Prediction of late failure after medical abortion from serial β-hCG measurements and ultrasonography

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BACKGROUND: Surgical treatment of failed medical abortion may be performed several weeks after initiation of the abortion. There are no recognized methods for early identification of these late failures. We assessed the prognostic values of β-hCG and ultrasonography in predicting late failure after medical abortion. METHODS: A total of 694 consecutive women with gestational age (GA) <63 days were followed up with β-hCG measurements initially on the day of treatment and on day 8 and day 15, after the medically induced abortion with mifepristone and gemeprost. Measurement of the endometrial thickness by ultrasonography was performed on day 15 after induction of medical abortion. Failures diagnosed after day 15 and within 15 weeks were identified and classified as late failures. All interventions in this group were due to bleeding problems. The predictive values of different absolute and relative β-hCG levels and different endometrial thickness were analysed. RESULTS: Of all failures in the study period, 65% (32) were diagnosed after the 2 week follow-up, and categorized as late failures. The absolute and the relative β-hCG values on days 8 and 15 as well as the endometrial thickness on day 15 were greater among late failures than successes. Used as a predictive test, the positive predictive values of these variables were low. CONCLUSION: Neither β-hCG nor endometrial thickness can be used clinically as diagnostic tests in predicting late failure after medical abortion.

Key words: β-hCG/diagnostic test/failure/medical abortion/prediction

Introduction

The frequency of failure after medically induced abortions, defined as subsequent surgical intervention, is 2–6% for regimens using mifepristone/vaginal prostaglandin analogue (UK Multicentre Trial, 1990; Ashok et al., 1998, 2002; Schaff et al., 1999, 2000a,b). A noticeable number of failures are diagnosed after the usual 2 week follow-up (Ashok et al., 1998; Schaff et al., 2000b; Knudsen, 2001; Rørbye et al., 2003). Compared with surgical termination, medical abortion seems to be associated with a lower risk of pelvic inflammatory disease, probably due to the avoidance of instrumentation of the uterus (Henshaw et al., 1994; Winikoff et al., 1997; Jensen et al., 1999; Child et al., 2001). Incomplete medical abortion may, however, increase the risk of infection and is furthermore associated with discomfort as persistent or recurrent bleeding and pain. Early identification of women with retained tissue would allow early intervention. The risk of failure is related to high gestational age (McKinley et al., 1993), high body mass index (Grimes et al., 1990) and multiparity (Bartley et al., 2000). Few prospective studies have addressed prediction of failure after medical abortion, and no prospective tests have been suggested.

Failures diagnosed after the 2 week follow-up, defined as late failures, are associated with retained products of conception and heavy or prolonged bleeding. The absolute and/or relative β-hCG might therefore be higher in failures than successes, and could perhaps be an indicator of late failure. This hypothesis is supported by Honkanen et al. (2002), who found that the decline in β-hCG after a medically induced abortion is inversely correlated with the time taken to abort. The thickness of the endometrium is a useful parameter in diagnosing incomplete abortion after first trimester spontaneous abortion (Wong et al., 2002), and is also expected to be useful in diagnosing failure after medical abortion.

With this background, we wanted to compare the absolute and the relative β-hCG values and the endometrial thickness after 1–2 weeks in successes and late failures after medical abortion, and to analyse the prognostic value of these variables.

Materials and methods

A total of 871 women aged >18 years had a medical abortion in the period of August 1999 to May 2001. The women were included at H:S Copenhagen University Hospital; Hvidovre and Frederiksberg. Contraindications for medical abortion in our facility and exclusion
Table I. Baseline characteristics for women excluded from the study and women followed-up as intended

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Excluded (n = 177)</th>
<th>Followed up (n = 694)</th>
<th>Failures (n = 32)</th>
<th>Successes (n = 662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>27 (18–44)</td>
<td>28 (18–50)</td>
<td>29 (19–38)</td>
<td>28 (18–50)</td>
</tr>
<tr>
<td>Median gestational age in days (range)</td>
<td>51 (35–63)</td>
<td>50 (32–63)</td>
<td>52 (38–63)</td>
<td>50 (32–63)</td>
</tr>
<tr>
<td>Median β-hCG day 1 (IU/l) (quartiles)</td>
<td>89 915</td>
<td>87 057</td>
<td>113 519</td>
<td>86 827</td>
</tr>
<tr>
<td>Parous (%)</td>
<td>42</td>
<td>40</td>
<td>59*</td>
<td>39</td>
</tr>
<tr>
<td>Prior induced abortion (%)</td>
<td>47**</td>
<td>36</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>Prior miscarriage (%)</td>
<td>18</td>
<td>13</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

Same baseline characteristics are shown for medical abortion failures and successes.

