

v1: 12 December 2023

## Review Article

# Impact of medical, surgical and expectant management on spontaneous miscarriage/abortion on first trimester: A systematic review and meta-analysis of randomized, controlled trials

Peer-approved: 12 December 2023

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Qeios, Vol. 5 (2023)  
ISSN: 2632-3834

Shivali Negi<sup>1</sup>, Kavya Sharma<sup>1</sup>, Anwesa Acharya<sup>2</sup>, Ananya Prabhu<sup>3</sup>, Rinshu Dwivedi<sup>4</sup>, Ramesh Athe<sup>5</sup>

1. Department of Public Health, Punjabi University, Patiala, India; 2. Department of CSE, CMR University, Bengaluru, India; 3. Manipal College of Dental Sciences (MCODS), Manipal, India; 4. Indian Institute of Information Technology (IIIT), Trichy, India; 5. Indian Institute of Information Technology (IIIT), Dharwad, India

An increase in miscarriage in the first trimester of gestation and its associated complications is burdensome 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 in choosing an appropriate treatment plan. The 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 of bias by using the guidelines of PRISAM (Preferred Report Items for Systematic Review and Meta-Analysis). Twenty-one eligible articles were included in this systematic review, comprising 7,931 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 higher 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.

**Corresponding author:** Ramesh Athe,  
[dr.athe9@gmail.com](mailto:dr.athe9@gmail.com)

## 1. 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][2][3].

As a preventive measure for the evacuation of the retained products of conception in missed miscarriage and incomplete miscarriage, therapeutic alternatives 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 a 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. Gemeprost and Dinoprost are less prevalent. 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 procedures have 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. 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.

## 2. Methodology

The systematic review and meta-analysis were performed in accordance with the PRISMA guidelines and registered in Prospero CRD42020154395 [12][13][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 effects of medical, surgical, and expectant management of first-trimester spontaneous miscarriage.

### 2.1. Eligibility

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

#### a. 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 was searched [14][15]. Randomized case-control, cohort studies, and quasi-trials of women with first-trimester miscarriage were included, and 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 from 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 that could potentially meet the inclusion criteria for this review were identified at this stage and accessed in their entirety. Cases of disagreement were resolved by consensus.

## 2.2. Data Extraction

Randomized trials, quasi-randomized studies, cohort studies, and case-control studies that evaluated medical treatment, surgical treatment, and expectant treatment management of first-trimester miscarriage, which was defined as a spontaneous loss of a non-viable intrauterine pregnancy between 0 and 13<sup>th</sup> weeks gestation, were included. Studies that evaluated a 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 an 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<sup>[14][15]</sup>.

## 2.3. Assessment of risk of bias in included studies

The risk of bias for the chosen studies was evaluated with Joanna Briggs Institute (JBI) criteria<sup>[16]</sup>. Two reviewers independently decided whether there was a “High risk,” “Low risk,” or “unclear risk” of bias. The risk of bias was ranked high when the study reached up to 49% of yes, moderate when it was (50–69)%, and low when it was above or equal to 70%.

## 2.4. 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 variables were success rate, vaginal bleeding, abdominal pain, and infection rate<sup>[14][15][17][18][19][20][21]</sup>. 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).

## 3. 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, 21 eligible articles were included in this systematic review, comprising 7931 patients undergoing medical, surgical, or expectant management for early spontaneous miscarriage<sup>[22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42]</sup> and depicted in Figure 1, with summary statistics tabulated in Table 1.

