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THE ROLE OF ENDOMETRIAL THICKNESS AND SERUM BETA-HUMAN CHORIONIC GONADOTROPIN LEVELS AS PREDICTIVE MARKERS OF DELAYED FAILURE IN MEDICAL ABORTION

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Abstract

Introduction: Medical abortion, also known as medical termination of pregnancy (MToP) or MA, employs pharmaceutical agents to trigger a process similar to miscarriage, serving as an alternative to surgical methods. Extensive evidence, global practices and guidelines from the World Health Organization (WHO) validate the effectiveness of administering 200mg of mifepristone followed by 800mcg of misoprostol taken 24-48 hours later for pregnancies up to nine weeks in gestation.

Objective: This study aims to assess the predictive value of ultrasonographic measurements of endometrial thickness and serum human beta chorionic gonadotropin (β-hCG) levels in identifying late failure in patients undergoing medical abortion with mifepristone and misoprostol.

Material and Methods: A prospective observational study was carried out at the University Clinic for Gynecology and Obstetrics in Skopje from January to June 2023. The research involved 97 women seeking medical abortions who reported experiencing residual vaginal bleeding lasting 15 days or longer following outpatient medical induction for pregnancies not exceeding nine weeks. Each participant underwent transvaginal ultrasound and serum β-hCG testing prior to cervical dilation and endometrial curettage performed under anesthesia. Based on histopathological analysis of uterine contents, participants were categorized into those with incomplete abortions (19 cases; 19.59%) showing products of conception, and those with complete abortions (78 cases; 80.41%) lacking such evidence. Correlations between transvaginal ultrasound findings and quantitative β-hCG levels with histopathological results were analyzed to determine the reliability of these markers in predicting complete abortion.

Results: Baseline characteristics were comparable across both groups. Endometrial thickness measurements showed significant differences: averaging 11.2±3.9mm in the complete abortion group compared to 14.6±6.1mm in the incomplete group (P=0.003). Serum β-hCG levels also varied significantly: averages were found at 73.92±23.86 IU/L for complete abortions versus 109.37±68.36 IU/L for incomplete ones (P<0.001). An endometrial thickness threshold of ≥12mm yielded a sensitivity of 88.46%, specificity of 73.68%, positive predictive value (PPV) of 93.24%, and positive likelihood ratio (LR+ve) of 85.57%. Similarly, a serum β-hCG level ≥100 IU/L indicated incomplete abortion with a sensitivity of 87.2%, specificity of 78.9%, PPV of 94.4% and LR+ve of 85.6.

Conclusion: Quantitative serum β-hCG levels along with measurements of endometrial thickness are valuable diagnostic tools for predicting late failure after medical abortion; however, they should be employed as complementary assessments alongside thorough clinical evaluations.

Key Words: *Transvaginal ultrasonography, Endometrial thickness, Serum β-hCG, Oral misoprostol, Early pregnancy failure.*

Introduction

Medical abortion refers to the use of medications to terminate a pregnancy in a manner akin to a miscarriage. Despite an overall decline in abortion rates, the prevalence of medical abortion has markedly increased since its approval by the FDA in 2000. While some nations continue to enforce regulations that limit access, others are investigating methods to enhance accessibility by permitting non-physician clinical providers to prescribe mifepristone, and evaluating the effectiveness of telemedicine in widening access to abortion services for those who need them. Medical abortion serves as an alternative to surgical abortion (1. It is recognized as an effective and acceptable option for abortion care (2-3). Due to minimal medical requirements for the safe administration of medical abortion drugs and the fact that women can generally manage the process themselves, there is a rising percentage of induced abortions in both the United States (US) and globally that are classified as medical abortions (4-5). Expanding access to medical abortion, including increasing the gestational ages at which it can be safely administered, is one approach aimed at reducing unsafe abortions, particularly in areas where trained surgical providers are scarce. The most efficacious regimen for medical abortion combines mifepristone with misoprostol; however, differences exist regarding dosage, timing and method of administration for these two medications. Extensive evidence, international practices, and recommendations from the World Health Organization (WHO) endorse a regimen consisting of a 200mg dose of mifepristone followed by 800μg of misoprostol for pregnancies up to 63 days gestation (6-7), with recent findings suggesting its application could extend to 70 days gestation (8). Misoprostol is taken 24-48 hours following mifepristone, and facilitates uterine emptying through cramping and bleeding similar to early miscarriage. A follow-up appointment is usually arranged one or two weeks later to verify pregnancy termination using ultrasound or blood tests. The efficacy of all regimens is influenced by gestational age, showing reduced effectiveness after nine weeks; hence, it is recommended that misoprostol doses be repeated starting late in the first trimester. Home administration of misoprostol demonstrates comparable effectiveness to clinical administration up to 63 days gestation and is recognized as a safe practice (9,10). Future studies on later gestational ranges would also need to prove similar efficacy, acceptability, and adverse event rates associated with home use of medical abortion medications (11). As avenues for providing abortions have been streamlined and enhanced, several affluent countries have seen an uptick in medication abortions compared to aspiration procedures while simultaneously experiencing improved access and fewer complications related to medical abortions (12). In regions where abortive medications (mifepristone/ misoprostol) can be obtained directly from pharmacies - bypassing physician dispensations - abortions tend to occur significantly earlier in gestation (13). In the United States, approximately 40 percent of all abortions were classified as medical abortions in 2018; notably, most occurred at or before nine weeks of gestation (14-16). When conducted according to established guidelines, medical abortion constitutes a safe method for terminating pregnancies. Although numerous studies have explored acceptance levels concerning medical abortions, considerably less research has focused on factors affecting

