stems from both low-income to high-income countries. In present study we tried to minimize bias assigning two independent reviewers to assess the eligibility for inclusion criteria, data extraction, and assessed risk of bias independently. Data extraction was undertaken by one review

author and checked by another. However, many of these steps involve subjective assessments and thus may carry there is no risk of bias.

CONCLUSION

Although it would be critical to have more data, the current evidence suggests medical treatment is superior to expectant care in terms of success rate and less frequent side effects and can be an alternative to surgery management of first trimester miscarriage. Study has identified high risk of nausea and vaginal bleeding with the use of medical intervention which can be explained to the women during treatment counseling. Multicenter trials should be carried in future to compare the use of medical treatments, by the various formulations, routes and doses, with expectant care and surgery to confirm or refute these findings. This should provide more evidence on the effectiveness and adverse effects, so women can be provided with better information in order to support their choices. Future trials should consider women's views and quality of life measures alongside the clinical outcome.

Declaration: We confirm that the manuscript has been read and approved by all the listed authors. We further confirm that the order of authors listed in the manuscript has been approved by all.

Ethics approval and consent to participate: Ethical approval was not required for the present study as it is based on the secondary data/information.

Consent for publication: All the listed authors give their due consent for the publication

Availability of data and material: The present study is based on the secondary data sources which are available at mentioned databases in public domain. We have used the data from published articles for our research. Please refer Table1.

Competing interests: There are no conflicts of interest declared by authors.

Funding: The authors acknowledge the Vritika Research Internship sponsored by the Science & Engineering Research Board (SERB), Department of Science and Technology (DST), Govt. of India, under Accelerate Vigyan Vritika scheme for carrying out the study.

Authors' contributions: Ananya Prabhu, Kavya Sharma, Anwesa Acharya, and Shivali Negi have contributed the data collection, analysis, and manuscript preparation. Ramesh Athe developed the study protocol, secured funds, supervised the study, and guided in manuscript preparation. Rinshu Dwivedi and Pushpdant Jain contributed to the development of study protocol and manuscript writing.

Acknowledgements: The authors express their sincere acknowledgement to the SERB Vritika and Indian Institute of Information Technology Dharwad (IIIT Dharwad) for their support and insightful inputs. The authors are grateful to the

Department of Data Sciences and Intelligent Systems, IIIT Dharwad for their support and encouragement, which has helped in improving this study.

AI Statement: We confirm that the AI hasn't been used to prepare the manuscript and approved by all the listed authors.

REFERENCES

Athe, R., Mendu, V. V., & Krishnapillai, M. N. (2015). A meta-analysis combining parallel and cross-over randomized controlled trials to assess impact of iodine fortified foods on urinary iodine concentration among children. *Asia Pacific Journal of Clinical Nutrition*, 24(3), 496–503. 10.6133/apjcn.2015.24.3.1026420192

Athe, R., Rao, M. V., & Nair, K. M. (2014). Impact of iron-fortified foods on Hb concentration in children (<10 years): A systematic review and meta-analysis of randomized controlled trials. *Public Health Nutrition*, 17(3), 579–586. 10.1017/S1368980013000062233881 59

Basu, R., Gundlach, T., & Tasker, M. (2003). Mifepristone and misoprostol for medical termination of pregnancy: The effectiveness of a flexible regimen. *The Journal of Family Planning and Reproductive Health Care*, 29(3), 139–141. 10.1783/147118903101197818128853 07

Fernlund, A., Jokubkiene, L., Sladkevicius, P., & Valentin, L. (2018). Misoprostol treatment vs expectant management in women with early non-viable pregnancy and vaginal bleeding: A pragmatic randomized controlled trial. *Ultrasound in Obstetrics & Gynecology*, 51(1), 24–32. 10.1002/uog.1894029072372

Ibiyemi, K. F., Ijaiya, M. A., & Adesina, K. T. (2019). Randomised Trial of Oral Misoprostol Versus Manual Vacuum Aspiration for the Treatment of Incomplete Abortion at a Nigerian Tertiary Hospital. *Sultan Qaboos University Medical Journal*, 19(1), e38–e43. 10.18295/squmj.2019.19.01.00831198594

Jain, J. K., Dutton, C., Harwood, B., Meckstroth, K. R., & Mishell, D. R.Jr. (2002). A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. *Human Reproduction (Oxford, England)*, 17(6), 1477–1482. 10.1093/humrep/17.6.147712042265

Joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists. (1985). Induced abortion operations and their early sequelae. Joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists. *The Journal of the Royal College of General Practitioners*, 35(273), 175–180.3989781

Li, Y. T., Chen, F. M., Chen, T. H., Li, S. C., Chen, M. L., & Kuo, T. C. (2006). Concurrent use of mifepristone and misoprostol for early medical abortion. *Taiwanese Journal of Obstetrics & Gynecology*, 45(4), 325–328. 10.1016/S1028-4559(09)60252-717175491

