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A Meta-Analysis Approach on Medical, Surgical and Expectant Management on Abortion of First Trimester

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SUMMARY

An increase in miscarriage in the first trimester of gestation and its associated complication is burden-some on the quality of life of a woman. Medical, surgical, and expectant care are carried out after the miscarriage to remove any remaining tissues in the uterus. Understanding the efficacy and safety of these interventions will raise awareness and be a deciding factor to choose an appropriate treatment plan. Present review aims to determine the efficacy and safety of medical, surgical, and expectant care of various medical and surgical methods for first-trimester miscarriage. This review included studies that allocated women to medical, surgical or expectant management in the first trimester. PubMed, Cochrane Library, MEDLINE, and Embase Library were searched for the literature. The primary outcome was the complete evacuation of products of conception. Data were independently reviewed, graded for evidence quality, and assessed for risk bias by using the guidelines of PRISMA (Preferred Report Items for Systematic Review and Meta-Analysis). 21 eligible articles were included in this systematic review, comprising of 7931 patients undergoing medical, surgical or expectant-management for early spontaneous-miscarriage. The success rate in surgical intervention was higher when compared with medical intervention (OR: 16.12 [9.11, 28.52]) and expectant management (OR: 2.78 [2.13, 3.61]). Whereas medical intervention had a high success rate when compared with expectant-management (OR: 4.29 [2.31, 7.97]). The review determines the effect of medical, surgical, and expectant-management procedures on women who have had spontaneous-miscarriages in their first-trimester. PROSPERO-International prospective register of systematic reviews–CRD42020154395.

Keywords: Surgery; Medical; Expectant management; Spontaneous Abortion; First trimester; Systematic review.

INTRODUCTION

A miscarriage is a common occurrence defined as a nonviable pregnancy with an empty/incomplete gestational sac, an embryo without cardiac action, or a gestational trophoblastic illness with molar placental degradation. It occurs in 15% to 20% of pregnancies, according to estimates. Approximately 80% of these spontaneous miscarriage pregnancies occur between the first and thirteenth weeks of gestation, with the risk decreasing after 12 weeks. Most patients are unaware of how frequently spontaneous miscarriages occur in the first trimester, which can lead to anxiety (30%), post-traumatic stress disorder (34%), and sadness (10%), all of which can disrupt mental harmony [1-3].

As a preventive measure for the evacuation of the retained products of conception in missed miscarriage and incomplete miscarriage, therapeutic alternatives

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such as surgical evacuation, expectant management, and medicinal management are used[4]. Vacuum aspiration is a type of surgical uterine evacuation that involves a vacuum source. It is also known as suction curettage, endometrial aspiration, or mini-suction. It is possible to utilize a handheld vacuum syringe or mechanical pump that is operated by foot (Manual Vacuum Aspiration) or electricity (Electric Vacuum Aspiration)[5]. Sharp metal curettage (also known as dilatation and curettage) is commonly performed in an operating room while the patient is sedated or under a general or regional anesthetic[6].

Miscarriage medications typically involve synthetic prostaglandins such as Misoprostol, which is used primarily in incomplete miscarriages. Mifepristone, a progesterone antagonist, is used in conjunction with misoprostol to treat early miscarriage, particularly missed/silent miscarriage. Misoprostol, a safe and cheap medication, may allow for early POC ejection while avoiding complications[7,8]. The approach of expectant management allows the retained tissues of gestation to usually pass naturally, outside the hospital, and is an alternative to standard treatment with medication or surgery[9].

Surgical procedure has a 95% success rate for missed abortion but an important unresolved issue is the cost of surgery and the risks associated with anesthesia[5]. Medical management of miscarriages has been demonstrated to be advantageous, particularly in women who have had a missed miscarriage or an empty sac. Misoprostol, on the other hand, is not approved for usage in all countries[10]. If a miscarriage is not handled, the fetal tissue will normally pass naturally, as it did for more than 65% of women who suffered a miscarriage with may take up to two weeks. Unexpected hospitalizations and surgical curettage, on the other hand, occurred significantly more frequently during expectant and medicinal management than following surgical management[5,11].