women's satisfaction with surgical procedures over the past fifteen years. Evidence suggests high acceptability rates among women who obtain accessible abortion services; these data indicates general contentment among women who successfully secure an abortion (17).

In Republic of North Macedonia, abortion has been legal since 1972; however, medical abortion was only legalized for use in May 2019 under the Law on Pregnancy Termination, Republic of North Macedonia (18). Following the implementation of Clinical Guidelines on Safe Abortion in December 2020, we initiated a pilot project focusing on medical abortions during both the first and second trimesters (19). Even though medical abortive drugs lack formal registration within the country's healthcare system due largely to favorable political attitudes toward reproductive rights observed over recent years, the government allocated funds through its Preventive Program for Mother and Child Health Care budget specifically aimed at acquiring these drugs for introduction into services at the University Clinic for Gynecology and Obstetrics.

The primary objective when monitoring patients undergoing medical abortion is confirming successful termination without complications. Post-abortion monitoring parameters may encompass serum-hCG levels assessment alongside sonographic evaluations regarding endometrial thickness patterns observed during bleeding episodes or serial hemoglobin/ hematocrit measurements(20). Furthermore, sonographic assessments measuring endometrial thickness serve as crucial indicators when diagnosing incomplete abortions post-first trimester spontaneous losses; they may also assist clinicians assessing potential treatment needs following medicated terminations (21). Nonetheless, a clear strategy remains elusive concerning whether women with ultrasound indications suggestive of incomplete termination truly necessitate any intervention based solely on retained products diagnosis.

Objectives

The objectives of the study were to evaluate the serum-hCG levels and ultrasonographic measurement of endometrial thickness as predictors of failure to complete abortion in patients designated for medical abortion using mifepristone and misoprostol.

Materials and Methods

We carried out a prospective observational study involving 97 women who sought medical abortion at the University Clinic of Gynecology and Obstetrics in Skopje, Republic of North Macedonia, from January to June 2023. Following gynecological assessment and ultrasound evaluations to confirm gestational age, participants were administered 200mg of mifepristone orally, followed by 800μg of misoprostol sublingually after a 24-hours period for at-home use. Data regarding socioeconomic status, body mass index (BMI), reproductive history, outcomes of the medical abortions during follow-up examinations, requirements for surgical intervention due to retained uterine contents, side effects experienced and other relevant information were collected through dedicated questionnaires. Prior to any procedure, written informed consent was secured from all participants involved in the study. Serum human chorionic gonadotropin (hCG) levels were measured on days 7 and 14 post-treatment. Transvaginal ultrasounds were conducted during each follow-up visit to assess the presence of the gestational sac. Women exhibiting minimal bleeding with an empty uterus on ultrasound were monitored until day 15;

those who continued to bleed beyond this point were included in the study. Participants experiencing significant bleeding received a clinical diagnosis of incomplete abortion confirmed through ultrasonography and subsequently underwent surgical evacuation of the uterus. Individuals with severe vaginal bleeding (with or without signs of shock), those presenting with a dilated cervical os or indications of cervical abortion were excluded from the analysis. After providing explanations about the procedures and objectives of the study, all subjects underwent transvaginal ultrasound scans as well as serum hCG assays before proceeding with cervical dilation and endometrial curettage or uterine evacuation under general anesthesia. Based on histopathological examination results of the uterine contents, participants were classified into two groups: those with incomplete abortions (19 cases; 19.6% showing evidence of products of conception) and those with complete abortions (78 cases; 80.4% showing no evidence of products of conception). The findings from transvaginal ultrasound examinations and quantitative serum hCG levels were compared to histopathological results to determine their effectiveness in predicting complete abortion outcomes.

