The Role and Efficacy of Misoprostol in Pregnancy Termination – A Review Article

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ABSTRACT

Various routes of misoprostol have been employed in order to induction abortion. Several studies have demonstrated that misoprostol can be given either in combination with mifepristone or alone. Higher success rate have been reported in several investigations in regimens that include a combination of misoprostol and mifepristone in the second trimester. However, evidences in early pregnancy are controversial. Evidences have shown that higher and frequent doses of misoprostol are more effective. Vaginally administrated misoprostol in both first and second trimester pregnancies had higher expulsion rate and less complication compared to oral routes. The majority of participants preferred oral routes due to more convenient and privacy. Regimens that include an initial high dose of vaginally administrated misoprostol followed by frequent doses of orally administrated misoprostol had the highest acceptability and response rate.

INTRODUCTION

Pregnancy termination is not a novel matter in medicine and it has been practiced since ancient times [1]. In the past decades, surgical methods have been widely used for termination of pregnancy. However, their usage is limited nowadays due to their critical and fatal complications [2]. Thus, so many medical treatments have been emerged for induced abortion. Several advantages, including high efficacy, safety, affordability and availability have been recommended for medical termination [3, 4]. The medications which are widely used are methotrexate, mifepristone and misoprostol [5]. Combination therapy of misoprostol either with mifepristone or methotrexate have reported to be more effectual than misoprostol alone [6, 7]. Accordingly, these regimens are known as gold standard medications for induction abortion [8, 9]. An important issue about the combination therapy is the high cost of mifepristone and methotrexate. Also, the aforesaid drugs may not be available in some countries [10]. Thus, misoprostol is the treatment of choice in patients who prefer cheaper medications or in conditions in which other drugs are not available [10, 11]. In addition, it has been reported that the efficacy of misoprostol depends on several factors, including route of administration, dosage, frequency of doses and gestational age [12]. In this review we discussed the role of misoprostol in induction of abortions.

Pharmacokinetics:

Misoprostol [15-deoxy-16-hydroxy-methyl PGE1] is a synthetic analogue of prostaglandin E1 that was initially produced for the prevention of peptic ulcer disease. Misoprostol binds to the prostaglandin receptors on the myometrial surface [13]. Consequently, the endoplasmic reticulum produces calcium and results in uterine contraction [14, 15]. Misoprostol can also lead to cervical effacement during pregnancy and therefore assist in evacuation of uterus by simultaneous uterine contraction [16].

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Route of administration:

Misoprostol tablets are provided for orally administration however, it can be used in other routes such as vaginally, rectally and sublingually [17, 18]. Evidence showed that the mean times to peak concentrations for oral, sublingual, vaginal and rectal administrated misoprostol are about 8, 11, 20 and 100 min, respectively. The mean duration of action for oral and sublingual administrated misoprostol are up to 2 and 3 h, respectively and for both vaginal and rectal administrated type are reported to be up to 4 h [19]. According to the information above, vaginally administrated misoprostol takes more time to achieve peak serum levels and remains elevated longer than other routes. It is estimated that this could be due to inconsistent absorption of vaginally administrated misoprostol tablets. Vaginally administrated misoprostol can lead to regular and stronger uterus contraction and consequently mechanical dilatation of the cervix in comparison with other forms. Evidences have indicated that absorption of vaginally administrated misoprostol depends on the PH of the vaginal discharge and its volume. Therefore, the efficacy of misoprostol tablets in acidic media is estimated to be higher than other routes. Some other studies have demonstrated that misoprostol absorption may be affected by the amount of vaginal bleeding during abortion [17, 20-22].

First trimester pregnancy termination:

Orally administrated misoprostol tablets are rapidly absorbed in gastrointestinal tract. Evidences regarding the oral misoprostol for termination pregnancy are less emphasized on first trimester pregnancies and have focused more on the cervical ripening before surgical evacuation [23, 24]. However, a study demonstrated that expulsion rate with single dose of 400 mcg oral misoprostol was about 13 % [25], while, another study demonstrated that repeated doses of 400 mcg misoprostol can lead to increased expulsion rate up to 70% [26, 27]. In a study, 800 mcg orally misoprostol was administrated and its efficacy was reported to be 89% [28]. Several studies have compared the efficacy of combination therapy of misoprostol and mifepristone with misoprostol alone in early pregnancy termination. But, there was no significant difference in expulsion rate among the both groups [29, 30]. Another study compared the efficacy of single 800 mcg vaginal dose of misoprostol with 200 mcg mifepristone followed by 400 mcg oral misoprostol. The authors declared that the expulsion rate was similar in both groups [about 80%]. Parveen and colleagues administered 400 mcg of vaginally misoprostol and reported a success rate of 72% [31]. Although the success rate increased by higher doses of misoprostol, it seems that this differences may not be beneficial in clinic [32] Several investigators have demonstrated that vaginal misoprostol is a safe and effective medication for pregnancy termination in first trimester [28, 33]. In a study that Ngoc and colleagues conducted among patients with confirmed missed abortion, 800 mcg of vaginally administrated misoprostol was given to patients. The expulsion rate among this subjects was reported about 93% [28]. Evidences have established that higher serum concentration of misoprostol and increased bioavailability will be achieved, when it is administrated vaginally. Nausea and diarrhea were more reported in orally administrated misoprostol [19].