The main aim of this systematic review is to determine the efficacy and safety of medical, surgical, and expectant care of different medical and surgical methods for first-trimester miscarriage.

METHODOLOGY

The systematic review and meta-analysis were performed interpretation to the PRISMA and registered in Prospero CRD42020154395[12-14]. The PICO strategy (population, intervention, comparison, and outcome) was used to build the research question. Thus, this systematic review is required to clarify the safety, efficacy, and side effect of medical, surgical, and expectant management on first-trimester spontaneous miscarriage.

Eligibility

The review included original articles that evaluated the safety, efficacy, and side effect of pharmacological, surgical and expectant management on first-trimester spontaneous miscarriage. Studies that patients did not receive medical, surgical and expectant interventions for miscarriage, review articles, letters to the editor; in vitro studies, conference articles and case reports or series were excluded from the present study[15].

Search strategy

A literature search on Medline/PubMed, Cochrane Library, MEDLINE, and Embase Library was performed using mesh terms mentioned in **Supplementary material S1** and were searched[14,15]. Randomized case-control, cohort studies, and quasi-trials of women with first-trimester miscarriage were included, and directed a systematic review and meta-analysis generated both direct and mixed evidence on the effectiveness and side effects of medical, surgical, and expectant management. 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. The studies which could potentially cover the inclusion criteria for this review were identified at this stage and accessed in their entirety. Cases of disagreement were resolved by consensus.

Data Extraction

Randomized trials, quasi-randomized studies, cohort study and case-control studies that evaluated medical treatment, surgical treatment and expectant 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 combination of two treatment options (e.g. medical, expectant and surgical management) 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, bleeding, abdominal pain, and infection rate[14,15].

Assessment of risk of bias in included studies

The risk of bias for the chosen studies was evaluated with Joanna Briggs Institute (JBI) criteria[16]. Two reviewers independently will decide whether there is a "High risk", "Low risk" or "unclear risk" of bias. The risk of bias will be ranked high when the study reached up to 49% of yes, moderate when it is (50-69) % and low when it is above or equal to 70%.

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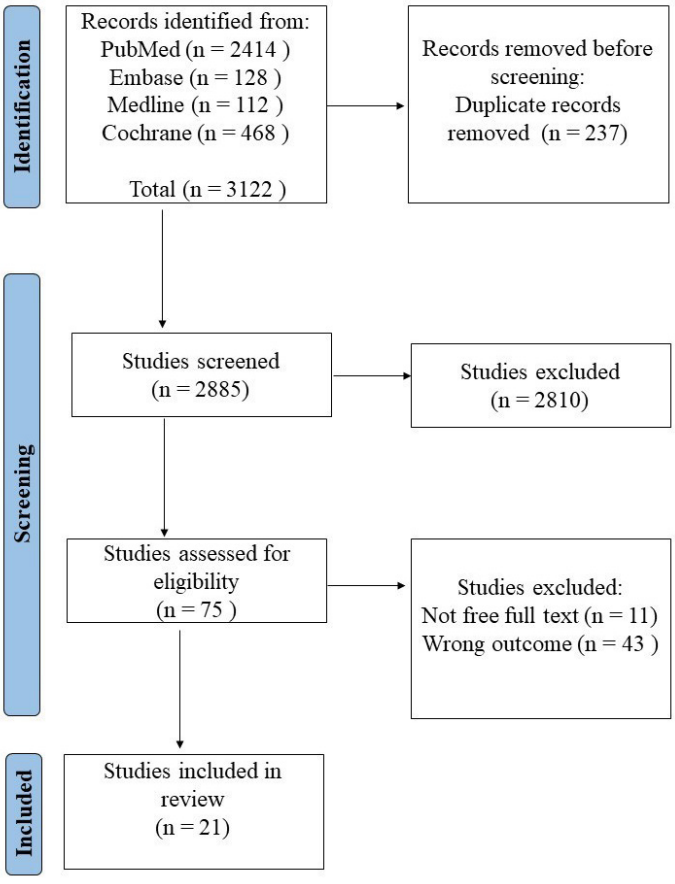
2.5 Statistical Analysis