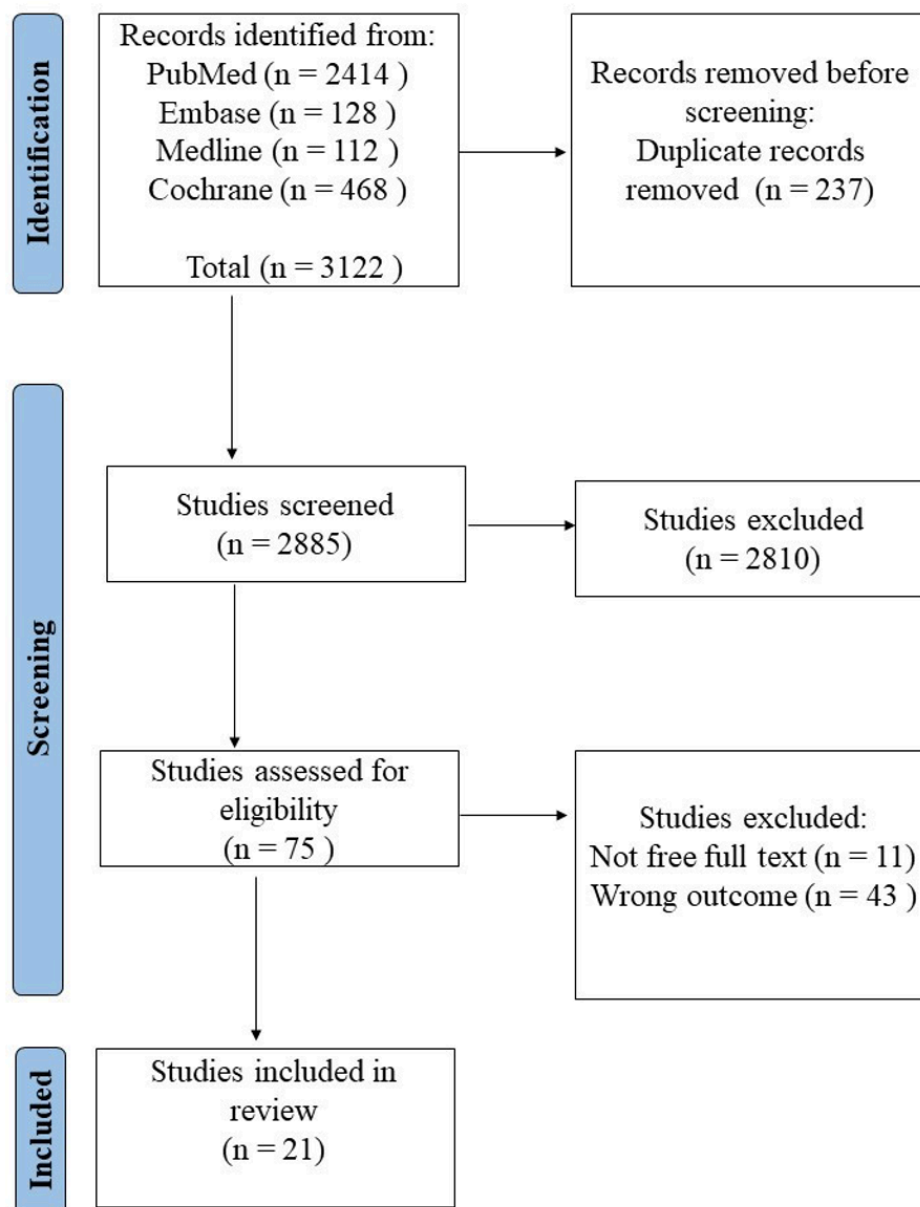


Figure 1. Represents the PRISMA flowchart for study selection

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

**Table 1.** Summary of the trials assessing the characteristics abortion

### 3.1. Study characteristics

Eleven studies compared medical intervention with surgical [23][27][31][33][34][35][36][37][38][39][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][40][41]. Out of the 21 articles included, sixteen had a randomized controlled trial design [22][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][41][42], two had a 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 the 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.

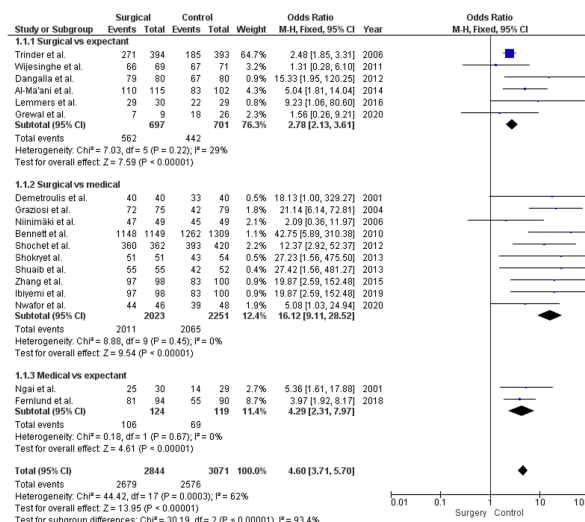
### 3.2. Risk of bias assessment

The risk of bias was estimated using the JBI scale; most studies showed a low to moderate risk of bias. The lowest risk of bias was seen in the study by Demetroulis [25] et al., and the 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**.

