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ORIGINAL ARTICLE

The efficacy of misoprostol in the first trimester miscarriage treatment – an individual patients' data analysis

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Abstract

INTRODUCTION: The study aimed to detect factors predicting a successful pharmacological induction of first-trimester miscarriage.
MATERIAL AND METHODS: A prospective, cohort research was conducted at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, between years 2011–2015. 642 women diagnosed with first trimester miscarriage qualified for pharmacological induction with misoprostol were included in the study. Each patient underwent repeatable doses of 800mcg misoprostol vaginally. The endpoint was complete excretion of all tissues, with no need to perform surgical curettage. Type of miscarriage, gravidity, parity, number of doses, time of drug administration and side effects were analysed as possible factors influencing the results. The statistical analysis was performed with STATISTICA 10.0 software.
RESULTS: The percentage of successful miscarriage induction was 83.6%. Two main factors corresponded with successful pharmacological treatment in regression analysis: number of administered doses (adjusted OR 1.64; 95% CI 1.18–2.29) and week of gestation (aOR 1.22; 95%CI 1.03–1.44). The success of the pharmacological induction of miscarriage was significantly decreased if the woman had a history of caesarean section (aOR 0.34; 95% CI 0.2–0.57). 2.2% of patients experienced benign side effects of the therapy.
CONCLUSIONS: Pharmacological induction is an effective and safe treatment method of first trimester abortion in the majority of cases. The knowledge of factors influencing the efficacy of misoprostol may help clinicians in proper counselling and individualisation of therapy.

INTRODUCTION

First trimester miscarriage, defined as pregnancy failure up to 13 completed weeks, affects nearly 25% of women in their reproductive age (Robledo *et al.* 2007). Clinical presentation of spontaneous miscarriage most commonly includes bleeding from the genital tract and spontaneous expulsion of an embryo/fetus from the uterine cavity. Expectant management is adequate in cases with small or moderate bleeding. However, in some cases - incomplete, inevitable, missed abortion - fetal or placental tissues may remain in the uterine cavity. In such conditions 3 different approaches are possible: expectant management, dilatation and curettage (D&C) and pharmacological induction of abortion with misoprostol.

In the past, D&C was the method of choice in cases of missed abortion or anembryonic pregnancy – as a quick, efficient intervention, with the possibility of histological examination (Tang & Ho 2006; Neilson *et al.* 2013) . Despite its high effectiveness, it is an invasive treatment with the risk of serious complications, such as uterine perforation or intrauterine adhesions (Asherman's syndrome) (Tang & Ho 2006).

Nowadays, the contemporary medicine offers less invasive methods of treatment in the above mentioned conditions. Pharmacological induction of abortion is an acceptable, effective and safe method of treatment (Neilson *et al.* 2013). Preparations of prostaglandins stimulate uterine muscle contractility (Wielgos *et al.* 2007). Misoprostol, a synthetic analogue of E1 prostaglandin, has good physical and chemical properties. It has a short half-life of 20–40 minutes and does not accumulate in the serum. It can be administered as a separate formulation or in combination with NSAIDs (non-steroidal anti-inflammatory drugs). Such induction can also be performed as an outpatient procedure with no need for hospital admission.

The aim of the study was to determine individual patients' factors affecting the effectiveness of misoprostol induction of the first trimester miscarriage.

MATERIALS AND METHODS

Study design and patients' characteristics

A prospective, single-centre cohort study was conducted at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. 642 patients admitted to the Department due to the first trimester miscarriage (prior to 14th week of gestation) between 2011–2015 were included in the study. Once the diagnosis of either missed abortion or blighted ovum miscarriage was confirmed, the eligible patients were qualified to pharmacological induction of abortion and gave a written consent to participate in the study. In each case the diagnosis was confirmed by ultrasound with one of the following: an intrauterine sac with a diameter >20mm without a fetal pole or yolk sac, classified as anembryonic sac; the presence of fetal pole without heartbeat or crown-rump length (CRL) at least 6mm with no cardiac activity and no change at the time of a second ultrasound one week later. The exclusion criteria comprised of: incomplete miscarriage or termination of pregnancy due to maternal or fetal indications, an allergy to misoprostol or other prostaglandins, an ectopic pregnancy, a suspicion of gestational trophoblastic disease, high risk of uterine rupture, severe vaginal bleeding, pelvic infection, sepsis and hemodynamic instability. After collecting all data the cohort was divided into 2 groups: A - with successful pharmacological induction of abortion and B – the group of patients requiring additional procedures to finalize the treatment of the first trimester miscarriage.