The meta-analyses were performed for suitable outcomes using Review Manager Software 5.4.1. The odds Ratio (OR) was used as an effective measure for dichotomous variable outcomes in the study such as success rate, surgery required abdominal pain, blood diffusion, infection rate, nausea, and vaginal bleeding. The weighted mean difference was used for vaginal bleeding in days. The heterogeneity between the medical, surgical, and expectant studies was verified by the inconsistency test (I^2). I^2 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 I^2 was equal to 0 the fixed effects model was used, when I^2 was greater than 0 the random effects model was used. The dependent variable was success rate, vaginal bleeding, abdominal pain and infection rate [14,15,17-21]. Statistical analyses were performed with Review Manager (RevMan) software version 5.4.1, and Comprehensive Meta-Analysis (CMA) software trial version (www.meta-analysis.com).

Figure 1. Represents the PRISMA flowchart for study selection



RESULTS

3122 articles were identified from the literature, 2414 in PubMed, 112 in Medline, 128 in Embase and 468 in Cochrane. 237 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 21 eligible articles were included in this systematic review, comprising of 7931 patients undergoing medical, surgical or expectant management for early spontaneous miscarriage[22-42] and depicted in **Figure 1** and also and summary statistics tabulated in **Table 1.** Represents the PRISMA flowchart for study selection.

Study characteristic

Eleven studies compared medical intervention with surgical [23,27,31,33-40], three studies compared medical management with expectant management[26,32,39], and 8 studies compared surgical with expectant management [22,24,28,30,31,39-41]. Out of the 21 articles included, sixteen had randomized controlled trial design [22,24-39,41,42], two had quasi controlled design [28,40] and three were cohort studies [23,36,37]. The primary demographic characteristics of all the included 21 studies are tabulated**.** Complete abortion was defined as complete expulsion of the products of conception without any additional management. We could compare the success rate of the intervention, and for the reported side effects, we could only compare the incidence of abdominal pain, vaginal bleeding and infection.

Risk of bias assessment

The risk of bias was estimated using the JBI scale; most studies showed low to moderate risk of bias. The lowest risk of bias was seen in study by Demetroulis[25] et al., and highest risk of bias was seen among Fernlund[26] et al. Most studies did not conduct statistical analysis for confounding factors. Blinding of participants and clinicians was not possible due to the type of intervention. The results of the quality assessment of the studies are shown in the **Supplementary Table S2.**

Meta-analysis

The results of meta-analysis for the outcomes are presented as forest plots in **Figure 2**. The forest plot indicated that the odds of success in surgical intervention was higher when compared with medical intervention (N= 4274, OR: 16.12 [9.11, 28.52], Heterogeneity: Chi^2 = 7.03, df = 5 (P = 0.22); I^2 = 29%) and expectant management (N=1398, OR: 2.78 [2.13, 3.61], Heterogeneity: Chi^2 = 7.03, df =