Li, Y. T., Hsieh, J. C., Hou, G. Q., Chen, T. H., Chu, Y. C., Lin, T. C., Kuan, L. C., Lin, M., Tang, H. H., & Kuo, T. C. (2011). Simultaneous use of mifepristone and misoprostol for early pregnancy termination. *Taiwanese Journal of Obstetrics & Gynecology*, 50(1), 11–14. 10.1016/j.tjog.2010.09.00221482367

Lin, M., Li, Y. T., Chen, F. M., Wu, S. F., Tsai, C. W., Chen, T. H., & Kuo, T. C. (2006). Use of mifepristone and sublingual misoprostol for early medical abortion. *Taiwanese Journal of Obstetrics & Gynecology*, 45(4), 321–324. 10.1016/S1028-4559(09)60251-517175490

Lohr, P. A., Starling, J. E., Scott, J. G., & Aiken, A. R. A. (2018). Simultaneous Compared With Interval Medical Abortion Regimens Where Home Use Is Restricted. *Obstetrics and Gynecology*, 131(4), 635–641. 10.1097/AOG.0000000000000253629528933

Ngai, S. W., Chan, Y. M., Tang, O. S., & Ho, P. C. (2001). Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. *Human Reproduction (Oxford, England)*, 16(7), 1493–1496. 10.1093/humrep/16.7.149311425836

Niinimäki, M., Jouppila, P., Martikainen, H., & Talvensaari-Mattila, A. (2006). A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertility and Sterility*, 86(2), 367–372. 10.1016/j.fertnstert.2005.12.07216764872

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, 5(1), 210. 10.1186/s13643-016-0384-427919275

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., & Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, 372(71), n71. Advance online publication. 10.1136/bmj.n7133782057

Porritt, K., Gomersall, J., & Lockwood, C. (2014). JBI's Systematic Reviews: Study selection and critical appraisal. *The American Journal of Nursing*, 114(6), 47–52. 10.1097/01.NAJ.0000450430.97383.6424869584

Prasad, S., Kumar, A., & Divya, A. (2009). Early termination of pregnancy by single-dose 800 microg misoprostol compared with surgical evacuation. *Fertility and Sterility*, 91(1), 28–31. 10.1016/j.fertnstert.2007.11.02818295212

Shelley, J. M., Healy, D., & Grover, S. (2005). A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 45(2), 122–127. 10.1111/j.1479-828X.2005.00357.x15760312

Shuaib, A. A., & Alharazi, A. H. (2013). Medical versus surgical termination of the first trimester missed miscarriage. *Alexandria Journal of Medicine*, 49(1), 13–16. 10.1016/j.ajme.2012.08.004

Torky, H. A., Marie, H., ElDesouky, E., Gebreel, S., Raslan, O., Moussa, A. A., Ahmad, A. M., Zain, E., & Mohsen, M. N. (2018). Letrozole vs. Placebo Pretreatment in the Medical Management of First Trimester Missed Miscarriage: A Randomized Controlled Trial. *Geburtshilfe und Frauenheilkunde*, 78(1), 63–69. 10.1055/s-0043-12249929375147

Trinder, J., Brocklehurst, P., Porter, R., Read, M., Vyas, S., & Smith, L. (2006). Management of miscarriage: Expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). *BMJ (Clinical Research Ed.)*, 332(7552), 1235–1240. 10.1136/bmj.38828.593125.5516707509

Wijesinghe, P. S., Padumadasa, G. S., Palihawadana, T. S., & Marleen, F. S. (2011). A trial of expectant management in incomplete miscarriage. *The Ceylon Medical Journal*, 56(1), 10–13. 10.4038/cmj.v56i1.288821542427

Zikopoulos, K. A., Papanikolaou, E. G., Kalantaridou, S. N., Tsanadis, G. D., Plachouras, N. I., Dalkalitsis, N. A., & Paraskevaidis, E. A. (2002). Early pregnancy termination with vaginal misoprostol before and after 42 days gestation. *Human Reproduction (Oxford, England)*, 17(12), 3079–3083. 10.1093/humrep/17.12.307912456606

