

Endometrial Thickness and Serum β -hCG as Predictors of the Effectiveness of Oral Misoprostol in Early Pregnancy Failure

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Abstract

Objective: To evaluate ultrasonographic measurement of endometrial thickness and serum levels of chorionic gonadotropin (β -hCG) as predictors of failure to abort completely in patients designated for uterine evacuation using oral misoprostol.

Methods: Women attending an obstetric outpatient clinic who complained of residual vaginal bleeding 15 days or more after taking oral misoprostol for medical induction of abortion for early pregnancy failure were evaluated by transvaginal ultrasound scan and assay of serum β -hCG. They subsequently underwent dilatation and curettage under general anaesthesia. According to the results of histopathological examination of uterine contents, the study cohort was divided into women with incomplete abortion (19 cases, 19.6%) and cases with complete abortion (78 cases, 80.4%). The results of the ultrasound scan and the assay of serum β -hCG were correlated with the histopathological results to determine the accuracy of these markers in predicting complete abortion.

Results: Baseline characteristics for both groups were similar. The endometrial thickness in the two groups ranged from 11.2 ± 3.9 mm in the complete abortion group to 14.6 ± 6.1 mm in the incomplete abortion group, a statistically significant difference ($P = 0.003$). Serum β -hCG levels were statistically different in the two groups (complete abortion 73.9 ± 23.9 IU/L vs. incomplete abortion 109.4 ± 68.4 IU/L, $P < 0.001$). Measured endometrial thickness ≥ 12 mm predicted incomplete abortion with a sensitivity of 88.5%, a specificity of 73.7%, a positive predictive value (PPV) of 93.2%, and a positive likelihood ratio (LR+ve) of 85.6. A serum β -hCG ≥ 100 IU/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.

Conclusion: Quantitative assay of serum β -hCG and ultrasound measurement of endometrial thickness are clinically useful measures for predicting late failure of medical abortion, but should be used as supplements to clinical assessments.

Key Words: Transvaginal ultrasonography, endometrial thickness, serum β -hCG, oral misoprostol, early pregnancy failure

Competing Interests: None declared.

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Résumé

Objectif : Évaluer la mesure échographique de l'épaisseur endométriale et les taux sériques de gonadotrophine chorionique (β -hCG) à titre de prédicteurs de l'échec de l'avortement complet chez les patientes pour lesquelles une évacuation utérine au moyen de misoprostol oral est indiquée.

Méthodes : Les femmes fréquentant une clinique externe d'obstétrique qui s'étaient plaintes de saignements vaginaux résiduels 15 jours ou plus après avoir pris du misoprostol par voie orale, en vue d'un avortement thérapeutique motivé par l'échec précoce de la grossesse, ont été évaluées par échographie transvaginale et dosage de la β -hCG sérique. Elles ont par la suite subi une dilatation-curetage sous anesthésie générale. En fonction des résultats de l'examen histopathologique du contenu utérin, la cohorte d'étude a été divisée en deux groupes : « femmes ayant connu un avortement incomplet » (19 cas, 19,6 %) et « femmes ayant connu un avortement complet » (78 cas, 80,4 %). Les résultats de l'échographie et du dosage de la β -hCG sérique ont été corrélés aux résultats histopathologiques afin de déterminer la précision de ces marqueurs en matière de prédiction de l'avortement complet.

Résultats : Les caractéristiques de base des deux groupes étaient semblables. Au sein des deux groupes, l'épaisseur endométriale allait de $11,2 \pm 3,9$ mm (groupe « avortement complet ») à $14,6 \pm 6,1$ mm (groupe « avortement incomplet »), soit une différence significative sur le plan statistique ($P = 0,003$). Les taux sériques de β -hCG étaient statistiquement différents au sein des deux groupes (avortement complet : $73,9 \pm 23,9$ UI/L, par comparaison avec avortement incomplet : $109,4 \pm 68,4$ UI/L, $P < 0,001$). Une mesure d'épaisseur endométriale ≥ 12 mm permettait de prédire un avortement incomplet selon une sensibilité de 88,5 %, une spécificité de 73,7 %, un coefficient de prévision d'un test positif (CPTP) de 93,2 % et un rapport de vraisemblance positif (RV+) de 85,6. Un taux sérique de β -hCG ≥ 100 UI/L permettait de prédire un avortement incomplet selon une sensibilité de 87,2 %, une spécificité de 78,9 %, un CPTP de 94,4 % et un RV+ de 85,6.