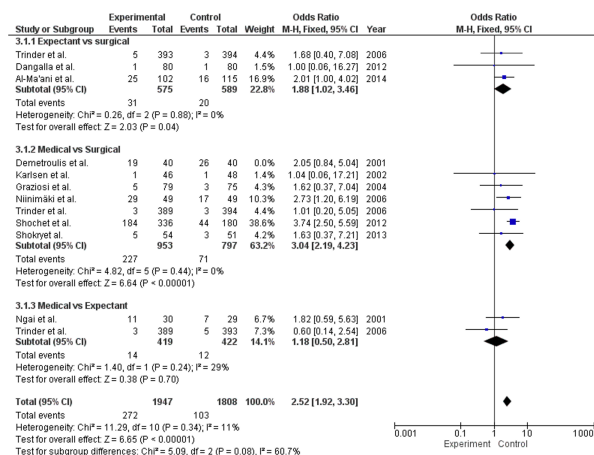
### 3.3. Meta-analysis

The results of the 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 were higher when compared with medical intervention (N= 4274, OR: 16.12 [9.11, 28.52], Heterogeneity:  $\text{Chi}^2 = 7.03$ ,  $\text{df} = 5$  ( $P = 0.22$ );  $I^2 = 29\%$ ) and expectant management (N=1398, OR: 2.78 [2.13, 3.61], Heterogeneity:  $\text{Chi}^2 = 7.03$ ,  $\text{df} = 5$  ( $P = 0.22$ );  $I^2 = 29\%$ ). Whereas medical intervention had a high success rate when compared with expectant management (N=243, OR: 4.29 [2.31, 7.97], Heterogeneity:  $\text{Chi}^2 = 0.18$ ,

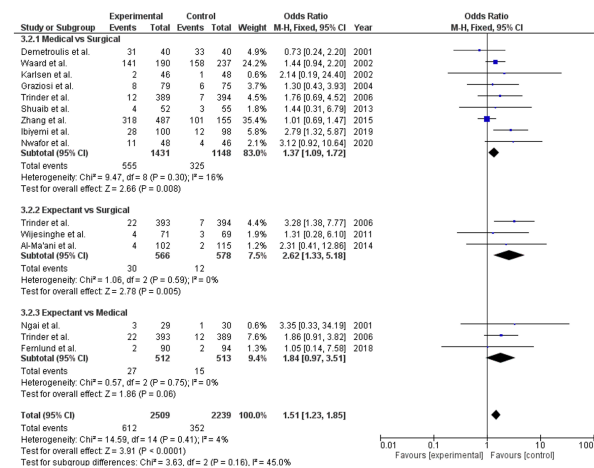
$\text{df} = 1$  ( $P = 0.67$ );  $I^2 = 0\%$ ). The studies showed that the risk of abdominal pain was higher in medical when compared to surgical (OR: 3.04 [2.19, 4.23]) and expectant management (OR: 1.18 [0.50, 2.81]), whereas the risk was higher in expectant compared to surgical (OR: 1.88 [1.02, 3.46]). The studies showed that the risk of vaginal bleeding was higher in the expectant group when compared with surgical (OR: 2.62 [1.33, 5.18]) or medical (OR: 1.84 [0.97, 3.51]), while there was an increased risk in the medical compared to the 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]).



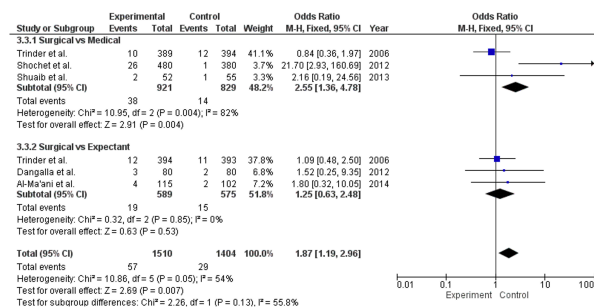
**Figure 2a.** Forest plot comparing success rates of Surgical vs Medical vs Expectant



**Figure 2b.** Forest plot comparing abdominal pain of Surgical vs Medical vs Expectant



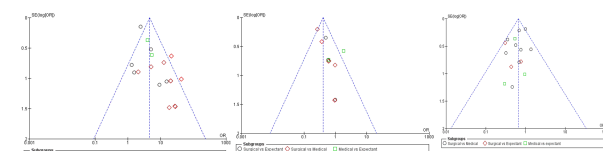
**Figure 2c.** Forest plot comparing vaginal bleeding of Surgical vs Medical vs Expectant