Table 1: Summary of the trials assessing the characteristics abortion

S.No.	Year	Authors	Location	Study design	Study Duration	Intervention/ Control	Mean age	Gestation mean	Parity
1	2014	Al-Ma'ani et al.22	Germany	RCT	30	Expectant vs surgical	32.5	62.5 days	N/A
2	2010	Bennett et al.23	US	Cohort	3	Medical, MVA	2.5	N/A	N/A
3	2012	Dangalla et al.24	Sri Lanka	RCT	14	Expectant care vs ERPC	29	9.2	52 (64.6)
4	2001	Demetroulis et al.25	UK	RCT	10	Misoprostol and D&C	28.4	72.8	12
5	2018	Fernlund et al.26	Sweden	RCT	30	Misoprostol vs expectant	32.2	76.5	45
6	2004	Graziosi et al.27	Netherlands	RCT	2	Misoprostol, Cutterage	32.1	71.4	34
7	2020	Grewal et al.28	London	QCT	21	Expectant vs surgical	34	42 days	N/A
8	2019	Ibiyemi et al.29	Nigeria	RCT	7	Misoprostol vs surgery	28.38 (5.51)	N/A	N/A
9	2001	Karlsen et al.30	Norway	RCT	10	Expectant Management, Surgical Evacuation	30.8	59.5	1.1
10	2016	Lemmers et al.31	Netherlands	RCT	42	Cutterage, Expectant Management	31.8	N/A	16
11	2001	Ngai et al.32	China	RCT	15	Misoprostol vs expectant	31.5 (7.7)	43.5	14
12	2006	Niinimäki et al.33	Finland	RCT	30	Mifepristone+ misoprostol vs surgery	30.9 (6.9)	74.7	
13	2020	Nwafor et al.34	Nigeria	RCT	7	Misoprostol , MVA	N/A	58.8	1.6
14	2009	Prasad et al.35	India	RCT	8	Misoprostol vs surgery	N/A	48	N/A
15	2012	Shochet et al.36	Africa	Cohort	7 days	Surgical vs Medical	287	N/A	11
16	2013	Shokryet al.37	Egypt	Cohort	0.5	Misoprostol, Surgical Evacuation	27.1	58.8	11
17	2013	Shuaib et al.38	Yemen	RCT	7	Misopristole	28.9	N/A	43
18	2006	Trinder et al.39	United Kingdom	RCT	14	Misoprostol vs expectant vs Surgery	31.2 (5.9)	N/A	226
19	2002	Wieringa-de Waard, M et al.40	Amsterdam	QCT	42	Surgical Curettage, Expectant Management	32.8	54	14
20	2011	Wijesinghe et al.41	Sri Lanka	RCT	14	Expectant vs surgical	29.19 (5.67)	73.13 days	33 (46%)
21	2015	Zhang et al.42	US	RCT	84	Misoprostol, Surgical Evacuation	30.9	53.2	N/A
RCT: Randomized controlled trials; QCT: Quasi randomized controlled trials									

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Figure 2 a. Forest plot comparing success rate of surgical vs medical vs expectant

