The efficacy of vaginal Misoprostol in second trimester medical termination of pregnancy a cohort study

A eficácia do Misoprostol vaginal na interrupção médica da gravidez realizada no segundo trimestre

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Abstract

Overview and Aims: To determine the efficacy of vaginal misoprostol as standard protocol in second trimester medical termination of pregnancy.
Study Design: Retrospective cohort analysis.
Population: Women who underwent pregnancy termination between 12 and 24 weeks for medical reasons, over a 5-year period.
Methods: A standard 400mcg misoprostol dosage was given intravaginally every 6 hours until a maximum of 6 doses in a 48h period. We analyzed the failure of treatment rate, the elapsed time until resolution of pregnancy, the related complications and the influence of possible bias in the success of treatment.
Results: In this study period 333 women underwent second trimester termination of pregnancy. The failure rate at 48h of the established protocol was 11.1%, with a success rate of 73% in the first 24h of treatment. Side effects and complications, such as excessive blood loss, need for transfusion, placental retention, fever or vomiting, were registered in 25.2% of the cases. There were no cases of uterine rupture or need for hysterectomy.
Conclusions: Vaginal misoprostol is a safe, efficient and acceptable method for second trimester medical termination of pregnancy.

Keywords: Second trimester termination of pregnancy; Misoprostol; Vaginal prostaglandins; Treatment success.

INTRODUCTION

Second trimester pregnancy termination is a common problem in obstetrics practice. Although constituting only 10 to 15% of all induced abortions worldwide, they are responsible for more than two-thirds of all major-abortion related complications[1].

The optimal method of second trimester abortion continues to be debated, with different surgical and medical procedures being used over the time. Medical abortion – defined as termination of pregnancy by the use of a drug or combined drugs – has the potential to reduce complications and expand access to abortion, and prostaglandins figure as the most commonly agents used for that propose[1,2].

Misoprostol, a prostaglandin E1 analogue originally designed for the prevention and treatment of gastroduodenal ulcers, has gained a wide popularity in obstetrics – it can be used for cervical ripening and labor induction at term, for treatment of post-partum hemorrhage, and also for first and second trimester abortions[3,4]. Misoprostol has advantages over other prostaglandins and other drugs in the set of pregnancy termination – it is inexpensive, it is widely available in many countries, it is stable at room temperature and it has multiple routes of administration (oral, vaginal, rectal or sublingual)[4-7].

Termination of pregnancy in the second trimester using misoprostol has been shown to be safe and effec-

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tive, with a success rate up to 90% in some of the published series[6,8-11]; however the ideal regimen of misoprostol still remains to be determined, with more than thirty different dosage regimens described in the literature for its use in obstetrics[2,8,12,13].

The aim of this study was to evaluate the efficacy of the misoprostol protocol used in our Department for second trimester medical termination of pregnancy.

METHODS

We conducted a retrospective cohort analysis of second trimester medical terminations of pregnancy occurring in our department between January 2005 and December 2010. Data were collected from a department database and completed by medical records.

All single pregnancies between 12 and 24 complete weeks were included. Gestational age was determined by last menstrual period unless a difference of more than 7 days was established by crown-rump length at first trimester ultrasound. In all cases the protocol in use for second trimester termination of pregnancy was applied, consisting in the administration of 400mcg misoprostol (2 tablets of 200mcg) vaginally every 6h up to 6 doses, completing 48h of treatment after a final expecting period of 12h. Before the procedure a complete blood count, C reactive protein and clotting times analysis was performed. Pain control with tramadol was prescribed on maternal request. Prophylactic antibiotics were not administrated.

Failure of the treatment was defined as absence of fetal expulsion in the 48h (2880min) period of the protocol. For each case, the decisions regarding the need for mechanical uterine cavity revision were taken by the obstetricians on call.

We analyzed the failure of treatment rate and the elapsed time between the beginning of treatment and fetal expulsion and analyzed the variables – maternal age, ethnicity, previous gestations, parity, previous abortions, gestational age (in completed weeks) and reason for termination of pregnancy (fetal malformation or aneuploidy, fetal death, premature rupture of membranes or maternal disease) – that could be associated with the success rate and/or shorter interval to resolution.

