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EFFECTIVENESS OF DIFFERENT METHODS OF TERMINATION IN MISSED ABORTION OF THE FIRST TRIMESTER

Abstract. This article presents comparative results of using the prostaglandin analogue misoprostol by vaginal and oral ways and antiprogestagen mifepristone in combination with misoprostol for termination of missed abortion. It was found that the vaginal route of administration of misoprostol was more effective in comparison with other methods, and it had minimal side effects.

Keywords: missed abortion, misoprostol, mifepristone, termination of pregnancy.

Introduction. Missed abortion (MA) in the first trimester is characterized by delayed embryonic or fetal development by results of US blighted ovum (anembryonic gestation) or the embryo/fetus without cardiac activity [1]. The frequency of occurrence of this complication in the structure of reproductive loss is quite high (10-20%), and among the early reproductive losses is 45-88,6% [2]. Nowadays, a large percentage of these cases are diagnosed by routine ultrasound scanning in the first trimester of pregnancy.

Surgical evacuation remains the gold standard of medical care in missed abortion, being fast and very effective if performed by an experienced specialist. However, the relevant complications (trauma to the cervix, leading to cervical incompetence, severe pain, structural and functional inferiority of endometrium) dictate the search for alternative ways of case management [3].

In this regard, nowadays, primarily medical methods are used for the termination of pregnancy, which as shown by randomized trials [4] have advantages compared with traditional surgery. Researchers have attempted to compare the effectiveness of different routes of administration (oral and vaginal tract) of prostaglandin analogues; however, the obtained data is ambiguous [5].

Aim of the study: to compare the efficacy of the prostaglandin analogue misoprostol 200 mcg for various routes of administration and mifepristone antiprogestagen 200 mg in combination with a prostaglandin analogue misoprostol 200 mcg to terminate the missed abortion in the first trimester.

Material and methods. A randomized, prospective study of 94 pregnant women with a diagnosis of missed abortion up to 12 weeks, after obtaining informed consent was conducted. The study was conducted on the basis of City Hospital №2 in Astana and on the basis of the Department of Obstetrics and Gynecology №1 JSC "Astana Medical University" during 2015-2016. Inclusion criteria were: 1) 18-45 years old; 2) gestational age ≤12 weeks on last menstrual period; 3) established diagnosis of missed abortion according to ultrasound; 4) the cervix is closed with a vaginal examination; 5) hemoglobin ≥ 90 g\l; 6) the normal body temperature; 7) informed consent. Exclusion criteria: 1) excessive uterine bleeding; 2) unstable hemodynamics; 3) violation of coagulation (PTI ≤ 85%, fibrinogen <2.0 g\l); 4) the signs and symptoms of infection; 5) a history of extragenital pathology in which the use of prostaglandins is contraindicated, 6) active lactation period; 7) a multiple pregnancy.

By random sample, surveyed women were divided into 3 groups: Group A: 32 patients treated with 200 mcg misoprostol intravaginally into the posterior vaginal fornix every 3 hours up to six doses; Group B: 31 patients, treated with 200 mcg misoprostol orally every three hours up to six doses, group C: 31 patients who treated with 200 mg mifepristone and after 24 hours - 200 mcg of oral misoprostol, repeating every three hours up to six doses.

All patients were monitored and observed for vaginal bleeding and the process of expulsion of the ovum, noted side effects of the drug. Over the next 12-36 hours, following results were evaluated: complete miscarriage, incomplete miscarriage (echogram did not indicate an empty uterine cavity) or the absence of expulsion of products of conception, which subsequently required the use of a surgical abortion. Each woman was informed of the expulsion of the ovum and the possible symptoms. If the fertilized egg has been expelled, she was explored vaginally, and then there was conducted a transvaginal US. If the fertilized egg remained, then the administration of additional doses of misoprostol continued as long as there was a full expulsion of the ovum or patient took the maximum dose of misoprostol. If the patient's pregnancy was terminated earlier, additional doses were not administered.

Patients were observed for 6 hours after complete abortion, and then dismissed. They received prophylactic antibiotics for 3-5 days.

Control examination was conducted after 14 days; they were surveyed, conducted transvaginal ultrasound, pelvic examination. Bleeding was divided by duration – as the short (up to 5 days), medium (5-10 days) or long (over 10 days), by number – as severe, moderate or weak. During the conversation with the patient there were refined side effects or any additionally received treatment. Follow-up visit was appointed to the 6^{th} week to determine the time necessary for the resumption of menstruation, other side effects (if experienced) and tolerability.