Table 1. Baseline characteristics of the study groups.

	Complete abortion (n=78)	Incomplete abortion (n=19)	P
Maternal age (years ± SD)	29.15±4.4	28.73±4.8	0.715
Parity (n (%))			
Primipara	37 (47.4%)	8 (42.1%)	0.676
Multipara	41 (52.6%)	11 (57.9%)	
Maternal BMI (Kg/m2± SD)	31.4 ± 4.1	30.6 ± 4.4	0.448
Gestational age in days at induction*	38.5 (33–46)	46.5 (39–56)	0.026†
History of previous miscarriage*	1 (0–3)	1 (0–3)	0.751
Induction–presentation interval in days*	18.5 (14–22)	15 (14–24)	0.624

BMI: Body mass index; *Data are given in median (range);†statistically significant difference.

Endometrial thickness was measured using a 5–7.5MHz transvaginal ultrasound probe. The method of examination was consistent with published recommendations (13). When ultrasonography confirmed that the gestational sac had been expelled, the maximal anteroposterior endometrial thickness, including any blood and clots, in the longitudinal plane of the uterus was measured. If the sac had not been expelled, the endometrial thickness was not measured. Quantitative-B hCG (Betha chorionic gonadotropin) Assay - Venipuncture samples were transferred within 30 minutes to the laboratory, where centrifugation was performed to separate serum. The results were expressed as IU/L. This assay can detect whole molecule (intact) hCG as well as free-hCG subunits. The analytical sensitivity of hCG detection in serum is 2 IU/L (with a correlation coefficient of 0.95), and the cut-off level for a positive test in serum is 25 IU/L. The comparison of quantitative variables across the study groups was conducted utilizing the Mann Whitney U test for independent samples. Categorical data comparisons were carried out using the chi-square test, and Yates correction was applied when the expected frequency fell below 5. The accuracy of the results was expressed through sensitivity, specificity, positive predictive

value, negative predictive value, as well as the likelihood ratios for both positive and negative tests. To identify the optimal cut-off values for the diagnostic markers under investigation, receiver operating characteristic analysis was employed. A statistical significance threshold was established at P<0.05.

Results

Out of the 97 women enrolled in the study, 78 were found to have had a complete abortion (80.4%) and 19 to have had an incomplete abortion (19.6%), as determined by histopathological examination of uterine curetting. The baseline characteristics of women in each group were similar (Table 1). There was a statistically significant difference in estimated gestational age between the complete abortion and incomplete abortion groups (38.5 days and 46.5 days, respectively; P=0.026). The mean endometrial thickness in the two groups was 11.2±3.9mm in the complete abortion group and 14.6±6.1mm in the incomplete abortion group, a statistically significant difference (P=0.003) (Table 2). Mean serum-hCG levels also were statistically different in the two groups (73.9±23.9 IU/L in the complete abortion group and 109.4±68.4 IU/L in the incomplete abortion group; P<0.001). The accuracy of the studied markers in predicting complete abortion is shown in Table 3. An endometrial thickness of 12mm predicted incomplete abortion with a sensitivity of 88.5%, a specificity of 73.7%, a PPV of 93.2% and an LR+ve of 85.6. On the other hand, a serum-hCG level 100IU/L predicted incomplete abortion with a sensitivity of 87.2%, a specificity of 78.9%, a PPV of 94.4% and a LR+ve of 85.6.

Table 2. Ultrasonographic results and quantitative-hCG assay in the study groups.

	Complete abortion (n =78)	Incomplete abortion (n = 19)	P
Endometrial thickness (mm)*	11.2 ± 3.9	14.6 ± 6.1	0.003†
Serum-hCG (IU/L)*	73.9 ± 23.9	109.4 ± 68.4	< 0.001†

*Data are given in mean ± SD; † statistically significant difference.

Table 3. Accuracy of the studied markers in diagnosing complete abortion.

