Mifepristone does not induce cervical softening in non-pregnant women

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BACKGROUND: Many techniques have been developed to soften the cervix to reduce complications following surgical dilatation. Progesterone inhibits myometrial contractility and its secretion during pregnancy ensures cervical competence. We used the progesterone antagonist mifepristone as a cervical ripening agent and evaluated its effect prior to office hysteroscopy. METHODS: Fifty-eight healthy non-pregnant women aged 18–50 were studied in a randomized double-blind study. They received mifepristone (200 mg) or placebo 30 h prior to hysteroscopy. A Hegar test was performed prior to drug administration and again before hysteroscopy. A visual analogue pain scale was used to assess pain. RESULTS: Medical history, physical examination and blood tests were similar in both groups, except for serum progesterone which was higher in the study group. Hegar measurement prior to drug ingestion was similar in both groups and after a mean time of 30.3 h increased in both groups. Neither the ΔHegar measurement nor the pain scale was different in the two groups. There was also no effect of the high progesterone levels. CONCLUSIONS: Unlike its dramatic effect in the pregnant uterus, mifepristone administered 30 h prior to hysteroscopy was not effective in ripening the cervix of non-pregnant women.

Key words: mifepristone/office hysteroscopy/pain scale/RU-486

Introduction

In the last few years, several pharmacological and mechanical methods have been developed to ripen and soften the uterine cervix. The purpose is to reduce the risk of cervical tears, uterine perforation and haemorrhage, complications that may occur following surgical cervical dilatation. Prostaglandins (Embrey and Tait, 1977; MacKenzie and Embrey, 1977), relaxin (MacLennan et al., 1980), estrogens (Gordon and Calder, 1978) and laminaria tents (Johnson, 1989) are commonly used in pregnancy, either as part of induction of labour at term, or as the first step of dilatation prior to curettage or vacuum aspiration. Recently, sodium nitroprusside has also been used since nitric oxide is involved in the process of cervical ripening (Facchinetti et al., 2000; Piccinini et al., 2003).

Progesterone inhibits myometrial contractility, and its ongoing secretion during pregnancy ensures cervical competence (Csapo and Pulkkinen, 1978). This is the rationale for attempting to use a progesterone receptor antagonist as a cervical ripening agent (Durlot et al., 1988). Mifepristone (RU486) is a synthetic steroid hormone analogue that has both antiprogesterone and antiglucocorticoid activities. Several studies have shown that by enhancing uterine contractility and promoting cervical softening, mifepristone followed by the prostaglandin, misoprostol, can terminate pregnancies of <9 weeks duration. Mifepristone is also most useful in promoting cervical dilatation in women with later gestational ages whose pregnancies are terminated with prostaglandins or surgery (Jannet et al., 1996; Ashok and Templeton, 1999). In these studies, maximum cervical dilation was usually seen 30–48 h after mifepristone administration (Jannet et al., 1996). Mifepristone also causes expulsion of the uterine contents following intrauterine fetal death (Cabrol et al., 1990).

There is only one study reported to date which investigated the role of mifepristone in cervical ripening of non-pregnant women (Gupta and Johnson, 1990). This randomized, placebo-controlled trial demonstrated that mifepristone (600 mg) increased the mean pre-operative cervical dilatation and decreased the force required to dilate the cervix of post-menopausal women. Snijders et al. (1992) have reported that cervical stroma showed a fairly constant expression of progesterone receptors at a moderate concentration during the different menstrual cycle phases and after menopause. Based...
on these data and encouraged by the study published by Gupta and Johnson (1990), we postulated that mifepristone may also affect non-pregnant women.

In our randomized double-blind placebo-controlled study, we evaluated the efficacy of mifepristone in inducing cervical softening prior to office hysteroscopy in non-pregnant pre-menopausal women who require office hysteroscopy.

**Material and methods**

**Patients**

A total of 58 pre-menopausal women participated in the study (Figure 1). Their hysteroscopy was scheduled during the follicular phase of their menstrual cycle. Each participant in the study underwent a preliminary evaluation including medical history, physical examination, vaginal examination and ultrasonographic ovarian evaluation. Routine laboratory testing for liver and kidney function and blood count was performed 7–10 days prior to hysteroscopy. All of these results were within the normal range. None of the patients had menorrhagia. A few had irregular bleeding due to polycystic ovaries (PCO). The reasons for performing the hysteroscopy are shown in Table I.

**Inclusion and exclusion criteria**

Normal, healthy, non-pregnant women, aged 18–50 years who were scheduled to undergo hysteroscopy for a medical indication were recruited for the study. Pregnant women or women who used corticosteroid, hormonal contraception or any other steroid hormones were excluded from the study, as were women who suffered from adrenal, liver, renal or cardiovascular disease or insulin-dependent diabetes mellitus. In addition, women who had undergone any cervical intervention or surgery in the past and women who had undergone hysteroscopy because precise endometrial dating was required were also excluded from the study.

