Misoprostol for termination of first trimester missed abortion.

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الملخص

الميزوبرستول هو مثيل البروستوكلاندين- اي 1 ويمكن ان يعطى عن طريق الفم وتحت اللسان و عن طريق المهبل وعن طريق الشرج. يعتبر هذا العقار رخيصا و ممكن خزنه في درجة حرارة الغرفه و بسبب فعاليته في احداث تقلصات رحميه اصبح عقارا مهما في مجال النسائيه و التوليد. الهدف من الدراسة هو لتقييم فعالية الميزوبرستول وذلك بأعطائه عن طريق المهبل يليه اعطائه عن طريق الفم لانهاء الاسقاط المنسي طبيا بين 8 – 13 اسبوع. هذهِ دراسه مستقبليه تضمنت ستون امرأه مشخصه بحالة اسقاط منسي ادخلوا مستشفى الزهراء العام في محافظة واسط / العراق للفتره بين تموز 2006 و تموز 2007 . 800 مايكروكرام (اربع حبوب) من الميزوبرستول توضع في الجزء الخلفي من المهبل بعد ترطيبها بالنورمال سلاين تليها جرعه عن طريق الفم (400 مايكروكرام) بعد ستة ساعات . وجرعه فمويه اخرى بعد ستة ساعات من الجرعه الاخيره للمرضى الذين لم يستجيبوا للجرعتين الاوليتين.النتائج 48 مريضه (80%) حصل اسقاط كامل. 21 منهن(35%) بعد الجرعه الاولى. 15مريضه (25%) بعد الجرعه الفمويه الاولى و 12 مريضه (20%) بعد الجرعه الفمويه الثانيه .6مريضات (10%) انتهوا بأسقاط ناقص و 6 مريضات (10%) لم يستجيبوا للعلاج بعد مرور 24 ساعه على بدأ العلاج واحتاجوا الى تداخل جراحي لانهاء الحمل. كان معدل وقت انهاء الاسقاط المنسي هو عشرة ساعات .يستنتج من الدراسة انهاء الحمل الطبي في حالات الاسقاط المنسي في الجزء الاول من الحمل بواسطة الميزوبرستول هي طريقه فعاله و امينه وعمليه.

Abstract

Background: misoprostol is prostaglandin E1 analogue that can be given by oral, sublingual, vaginal or rectal route. It is cheap and can be stored at room temperature and because of its utero-tonic action, it become an important drug in obstetric and gynecological practice.

Objectives: to evaluate the effectiveness of intravaginal followed by oral misoprostol tablets for medical termination of missed abortion between 8 – 13 weeks.

Methods : a prospective study of (60) women with diagnosed missed abortion admitted to AL- Zahraa General hospital – Wassit Governorate Iraq from July 2006 through July 2007 . 800 micrograms (4 tablets) of misoprostol inserted in the posterior fornix of the vagina after moisture with normal saline followed by oral 400 micrograms (2 tablets) 6 hours later. Another 400 micrograms were given orally 6 hours from the last dose for those patients whodid not respond to the previous two doses.

Results: (48) patients (80%) had complete expulsion . (21) Patients (35%) after the vaginal dose. (15) Patients (25%) respond after the first oral dose and (12) patients (20%) after the second oral dose. (6)

Patients (10%) had incomplete abortion; the remainder (6) patients (10%) failed to respond within 24 hours of starting treatment and require surgical evacuation. The mean time for expulsion was 10 hours.
Conclusion: first trimester missed abortion medical termination by misoprostol is effective, save and a practical Methods .
Keywords: misoprostol , first trimester missed abortion, termination

Introduction

Termination of pregnancy is one of the most common procedures in gynecological practice. About 30 million abortion are performed worldwide each year therefore the safety of the procedure is of global public importance.An increasing proportion (10%) of unsuccessful pregnancies are now diagnosed on routine first trimester ultrasonography and designed as missed abortions. (1)

Missed abortion

Refers to the clinical situation in which an intrauterine pregnancy is present but is no longer developing normally. This can manifest as an anembryonic gestation (empty sac or blighted ovum) or with fetal demise prior to 20 weeks gestation. The gestation is termed a missed only if the diagnosis of incomplete abortion or inevitable abortion is excluded (cervical os is closed).
Before widespread use of ultrasounography, the term missed abortion was applied to pregnancies with no uterine growth over prolonged period of time, typically 6 weeks.