At admission the patients underwent all necessary diagnostic tests: blood pressure, pulse and temperature measurements, general and vaginal examination, ultrasound examination, blood tests including full blood count and blood type with Rhesus (Rh) factor if missing.

All women included in the study had signed a written informed consent for the treatment with misoprostol approved by FIGO Organization. The 2012 FIGO guidelines recommend vaginal misoprostol 800μg or alternatively 600μg sublingually, with repeatable doses after 3 hours, maximum twice daily (FIGO 2012). In some cases also rectal administration was performed, but with an equal dose. Both rectal and sublingual routes were proposed when bleeding occurred or at patients' request. The endpoint was successful pharmacological miscarriage induction considered as bleeding with the excretion of all tissues, without the need to perform dilatation and curettage (D&C). Ultrasound (US) examination was performed in each patient with bleeding before discharge to confirm that there were no retained products of conception. The absence of chorionic or fetal tissues and anterior-posterior thickness of endometrium of less than 15mm were significant factors pointing to successful induction of miscarriage. The D&C intervention was performed in cases of unsuccessful induction, severe bleeding accompanied by the drop of blood pressure or deterioration of general condition, and at patients' request. The presence of any side effects of prostaglandins, such as fever, nausea, vomiting, diarrhoea or skin rash was recorded in medical history. All Rhesus-negative patients were also qualified for immunoglobulin injection before discharge.

Every patient with successful induction was instructed to repeat US examination and to measure blood beta hCG concentration within one month from discharge to assess if any of them required delayed curettage and to exclude persistent trophoblastic disease. The follow up was carried out by phone to find out if any of them had been admitted to other hospitals.

Various factors, which could possibly influence the success of miscarriage induction were taken into account while analysing the results. Data including age, body mass index (BMI), parity, mode of previous

deliveries, history of previous surgical procedures on the uterus were collected. In addition, the details concerning current pregnancy, such as the week of gestation based on the date of the last menstrual period, type of miscarriage – missed abortion or blighted ovum, presence of bleeding at admission, doses, time and way of misoprostol administration were precisely analysed.

The study was approved and gained the positive opinion from the Ethics Committee at Medical University of Warsaw.

Statistical analysis

Statistical analyses were performed with STATISTICA 10.0 software. Patients' characteristics were presented as numbers of cases and percentages for categorical data, and as means with standard deviations (SD) for continuous data or – for non-continuous – medians and quartiles. The groups were compared by chi-squared test and exact Fisher's test for categorical variables. Mann-Whitney U-test was performed for continuous variables. The value of $p<0.05$ was considered significant. Multiple logistic regression model was built to estimate which factors influence the efficacy of pharmacological induction.

RESULTS

Baseline characteristics of the patients

All 642 patients included in the study did fulfil the eligibility criteria and made up the final analytical sample (the flow chart of patients' recruitment and treatment is presented in Figure 1). The group A – with successful induction consisted of 545 patients (84.9%), while group B (requiring instrumental treatment) comprised of 97 women (15.1%). There were no significant differences in the age of patients from groups A and B, nor in their BMI. Complete data regarding patients' characteristics are presented in Table 1.

On the day of miscarriage diagnosis the median age of gestation was 9.67 (± 1.7) weeks. The majority of cases suffered from missed abortion (n=545; 84.9%). At admission, 95 patients (14.8%) reported bleeding, subjectively divided by doctors into spotting or moderate bleeding (heavy bleeding was an exclusion criterion).

Factors influencing successful pharmacological treatment

Women in group B received more drug doses in total (A 2.30 vs B 3.97; $p<0.0001$) and more prior to the onset of bleeding (A 1.51 vs B 2.04; $p=0.028$). In comparison to the successful group, patients in group B required a longer period of drug administration (mean 1.30 vs 2.04 days; $p<0.0001$). A multiple logistic regression model was applied to evaluate the factors influencing the rate of successful treatment. The number of administered doses of misoprostol had a significant impact according to the analysis (adjusted OR 1.64; 95% CI 1.18–2.29). In addition, the lower the week of gestation at misoprostol administration, the better the efficacy of misoprostol treatment (aOR 1.22; 95%CI 1.03–1.44). The success of the pharmacological induction of miscarriage was significantly decreased if the woman had a history of caesarean section (aOR 0.34; 95% CI 0.2–0.57). The results of multiple regression analysis for all the variables are presented in Table 2.

