UPDATES ON MANAGEMENT OF MISSED ABORTION AND ITS PSYCHOLOGICAL OUTCOMES: A SYSTEMATIC REVIEW

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Abstract

Objectives: To study the recently published literature on the diagnosis and management of missed abortion.

Methods: We conducted a thorough search of PubMed, SCOPUS, Web of Science, and Google Scholar to find pertinent literature. Rayyan QRCI was utilized during the entire process.

Results: We included eight studies with a total of 931 participants. High antimullerian hormone (AMH) levels and low neutrophile count were demonstrated as predictive factors for missed abortion. Combining aromatase inhibitor medication (letrozole) or blocking progesterone (mifepristone) with misoprostol had favorable results than misoprostol alone regarding lower odds of non-expulsion, shorter time required for expulsion Regarding the route of administration, two studies found that vaginal misoprostol was more effective and smaller mean pain score. Transdermal electrical stimulation in conjunction with mifepristone plus methyl carboprost suppository can decrease the bleeding duration and volume, and encourage the thickening of the endometrium.

Conclusion: We found a lack of data that investigates the diagnosis and prediction of missed abortion. However, AMH level and neutrophil count were documented as significant prediction factors for the incidence of missed abortion. Misoprostol was effective in managing our condition, but combining progesterone blockade agents and aromatase inhibitors showed better responses. Additionally, vaginal misoprostol was found to be the best route of administration regarding the response and complications. Further research, especially prospective RCTs are required for better understanding and more results.

Keywords: Missed abortion; Diagnosis; Management; Systematic review.

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Introduction

In the first and second trimesters, 15–20% of all known pregnancies terminate spontaneously [1]. While most of these losses are clear-cut cases of spontaneous miscarriages, some pregnancies end abruptly without any noticeable symptoms. Historically, surgical dilatation and curettage or manual vacuum aspiration have been used to treat asymptomatic non-viable pregnancies (missed abortions). When carried out by a skilled provider in the right environment, these surgical procedures have shown to be very effective and have a low rate of complications. Periodically, serious side effects like infection, uterine perforation, and cervical laceration can happen, especially in places where facilities and care may be scarce. The medical management of non-viable pregnancies is gaining traction [2].

Surgical evacuation, which has been performed extensively worldwide over the past 50 years, is considered the standard treatment for missed abortions, with a success rate of about 95% [3]. One significant unanswered issue, though, is the expense of hospitalization and surgery, as well as the risks connected to anesthesia and surgery. In addition to infection and bleeding, women who have missed abortions and have not yet achieved their dream of motherhood may find that reduced fertility brought on by intrauterine adhesions is intolerable. Thus, some research suggests that rather than surgical evacuation, medicinal care or pregnancy could be a better option [4].

The absence of heartbeats during early pregnancy is the basis for an ultrasound diagnosis of a dead fetus. A dead fetus moves because of passive fluctuation. There may be later secondary changes in the dead fetus that point to a pregnancy-related issue. These are all contingent upon the amount of time that elapses between the time of intrauterine death and the diagnosis [5].

A missed abortion should only be evacuated if the mother's blood fibrinogen level is more than 1 g/L. Parenteral fibrinogen or heparin, which stops additional coagulation and enables intravascular fibrinogen value improvement, can be used to accomplish this. Nowadays, misoprostol is used in a procedure known as "drug curettage" to end pregnancies [6]. Although Cytotec, a synthetic prostaglandin analog with E1 features, can be given at any point in a pregnancy, its best results come from early pregnancy terminations that occur no later than week 12 [7]. This systematic review investigated the recently published literature on the diagnosis and management of missed abortion.

Methodology

Study Design and Duration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review [8]. In April 2024, the systematic review got started.

Search strategy

To find relevant material, a comprehensive search was conducted using four key databases: PubMed, SCOPUS, Web of Science, and Google Scholar. We searched through databases that contained only English content, paying attention to the unique requirements of each. To find the relevant papers, we converted the following keywords to PubMed Mesh terms; "Missed abortion," "Medical treatment," "Surgical evacuation," and "Diagnosis." "OR," "AND," and "NOT," three boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Any study design that discussed the recent literature on the diagnosis and management of missed abortion.
- Studies conducted in the last five years (2020-2024).
- We did not include studies that discussed the treatment of missed abortion with complications.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

Two output verifications of the search method were conducted using Rayyan (QCRI) [9]. By using inclusion/exclusion criteria, the researchers evaluated how relevant the abstracts and titles were to the combined search results. The reviewers carefully considered every manuscript that met the inclusion requirements. The authors talked about ways to resolve conflicts. A pre-made data extraction form was used to upload the approved study. The authors extracted data on the study title, authors, study year, country, participants, age, gender, gestational age (GA), history of previous abortions, diagnosis, and management. A separate sheet was built for the risk of bias assessment.