Causes

Causes of missed abortion are generally the same as those causing spontaneous abortion or early pregnancy failure. Include anembryonic gestation (blighted ovum), fetal chromosomal abnormalities , maternal disease , embryonic anomalies , placental abnormalities , and uterine anomalies. Most spontaneous abortions are preceded by missed abortion with the exception of expulsion of a normal pregnancy because of a uterine abnormality. (2)

Frequency

Closely correlates with frequency of failed pregnancy in general. In clinically recognized pregnancies , spontaneous abortion occurs in up to 15% of cases. The rate is much higher for preclinical pregnancies. Diagnosis is made much more frequently because of increased use of early ultrasonography.

Morbidity and mortality

Associated morbidity is similar to that associated with spontaneous abortion and includes bleeding , infection , and retained products of conception . Previously , before the diagnosis of fetal demise could be made and before the condition could be treated easily, disseminated intravascular coagulation (DIC) syndrome associated with prolonged retention of a dead fetus (>6-8 wk) was reported. With early diagnosis and treatment, DIC is extremely rare.

Race: **Incidence is similar among all races**

Age: **Pregnancy failure rates increase with age and rise significantly in women older than 40 years[(2)].**

Diagnosis

History:

History is of limited value . Obtaining information about the first diagnosis of pregnancy, any human chorionic gonadotropin (hCG) tests, or abatement of symptoms of pregnancy may help increase the index of suspicion for the diagnosis of missed abortion.

Physical examination:

Physical examination is of limited value. A uterus that is small for dates or not increasing in size suggests missed abortion.Vaginal bleeding is suggestive of missed abortion . Loss of fetal heart tones or inability to obtain heart tones at the appropriate time leads to suspicion of the diagnosis .Coagulation studies are generally not indicated prior to evacuation of the uterus.

Documenting Rh status and treating appropriate-ely if the woman is Rh negative is important. [(2)]

Imaging study:

Ultrasonography : Once the hCG level has reached the discriminatory level , vaginal ultrasonography replaces blood tests as the primary means of evaluation.If a true intrauterine gestational sac is observed, ectopic pregnancy is ruled out. For naturally conceived pregnancies, the coexistence of ectopic and intrauterine pregnancy is extremely rare (1out of 30000 pregnancies) .However, with assisted reproduction technology,consider the coexistence of an ectopic and intrauterine pregnancy.After a sac has been demonstrate - ed in the uterus , the next step is to determine if the pregnancy is normal or abnormal. Transvaginal ultrasonography is the best imaging procedure to evaluate intrauterine contents. While some ultrasonography criteria strongly support the diagnosis , most patients and physicians prefer to use repeat ultrasonography to confirm that the pregnancy is a missed abortion and not simply an early normal pregnancy. In most cases, a repeat ultrasono- graphy in 1 week confirms lack of progressive development . In the case of a very

early pregnancy where the sac diameter is less than 5-6 mm, repeating the study in 10-14 days may be more effective. Serial Ultrasonography is unnecessary if ultrasonography reveals loss of previously documented heart activity . Transvaginal ultrasonography Criteria that strongly suggest embryonic demise include a crown-rump length that is greater than 5 mm without cardiac activity. The criterion that suggests a blighted ovum is a mean gestational sac diameter greater than 16 mm with absence of embryo or a mean gestational sac diameter greater than 8 mm and no yolk sac. More extensive tests, such as chromosomal analysis , are not usually indicated.However,in cases of recurrent losses, karyotyping of the parents can be useful. [3]

Methods of termination

Surgical:

Surgical evacuation is the standard of care in treating missed abortion, with suction curettage being the most common Methods . Advantages to surgical evacuation include immediate and definitive treatment with fewer medical visits . Although complications are uncommon , surgical termination has been shown to be associated with uterine perforation,cervical injuries with overall complication rate varies between 4 and 10 percent.