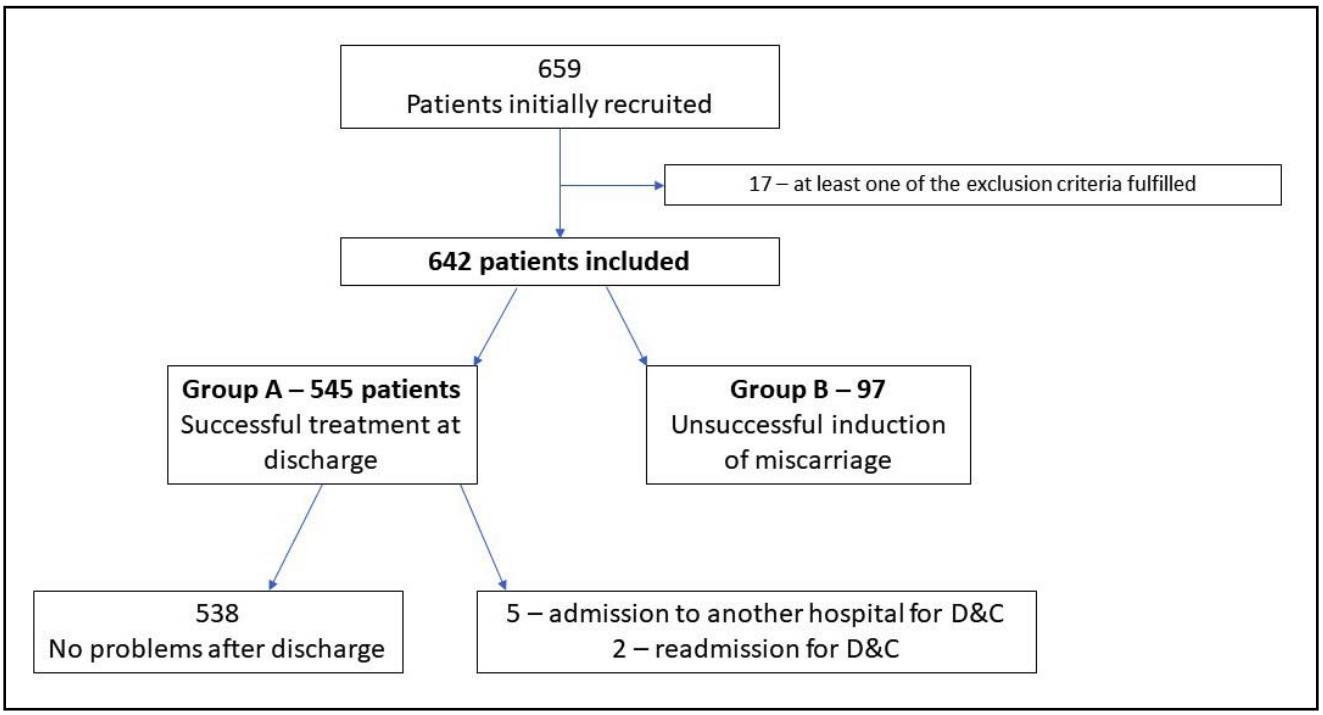

Fig. 1. Flow chart of patients with first trimester miscarriage treated with misoprostol in the study group

Tab. 1. Baseline characteristics of the study group (successful and unsuccessful induction)

Variable	Total (n=642)	Successful induction (n=545)	Unsuccessful induction (n=97)	*p*-value
Age [years]	32.21 ± 5.05	32.20 ± 5.09	32.23 ± 4.91	0.93
BMI [kg/m^2]	22.69 ± 3.75	22.71 ± 3.82	22.59 ± 3.35	0.92
Time from previous delivery [years]:				
• mean & SD	3.67 ± 3.13	3.60 ± 3.12	3.96 ± 3.13	
• median & IQR	3 [1-5]	3 [1-5]	4 [2-5]	0.07
History of miscarriages				
• 1	19.78% (n=127)	20.37% (n=111)	16.49% (n=16)	0.50
• ≥2	5.30% (n=34)	4.95% (n=27)	7.22% (n=7)	
Type of miscarriage				
• missed abortion	84.89% (n=545)	85.13% (n=464)	83.51% (n=81)	0.68
• blighted ovum	15.11% (n=97)	14.86% (n=81)	16.49% (n=16)	
Previous surgical interventions on uterus*	19.16% (n=123)	17.98% (n=98)	25.77% (n=25)	0.07
Presence of bleeding on admission	14.80% (n=95)	15.05% (n=82)	13.40% (n=13)	0.67

*Defined as all surgical procedures performed on uterus other than caesarean section.
IQR – interquartile rate; SD – standard deviation*BMI = Body Mass Index

In the majority of cases in group B, the pharmacological treatment was discontinued in favour of D&C due to the lack of effect (67/97 patients, 69.1%) or severe bleeding requiring instrumental procedure (14/97 patients, 14.4%). Six women out of 97 (6.2%) required curettage due to the retained tissues in control ultrasound examination at the end of the third day of induction and 8 (8.25%) underwent the procedure at patients' request (psychological or physical difficulties to continue the induction). Most of the women with unsuccessful induction had been administered misoprostol for more than one day (71.1%, n=69), in comparison to group A, where in 411 patients (75.41%) duration of treatment equalled 1 day.