Results and their discussion. The average age of the examined patients ranged from 20 to 42 years, an average 30,75±1,03 years. Comparative analysis by age group showed no statistically significant differences between groups. Most patients were multiparous (66.7% – in Group A, 56.7% – in group B, 76.7% – in group C). Previous history of abortion in 33.3% were in group A, 36.7% – in Group B and 23.3% – in Group C. Missed abortion history was 23.3% of the women in Group A, 30% in group B and 16.7% in group C. The average gestational age at the time of the study was: 73,7±2,2 days in group A; 75.6±2.7 days in Group B and 73.674±1.268 days in Group C.

Majority of women found missed abortion with ultrasound when a random smearing dark brown discharge from the genital tract, when applied to a gynecologist at the place of residence or with ambulance to emergency clinic. In our study, the final performance indicator defined as complete evacuation of the uterine cavity without need for surgical intervention. Also there were considered transvaginal ultrasound data, according to it, the endometrial thickness should be no more than 15-17 mm, without hyperechoic inclusion.

The results of the study showed (Table 1), that misoprostol at two routes of administration, and the combined use of mifepristone and misoprostol is an effective non-surgical method, and has a highly effectiveness for vaginal administration of misoprostol. Application of misoprostol, PGE-1 analogue without antiprogestagen also shows high performance. This once again confirms the hypothesis that antigestagens are not really necessary for the termination of missed abortion as progesterone level is usually low and therefore only the PGE-1 is required to initiate uterine contractions and expulsion of the ovum.

Table 1 – Clinical outcome in the three groups

Outcome	Groups		
	A	B	C
Complete miscarriage	30 (93,75%)	25 (80,6%)	26 (83,87%)
Incomplete miscarriage	2 (6,25%)	5 (16,1%)	5 (16,1%)
Pregnancy is not terminated	0	1 (3.22%)	0
Total	32 (100%)	31 (100%)	31 (100%)

At the same time, there has been the ineffectiveness of medical termination: two patients in the vaginal misoprostol group had incomplete miscarriage, and surgical intervention was required in both cases. In the oral group, 6 patients had treatment failure.

We have analyzed the number of doses of misoprostol which is necessary to complete an abortion in the two groups (Table 2).

Table 2 – Dose number of misoprostol, which was necessary for complete miscarriage in the three groups

Dose number	Groups		
	A	B	C
One	2 (6.25%)	0 (%)	6 (19.3%)
Two	7 (21.8 %)	3 (9.67%)	19(61.3%)
Three	16 (50%)	10 (32.25%)	6 (19.3%)
Four	7 (21.87%)	14 (45.1%)	0 %
Five	0%	3 (9,67%)	0%
Six	0%	1 (3,22%)	0%
Total	30	25	26

The results showed that 2 (6.25%) patients in Group A, 0% - in group B, and 6 (19.3%) patients in Group C full miscarriage has occurred after the first dose, while 7 patients (21.8%) in group A, 3 (9.67%) in group B, and 19 (61.3%) in group C complete miscarriage occurred after the second dose. After third dose, full miscarriage has occurred in 16 (50%) patients in Group A, 10 (32.25%) patients in group B, and 6 (19.3%) patients in group C, and after the fourth dose in 7 patients (21.87 %) in group A, 14 (45.1%) patients in group B there was a complete miscarriage.

Thus, administration of vaginal misoprostol and mifepristone combined with misoprostol was more effective than oral administration of misoprostol, because complete miscarriage in those groups happened after the third or fourth dose of misoprostol, i.e additional doses were not necessary.

Mean interval (in hours) of the first dose of misoprostol till complete miscarriage was 10.8±3.4 hours in Group A; 13.2±3.1 hours in group B; 5.2±3.1 hours in Group C.

It is known [7], that the use of prostaglandin may be accompanied by various side effects. The results of our study have shown that a large percentage of side effects occurred in the oral and the combined group.

Table 3 – Side effects of the application of PGE-1 analogue misoprostol

Side effects	Groups			D1	D2	D3
	A	B	C			
Nausea/vomiting (requires treatment)	3 (9,4%)	21 (67,7%)	13 (41,9%)	<0,001	<0,05	<0,01
Headache	4(12,5%)	5(16,2%)	7(22,5%)	>0,05	>0,05	>0,05
Dizziness	2(6,25%)	5(16,2%)	11(35,5%)	>0,05	>0,05	3.047
Diarrhea	0 (0)	3(9,7%)	2 (6,25%)	>0,05	>0,05	>0,05
Cramping pain	7(21,9%)	16(51,6%)	17(54,8%)	<0,01	>0,05	2.85
Fever (requires treatment)	0 (0)	1 (3,22%)	0 (0)	0	0	0
Heavy bleeding	0 (0)	2 (6,25%)	2 (6,25%)	0	0	0
Hysterocervicorrhesis	0 (0)	0 (0)	0 (0)	0	0	0
Hysterorrhesis	0 (0)	0 (0)	0 (0)	0	0	0
Total	32	31	31			
D1 – difference between groups A and B; D2 – difference between groups A and C, D3 – difference between groups B and C.						