Medical:

The most common medical regimen used to evacuate the uterus is 400 -800 mcg per vagina of misoprostol in single or multiple doses. Trials have found success rates ranging from 70-90%. Some studies show that oral misoprostol is also an option . Sublingual administration has equivalent efficacy to vaginal misoprostol , although more diarrhea symptoms are experienced. Other medical agents, such as mifepristone (RU-486), are also used. Currently the data are conflicting on whether the combination of mifepristone and misoprostol is superior to using misoprostol alone. For now, medical treatment and expectant management are limited to clinical settings where a close association with hospital services exists or they are reserved for the patient who refuses surgical treatment.Some series have offered expectant management to patients with small amounts of tissue in the uterus . While these regimens are generally successful , a number of women require curettage because of retained tissue or bleeding . Studies have shown conflicting data on whether expectant management is as effective as medical management; however, the data tend to favor medical management. A large trial found a success rate of approximately 50% for missed abortion and anembryonic pregn-ancy within 14 days of presentation.

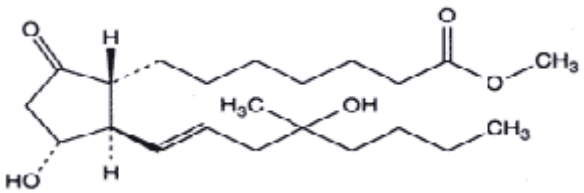
A recent meta-analysis that included 13 studies assessed the efficacy of expectant management compared with misoprostol treatment in missed abortion found complete evacuation rates of 28% and 81%, respectively.

A recent multicenter randomized controlled trial that included 1200 women who were randomized to expectant , medical , or surgical management for missed abortion found no increased risk for gynecologic infection , which was approximately 2-3% in all groups. However, the number of unplanned hospital admissions increased in the expectant and medical group compared with the surgical group . Furthermore , a follow–up economic evaluation of this study concluded that expectant and medical management were more cost – effective than traditional surgical management with expectant management being the most cost -effective.The awareness of risk and need for general anesthesia promoted the search for alternatives such as excepectant and medical Methods . Medical abortion offers great potential for improving abortion access and safety as it requires less extensive infrastructures than surgical abortion. Research has been continued to improve the medical abortion regimen since its inception. [4]

Further care:

Rho (D) - negative patients should receive anti-D immunoglobulin after a missed abortion. Emotional support and education are important. Assist the patient through the grieving process. Assure the patient that the prognosis for normal pregnancy in the future is excellent. [5]

Misoprostol



Misoprostol the synthetic analogue of PGE1 has radically changed the approach to first trimester missed abortion [6] . Misoprostol has been approved for administration by oral route for the prevention and treatment of gastroduodenal ulcers associated with the use of non-steroidal anti- inflammatory drugs [7]. The therapeutic potential of misopristol as an abortifacient has been clearly demonstrated in a randomized studies [7]. The first indication for its powerful uterotonic properties came from the Latin America when it was utilized to terminate pregnancy.

In Brazil in the 1980 they realize that uterine 'side effect' of cytotec made it a highly effective drug for 'bringing on periods' in cases of delayed menses. The knowledge that misoprostol was very effective at causing abortions spread rapidly and , and by the end of 1980s, a high proportion of abortions in Brazil were induced by misoprostol. In spite of all these advantages, misoprostol has not been approved for use in gynecology and obstetrics in most countries. However, there are signs that health regulators are embracing in the use of misoprostol [(8)]. It has also become an important drug in obstetric and gynecologic practice because of its uterotonic and cervical ripening actions . It is useful for elective medical abortion , cervical ripening before surgical abortion , evacuation of the uterus in cases of embryonic or fetal death and induction of labour . The drug may also be used to treat and prevent postpartum hemorrhage. Although, misoprostol is not approved for any of these indications in the United States.However,the FDA recognizes that, in certain circumstances , offlabel uses of approved products are appropriate rational, and accepted medical practice [(9)].

Although The World Health Organization provided the drugs for a large study in India for the comparison of oral versus vaginal misoprostol from 1998 – 2000 [(10)] ; questions remain about the route of administration, with almost every imaginable variant having been used. (Oral, vaginal, rectal, buccal, and sublingual use have all been reported.) Some studies suggest that vaginal application of misoprostol increases the success rate and reduces side effects as compared with oral or other routes, whereas the results of other studies indicate that the various routes are equally efficacious and have similar rates of side effects.In 2003 , the use of misoprostol in combination with mifepristone was approved by the United States Food and drugs Administration for the induction of labor and misoprostol has been added to the World Health Organization (WHO) Model List of Essential Drugs for the induction of labor and abortion.