Strategy for data synthesis

Summary tables using information from relevant studies were compiled to provide a qualitative assessment of the research's findings and components. The best technique for making use of the data from the included study articles was chosen after the data for the systematic review was gathered.

Results

Search results

The systematic search produced 714 study articles in total, of which 298 duplicates were eliminated. After 416 studies had their titles and abstracts screened, 366 were not included. After 50 reports were requested to be retrieved, 3 articles were not found. After screening 47 studies for full-text assessment, 27 were rejected due to incorrect study results, 8 were rejected due to incorrect population type, and 4 articles were editor's letters. This systematic review included eight eligible study articles. A synopsis of the procedure for choosing studies is provided in (Figure 1).

Characteristics of the included studies

Table (1) shows the sociodemographic details of the research articles that are included. Our results included eight studies with a total of 931 participants. Four studies were randomized control trials (RCTs) [10, 11, 12, 16, 17], two were case-controls [13, 15], and one was retrospective cohort [15]. Three studies were conducted in Iran [12, 16, 17], three in China [13, 14, 15], one in Egypt [10], and one in india [11].

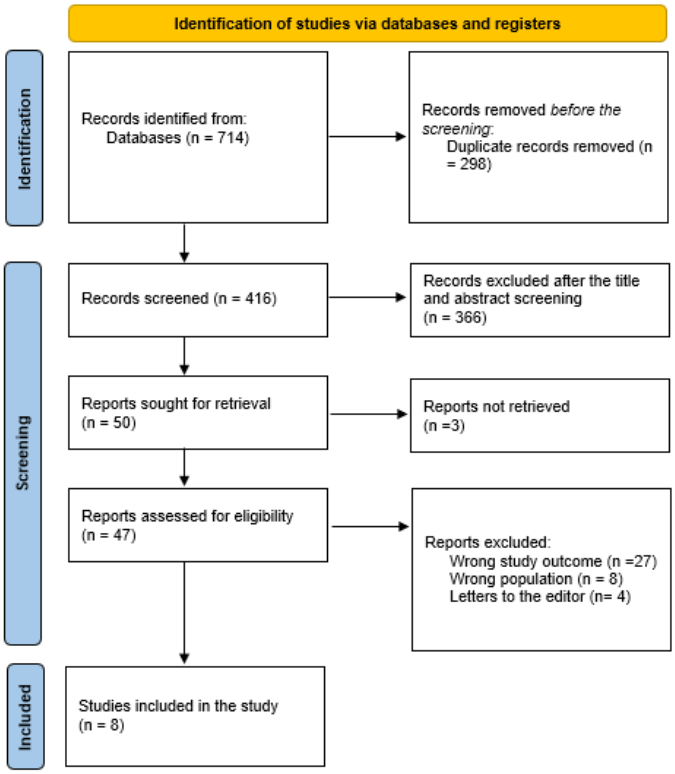

Figure 1. Study selection is summed up in a PRISMA flowchart.

Diagnosis

Table (2) presents the clinical characteristics. Only two studies discussed the diagnosis and predicting factors of missed abortion. High AMH levels [13] and low neutrophile count [14] were demonstrated as predictive factors for missed abortion.

Treatment

One study found that single- and multiple-dose letrozole regimens that were followed by misoprostol had a higher rate of abortion completion and a shorter time to complete [10], while another study stated that misoprostol alone was found to be just as effective as misoprostol with letrozole [17].

Other combinations such as mifepristone followed by misoprostol had lower odds of non-expulsion, shorter time required for expulsion, and surgical evacuation due to excessive bleeding than misoprostol alone [11].

Regarding the route of administration, two studies found that vaginal misoprostol was more effective and smaller mean pain score [12, 16].