*P < 0.05, **P < 0.01 for excluded women versus women followed up as intended, and failures versus successes compared by Mann–Whitney test and Fisher’s exact test.

days (n = 79) or surgical intervention before day 15 (n = 8). Late failure was defined as surgical intervention after day 15 and within 15 weeks. No interventions on women included in the study were performed as a consequence of either serum β-hCG values or ultrasonographic images.

All women were followed up by a unique personal identification number in a computer system 15 weeks after initiation of the abortion, allowing identification of all surgical interventions anywhere within the country due to abortion-related complications. No women were lost to follow-up in this study.

The median values of the different variables for late failures and successes were compared by Mann–Whitney U-test. The positive and negative predictive values as well as sensitivity and specificity were calculated and analysed at different threshold limits for absolute β-hCG values on days 1, 8 and 15 and for relative β-hCG values on days 8 and 15, and for different endometrial thicknesses on day 15. To characterize each parameter with respect to its accuracy to detect failures, sensitivity and specificity were calculated from 2×2 contingency tables for each possible threshold value and plotted as receiver operating characteristic (ROC) curves. The areas under the curves (AUC) were calculated as a test for the hypothesis that AUC is not significantly different from 0.5, the area under the straight line (sensitivity = 1 – specificity) that represents no discrimination between failure and success.

The local ethics committee approved the study, and all patients gave informed consent.

Results

Women excluded from the study had more often had prior, induced abortions than women who were followed up as intended, but the two groups were otherwise comparable (Table I).

The overall success rate for all women in the study period was 94.4% (95% CI: 92.9–96.1) (n = 822/871). Efficacy was significantly higher at gestational age (GA) <49 days: 97.5% (95.0–99.0) than at 49<GA<56 days: 93.3% (90.5–96.1) and at 56<GA<63 days: 89.7% (84.8–94.6) (P < 0.01). Among the women included for further analysis in this study, parity and gestational age were higher in the failure group than in the success group. The remaining baseline characteristics were similar (Table I). Sixty-five per cent (32/49) of all failures were diagnosed after day 15 and defined as late failures. Of the 32 late failures, six interventions were due to acute heavy bleeding and 26 due to prolonged bleeding. There were no ongoing pregnancies and no interventions on patient request not related
to bleeding. Late failures were diagnosed with a median interval of 23.5 days (range 15–103) after mifepristone administration. Twenty of the 32 failures were diagnosed after 30 days. Tissue from 20 women with late failure was examined histologically. Products of conception were found in 95% (19/20) of the curettages examined histologically. The points at the end of the whiskers represent the range of the values. *P < 0.01 for failures and successes compared by Mann–Whitney U-test.

The demands for a diagnostic test depend on the clinical situation, the consequences of a positive test result, and the risks connected with an overlooked condition. Diagnosing a failed medical abortion leads to surgical intervention often performed under general anaesthesia. To avoid unnecessary interventions, the positive predictive value of the applied test must be high. The specificity should not be <0.95, which is the approximate chance of a successful course using this medical abortion regimen.

We found that threshold levels of β-hCG and endometrial thickness with high positive predictive values had a low sensitivity, leading to identification of only a minority of the failures. As an example: using β-hCG >5000 on day 15 as a threshold, the specificity was 0.99, the positive predictive value was 0.69, but the sensitivity only 0.28. Used in a clinical situation, this means that 31% of performed interventions similar to other studies using the same regimen (UK Multicentre Trial 1990; Ashok et al., 1998; Schaff et al., 1999, 2000b; Ashok et al., 2002). Retained products of conception in 95% (19/20) of the curettages examined histologically indicate that the surgical interventions were medically justified. We do not know, however, how many of these would have resolved if left untreated. It is also possible that some of the cases categorized as successful would have had similar histological findings if a curettage had been performed. More than half of the failures 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 overall percentage decline in β-hCG is consistent with earlier findings (Walker et al., 2001; Honkanen et al., 2002). Both the absolute and the relative values of β-hCG as well as the endometrial thickness after medical abortion were higher in women who turned out to be late failures than in successfully treated women. However, we conclude that none of these variables can be used as diagnostic tests in predicting late failure after medical abortion.