In 2006 , the government of Nigeria registered misoprostol for the prevention and treatment of postpartum hemorrhage , and a national distribution program is underway in Ethiopia. Furthermore pharmacies exclusive rights to misoprostol ran out in 2005, and a number of generic alternatives to cytotec are now been produced [(11)].

The most adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain and fever.The effects of misoprostol on the reproductive tract are increased, and gastrointestinal adverse effects are decreased, if the oral preparation of misoprostol is given vaginally [(12)].Many studies of vaginal administration have used misoprostol tablets developed and registered for oral use. But the normal procedures of drug registration will make it impossible for a

Pharmaceutical company to register an oral tablet for vaginal use without considerable additional expenditure on studies and, possibly, reformulation of the tablet. So far, no company has made such an investment , in part because it would be almost impossible for such a product to compete successfully with the inexpensive misoprostol tablets currently available [13].When misoprostol tablets are placed in the posterior fornix of the vagina, the plasma concentrations of misoprostol acid peak in one to two hours and then decline slowly . Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than when administrated orally, but overall exposure to the drug is increased [14]. The greater effect on the uterus by the vaginal route is probably due to the direct access to the myometrium via the cervical canal and by transfer of drug from the perivaginal venous plexus to uterine arterioles. When complete drug induced drug expulsion does not occur, the cervical priming properties of misoprostol are helpful to perform surgical evacuation . A good cervical permeability was defined as the ability to pass a number 8 Hegar dilator [15].

Materials and Methods

The present study represents a prospective study carried in AL-Zahraa General Hospital Wassit Governorate / Iraq from July 2006 through July 2007.

(60) Patients where selected some where referred from private clinics and others came for routine antenatal care , a diagnosis of early pregnancy failure was made by an ultrasonography and defined as intrauterine gestational sac not showing any growth after a 7 days interval with or without an embryonic pole and absence of cardiac activity.

Inclusion criteria:

1 – Estimated gestational age between 8 - 13 weeks calculated from the first day of the last menstrual period(LMP)according to menstrual history.

2- No previous uterine scar

3- No previous cervical surgery.

4- No medical disorder prevent the usage of misoprostol

On examination they where found to have missed abortion without obvious symptoms . Full history including gynecological and obstetrical records was taken and a full general examination was made including measurement of blood pressure , pulse and temperature , along with necessary laboratory investigations including rhesus status. All patients admitted to the obstetric and gynecology department , consented to participate in the study, all those women had been informed about the possible risks and benefits of

medical abortion with the under standing that there would be a surgical abortion if the medical abortion failed.

800 micrograms of misoprostol (4 tablets) were digitally inserted, after moisture with normal saline , deep into the posterior vaginal fornix followed by oral 400 micrograms (2 tablets) 6 hours later if abortion does not occur .

Another 400 micrograms were given orally after 6 hours from the last dose for those patients who not respond to the previous two doses.

A complete evacuation rate was considered the primary end point. Misoprostol treatment was considered to have failed in cases of failure of uterine contraction and start of expulsion had not occurred within 24 hours from initiation of therapy or immediate interference because of abnormal bleeding. Failed cases treated by surgical evacuation.All women were followed up by an obstetrician, from admission until discharge.

They were assessed for complications that might occur during the termination process.

Results

Of the total (60) patients with missed abortion who were enrolled in this study, 48 patients (80%) had complete expulsion.(21)Of them (35%) with single vaginal dose and (15) patients (25 %) after the first oral dose (vaginal dose and one oral dose) and 12 patients (20%) after the second oral dose (complete schedule).The mean time of expulsion was 10 hours. (Table 1, 2).6 patients (10%) had incomplete expulsion , three of them after vaginal dose and one after the first oral dose and the remaining two after the second oral dose . Those (6) patients require evacuation under general anesthesia because of vaginal bleeding and retained product of conception . Table (3)