Conclusion : Bien que le dosage quantitatif de la β -hCG sérique et la mesure échographique de l'épaisseur endométriale soient des mesures utiles sur le plan clinique pour la prédiction de l'échec tardif de l'avortement médical, elles devraient être utilisées à titre de suppléments aux évaluations cliniques.

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INTRODUCTION

For more than 50 years, early pregnancy failure has typically been managed by surgical evacuation of the uterus.¹ In 1997, Chung et al. reported an overall complication rate of 6.6% in women who undergo surgical intervention.² Medical treatment to induce abortion has been shown to be a reasonable alternative to universal surgical evacuation. It avoids surgical complications, follows the natural history of the disease, and is likely to be cost effective.³ Incomplete medical abortion may, however, increase the risk of infection and has been associated with persistent or recurrent bleeding and pain.⁴

Use of the inexpensive synthetic prostaglandin E₁ analogue misoprostol for medical abortion results in complete expulsion of the gestational sac in more than 80% of women.^{5,6} Moreover, for those patients who subsequently require surgical evacuation, the risk of surgery-related complications and short-term complications has been shown to be significantly lower in patients who use misoprostol prior to surgical evacuation.⁷

Early identification of women treated with misoprostol who have retained products of conception would allow early intervention. The risk of failure of medical treatment appears to be related to advanced gestational age, high body mass index, and multiparity.^{8,9} Honkanen et al. reported that the decline in serum β -hCG levels after a medically induced abortion is inversely correlated with the time taken to abort.¹⁰

It is important to establish post medical abortion guidelines to prevent unnecessary surgical intervention. The primary purpose of monitoring patients during medical abortion is to confirm that abortion has been complete, without complications. Parameters that can be used to monitor the post-abortion course include serum β -hCG levels, sonographic evaluation of endometrial thickness, bleeding patterns, and serial measurements of hemoglobin and hematocrit.¹¹

The sonographic measurement of endometrial thickness is a useful parameter for diagnosing incomplete abortion after a first trimester spontaneous abortion, and can be expected to be useful in diagnosing failure after medical abortion.¹²

However, there is no clear means of determining whether or not women whose ultrasound findings suggest incomplete abortion or retained products of conception truly need any treatment. In this study we evaluated serum β -hCG levels and ultrasonographic measurement of endometrial thickness as predictors of failure to complete abortion in patients designated for medical abortion using oral misoprostol.

MATERIALS AND METHODS

We conducted a prospective observational study of 97 women attending the gynaecology outpatient clinic at Al Fayom and Cairo Universities between May 2007 and November 2007. All participants had taken misoprostol as treatment for early pregnancy failure (to a maximum of 56 days' gestation) and had either persistent or recurrent vaginal bleeding 15 days or more after use of misoprostol. Misoprostol had been given orally in an initial dose of 400 μ g, repeated every six hours if the patient had not passed the products of conception to a maximum of four doses. Follow-up visits were scheduled at five days (range 3–7) and 15 days (range 10–18) after misoprostol administration. Serum β -hCG was assayed on day 7 and day 14. Transvaginal ultrasonography was performed at each follow-up visit to determine if the gestational sac was still present. Women who had significant bleeding were given a clinical diagnosis of incomplete abortion, which was confirmed by ultrasonographic assessment, and had surgical evacuation of the uterus. Women with minimal bleeding and an empty uterus on ultrasound were followed to day 15. If bleeding persisted at that time, they were enrolled in the study. Women with severe vaginal bleeding (with or without evidence of shock), those who had a dilated cervical os, and those with evidence of cervical abortion were excluded from the study.

After explanation of the procedures and the aim of the study, all participants had transvaginal ultrasound scanning and an assay of serum β -hCG before undergoing cervical dilatation and endometrial curettage or uterine evacuation under general anaesthesia (at either Kasr El Aini Maternity Hospital or El Fayom General Hospital). Depending on the results of histopathological examination of the uterine contents, the study cohort was divided into women with incomplete abortion (who had evidence of products of conception; 19 cases, 19.6%) and women with complete abortion (who had no evidence of products of conception; 78 cases, 80.4%). The results of transvaginal ultrasound examination and quantitative serum β -hCG were correlated with the histopathological results to calculate the accuracy of these markers in predicting complete abortion.