Discussion
We have prospectively followed a large group of consecutive women undergoing medical abortion, and our failure rate is.
would be unnecessary, while 72% of the failures would be missed. Higher positive predictive values were achieved by combining changes in β-hCG and endometrial thickness, but still at the expense of sensitivity. As an example: a β-hCG value >5000 on day 8 combined with an endometrial thickness >10 mm on day 15 gave the positive predictive value 0.75, but the corresponding sensitivity was 0.28 and the specificity 1. Similar values were seen with other combinations of different threshold levels.

We found that none of the analysed parameters was acceptable as a diagnostic test because of the low positive predictive values. The consequences of overlooking a failure are limited, as 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 analysed variables used as diagnostic tests would lead to an unacceptable number of unnecessary interventions. If a positive test result could lead to a simple, risk-free, definitive test, a higher false positive rate could be acceptable, but such a definitive test has not been proven.

Since we did not intervene on either β-hCG values or on specific endometrial thicknesses, but followed the spontaneous courses after a 2 week follow-up, we were able to analyse the prognostic value of β-hCG and ultrasonography as predictors of late failure. Serum β-hCG was measured according to the internationally accepted standard reference, but the absolute values may vary with different assays. The use of relative changes allows comparison between centres using different assays. Resident doctors under the supervision of a specialist doctor performed the ultrasonography at follow-up. We have not analysed the validity of the measurements of the endometrial thickness and therefore cannot exclude a possible inter-observational discrepancy. To minimize this, all residents had to qualify before authorization was given to perform ultrasound examinations at our department. Furthermore, doctors were unaware of the final outcome. There is no reason to believe that a systematic error has been made, but rather a random incorrectness that does not influence the conclusion. Moreover, our findings are consistent with endometrial thicknesses after a tamoxifen/misoprostol regimen (Harwood et al., 2001).

Some of the cases excluded in this study were unavoidable, because surgical intervention was performed before follow-up on day 15, but the majority of exclusions was caused by a lack of serial β-hCG values or ultrasonography performed on the correct days. Similar frequencies of lost or incorrect follow-up after induced abortion are a recognized problem (Thonneau et al., 1998). However, the baseline characteristics were similar in the women included and those women excluded, and it is therefore unlikely that results from the excluded women would affect the overall conclusion. Comparing women in the failure group with women in the success group revealed more parous women among failures, which correspond to the increased risk of failure with increased parity (Bartley et al., 2000).

Following mifepristone administration, β-hCG continues to increase, but declines precipitously after administration of misoprostol (Somell et al., 1990; World Health Organization Task Force, 1991; Walker et al., 2001; Honkanen et al., 2002). The finding of significantly higher absolute and relative β-hCG values among late failures compared with successes on days 8 and 15 after a mifepristone/prostaglandin regimen has, to our knowledge, not been published previously. The only published predictive analysis concluded that a decrease in β-hCG of <50% within 24 h after misoprostol administration in methotrexate pre-treated women was associated with an increased risk of ending as a failure, but the positive and negative predictive values were not given (Creinin, 1996).

In conclusion, absolute and relative β-hCG values as well as endometrial thickness were significantly higher in late failures than successes after medical abortion, but none of these parameters is clinically useful as a diagnostic test in predicting late failure after medical abortion. β-hCG measurement and ultrasonography can be used to identify ongoing pregnancies, and might be helpful in a clinical situation of doubt, but are merely supplements to the general clinical evaluation. After ongoing pregnancy is excluded, only the clinical course will reveal the remaining failures. The women must therefore be informed to return for a clinical examination in cases of acute or prolonged bleeding, pain or fever, as these signs may be indicators of failure or other complications that need treatment.

References


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