Side effects

14 patients in the analyzed group (2.2%) experienced side effects of pharmacological induction – mostly in form of emesis (n=5), fever (n=3) or hypotonia (n=5), which in one case led to postural syncope and intensive muscle spasms (n=1). One of the patients reported dyspnoea (n=1), however, additional diagnostic procedures proved no signs of any perceptible pathological process.

No severe complications of miscarriage induction, such as uterine rupture, bleeding requiring blood transfusion, massive anaphylactic reaction or sepsis, being a potentially life-threating conditions, were reported.

Long-term outcome

Two patients in the analyzed group were readmitted to the Department and the following 5 women underwent the D&C procedure in another medical facility due to the retained fetal tissues or severe bleeding within one month after discharge. During the induction each of them received high doses (more than 4 doses – 3200mcg) of misoprostol vaginally. Those patients initially contributed to 1.3% of the primary successful group. In the end, the long-term successful rate of prostaglandin induction of miscarriage was 83.6%.

DISCUSSION

The final efficacy of misoprostol treatment of the first trimester miscarriage in the presented study equalled 83.6%. The findings are concordant with the previously published papers. In a large randomised trial by Davis *et al.* the success rate of missed miscarriage induction with prostaglandins reached nearly 85% (Davis *et al.* 2007). Most recently Fernlund *et al.* reported the final efficacy of such treatment with the rate of 86% (Fernlund *et al.* 2018). In other published papers the effectiveness varied between 62% and more than 90% (Sotiriadis *et al.* 2005; Sifakis *et al.* 2005; Peterson *et al.* 2013).
In the presented research maternal age and BMI did not impact the results of pharmacological treatment. Likewise, the type of miscarriage – missed abortion or anembryonic pregnancy was not the factor influencing misoprostol efficacy in the presented results. This note-worthy result is in accordance with research published by Barcelo *et al.* (Barcelo *et al.* 2012). In contrary, the largest US trial reported slightly lower success rate of misoprostol treatment in anembryonic pregnancies (81%) than in embryonic missed miscarriage (88%) (Zhang *et al.* 2005).

Most of the studies concerning the usefulness of misoprostol in the treatment of first trimester miscarriage focus on the efficacy of prostaglandins rather than on factors which may have an influence on overall results (McGee *et al.* 2016; Black *et al.* 2017).

Limited literature data revealed the association between parity and successful misoprostol treatment. In the cohort study by Reeves *et al.* parity was found to be a predictor of uterine evacuation, with the OR 1.30 (95% CI 1.11 – 1.52) for each additional birth (Reeves

Tab. 2. Variables with possible influence on the successful induction of first-trimester abortion with misoprostol

Variable	Adjusted odds ratio (aOR)	95% confidence intervals (CI)
BMI (body mass index)	1.00	0.93 - 1.08
Parity	1.10	0.64 - 1.89
Days of misoprostol administration	1.37	0.68 - 2.77
Gestational age at miscarriage induction	**1.22**	**1.03 - 1.44**
Number of misoprostol doses administered	**1.64**	**1.17 - 2.29**
The presence of bleeding on admission	1.22	0.84 - 1.78
Type of miscarriage (missed / blighted ovum)	0.94	0.43 - 2.05
History of delivery	1.27	0.72 - 2.25
History of vaginal delivery	0.84	0.5-1.4
History of cesarean section	**0.34**	**0.2-0.57**
History of miscarriage	1.05	0.55 - 1.98
History of D&C (dilatation and curettage)	1.42	0.65 - 3.08

et al. 2016). In other studies, parity and previous spontaneous abortions were risk factors of unsuccessful pharmacological management – Chien *et al.* described reversely proportional dependence between parity and positive response to prostaglandins therapy (Chien *et al.* 2009). According to Haimov-Kochman's *et al.* any abortion in the past significantly decreased the possibility for successful outcome (Haimov-Kochman *et al.* 2007). In the above publications the researchers did not find evidence concerning the influence of gravidity on the success rate of prostaglandins treatment. However, the presented study did not show the influence of parity / gravidity on the efficacy of pharmacological induction.

Few studies relate to the type of previous delivery and the success of misoprostol treatment. According to Chien *et al.* the history of prior caesarean section increased the risk of curettage due to ineffective misoprostol therapy (Chien *et al.* 2009). The presented research also confirmed such observation.