Sublingual misoprostol is also widely used for early pregnancy termination. In a study that compared the repeated doses of sublingual or vaginally administrated of 600 mcg misoprostol every 3 h up [up to three doses] the authors demonstrated the success rate was similar in both groups [about 87.5%]. But, diarrhea was significantly more prevalent in the sublingual group. They suggested to prescribe sublingual misoprostol for early pregnancy termination, when patients don’t prefer repeated vaginally administrated misoprostol [34]. A recently study compared the efficacy of various routes of single dose of 400 mcg misoprostol in cervical ripening and demonstrated that the mean time from induction to abortion, intraoperative pain score and duration of surgical evacuation in sublingual group was significantly lower than vaginal and oral routes. In contrast, some complications such as nausea, vomiting and loose motion were higher in sublingual subjects as compared to vaginal and oral routes [31]. Several investigators have demonstrated that although the effectiveness of vaginal misoprostol in early pregnancy is higher than sublingual and oral routes. However, sublingual and oral routes have more acceptability among participants due to more convenient and privacy [34, 35].

Second trimester pregnancy termination:

Numerous studies have demonstrated that various route of misoprostol are an effective agent for mid trimester pregnancy termination [36, 37]. Although, evidences have shown that uterine sensitivity to prostaglandin analogs rising with increased gestational age and consequently lower doses of these medications are needed for expulsion of pregnancy materials. But, Pregnancy termination in mid trimester, is associated with higher complications [38]. Many authors have indicated that vaginal misoprostol in second trimester pregnancy termination was also more effective than other routes. Higher complication rates have been reported for oral and sublingual administration of misoprostol.
Evidences have shown that vaginally administrated misoprostol had higher success rate and shorter induction abortion interval and also, a lower amount of misoprostol was required when it is administrated vaginally.

Several studies demonstrated that administration of vaginal misoprostol with longer interval has the same effect and has significantly lower side effects in comparison with those regimens with shorter intervals [17, 39]. Wong and colleagues demonstrated that 400 mcg misoprostol every 3h [up to 5 doses] among patients with previous pregnancy was more effective than primigravidae women, while nulliparous patients responded to 400 mcg misoprostol every 6h [for maximum of 3 doses] better than multigravidae patients [39].

Many authors have demonstrated that vaginally administrated misoprostol in second trimester is associated with higher uterine bleeding and consequently decreased absorption as opposed to orally or sublingually routes. Accordingly, orally or sublingually administrated misoprostol is recommended for patients who needed repeated doses of misoprostol, specially when the uterine started to bleed [12, 40]. In addition, some other studies have shown that cervical priming with single dose of 800 mcg vaginally administrated misoprostol was equivalent with those with subsequent similar doses of vaginal misoprostol [41, 42]. On the other hand, El-Refaey and colleagues indicated that expulsion rate and induction abortion interval with combination therapy of initial 600 mcg vaginally administrated misoprostol followed by subsequent doses of 400 mcg orally administrated misoprostol every 3h were comparable with similar repeated doses of vaginal misoprostol [43]. The safety and effectiveness of misoprostol alone has been well documented in several studies. However, many authors have indicated that, when misoprostol is administrated alone, it must be prescribed with higher doses and leads to a lower success rate, higher complications and longer induction abortion interval [44, 45]. Vrhkar and colleagues evaluated the efficacy of 200 mcg of orally administrated mifepristone and 2 days later prescribed 800 mcg of vaginally administrated misoprostol as initial dose followed by 400 mcg orally administrated misoprostol in order to induce abortion in the second trimester. The success rate in their study was above 99% which was higher compared to previous studies [7]. Another study conducted by Patel and colleagues [40] employed repeated doses of 200 mcg vaginally administrated mifepristone 24 h after 200 mcg orally administrated mifepristone. Their results were comparable with those reported by Vrhkar. But, induction to abortion interval and complications were lower compared to those by Vrhkar. It could be due to lower doses and the route of administration which were used by Patel.

The evidences are consensus regard to complications of various routes of misoprostol in second trimester termination [46, 47]. Vaginal administrated misoprostol is generally associated with fever, irregular bleeding, hot flushes and nausea and vomiting [39, 48]. On the other hand, Nausea, vomiting, diarrhea, headache, chills and rigors, unpleasant taste were more frequent in sublingual and oral routes [44, 48]. Although, oral route had higher complication rates compared to other routes but, most of the authors have indicated that the majority of patients preferred oral route [38].

Conclusion:

Many medical methods have been employed for induction of abortion during the last decade. Although, most reported evidences show a higher success rate for surgical methods, but, the majority of authors have agreed on medical methods compared to surgical routes due to their availability and lower complications [49, 50].

During the first trimester, misoprostol regimens were administrated vaginally had higher success rates compared to oral route. Also, there was no significant differences in success rate when misoprostol was prescribed in combination with mifepristone in first trimester [29]. Vice versa, this combination in second trimester showed a highly expulsion rate compared to other medications [40]. However, as previously mentioned the majority of patients preferred oral routes for termination of pregnancy in both first and second trimesters. It seems that the most effective, safe and convenient route in first trimester is orally administrated of 800 mcg misoprostol and in second trimester combination therapy with 200 mcg oral mifepristone and subsequently 800 mcg vaginally administrated misoprostol followed by 400 mcg of orally administrated misoprostol every 3 h for a maximum of 5 doses. In condition in which, mifepristone is not available, initial administration of 600 mcg vaginal misoprostol followed by 400 mcg orally administrated misoprostol has also showed high success rate.

REFERENCE

Sublingual misoprostol for cervical ripening before diagnostic hysterectomy in premenopausal women: a randomized, double blind, placebo-controlled trial. Fertility and sterility, 93[7]:2400-4.