**Figure 2d.** Forest plot comparing infection rates of Surgical vs Medical vs Expectant

### 3.4. Publication bias

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



**Figure 3(a-c).** Funnel plot showing symmetry.

## 4. 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 management when compared to expectant, whereas the medical treatment was inferior in comparison to surgical treatment. The reason for the failure of abortion in medical vs. surgical is due to the remaining residual sac, which would require surgical evacuation<sup>[26][39]</sup>.

Though higher success was observed in surgical trials, the results of the trial showed a greater risk of infection following surgical management with a requirement for hospitalization when compared to medical or expectant management. There were no studies that compared the infection rate between medical management and expectant management.

The most common side effects observed were the risk of vaginal bleeding and abdominal pain among the patients before and after the management of miscarriage. The studies included collected the history of vaginal bleeding and abdominal pain through self-report interviews or questionnaires. 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 gestational tissue. The risk of abdominal pain was higher in the misoprostol group when compared to other interventions<sup>[43][44]</sup>.

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<sup>[45]</sup>.

In the present study, we tried to minimize bias by assigning two independent reviewers to assess the eligibility for inclusion, data extraction, and 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.

## 5. Conclusion

Although it would be critical to have more data, the current evidence suggests that medical treatment is superior to expectant care in terms of success rate and less frequent side effects and can be an alternative to surgical management of first-trimester miscarriage. The study has identified a high risk of abdominal pain with the use of medical intervention, vaginal bleeding requiring blood transfusion in expectant management, and a higher infection rate in the surgical group requiring hospitalization or an antibiotic regimen. These side effects should be explained to women during treatment counselling. Further studies are required to compare medical with expectant care. Future trials should consider women's views and quality of life measures alongside the clinical outcome.

## Declarations

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 secondary data/information.

### *Consent for publication*

All the listed authors give their due consent for publication.

### *Availability of data and material*

The present study is based on secondary data sources that are available in the mentioned databases in the

public domain. We have used data from published articles for our research. Please refer to Supplementary material S1.

## Competing interests

There are no conflicts of interest declared by the 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 the Accelerate Vigyan Vritika scheme for carrying out the study.

## Authors' contributions

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

## AI Statement

We confirm that AI has not been used to prepare the manuscript and that it has been approved by all the listed authors.

## Acknowledgements

The authors express their sincere acknowledgement to SERB Vritika and the 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.