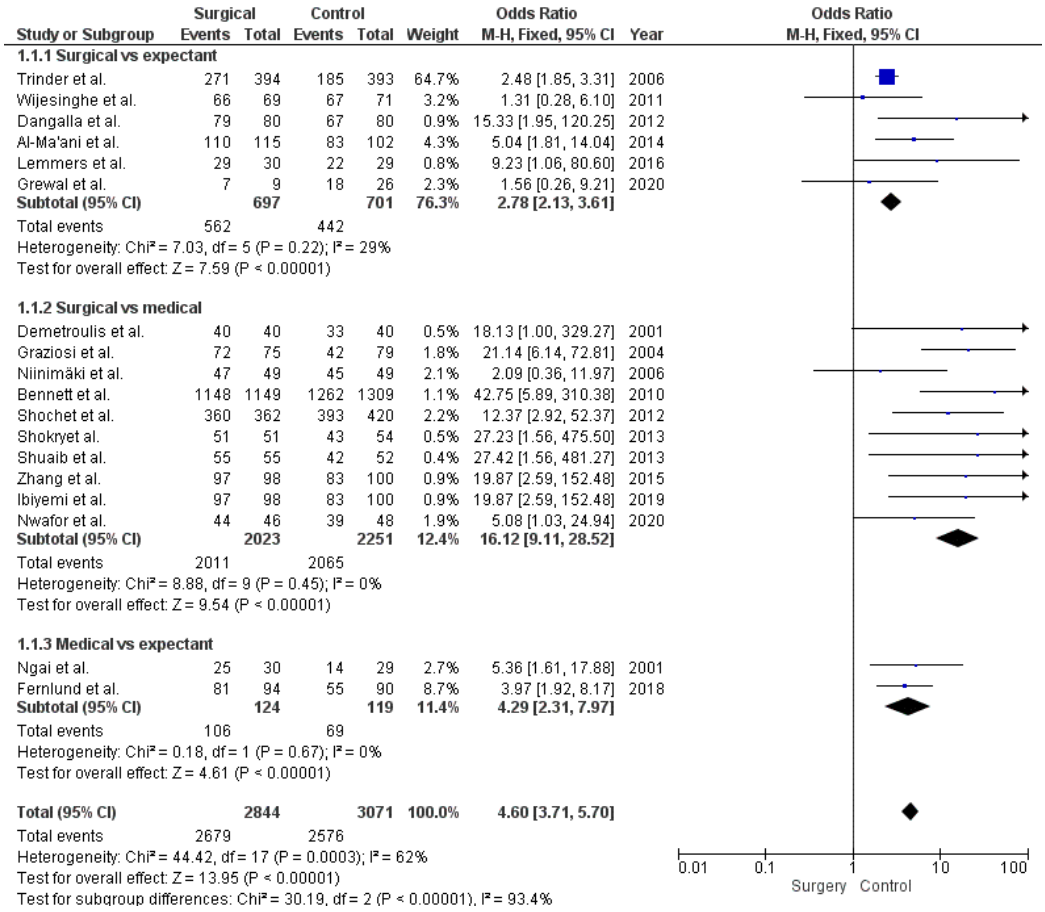


Figure 2b. Forest plot comparing abdominal pain of surgical vs medical vs expectant

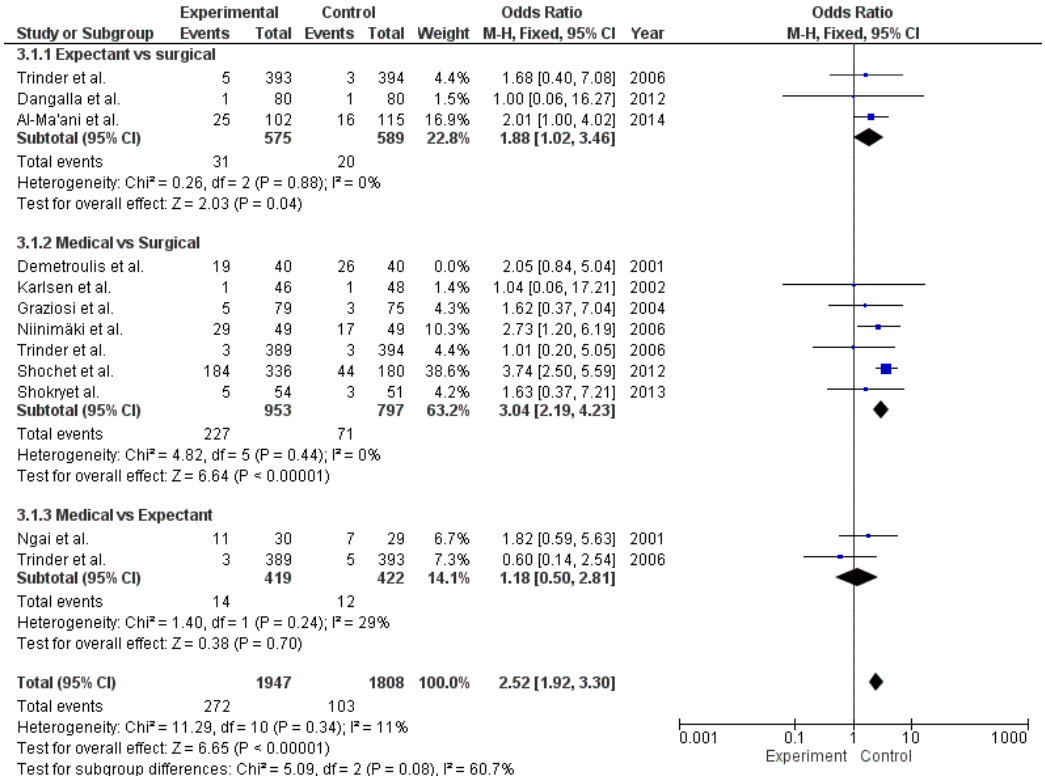


Figure 2c. Forest plot comparing Vaginal bleeding of surgical vs medical vs expectant