APPENDIX

Table 2. Summary statistics of included studies in systematic review

	Authors			Study		Dose	Route	Mean age		Previous
	Ngai et al.	China	RCT	15	Misoprostol vs expectant	Misoprostol 400 µg	Vaginal	31.5 (7.7)	43.5 (17.6) days	3
	Zikopoulos et al.	Greece		4	Misoprostol	Misoprostol 800 µg	Vaginal	22.4 (2.4)	38.9 days	0
	Jain et al.	US	RCT	15		200 mg	Vaginal	26.0 (6.0)	47.0 days	39
	Basu et al.	United		10			Vaginal	N/A	N/A	N/A
	Bagratee et al.	South Africa	RCT	14	Misoprostol vs placebo	600 µg misoprostol	Vaginal	33.2 (6.9)	73.8	12
	Ravn et al.	Denmark		14		400 mg oral	Oral	N/A	N/A	0.6
	Li et al.	Taiwan		14		200 mg	Vaginal	N/A	36 day	N/A
	Lin et al.	Taiwan		14		200 mg	Sublingual	N/A	36 days	previous 98.3% (350 women)
	Stockheim et al.	Israel	RCT	14		600 mg	Oral	32 (6)	N/A	31%
	Niinimäki et al.	Finland	RCT	30		200 mg	Vaginal	30.9 (6.9)	74.7 (14.2)	0.4 (0.7)
	Trinder et al.	United	RCT	14	Misoprostol vs expectant vs Surgery	800 µg misoprostol	Vaginal	31.2 (5.9)	N/A	N/A
	Tang et al.	China	RCT	9	Misoprostol	600 mg misoprostol	Sublingual	31.7 (6.7)	50.1 (9.6) DAYS	20 (22.2)
	Prasad et al.	India	RCT	8	Misoprostol vs surgery	800 µg of misoprostol	Vaginal	N/A	48 days	N/A
	Hertzen et al.	china,	RCT	14		200 mg	Sublingual vs vaginal	27.0 (6.3)	N/A	322
	Li et al.	Taiwan		14		oral	Vaginal	N/A	45.2 days	N/A
	Shuaib	Yemen	RCT	7	Misopristole	misopristole (400 µg)	vaginally	28.9	N/A	19
	Rouzi et al.	Saudi Arabia		1		50 µg of misoprostol dissolved in 5 ml of normal saline		34.6	54.6 days	N/A

continued on following page

Table 2. Continued

	Authors			Study		Dose	Route	Mean age		Previous
	Bracken et al.	Ukraine, Georgia, India and Tunisia		14	mifepristone + misoprostol	200 mg	Sublingual	27.7 (5.7)	N/A	173
	Løkeland et al.	Norway		30	mifepristone + misoprostol		vaginal	27	N/R	N/A
	Gatter et al.	United States		14	mifepristone + misoprostol	200 mg of	oral	N/A	N/A	N/A
	Li et al.	china	RCT	3	150 mg mifepristone + 200 µg misoprostol	150 mg	Vaginal	27.2	31.1	N/A
	Iyengar et al.	India	RCT	14	mifepristone + misoprostol		oral	26.6	41.65 days	113
	Marwah et al.	India	RCT	14	misoprostol	400µg of misoprostol		23.7	N/A	18
	Lohr et al.	United		14	mifepristone + misoprostol	200mg oral	Vaginal	27	48	37.2
	Fernlund et al.	Sweden	RCT	30	Misoprostol vs expectant	single dose of 800µg misoprostol	Vaginal	32.2	76.5	24
	Schreiber et al.	US	RCT	30	mifepristone + misoprostol	200 mg of	Vaginal	30.7(6.3)	N/A	53
		Iran	RCT	15	Letrozole vs placebo	10 mg oral letrozole for 3 days+600 microgram single dose oral misoprostol	Oral	29.21 (4.08)	54.18 days	N/A
	Torky et al.	Egypt	RCT	14	Letrozole vs placebo	800 micrograms of misoprostol vaginally on the fourth day	Vaginal	26.62 (4.30)	48.83	N/A
	Larsson et al.	Sweden		14	mifepristone + misoprostol	200 mg of	Vaginal	28.3 (6.9)	59.4 (1.9)	44
	Shaamash et al.	Egypt	RCT	14	Misoprostol	800 µg of misoprostol	Vaginal		9.7	0.59 ± 0.90
	Ibiyemi et al.	Nigeria	RCT	7	Misoprostol vs surgery	600 µg of oral misoprostol	Oral	28.38 (5.51)	N/A	N/A
	Souizi et al.	Iran	RCT	7	Misoprostol	600 µg of misoprostol every 6 h (maximum of 4 doses)-vaginal	Vaginal vs oral vs sublingual	29.2(6.0)	58.8 DAYS	17

Table 3. Medical intervention versus surgical intervention

Authors		Study	Intervention			Surgical treatment required	Ppl with	Abdominal pain	Gestational sac or decidual tissue	
Niinimäki et al.		30	Medical	49	45	5	1	29	N/A	1
			Surgical	49	47	2	7	17	N/A	7
Trinder et al.		14	Medical	389	240	32	12	3	78	10
			Surgical	394	271	8	7	3	41	12
Prasad et al.		7	Medical	69	65	4	3	37	4	N/A
			Surgical	68	65	2	0	68	2	N/A
Shuaib et al.		7	Medical	52	42	10	4	N/A	N/A	2
			Surgical	55	55	0	3	N/A	N/A	1
Ibiyemi et al.		7	Medical	100	83	17	28	32	8	N/A
			Surgical	98	97	1	12	97	1	N/A

Table 4. Medical intervention versus expectant intervention

Authors		Intervention	Sample size	Success rate	Surgical treatment required		Abdominal pain	Residual tissue		
Ngai et al.		Medical	30	25	1	14.6 days	11	N/A	N/A	14
		Expectant	29	14	3	15 days	7	N/A	N/A	7
Trinder et al.		Medical	389	240	32	11 days	3	78	10	N/A
		Expectant	393	185	82	12 days	5	145	11	N/A
Fernlund et al.		Medical	94	81	10	12.7 days	90	N/A	N/A	57
		Expectant	90	55	31	15 days	71	N/A	N/A	45