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<sup>ir</sup> <sup>is</sup> <sup>it</sup> <sup>iu</sup> <sup>iv</sup> <sup>iw</sup> <sup>ix</sup> <sup>iy</sup> <sup>iz</sup> <sup>ja</sup> <sup>jb</sup> <sup>jc</sup> <sup>jd</sup> <sup>je</sup> <sup>jf</sup> <sup>jj</sup> <sup>jk</sup> <sup>jl</sup> <sup>jm</sup> <sup>jn</sup> <sup>jo</sup> <sup>jp</sup> <sup>jq</sup> <sup>jr</sup> <sup>js</sup> <sup>jt</sup> <sup>ju</sup> <sup>jv</sup> <sup>jw</sup> <sup>jx</sup> <sup>jy</sup> <sup>jz</sup> <sup>ka</sup> <sup>kb</sup> <sup>kc</sup> <sup>kd</sup> <sup>ke</sup> <sup>kf</sup> <sup>kg</sup> <sup>kh</sup> <sup>ki</sup> <sup>kj</sup> <sup>kk</sup> <sup>kl</sup> <sup>km</sup> <sup>kn</sup> <sup>ko</sup> <sup>kp</sup> <sup>kq</sup> <sup>kr</sup> <sup>ks</sup> <sup>kt</sup> <sup>ku</sup> <sup>kv</sup> <sup>kw</sup> <sup>kx</sup> <sup>ky</sup> <sup>kz</sup> <sup>la</sup> <sup>lb</sup> <sup>lc</sup> <sup>ld</sup> <sup>le</sup> <sup>lf</sup> <sup>lg</sup> <sup>lh</sup> <sup>li</sup> <sup>lj</sup> <sup>lk</sup> <sup>ll</sup> <sup>lm</sup> <sup>ln</sup> <sup>lo</sup> <sup>lp</sup> <sup>lq</sup> <sup>lr</sup> <sup>ls</sup> <sup>lt</sup> <sup>lu</sup> <sup>lv</sup> <sup>lw</sup> <sup>lx</sup> <sup>ly</sup> <sup>lz</sup> <sup>ma</sup> <sup>mb</sup> <sup>mc</sup> <sup>md</sup> <sup>me</sup> <sup>mf</sup> <sup>mg</sup> <sup>mh</sup> <sup>mi</sup> <sup>mj</sup> <sup>mk</sup> <sup>ml</sup> <sup>mm</sup> <sup>mn</sup> <sup>mo</sup> <sup>mp</sup> <sup>mq</sup> <sup>mr</sup> <sup>ms</sup> <sup>mt</sup> <sup>mu</sup> <sup>mv</sup> <sup>mw</sup> <sup>mx</sup> <sup>my</sup> <sup>mz</sup> <sup>na</sup> <sup>nb</sup> <sup>nc</sup> <sup>nd</sup> <sup>ne</sup> <sup>nf</sup> <sup>ng</sup> <sup>nh</sup> <sup>ni</sup> <sup>nj</sup> <sup>nk</sup> <sup>nl</sup> <sup>nm</sup> <sup>nn</sup> <sup>no</sup> <sup>np</sup> <sup>nq</sup> <sup>nr</sup> <sup>ns</sup> <sup>nt</sup> <sup>nu</sup> <sup>nv</sup> <sup>nw</sup> <sup>nx</sup> <sup>ny</sup> <sup>nz</sup> <sup>oa</sup> <sup>ob</sup> <sup>oc</sup> <sup>od</sup> <sup>oe</sup> <sup>of</sup> <sup>og</sup> <sup>oh</sup> <sup>oi</sup> <sup>oj</sup> <sup>ok</sup> <sup>ol</sup> <sup>om</sup> <sup>on</sup> <sup>oo</sup> <sup>op</sup> <sup>oq</sup> <sup>or</sup> <sup>os</sup> <sup>ot</sup> <sup>ou</sup> <sup>ov</sup> <sup>ow</sup> <sup>ox</sup> <sup>oy</sup> <sup>oz</sup> <sup>pa</sup> <sup>pb</sup> <sup>pc</sup> <sup>pd</sup> <sup>pe</sup> <sup>pf</sup> <sup>pg</sup> <sup>ph</sup> <sup>pi</sup> <sup>pj</sup> <sup>pk</sup> <sup>pl</sup> <sup>pm</sup> <sup>pn</sup> <sup>po</sup> <sup>pp</sup> <sup>pq</sup> <sup>pr</sup> <sup>ps</sup> <sup>pt</sup> <sup>pu</sup> <sup>pv</sup> <sup>pw</sup> <sup>px</sup> <sup>py</sup> <sup>pz</sup> <sup>qa</sup> <sup>qb</sup> <sup>qc</sup> <sup>qd</sup> <sup>qe</sup> <sup>qf</sup> <sup>qg</sup> <sup>qh</sup> <sup>qi</sup> <sup>qj</sup> <sup>qk</sup> <sup>ql</sup> <sup>qm</sup> <sup>qn</sup> <sup>qo</sup> <sup>qp</sup> <sup>qq</sup> <sup>qr</sup> <sup>qs</sup> <sup>qt</sup> <sup>qu</sup> <sup>qv</sup> <sup>qw</sup> <sup>qx</sup> <sup>qy</sup> <sup>qz</sup> <sup>ra</sup> <sup>rb</sup> <sup>rc</sup> <sup>rd</sup> <sup>re</sup> <sup>rf</sup> <sup>rg</sup> <sup>rh</sup> <sup>ri</sup> <sup>rj</sup> <sup>rk</sup> <sup>rl</sup> <sup>rm</sup> <sup>rn</sup> <sup>ro</sup> <sup>rp</sup> <sup>rq</sup> <sup>rr</sup> <sup>rs</sup> <sup>rt</sup> <sup>ru</sup> <sup>rv</sup> <sup>rw</sup> <sup>rx</sup> <sup>ry</sup> <sup>rz</sup> <sup>sa</sup> <sup>sb</sup> <sup>sc</sup> <sup>sd</sup> <sup>se</sup> <sup>sf</sup> <sup>sg</sup> <sup>sh</sup> <sup>si</sup> <sup>sj</sup> <sup>sk</sup> <sup>sl</sup> <sup>sm</sup> <sup>sn</sup> <sup>so</sup> <sup>sp</sup> <sup>sq</sup> <sup>sr</sup> <sup>ss</sup> <sup>st</sup> <sup>su</sup> <sup>sv</sup> <sup>sw</sup> <sup>sx</sup> <sup>sy</sup> <sup>sz</sup> <sup>ta</sup> <sup>tb</sup> <sup>tc</sup> <sup>td</sup> <sup>te</sup> <sup>tf</sup> <sup>tg</sup> <sup>th</sup> <sup>ti</sup> <sup>tj</sup> <sup>tk</sup> <sup>tl</sup> <sup>tm</sup> <sup>tn</sup> <sup>to</sup> <sup>tp</sup>  <sup>tq</sup> <sup>tr</sup> <sup>ts</sup> <sup>tt</sup> <sup>tu</sup> <sup>tv</sup> <sup>tw</sup> <sup>tx</sup> <sup>ty</sup> <sup>tz</sup> <sup>ua</sup> <sup>ub</sup> <sup>uc</sup> <sup>ud</sup> <sup>ue</sup> <sup>uf</sup> <sup>ug</sup> <sup>uh</sup> <sup>ui</sup> <sup>uj</sup> <sup>uk</sup> <sup>ul</sup> <sup>um</sup> <sup>un</sup> <sup>uo</sup> <sup>up</sup> <sup>uq</sup> <sup>ur</sup> <sup>us</sup> <sup>ut</sup> <sup>uu</sup> <sup>uv</sup> <sup>uw</sup> <sup>ux</sup> <sup>uy</sup> <sup>uz</sup> <sup>va</sup> <sup>vb</sup> <sup>vc</sup> <sup>vd</sup> <sup>ve</sup> <sup>vf</sup> <sup>vg</sup> <sup>vh</sup> <sup>vi</sup> <sup>vj</sup> <sup>vk</sup> <sup>vl</sup> <sup>vm</sup> <sup>vn</sup> <sup>vo</sup> <sup>vp</sup> <sup>vq</sup> <sup>vr</sup> <sup>vs</sup> <sup>vt</sup> <sup>vu</sup> <sup>vv</sup> <sup>vw</sup> <sup>vx</sup> <sup>vy</sup> <sup>vz</sup> <sup>wa</sup> <sup>wb</sup> <sup>wc</sup> <sup>wd</sup> <sup>we</sup> <sup>wf</sup> <sup>wg</sup> <sup>wh</sup> <sup>wi</sup> <sup>wj</sup> <sup>wk</sup> <sup>wl</sup> <sup>wm</sup> <sup>wn</sup> <sup>wo</sup> <sup>wp</sup> <sup>wq</sup> <sup>wr</sup> <sup>ws</sup> <sup>wt</sup> <sup>wu</sup> <sup>wv</sup> <sup>ww</sup> <sup>wx</sup> <sup>wy</sup> <sup>wz</sup> <sup>xa</sup> <sup>xb</sup> <sup>xc</sup> <sup>xd</sup> <sup>xe</sup> <sup>xf</sup> <sup>xg</sup> <sup>xh</sup> <sup>xi</sup> <sup>xj</sup> <sup>xk</sup> <sup>xl</sup> <sup>xm</sup> <sup>xn</sup> <sup>xo</sup> <sup>xp</sup> <sup>xq</sup> <sup>xr</