Transdermal electrical stimulation in conjunction with mifepristone plus methyl carboprost suppository can decrease the bleeding duration and volume, and encourage the thickening of the endometrium [15] (Table 1, Table 2).

Discussion

This review represents the most recent and comprehensive synthesis of data for the management and diagnosis of missed abortion. We found that high AMH levels [13] and low neutrophile count [14] were demonstrated as predictive factors for missed abortion. According to a recent study, patients frequently experience inflammatory reactions, and inflammation is one of the main causes of missed abortions [18]. According to Zhang et al. [19], rats transplanted with human amniotic epithelial cells showed considerable improvements in their ovarian reserve and fertility, as well as an increase in AMH and a decrease in inflammation. Therefore, patients with missed abortions may see a drop in their AMH level due to inflammatory reactions, as opposed to normal pregnant women. AMH is regarded as a reliable indicator of the function of ovarian reserve. Meanwhile, new studies have revealed that AMH is expressed in the endometrium as well. AMH controls the viability and proliferation of endometriosis cells, suggesting that it could be a potential treatment for endometriosis [20].

Elevated white blood cell and neutrophil counts could indicate the presence of inflammation, infection, bleeding, necrosis of tissue, stressful conditions, or gestational diabetes [21, 22]. In a variety of domains, neutrophil-to-lymphocu=yte ratio (NLR) has recently gained popularity as a viable substitute diagnostic technique for systemic inflammatory response [23-25]. Previous research revealed that leucocytosis during pregnancy was mostly caused by neutrophilia [26], and that total leukocyte counts in normal pregnancy were much greater than those in nonpregnant controls [27]. Therefore, it makes sense that NLR changed as the study's neutrophil levels changed. On the other hand, prior research has indicated that NLR is raised in a number of pregnancy problems that can impact the course of the pregnancy, including hyperemesis gravidarum, gestational diabetes, HELLP syndrome, preeclampsia, and miscarriage.

A recent systematic review and meta-analysis conducted by Abu-Zaid et al. stated that misoprostol was given before surgery to patients having abdominal hysterectomy, and it was found to be generally safe and significantly reduce blood loss-related morbidities. The current study found that combining aromatase inhibitor medication (letrozole) or blocking progesterone (mifepristone) with misoprostol had favorable results than misoprostol alone

Table 1. Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age
Tadros et al., 2023 [10]	Prospective RCT	Egypt	Group 1 Single dose letrozole (n=32), Group 2 Multiple dose letrozole (n=32), and Group 3 Misoprostol (n=32)	29.8 ± 6.8
Gupta et al., 2023 [11]	Prospective RCT	India	Group A (n=49) (Mife + Miso) and Group B (n=49) (Miso)	Less than 25-40 (range)
Mahmoodinasab et al., 2023 [12]	RCT	Iran	Intervention (Evening Primrose and misoprostol) (n=70) and Control (misoprostol alone) (n=70)	25.8 ± 4.4
Xia et al., 2021 [13]	Case-control	China	Control group (n=51) and Observation Group (n=46)	28.9 ± 5.7
Wang et al., 2020 [14]	Retrospective cohort	China	Normal group (n = 53) and missed abortion group (n = 69)	28.6 ± 5.8
Nie and Chen 2020 [15]	Case-control	China	Observation group (n=44) and Control group (n=42)	27.8 ± 5.2
Souizi et al., 2020 [16]	RCT	Iran	Vaginal (n=63), Oral (n=53), and Sublingual (n=56)	29.8 ± 6.7
Allameh et al., 2020 [17]	RCT	Iran	Misoprostol alone (n=60) and Misoprostol + letrozole (n=60)	22-41 (range)

Table 2. Clinical characteristics and outcomes of the included studies.