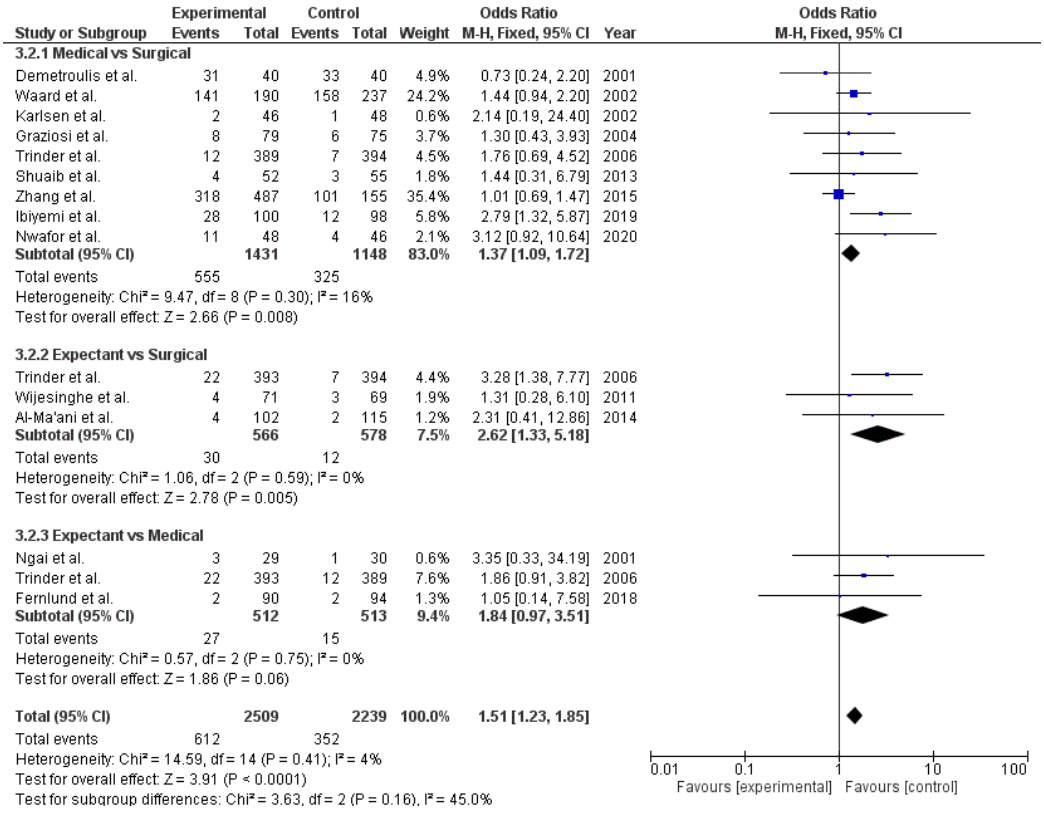
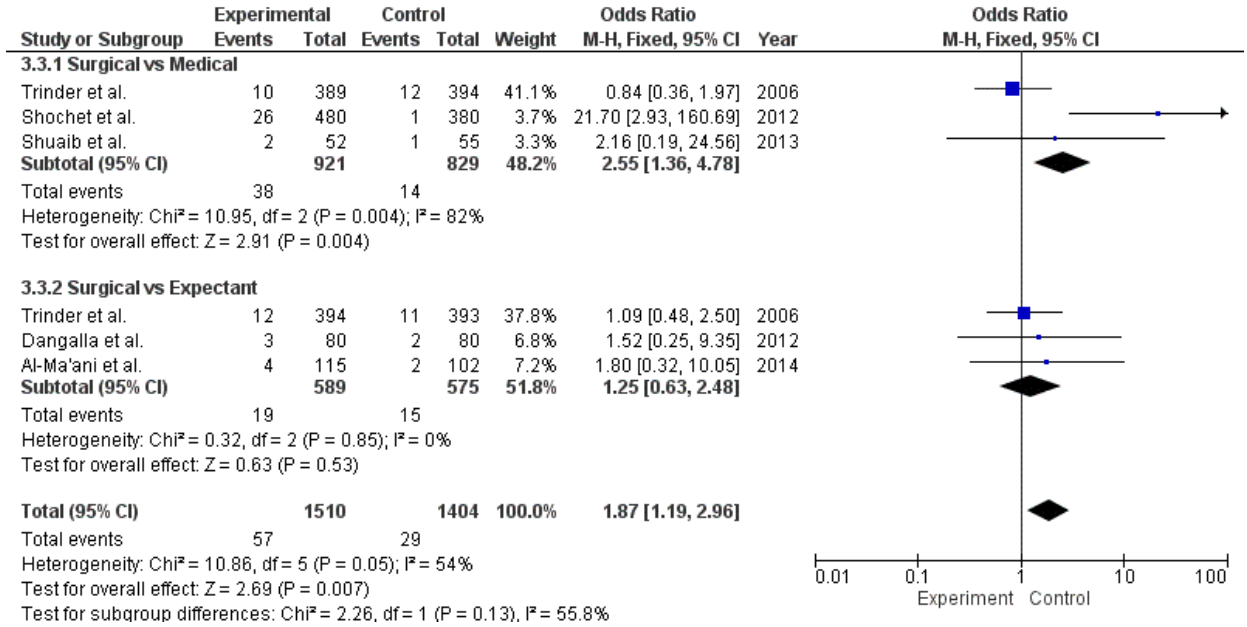