sup> <sup>xs</sup> <sup>xt</sup> <sup>xu</sup> <sup>xv</sup> <sup>xw</sup> <sup>xx</sup> <sup>xy</sup> <sup>xz</sup> <sup>ya</sup> <sup>yb</sup> <sup>yc</sup> <sup>yd</sup> <sup>ye</sup> <sup>yf</sup> <sup>yg</sup> <sup>yh</sup> <sup>yi</sup> <sup>yj</sup> <sup>yk</sup> <sup>yl</sup> <sup>ym</sup> <sup>yn</sup> <sup>yo</sup> <sup>yp</sup> <sup>yq</sup> <sup>yr</sup> <sup>ys</sup> <sup>yt</sup> <sup>yu</sup> <sup>yv</sup> <sup>yw</sup> <sup>yx</sup> <sup>yy</sup> <sup>yz</sup> <sup>za</sup> <sup>zb</sup> <sup>zc</sup> <sup>zd</sup> <sup>ze</sup> <sup>zf</sup> <sup>zg</sup> <sup>zh</sup> <sup>zi</sup> <sup>zj</sup> <sup>zk</sup> <sup>zl</sup> <sup>zm</sup> <sup>zn</sup> <sup>zo</sup> <sup>zp</sup> <sup>zq</sup> <sup>zr</sup> <sup>zs</sup> <sup>zt</sup> <sup>zu</sup> <sup>zv</sup> <sup>zw</sup> <sup>zx</sup> <sup>zy</sup> <sup>zz</sup> <sup>aa</sup> <sup>ab</sup> <sup>ac</sup> <sup>ad</sup> <sup>ae</sup> <sup>af</sup> <sup>ag</sup> <sup>ah</sup> <sup>ai</sup> <sup>aj</sup> <sup>ak</sup> <sup>al</sup> <sup>am</sup> <sup>an</sup> <sup>ao</sup> <sup>ap</sup> <sup>aq</sup> <sup>ar</sup> <sup>as</sup> <sup>at</sup> <sup>au</sup> <sup>av</sup> <sup>aw</sup> <sup>ax</sup> <sup>ay</sup> <sup>az</sup> <sup>ba</sup> <sup>bb</sup> <sup>bc</sup> <sup>bd</sup> <sup>be</sup> <sup>bf</sup> <sup>bg</sup> <sup>bh</sup> <sup>bi</sup> <sup>bj</sup> <sup>bk</sup> <sup>bl</sup> <sup>bm</sup> <sup>bn</sup> <sup>bo</sup> <sup>bp</sup> <sup>bq</sup> <sup>br</sup> <sup>bs</sup> <sup>bt</sup> <sup>bu</sup> <sup>bv</sup> <sup>bw</sup> <sup>bx</sup> <sup>by</sup> <sup>bz</sup> <sup>ca</sup> <sup>cb</sup> <sup>cc</sup> <sup>cd</sup> <sup>ce</sup> <sup>cf</sup> <sup>cg</sup> <sup>ch</sup> <sup>ci</sup> <sup>cj</sup> <sup>ck</sup> <sup>cl</sup> <sup>cm</sup> <sup>cn</sup> <sup>co</sup> <sup>cp</sup> <sup>cq</sup> <sup>cr</sup> <sup>cs</sup> <sup>ct</sup> <sup>cu</sup> <sup>cv</sup> <sup>cw</sup> <sup>cx</sup> <sup>cy</sup> <sup>cz</sup> <sup>da</sup> <sup>db</sup> <sup>dc</sup> <sup>dd</sup> <sup>de</sup> <sup>df</sup> <sup>dg</sup> <sup>dh</sup> <sup>di</sup> <sup>dj</sup> <sup>dk</sup> <sup>dl</sup> <sup>dm</sup> <sup>dn</sup> <sup>do</sup> <sup>dp</sup> <sup>dq</sup> <sup>dr</sup> <sup>ds</sup> <sup>dt</sup> <sup>du</sup> <sup>dv</sup> <sup>dw</sup> <sup>dx</sup> <sup>dy</sup> <sup>dz</sup> <sup>ea</sup> <sup>eb</sup> <sup>ec</sup> <sup>ed</sup> <sup>ee</sup> <sup>ef</sup> <sup>eg</sup> <sup>eh</sup> <sup>ei</sup> <sup>ej</sup> <sup>ek</sup> <sup>el</sup> <sup>em</sup> <sup>en</sup> <sup>eo</sup> <sup>ep</sup> <sup>eq</sup> <sup>er</sup> <sup>es</sup> <sup>et</sup> <sup>eu</sup> <sup>ev</sup> <sup>ew</sup> <sup>ex</sup> <sup>ey</sup> <sup>ez</sup> <sup>fa</sup> <sup>fb</sup> <sup>fc</sup> <sup>fd</sup> <sup>fe</sup> <sup>