The remaining (6) patients(10%) failed to respond 24 hours after starting medical treatment , those treated by surgical evacuation under general anesthesia in the next day , all of them had good cervical permeability.Like other prostaglandins misoprostol has adverse effects like nausea , vomiting , abdominal pain ,diarrhea, shivering and fever, although gastro- intestinal tract symptoms were reported more frequently, hemorrhage was the most serious complication which was reported in 3 patients(5%) in our study none of them required blood transfusion. pain was experienced in almost all but it was sever in 2 patients (3.3%) and required treatment. high fever another uncommon side effect was observed in 1 patient. As shown in table (4)

Table -1: Clinical outcome.

outcome	Patients number	percentage
successful	48	80 %
unsuccessful	12	20 %
total	60	100 %

Table -2: Clinical response to misoprostol.

expulsion	Patients number	Percentage %
complete	48	80 %
incomplete	6	10 %
No expulsion	6	10 %
total	60	100 %

Table-3: Relationship of number of doses and outcome in successful cases.

misoprostol doses	Successful cases	Percentage %
Vaginal dose	21	44%
First oral dose	15	31%
Second oral dose	12	25 %
total	48	100 %

Table-4: Effect of misoprostol on cervical permeability in non-responsive patients.

permeability	Patients number	percentage
permeable	6	100%
Non-permeable	0	0
total	6	100%

Table-5: The in incidence of side effects

Side effects	Patients number	percentage
nausea	4	6.6 %
vomiting	2	3.3 %
Sever pain	2	3.3 %
fever	1	1.6 %
Excessive blood loss	3	5%

Discussion

The success rate of misoprostol for early pregnancy failure appears to be advance in medical treatment and because women generally prefer some treatment to no treatment , Misoprostol treatment of women with early pregnancy failure provides an opportunity for women who desire active management to have a timed expulsion and avoid a surgical termination[16]. Overall, comparison of trials using misoprostol for early pregnancy failure is difficult because the studies included various patient populations and dosing regimens , different routes of administration , varying definitions of success and the time allowed until curettage was performed [17, 18]. It has been shown that the route of administration of misoprostol has strong impact on the pharmacokinetics profile and result in different clinical efficacy [19]. This study was done to find out an effective medical Methods to induce first trimester missed abortion within a reasonable time and with least possible complications.Of the total 60 patients enrolled in

this study, complete expulsion were achieved in (80%) who are higher than the results in the study of Graziosi et al [17] who reported 53 % success rate with 800 microgram vaginal misoprostol repeated after 24 hours . Also it is higher than the result of Ayres -de-campos et al [18] who reported 58.6% with vaginal misoprostol, our results is lower than the results of Crenin et al[16] who reported initial success of 71 % after single 800 mcg and overall all result of 84% with repeated vaginal dose at day 3 and similar the study of Rita et al[15] who report a success rate of 80 % following 2 vaginal doses of 600 mcg misoprostol 4 hours apart and 36% after 3 doses of 400mcg misoprostol given in 4 hours apart but with a higher side effects and lower cervical permeability rate than our study. But Kovaviscarch et al [20] in their study suggest intravaginal dose of 800mcg is more effective than 600mcg dose.These differences might be due to different doses and regimens.There are significant differences in the pharmacokinetics of misoprostol administrated by vaginal and oral routes that may explain the difference observed in clinical efficacy . Prolonged serum concentration following vaginal misoprostol suggests that vaginal administration could be dosed at longer interval than oral. [21] Moistening of the misoprostol tablet with normal saline before vaginal administration may be another important factor. although randomized studies have shown that moistening dose not improve the efficacy of the regimen Creinin K et al. [22] Ngai SW.et al shows higher abortion rate when water was added but difference does not reach a statistical significance [23]. B. Yilmaz et al shows misoprostol moistened with acetic acid significantly more effective than misoprostol moistened with saline [24]. Spitz et al has been reported that the efficacy of oral misoprostol decreases as pregnancy advances[25],nevertheless , El -Refae et al in previous studies have shown that the efficacy of vaginal misoprostol not affected by duration of pregnancy [26]. Missed abortion appears to be slightly less easily and less successfully resolved with the use of misoprostol therapy than is incomplete abortion [27].In addition , the lowest effective dose of misoprostol for each condition for which it is used is not yet clear, and this dose may turn out to be different for different categories of pregnancy loss (3).Our results were still lower than the results of El-Rafaey et al (26) who reported 93% success after vaginal misoprostol and again lower than the results of WHO studies in Suneeta Mittal et al [10] who reported 96-100% with the vaginal misoprostol. This high difference might be attributed to the use of the expensive mifepristone in combination with misoprostol in their studies (Iraq is a country with no access to mifepristone and the use of misoprostol alone is a reasonable strategy for medical abortion). A lot of work have shown the combination of misoprostol and mifepristone to be an effective Methods of achieving therapeutic medical termination of pregnancy in both first and second trimesters [28].