	Sensitivity	Specificity	PPV	NPV	LR+ve	LR-ve
Endometrial thickness (12mm)	88.5%	73.7%	93.2%	60.9%	85.6	3.4
Serum-hCG (100 IU/L)	87.2%	78.9%	94.4%	60.0%	85.6	4.1

Discussion

The safety and efficacy of medical termination of early pregnancy with mifepristone and misoprostol has been previously demonstrated in multiple studies (5,6). With the availability of mifepristone and misoprostol, it is expected that many women experiencing abortion may prefer a medical method of uterine evacuation because it allows them to avoid a surgical procedure. The clinical course of medical abortion closely resembles that of a spontaneous miscarriage.14 hCG values or measured endometrial thickness but following the patients' clinical course after two weeks follow-up, we were able to analyze the prognostic value of serum-hCG assay and ul-

trasonography as predictors of late failure. Serum-hCG was measured according to the internationally accepted standard reference. The overall percentage decline in-hCG is consistent with earlier findings (22, 20). In the present study, both the quantitative values of serum-hCGand and the endometrial thickness after medical abortion were higher in women who proved to be late failures than in women whose treatment was successful. Although most of the studies have reported an average duration of bleeding after medical abortion of approximately seven days, bleeding may last for as long as 21 days (23,24,25). In the event of persistent bleeding, surgical intervention should be applied. In addition to ordinary sonographic parameters, Markovitch et al., performed Doppler flow studies in patients after medically induced abortion (26). These authors found no correlation between the patients' reports of symptoms and the sonographic findings, and they found that an intrauterine echogenic mass with or without Doppler flow signals may not infrequently be detected two weeks after medical termination of pregnancy. Because most of the women with this finding subsequently resumed normal menses, they concluded that this finding could indicate remnants of trophoblastic tissue that will pass spontaneously without the need for dilatation and curettage (26). Steier et al., studied serum-hCG levels in women following the first trimester surgical abortion and demonstrated that the median time to reach a level of less than 10IU/L after surgical abortion was 30 days (range 16–60 days), compared to a median of 19 days (range 9–35 days) after spontaneous abortion (27). Honkanen et al., reported that serum-hCG concentrations have declined by 99.4% ±10% by day 14 after medical abortion, and that the route of medication administration (oral or vaginal) has no effect on the kinetics of serum-hCG (28). Another study reported that failed or incomplete abortion occurs when pregnancy tests with sensitivities of at least 1000 IU/L are positive within two weeks after surgical abortion (29). In our study we found that threshold levels of serum-hCG and endometrial thickness with high positive predictive values had a low sensitivity, leading to identification of only a minority of the failures. Higher positive predictive values were achieved by combining changes in serum-hCG levels and endometrial thickness, but still at the expense of sensitivity. Nevertheless, both parameters were acceptable as a diagnostic test because of their high positive predictive value. Based on the results of this study, we recommend the use of ultra-sonography and serum-hCG assays to help prompt diagnosis and management if patients have an uncertain outcome or suspected retained products of conception should be considered only after careful evaluation of the patient. The suspected late failures in the present study were identified after day 15, reflecting a long and tiring course of bleeding and/or pain. Being able to diagnose these failures earlier would optimize the medical abortion procedure. The data presented in this report, describing the regression of serum-hCG levels and endometrial thickness measurements, may be useful adjuncts for clinical management, especially when vaginal bleeding is prolonged or when serum-hCG levels and endometrial thickness measurements are much above expected values. The consequences of overlooking failed uterine evacuation are limited, because the risk of serious morbidity associated with retained tissue is minimal and because failures ultimately will be revealed clinically. With this background we conclude that the analyzed variables used as diagnostic tests would lead to a reduced number of unnecessary interventions. A thickened endometrium after miscarriage is a normal finding. An understanding of the relationship between endometrial thickness and the need for future surgical intervention is important. Our findings suggest that such a relationship exists, and that endometrial thickness measurements are likely to be predictive of incomplete abortion or the need for further treatment. In this study, a wide range of endometrial thickness was observed after expulsion of the gestational sac, and we observed a statistically significant difference in the mean endometrial thickness between women who had a complete termination and those who had an incomplete termination (11.2±3.9mm and 14.6±6.1mm, respectively). It should be emphasized that choosing a low endometrial thick-

ness cut-off point for clinical intervention would lead to unnecessary surgical treatment for a significant number of patients. Increasing the cut-off would decrease the false positive rate and improve the specificity of the test measurement. In our study, when the cut-off point for endometrial thickness was 12mm, the positive likelihood ratio was 85.57 and the negative likelihood ratio was 3.36.

Conclusion

Quantitative serum-hCG levels and endometrial thickness, both were significantly higher in women with failed medical abortion than in women whose treatment was successful. Both of these measures are clinically useful in predicting late failure after medical abortion, and can be helpful in uncertain clinical situations, but should be considered as supplementary to a general clinical evaluation.

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