ff</sup> <sup>fg</sup> <sup>fh</sup> <sup>fi</sup> <sup>fj</sup> <sup>fk</sup> <sup>fl</sup> <sup>fm</sup> <sup>fn</sup> <sup>fo</sup> <sup>fp</sup> <sup>fq</sup> <sup>fr</sup> <sup>fs</sup> <sup>ft</sup> <sup>fu</sup> <sup>fv</sup> <sup>fw</sup> <sup>fx</sup> <sup>fy</sup> <sup>fz</sup> <sup>ga</sup> <sup>gb</sup> <sup>gc</sup> <sup>gd</sup> <sup>ge</sup> <sup>gf</sup> <sup>gg</sup> <sup>gh</sup> <sup>gi</sup> <sup>gj</sup> <sup>gk</sup> <sup>gl</sup> <sup>gm</sup> <sup>gn</sup> <sup>go</sup> <sup>gp</sup> <sup>gq</sup> <sup>gr</sup> <sup>gs</sup> <sup>gt</sup> <sup>gu</sup> <sup>gv</sup> <sup>gw</sup> <sup>gx</sup> <sup>gy</sup> <sup>gz</sup> <sup>ha</sup> <sup>hb</sup> <sup>hc</sup> <sup>hd</sup> <sup>he</sup> <sup>hf</sup> <sup>hg</sup> <sup>hh</sup> <sup>hi</sup> <sup>hj</sup> <sup>hk</sup> <sup>hl</sup> <sup>hm</sup> <sup>hn</sup> <sup>ho</sup> <sup>hp</sup> <sup>hq</sup> <sup>hr</sup> <sup>hs</sup> <sup>ht</sup> <sup>hu</sup> <sup>hv</sup> <sup>hw</sup> <sup>hx</sup> <sup>hy</sup> <sup>hz</sup> <sup>ia</sup> <sup>ib</sup> <sup>ic</sup> <sup>id</sup> <sup>ie</sup> <sup>if</sup> <sup>ig</sup> <sup>ih</sup> <sup>ii</sup> <sup>ij</sup> <sup>ik</sup> <sup>il</sup> <sup>im</sup> <sup>in</sup> <sup>io</sup> <sup>ip</sup> <sup>iq</sup> <sup>ir</sup> <sup>is</sup> <sup>it</sup> <sup>iu</sup> <sup>iv</sup> <sup>iw</sup> <sup>ix</sup> <sup>iy</sup> <sup>iz</sup> <sup>ja</sup> <sup>jb</sup> <sup>jc</sup> <sup>jd</sup> <sup>je</sup> <sup>jf</sup> <sup>jj</sup> <sup>jk</sup> <sup>jl</sup> <sup>jm</sup> <sup>jn</sup> <sup>jo</sup> <sup>jp</sup> <sup>jq</sup> <sup>jr</sup> <sup>js</sup> <sup>jt</sup> <sup>ju</sup> <sup>jv</sup> <sup>jw</sup> <sup>jx</sup> <sup>jy</sup> <sup>jz</sup> <sup>ka</sup> <sup>kb</sup> <sup>kc</sup> <sup>kd</sup> <sup>ke</sup> <sup>kf</sup> <sup>kg</sup> <sup>kh</sup> <sup>ki</sup> <sup>kj</sup> <sup>kk</sup> <sup>kl</sup> <sup>km</sup> <sup>kn</sup> <sup>ko</sup> <sup>kp</sup> <sup>kq</sup> <sup>kr</sup> <sup>ks</sup> <sup>kt</sup> <sup>ku</sup> <sup>kv</sup> <sup>kw</sup> <sup>kx</sup> <sup>ky</sup> <sup>kz</sup> <sup>la</sup> <sup>lb</sup> <sup>lc</sup> <sup>ld</sup> <sup>le</sup> <sup>lf</sup> <sup>lg</sup> <sup>lh</sup> <sup>li</sup> <sup>lj</sup> <sup>lk</sup> <sup>ll</sup> <sup>lm</sup> <sup>ln</sup> <sup>lo</sup> <sup>lp</sup> <sup>lq</sup> <sup>lr</sup> <sup>ls</sup> <sup>lt</sup> <sup>lu</sup> <sup>lv</sup> <sup>lw</sup> <sup>lx</sup> <sup>ly</sup> <sup>lz</sup> <sup>ma</</sup>

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**Supplementary data:** available at <https://doi.org/10.32388/DZS0QK.2>

## Declarations

**Funding:** 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.

**Potential competing interests:** No potential competing interests to declare.