Multi centre trails with different prostaglandin analogues have shown that the same effectiveness as seen with 600 mcg dose can be achieved by 200mcg mifepristone [29] , in addition we considered the need for surgical intervention 12 hours from the last misoprostol dose as representing failure of treatment, but abortion might have occurred later[30]. The mean time of termination was 10 hours in our study which is lower than the time of Zaid et al [31] who reported 14hours when used repeated vaginal dose of 400 mcg of misoprostol , and again lower than the expulsion time in the study of Diaa EL-Mowafi et al who reported 14.4 + - 5.1 hours with the use of misoprostol in maximum dose of 1200 mcg in 36 hours .This might be to the differences in the doses and the regimens. the study of Bugalho et al [32] showed that the mean duration from application to expulsion was 11.8 + - hours with an initial dose of 800 mcg while the total dose range from 1200 – 1600mcg. Cervical permeability is another important finding in our study , prostaglandin locally might bring ripening by one of two mechanisms , firstly, they could induce collagen breakdown due to increase collagenase . Secondarily, they could alter collagen binding and tissue hydration by altering the glycosaminoglycans (GAG) / proteoglycan composition [33].Cervical dilatation prior to surgical evacuation was confirmed in all of the six nonresponsive cases (100%) which are higher than the findings in the result of Rita et al who reported 87.5% in the oral group and 90% in the vaginal group. [13] Side effects were lower than the other studies as shown in table (6)this might be explained by that the main dose where given vaginally in our study and the interval between the doses.

Table -6: The comparism of misoprostol side effects

complications	El-Refae et al 1995	Webster et al 1996	Diaa m. et al 1997	Our study 2007
nausea	-	-	6.7%	6.6%
vomiting	58.6%	50%	6.7%	3.3%
diarrhea	31.4%	25.7%	-	-
Headache	-	-	-	-
Chills, fever	1.4%	-	6.7%	1.6%
pain	-	-	-	3.3%
Excess bleeding	-	-	-	5%

Table-7:Previous studies of similar gestational age but different regimens.

author	Sample size	year	Regimens	Efficacy
Bugalho A (34)	101 133	1996 1996	200 mcg vag. q12h up to 4 doses 400 mcq vag. q 12hup to 4 doses	66.0 % 46.0 %
KoopersmithTB (35)	58	1996	Varying doses vag misoprostol	61.0 %
Carbonell Jl (36)	120	1998	800mcg vag. q24 h up to3 doses	87.0 %
Carbonell Jl (37)	120	1999	800mcg vag. q12 h up to3 doses	85.0 %
Carbonell Jl (38)	150	2001	800mcg vag. q24 h up to3 doses	84.0 %
Tang OS (39)	25	2001	Varying d. sublingl. misoprostol	92.0 %
Tang OS (40)	50	2002	600mcg sublingual up to5 doses	86.0 %
Our study	60	2007	800 vag.+400oral+400 oral 24h	80.0 %

From table (7), the studies who allowed longer time until curettage performed were associated with higher efficacy rate, while those with lower infrequent doses were associated with lower efficacy rate.

Conclusions

Medical termination by vaginal followed by oral misoprostol alone is effective, safe and a practical Methods for termination of first trimester missed abortion within a reasonable time and with least possible complications. . It also provides good cervical dilatation in unsuccessful cases requiring surgical evacuation.

Recommendations

1- We recommend the use of our protocol as it is effective, safe and associated with lower side effects.

2- Because of the small number of women included in this study, we recommend to apply it to a larger scale to support our results.

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