Study	GA	History of previous abortions	Diagnosis	Management
Tadros et al., 2023 [10]	7.1 ± 0.6	NM	NM	Compared to misoprostol alone, single- and multiple-dose letrozole regimens that were followed by misoprostol had a higher rate of abortion completion and a shorter time to complete.
Gupta et al., 2023 [11]	NM	NM	NM	Using Fisher's exact test, it was found that misoprostol had significantly higher odds of non-expulsion of the resulting baby, longer time required for expulsion, and surgical evacuation due to excessive bleeding than mifepristone followed by misoprostol.
Mahmoodinasab et al., 2023 [12]	11.4 ± 3.9	43 (30.7%)	NM	In cases of missed abortion, administration of vaginal evening primrose before vaginal misoprostol was found to be more successful than misoprostol alone. Although there was a smaller mean pain score in the intervention group (p>0.05), there was no discernible difference between the two groups.
Xia et al., 2021 [13]	NM	14 (14.4%)	It is anticipated that a serum AMH level will be a reliable predictive factor for early missed abortion diagnosis.	NM
Wang et al., 2020 [14]	Jul-13	NM	At 8–13 weeks of gestation, the neutrophil counts in the missed abortion groups were considerably lower than in the normal controls. As early as week seven of gestation, neutrophil counts may be able to identify missed abortions as a prospective indication for missed abortion in the first trimester of pregnancy.	NM
Nie and Chen 2020 [15]	7.8 ± 2.1	NM	NM	In order to treat missed abortions, transdermal electrical stimulation in conjunction with mifepristone plus methyl carboprost suppository can decrease the duration, volume, and encourage the thickening of the endometrium.
Souizi et al., 2020 [16]	8.4 ± 2.2	49 (28.5%)	NM	The three groups (vaginal, oral, and sublingual) varied significantly in terms of the success rate of abortions and the period between drug administrations. For a full abortion, vaginal misoprostol administration is more effective than sublingual and oral administration.
Allameh et al., 2020 [17]	05-Dec	16 (13.3%)	NM	For missed abortions in the first trimester, misoprostol alone was found to be just as effective as misoprostol with letrozole.

*NM=Not-mentioned

regarding lower odds of non-expulsion, shorter time required for expulsion [10, 11].

Regarding the route of administration, two studies in this review found that vaginal misoprostol was more effective and smaller mean pain score [12, 16]. The National Institute for Health and Care Excellence (NICE) and certain professional guidelines recommended 800 ug of vaginal misoprostol for missed abortions [29, 30]. When misoprostol was taken orally or sublingually, side effects were most likely to occur. The least amount of side effects and a low likelihood of complete abortion were noted while using a modest dosage of vaginal misoprostol [31]. When sublingual misoprostol, either 600 ug or 400 ug, was administered instead of vaginally or orally, it was linked to a higher frequency of fever and diarrhea. The reason for this was revealed by the pharmacokinetics of misoprostol, which indicated that among the delivery routes, sublingual misoprostol had the quickest onset of action, the highest peak concentration, and the greatest bioavailability [32].

We also found that transdermal electrical stimulation in conjunction with mifepristone plus methyl carboprost suppository can decrease the bleeding duration and volume, and encourage the thickening of the endometrium [15].

A novel synthetic anti-progesterone drug is mifepristone. Its treatment for missed abortions involves the following mechanisms: affinity for the uterine progesterone receptors, blocking the effect of progesterone, and promoting necrosis and decidual degeneration; lowering HCG production, encouraging the dissolution of the corpus luteum, stimulating the increase of prostaglandin secretion, enhancing the sensitivity of uterine smooth muscle, and softening the cervix; controlling the ratio of progesterone to estradiol, stimulating the uterine muscle, and encouraging the contraction of the uterus, thereby encouraging the expulsion of embryos [33]. Methyl carboprost suppository stimulates the smooth muscle of the uterus, which in turn promotes the uterus's rhythmic contraction and speeds up the exfoliation and ejection of the embryo [34].

Synergistic enhancement produced by transcutaneous electrical stimulation in conjunction with mifepristone and methyl carboprost suppository can induce emphysema ejection and end a pregnancy. One of the contemporary physical therapies is transcutaneous electrical stimulation. It is frequently utilized in therapeutic practice and has a wide range of effects, including stimulating or inhibiting autonomic neurons, dilating blood vessels, analgesia, and stimulating or encouraging muscular contraction [35].

Conclusion

We found a lack of data that investigates the diagnosis and prediction of missed abortion. However, AMH level and neutrophil count were documented as significant prediction factors for the incidence of missed abortion. Misoprostol was effective in managing our condition, but combining progesterone blockade agents and aromatase inhibitors showed better responses. Additionally, vaginal misoprostol was found to be the best route of administration regarding the response and complications. Further research, especially prospective RCTs are required for better understanding and more results.

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