ABBREVIATIONS

LR+ve	positive likelihood ratio
LR-ve	negative likelihood ratio
NPV	negative predictive value
PPV	positive predictive value

Table 1. Baseline characteristics of the study groups

	Complete abortion (n = 78)	Incomplete abortion (n = 19)	P
Maternal age (years \pm SD)	29.15 \pm 4.4	28.73 \pm 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/m ² \pm SD)	31.4 \pm 4.1	30.6 \pm 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
Number of misoprostol doses*	2 (1–4)	2.5 (1–4)	0.264
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.

Transvaginal Ultrasonographic Scan

Endometrial thickness was measured using a 5–7.5 MHz 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 β -hCG Assay

Venepuncture samples were transferred within 30 minutes to the laboratory, where centrifugation was performed to separate serum. Serum samples were stored at -20°C until assayed. Serum β -hCG assay was performed using the Abbott AxSYM System, based on the microparticle enzyme immunoassay technology, using an AxSYM total hCG trade mark kit (Abbott Laboratories, Diagnostic Division, Abbott Park IL). The results were expressed as IU/L. This assay is capable of detecting whole molecule (intact) hCG as well as free β -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.

Statistical Analysis

Comparison of quantitative variables between the study groups was performed using the Mann Whitney U test for independent samples. For comparing categorical data, chi-square test was performed. Yates correction equation was used when the expected frequency was < 5 . Accuracy was represented using the terms sensitivity, specificity, positive predictive value, negative predictive value, the likelihood ratio of a positive test and the likelihood ratio of a negative test. Receiver operator characteristic analysis was used to determine the optimum cut-off value for the

studied diagnostic markers. Statistical significance was set at $P < 0.05$. All statistical calculations were performed using Microsoft Excel version 7 (Microsoft Corporation, NY) and the SPSS for Windows (version 13.0, Chicago, IL) statistical program.

RESULTS

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 curettings. 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 ± 3.9 mm in the complete abortion group and 14.6 ± 6.1 mm in the incomplete abortion group, a statistically significant difference ($P = 0.003$) (Table 2). Mean serum β -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 ≥ 12 mm 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 β -hCG level ≥ 100 IU/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 β -hCG assay in the study groups

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

*Data are given in mean \pm 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 (12 mm)	88.5%	73.7%	93.2%	60.9%	85.6	3.4
Serum β -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 misoprostol has been previously demonstrated in multiple studies.^{5,6} With the availability of 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 Oral misoprostol is inexpensive, stable, and effective for medical abortion. We chose to use oral misoprostol because the vaginal route is less preferred by patients, and it may be uncomfortable and painful.^{15,16}

Although most studies have reported an average duration of bleeding after medical abortion of approximately seven days, bleeding may last for as long as 21 days.^{14,17,18} In the event of persistent bleeding, surgical intervention 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 β -hCG levels and endometrial thickness measurements, may be useful adjuncts for clinical management, especially when vaginal bleeding is prolonged or when serum β -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. Since we did not intervene as a result of either specific

β -hCG values or measured endometrial thickness, but followed the patients' clinical course after a two week follow-up, we were able to analyze the prognostic value of serum β -hCG assay and ultrasonography as predictors of late failure. Serum β -hCG was measured according to the internationally accepted standard reference. The overall percentage decline in β -hCG is consistent with earlier findings.^{11,19} In the present study, both the quantitative values of serum β -hCG and the endometrial thickness after medical abortion were higher in women who proved to be late failures than in women whose treatment was successful.

Post-procedure ultrasonography is used by the majority of care providers to document the absence of a gestational sac and confirm a completed medical abortion. 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 \pm 3.9 mm and 14.6 \pm 6.1 mm, respectively).

It should be emphasized that choosing a low endometrial thickness 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 12 mm, the positive likelihood ratio was 85.57 and the negative likelihood ratio was 3.36.

In addition to ordinary sonographic parameters, Markovitch et al. performed Doppler flow studies in patients after medically induced abortion.²⁰ 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.²⁰

Steier et al. studied serum β -hCG levels in women following first trimester surgical abortion and demonstrated that the median time to reach a level of less than 10 IU/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.²¹ Honkanen et al. reported that serum β -hCG concentrations have declined by $99.4\% \pm 10\%$ by day 14 after medical abortion, and that the route of medication administration (oral or vaginal) has no effect on the kinetics of serum β -hCG.¹⁰ 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.²² In our study we found that threshold levels of serum β -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 β -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 ultrasonography and serum β -hCG assays to help prompt diagnosis and management if patients have an uncertain outcome or suspected retained products of conception.

CONCLUSION

Quantitative serum β -hCG levels and endometrial thickness were both significantly higher in women with failed medical abortion than in women whose treatment was successful. Both of these measurements 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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