The authors followed FIGO and WHO recommendations concerning medical management of early pregnancy loss, administering 800mcg of misoprostol vaginally, or, less commonly 600mcg sublingually, repeating doses no earlier than after 3 hours (FIGO 2012; Tang *et al.* 2013). Such approach was also described in other studies (Barcelo *et al.* 2012; Zhang *et al.* 2005). In the majority of publications the cut-off point of misoprostol effectiveness was set at 2 doses of 800mcg misoprostol (Barcelo *et al.* 2012; Dalton *et al.* 2015). In the presented research the mean of administered doses in the successful treatment group was 2.3 vs 3.97 in the group with failed misoprostol abortion. Therefore, it seems that if a patient does not start bleeding after the first two doses, the probability of successful treatment significantly decreases.

The effectiveness of misoprostol may also be strengthened by additional pharmacotherapy. According to recent data published by Schreiber *et al.* administering an additional dose of 200mg mifepristone orally before vaginal misoprostol increases the efficacy of pharmacological induction of first-trimester miscarriage (30-day follow up: complete abortion in 91.2% in mifepristone-pretreatment subgroup vs 75.8% in misoprostol alone subgroup). The above mentioned trial will most certainly make mifepristone/misoprostol protocol a standard of care (Schreiber *et al.* 2018). Unfortunately, mifepristone is not registered in Poland (drug was and still is considered illegal), thus, no research with such protocol is possible at the moment.

The adverse effects, such as pain, fever, diarrhoea, nausea, vomiting, severe bleeding during treatment with misoprostol usually occur rarely, and in the majority of cases are managed conservatively (McGee *et al.* 2016; Patua *et al.* 2013; Hentzen *et al.* 2017). The side effects, both in the presented study and available literature, did not reveal any association with the efficacy of misoprostol in the early pregnancy loss treatment.

In comparison to uterine curettage as a method of treatment in missed abortion/anembryonic pregnancy, pharmacological induction seems to be safe, effective, inexpensive and acceptable by patients. Besides strictly medical aspects of the two management options for early pregnancy loss, misoprostol has an advantage over D&C in two fields: patient's satisfaction and economy. The studies show that pharmacological treatment is the most preferred management option, followed by expectant management and curettage (54%, 43% and 24%, respectively) (Hentzen *et al.* 2017). In addition, 73% of women undergoing pharmacological treatment indicated that they would recommend such option to other patients (Peterson *et al.* 2013). Although the economic aspects are rarely appreciated in the individual

patient approach, the overall costs of managing patients with miscarriage are significant and should at least be considered. D&Cs performed in the operating room, under general anaesthesia, including potential complications do generate significant costs, as described by Strand (Strand 2015). Dalton *et al.* described a special economic model created to optimize costs of first trimester miscarriage treatment, including various management options (Dalton *et al.* 2015).

The sample size in the presented research (nearly 650 patients treated with misoprostol for EPL) is one of its major strengths. In addition, the management was performed in accordance with FIGO and WHO guidelines in all the studied women in one centre.

There are, however, several limitations. First of all, the studied subjects were not randomised, therefore, the authors cannot exclude bias. Furthermore, although each patient underwent transvaginal ultrasound examination after reporting bleeding, with careful assessment of endometrial thickness and residual tissues, not all of them verified serum beta hCG concentration as instructed to exclude persistent gestational trophoblastic disease. The authors also cannot exclude bias, because the follow-up was performed by telephone conversations.

In conclusion, the pharmacological management in early pregnancy loss is a safe, effective and inexpensive method of treatment. Undoubtedly, it should be recommended as a treatment of choice in the above condition. The knowledge of factors influencing the efficacy of misoprostol may help clinicians in proper counselling and individualisation of therapy.

Nevertheless, questions still emerge: Are there any other factors predicting successful pharmacological treatment? Will the best model of approach in early pregnancy loss be based on the individual patient's characteristics? Is there an impact of misoprostol administration on patients' fertility in the future? These – and many other aspects should be taken into consideration while designing further research.

STATEMENT OF AUTHORSHIP

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I Szymusik – creator of the study concept; data analysis, preparation and correction of the manuscript, literature review
M Zgliczynska – data collection, data analysis
K Szarla – data collection
M Kopylowska – data collection
S Piatek – creator of the study concept, preparation of the manuscript, literature review
M Wielgos – final corrections and acceptance of the manuscript
K Kosinska-Kaczynska – statistical analysis, final corrections of the manuscript

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CONFLICT OF INTERESTS

None to declare.

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