Figure 2d. Forest plot comparing Infection rate of surgical vs medical vs expectant



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5 (P = 0.22); I^2 = 29%). Whereas medical intervention had an high success rate when compared with expectant management (N=243, OR: 4.29 [2.31, 7.97], Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 = 0%). The studies showed that risk of abdominal pain was higher in medical when compared to surgical (OR: 3.04 [2.19, 4.23]) and expectant management (OR: 1.18 [0.50, 2.81]) whereas the risk was higher in expectant compared to surgical (OR: 1.88 [1.02, 3.46]). The studies showed that risk of vaginal bleeding was higher in expectant group when compared with surgical (OR: 2.62 [1.33, 5.18]) or medical (OR: 1.84 [0.97, 3.51]), while there in increased risk in medical compared to surgical group (OR:1.37 [1.09, 1.72]). The rate of infection is higher in the surgical group when compared to medical (OR: 2.55 [1.36, 4.78]) and expectant group (OR: 1.25 [0.63, 2.48]).

3.4 Publication bias

The funnel plot was symmetrical, indicating absence of publication bias as shown in **Figure 3.** Which was confirmed using Egger's regression method[21] (Egger test, P=0.621).

DISCUSSION

Among the 21 selected studies, eleven studies compared medical intervention with surgical, three compared medical management with expectant management and eight studies compared surgical with expectant management for the management of spontaneous miscarriage in the first trimester. 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. [26,39]

Mifepristone, an anti-progestin, works by blocking progesterone receptors, leading to softening and dilation of the cervix thus promoting the expulsion of pregnancy tissue. However, their effectiveness can vary depending on factors such as gestational age, dosage regimen, and individual patient response. [4,9] Surgical management use of suction or dilation and curettage (D&C) mechanically to scrape and remove tissue using surgical instruments provide direct and controlled removal of pregnancy tissue, ensuring a higher likelihood of complete abortion without the need for further intervention[4].