Of all the most significant side effects were nausea, vomiting, severe cramping, diarrhea, heavy bleeding.

Thus, the occurance of gastrointestinal side effects was higher in the oral group, which was easily stopped via antiemetic and antidiarrheal drugs. The most noticeable side effect connected with misoprostol was diarrhea, which is a natural reaction of the intestinal smooth muscle to increase the level of Prostaglandin, and it easily eliminated in several days despite continued treatment. In the oral misoprostol

group and the combined group of mifepristone with misoprostol, diarrhea was observed in 3 patients (10%) and 2 patients (6.6%), respectively. In the vaginal group, diarrhea was not observed. Hyperthermia was observed in one patient in the oral group, while in the other groups this symptom was not observed. All the groups felt dizziness, headache in small amounts from 6% to 36%. Severe cramping pain, requiring analgesics was greater in oral and combination group compared with the vaginal group (in the oral group and the combined group it was 51.6% and 54.8% vs. 21.9% in vaginal group). Also in this study, no patient had cervical rupture as a result of treatment. These results once again demonstrate the effectiveness of medical termination of missed abortion [5].

Heavy post-abortion bleeding that required surgical evacuation was observed in a few patients (in the oral group – 2 patients (6.6%), 2 patients in the combined group (6.6%), and vaginal group had no heavy bleeding), which increases the acceptability of medical treatment at missed abortion, which is suitable as a practical alternative to conventional surgical evacuation. The majority of patients (53.3% in the first group, 63.3% in the second group, 60% in the third group) had normal recovery of menstrual cycle in 30-45 days, and it emphasizes that the effect of misoprostol in the beginning of the first menstrual period after abortion does not depend on the route of administration.

Post-abortion bleeding in an average of all groups was observed according to the number of bleeding: moderate degree – in group A in 63.3% of patients, in group B in 60% of patients, in group C in 50% of patients, according to the duration of bleeding for 5-10 days: in group A in 56.6%, in group B – 33.3%, in group C – 60%. Resumption of menstrual time: most women had normal recovery time of 30 days and 30-45 days in group A (86.6%), in group B (79.9%), in Group C (83.3%).

The results of our study coincides with the findings of other researchers [5,6,8], which showed the effectiveness of the above methods separately, but unlike them, we performed a comparative analysis of particular application of prostaglandins, and their combined use with antiprogesteron.

Conclusion. Despite the different ways of administration of drugs, and the combined use of antiprogesteron (mifepristone) and misoprostol, performance indicators were high in all groups. At the same time, the method of vaginally administration of prostaglandins is more effective with minimum side effects.

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АЛҒАШҚЫ ТРИМЕСТРДЕГІ ДАМЫМАЙТЫН ЖҮКТІЛІК БАРЫСЫНДА ЖҮКТІЛІКТІ ТОҚТАТУДЫҢ ӘР ТҮРЛІ ӘДІСТЕРІНІҢ ТИІМДІЛІГІ

Аннотация. Мақалада простагландиннің аналогы - қынаптық және ауыздық жолдардың мизопростолы және мифепристон антипрогестагеннің простагландиннің басқа аналогы – мизопростолмен комбинациясын дамымайтын жүктілікті жою үшін қолдану тиімділігінің салыстырмалы нәтижелері келтірілген. Мизопростолды қынапты жолмен енгізу жанама әсерлері минимальды ең тиімдірек әдіс болатындығы анықталған

Түйін сөздер: дамымайтын жүктілік, мизопростол, мифепристон, жүктілікті тоқтату.

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ЭФФЕКТИВНОСТЬ РАЗЛИЧНЫХ МЕТОДОВ ПРЕРЫВАНИЯ БЕРЕМЕННОСТИ ПРИ НЕРАЗВИВАЮЩЕЙСЯ БЕРЕМЕННОСТИ ПЕРВОГО ТРИМЕСТРА

Аннотация. Представлены сравнительные результаты эффективности применения аналога простагландина мизопростола вагинального и перорального путей, и антипрогестагена мифепристона в комбинации с аналогом простагландина мизопростолом для прерывания неразвивающейся беременности. Установлено, что вагинальный путь введения мизопростола является более эффективным методом, с минимальными побочными эффектами.

Ключевые слова: неразвивающаяся беременность, мизопростол, мифепристон, прерывание беременности.