Complications of the procedure were defined as excessive blood loss (drop of 2g/dL in the hemoglobin level); need for blood transfusion; retained placenta (60 minutes or more without expulsion); uterine rupture and need for hysterectomy. Presence of fever (≥38ºC timpanic), vomiting, diarrhea or abdominal pain, were also evaluated.

For statistical purposes we used the Chi-square test for qualitative variables and the t-Student test for quantitative variables. We did a binary logistic regression to determinate the variables associated with success rate and shorter time interval to fetal expulsion. We considered statistically significant a $p \leq 0,05$. Statistical analysis was done using IBM Statistics 20 for Microsoft Windows (IBM Corporate; Chicago; USA).

RESULTS

In the study period there were 333 cases of second trimester medical termination of pregnancy and the population demographics are given in Table I.

There were 37 cases of treatment failure in this population, giving a failure rate of 11,1%.

In 113 cases (33,9%) fetal expulsion occurred in the first 12h of the protocol, with 243 cases (73%) being

TABLE I. POPULATION DEMOGRAPHICS*

Mean maternal age (min-max)	32,1 (18-45)
Mean gestational age (±SD)	18,26 (±3,2)
Ethnicity	
White	298 (89,5)
Black	35 (10,5)
Previous gestations	
Yes	123 (36,9)
No	210 (63,1)
Parity	
Nulipara	163 (48,9)
Multipara	170 (51,1)
Previous abortion	
Yes	116 (34,8)
No	217 (65,2)
Previous cesarean section	
Yes	42 (12,6)
No	291 (87,4)
Cause for termination of pregnancy	
Fetal malformation/aneuploidy	222 (66,7)
Intrauterine fetal death	59 (17,7)
Premature rupture of membranes	35 (10,5)
Maternal disease	17 (5,1)

*Results not discriminated are expressed in number of cases and percentage: n (%)

TABLE II. SUCCESS RATE BY TIME UNTIL FETAL EXPULSION*

≤12h	113 (33,9)
≤24h	243 (73)
≤48h	296 (88,9)

Results expressed in number of cases and percentages: n (%)

completed in less than 24h. By the end of the 48h protocol period de global success rate was 88,9% (296 cases) – results exposed in Table II.

We analyzed the possible influence of different variables in the treatment success rate (Table III), but none of them showed a statistically significant relation to this outcome. In the 296 cases of success we analyzed also possible factors that could be related with success in less than 24h – maternal age, parity, previous pregnancies or abortions, gestational age and reason for termination of pregnancy – only parity and previous pregnancies showed a statistically significant association with the outcome (Table IV).

In 84 cases (25,2%) there were treatment complications to register (Table V). The most frequent one was retained placenta for more than 60 minutes – 67 cases (20,1%). In 156 cases (46,8%) an aspiration or curettage of the uterine cavity was performed. Cases of severe diarrhea or severe abdominal pain resistant to analgesic therapy were not registered. There were also no cases of uterine rupture or need for hysterectomy. No maternal deaths were registered.

We analyzed the possible influence of different variables such as parity, gestational age or reason for termination of pregnancy, in the rate of complications – there were no statistically significant associations with the outcome.

DISCUSSION

Misoprostol has proved to be a valid, safe and efficient method for termination of pregnancy[2]. In this study series we registered a success rate of 88,9% for second trimester termination of pregnancy with vaginal misoprostol without major complications - as excessive

TABLE III. ANALYSIS OF VARIABLES IN THE TREATMENT SUCCESS RATE*

	Treatment success n= 296 (88,9)	Treatment failure n= 37 (11,1)	p value
Mean maternal age (years±SD)	32,19±0,98	32,06±0,35	0,90
Mean gestational age (weeks±SD)	18,3±0,19	17,4±0,53	0,13
Ethnicity			
White	264 (79,3)	34 (10,2)	0,78
Black	32 (9,6)	3 (0,9)	
Previous gestations			
Yes	188 (56,5)	22 (6,6)	0,72
No	108 (32,4)	15 (4,5)	
Parity			
Nulipara	143 (42,9)	20 (6,0)	0,60
Multipara	153 (46,0)	17 (5,1)	
Previous abortions			
Yes	105 (31,5)	11 (3,3)	0,58
No	191 (57,4)	26 (7,8)	
Cause for termination			
Fetal malformation	198 (59,5)	24 (7,2)	0,07
Intrauterine fetal death	55 (16,5)	4 (1,2)	
Premature rupture of membranes	31 (9,3)	4 (1,2)	
Maternal disease	12 (3,6)	5 (1,5)	