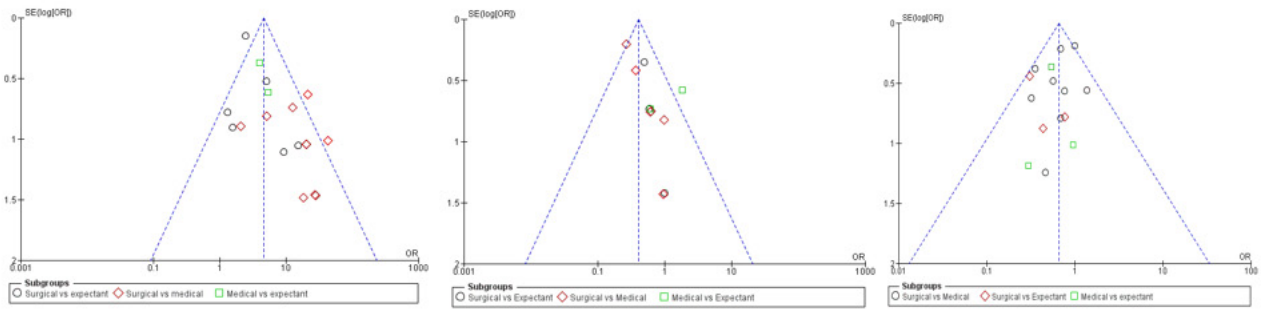
Though a higher success was observed in surgical trials, however the results of the trial a greater risk of infection following a surgical management with requirement for hospitalization when compared to medical or expectant management. Surgical methods involves invasive procedures that creates a channel for potential pathogens from the external environment or endogenous sources to enter the uterus, increasing the risk of infection.

Most common side effect observed in all three intervention was the risk of vaginal bleeding and abdominal pain among the patients before and after the management of miscarriage. The studies included collected history of vaginal bleeding and abdominal pain through self-report interviews or questionnaire. The pooled result of all the studies showed that the risk of vaginal bleeding was higher in the expectant group as this group needs to wait for the expulsion of the gestation tissue. The risk of abdominal pain was higher in the misoprostol group when compared to other intervention[43,44].

The risk of bias assessment of all the studies included in the systematic review was generally low to moderate. Blinding of participants and clinicians was not possible in most of the studies. There was no clarity regarding the selective reporting bias as the trial protocols were not assessed. Loss to follow-up and exclusions after randomization were low[45].

In present study we tried to minimize bias by assigning two independent reviewers to assess the eligibility for inclusion data extraction and assessed risk of bias independently. Data extraction was undertaken by one review author and checked by another. However, due to subjective assessments there might be some risk of bias.

Figure 3 a-c: Funnel plots of all individual studies in the meta-analysis



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 abdominal pain with the use of medical intervention, vaginal bleeding requiring blood transfusion in expectant management and higher infection rate in surgical group requiring hospitalization or antibiotic regimen. These side-effects should be explained to the women during treatment counselling. Further studies are required to compare the medical with expectant care. 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 Supplementary material S1.

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

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Authors' contributions: Shivali Negi, Kavya Sharma, Anwesa Acharya, and Ananya Prabhu 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 contributed to the development of study protocol and manuscript writing.

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

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Supplementary Table S 1

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)

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Table S2. Quality Assessment by using JBI checklists.

Authors	Study design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Ngai et al.	RCT	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Niinimäki et al.	RCT	Yes	Yes	No	N/A	Unclear	unclear	Yes	No	Yes	Yes	Yes	Yes	Yes
Trinder et al.	RCT	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prasad et al.	RCT	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Shuaib	RCT	Yes	Yes	Unclear	No	No	No	Yes	Yes	Yes	No	Unclear	Yes	Yes
Fernlund et al.	RCT	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No	No
Ibiyemi et al.	RCT	Yes	Yes	No	No	No	Unclear	Yes	Unclear	Yes	Unclear	No	Yes	Yes
Wijesinghe et al.	RCT	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dangalla et al.	RCT	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al-Ma'ani et al.	RCT	Yes	Yes	Yes	No	No	Unclear	Yes	No	Yes	Yes	Yes	No	Yes
Nwafor et al.	RCT	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al.	RCT	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lemmers et al.	RCT	Yes	Yes	Yes	No	No	No	No	Unclear	Yes	Yes	Yes	Yes	Yes
Graziosi et al.	RCT	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Demetroulis et al.	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Karlsen et al.	RCT	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**		
Bennett et al.	Cohort	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes		
Shokryet al.	Cohort	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	Unclear	No	Yes		
Shochet et al.	Cohort	Yes	Yes	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	Yes		
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**				
Grewal et al.	QCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes				
Waard et al.	QCT	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes				

RCT: Randomized Controlled Trials, QCT: Quasi Randomized Controlled Trials