*Results not discriminated are expressed in number of cases and percentage: n (%)

TABLE IV. ANALYSIS OF VARIABLES RELATED TO SUCCESS IN LESS THAN 24H*

	Fetal expulsion in less than 24h n= 243 (82,1)	Fetal expulsion between 24h and 48h n= 53 (17,9)	p value
Mean maternal age (years±SD)	32,04±0,4	32,15±0,78	0,92
Mean gestational age (weeks±SD)	18,2±0,21	18,7 ±0,44	0,28
Previous gestations			0,04**
Yes	161 (54,4)	27 (9,1)	
No	82 (27,7)	26 (8,8)	
Parity			0,033**
Nulipara	110 (37,2)	33 (11,1)	
Multipara	133 (44,9)	20 (6,8)	
Previous abortions			0,43
Yes	89 (30,1)	16 (5,4)	
No	154 (52)	37 (12,5)	
Cause for termination			0,09
Fetal malformation	155 (52,4)	43 (14,5)	
Intrauterine fetal death	49 (16,6)	6 (2)	
Premature rupture of membranes	29 (9,7)	2 (0,7)	
Maternal disease	10 (3,4)	2 (0,7)	

*Results not discriminated are expressed in number of cases and percentage: n (%)
**Statistical significance (p<0,05)

TABLE V. COMPLICATIONS OF TREATMENT*

Retained placenta	67 (20,1)
Fever	7 (2,1)
Excessive blood loss	5 (1,5)
Nausea and vomiting	3 (0,9)
Blood transfusion	2 (0,6)

Results expressed in number of cases and percentages: n (%)

blood loss, need for transfusion, uterine perforation or need for hysterectomy - in more than 95% of cases. These results are consistent with previous studies using the same misoprostol regimen[6,8,9].

Since there were no previously defined criteria for surgical intervention, the elevated rate (47%) of uterine cavity mechanical reviews in this series was probably influenced by an operator bias. Only in 67 cases (20,1%) the diagnosis of complete retained placenta was establish, leaving the remaining 89 cases of mechanical uterine cavity reviews with no direct diagnosis unless what we hypothesized to be echographic evidence of retained products of the placenta.

The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines recommend the use of combined regimens of mifepristone and misoprostol for medical termination of pregnancy[14].

Nevertheless, it is important to underline that – unlike misoprostol – mifepristone is a drug of limited distribution worldwide, making the combination regimens a reality available only for a restricted set of developed countries and emphasizing the use of misoprostol alone as a cost/effective approach to medical termination of pregnancy in developing countries.

Before the widespread use of misoprostol, other prostaglandins, such as prostaglandin F2 injections or vaginal prostaglandin E2, were most commonly used for termination of pregnancy. These drugs, although efficient, were associated with many side effects like fever, nausea, vomiting and diarrhea, often requiring premedication with antiemetic, antipyretic and anti-diarrheal drugs. Misoprostol has shown in this study – as well as in other publications – to be well tolerated, with a reduced rate of side effects[5,10,11].

Previous studies have demonstrated that serum levels of misoprostol could accumulate with repeated administrations at intervals shorter than 6h, in favor of the prolonged half-life registered with the vaginal route (80 minutes) compared to the oral route (30 mi-

nutes) – giving to the 6h interval a better side effect profile[17]. Also, a vaginal 400mcg misoprostol dose is more effective than a 200mcg regimen and has lower side effects than a 600mcg dose, justifying the selection of the protocol in use for this study[12,13,15].

There have been suggestions that a higher parity favors the response to misoprostol and that advancing gestational age decreases that response[5,12]. In our series only parity and previous pregnancies showed a significant relation with the elapsed time to resolution but not to the rate of failure. Others – such as maternal age, ethnicity or the cause for termination of pregnancy –did not showed any significant relation to the rate of failure or elapsed time to resolution. This lack of correlation may be related to an insufficient number of cases for statistical significance and to a diversity of selection and procedure bias that cannot be controlled in the setting of a retrospective analysis.

In conclusion, vaginal misoprostol figures as a valid, safe and efficient choice for second trimester medical termination of pregnancy.

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