**Randomization and study protocol**

Both our Institutional Human Subjects Review Board and that of the Israeli Ministry of Health approved the study. After explaining the nature of the study, all women signed an informed consent. They were then randomized to one of two groups: a study group who received 200 mg of mifepristone and a control group receiving identical placebo tablets. The randomization list comprising 60 women was prepared by using a randomization plan generator prepared by Tuft University, Boston, MA (http://www.randomization.com). This randomizes each subject to a single treatment by using the method of randomly permuted blocks. The randomization list was obtained prior to the commencement of the study. The medication was prepared in a blinded fashion and neither the patient nor the staff knew whether mifepristone or placebo was administered. The medication was given to the woman in a sealed bag, marked only by the participant number.

Thirty hours before the hysteroscopy, the women reported to the clinic, blood for 17β-estradiol (E2) and progesterone levels was drawn, and a urinary pregnancy test was performed. The degree of cervical resistance as well as the cervical diameter were determined by conducting a baseline Hegar test. In this procedure, Hegar dilators of increasing size (commencing with Hegar 2 mm) were passed through the cervical os until meeting resistance. Up to this point, the procedure is painless. For this reason, when resistance occurs, no further dilators were used. Cervical dilatation was assessed by the size of the largest dilator that could be passed through the cervical os without resistance (expressed in mm). Following this Hegar test, the tablet (mifepristone or placebo) was taken orally under supervision. The participants refrained from ingesting food 1 h pre- and post-tablet ingestion. Hysteroscopy was scheduled for the next afternoon (i.e. 30h later). Prior to commencing the hysteroscopy, cervical resistance was again determined by conducting a Hegar test (as described above).

**Procedure**

A 2.9 mm rigid hysteroscope was used in all the women. The cervix was held by a tenaculum prior to all hysteroscopies. Neither anaesthesia nor analgesics were used in the procedure. The total time of the hysteroscopy itself was generally less than 45 s.

**Pain assessment**

Pain intensity during the hysteroscopy was assessed by a visual analogue scale (VAS), a simple commonly used method (Chapman et al., 1985). The women were instructed to indicate the intensity of the pain by marking a 100 mm line anchored with terms describing the extremes of pain intensity (‘no pain’ on one side and ‘worst imaginable pain’ on the other side). The women were asked to report, and the nurse marked the pain intensity the moment the hysteroscope passed the internal os of the cervix and the hysteroscopist could view the uterine lumen.

The examiner also objectively evaluated the intensity of the pain of the patient using a score system (0 = relaxed with no pain, 2 = verbal expression of mild pain, 4 = expression of severe pain).

During hysteroscopy, if a polyp or suspected abnormal area was found, a biopsy was taken. At the conclusion of the hysteroscopy,

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**Table I. Indications for hysteroscopy**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study group (n = 28)</th>
<th>Control group (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>18</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Suspected polyp</td>
<td>6</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrent abortion</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Irregular bleeding</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Suspected uterine abnormality</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

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Figure 1. Flow chart of participants through the stages of randomization.
the examiner also made a calculated determination as to whether the woman received mifepristone or placebo. All hysteroscopies were performed by one physician (A.B.-C.).

**Statistical evaluation**

The PEPI statistical program (Gahlinger PM & Abramson JH, Version 4.0, 1993–2001) was used. The number of women studied was determined by power calculation performed prior to beginning the study by ‘samples’ in the PEPI software. According to an unpublished pilot study conducted by the principal investigator, it was observed that in normal untreated women, the cervix is open to Hegar 2 ± 2 mm. We thus assumed that the cervix in the placebo group would be dilated to a similar degree and expected that mifepristone would cause an additional dilatation of up to 1.5 mm. To achieve a power of 80% and \( P < 0.05 \), we calculated that 30 patients should be recruited for each group (Gahlinger PM & Abramson JH, Version 4.0, 1993–2001). Data were analysed by \( t \)-test where appropriate. A difference of \( P < 0.05 \) was considered to be significant. All values are given as mean ± SD. The degree of cervical dilatation (cervical diameter) before drug administration was compared in the two groups, as was the degree of cervical dilatation after drug administration at the time of hysteroscopy. An analysis of covariance comparison between the two groups was also carried out. The degree of pain in the two groups was also compared. The Spearman correlation test was used to determine the association between the (non-parametric) examiner score and the (parametric) pain scale.

**Results**

During the first 8 months of 2003, 58 women participated in the study; 28 received mifepristone (study group) and 30 received placebo (control group). Mean age, weight, height, age of menarche, parity, gravidity and indication for hysteroscopy were similar in both study and control groups. Similarly, there was no difference in the two groups with regard to serum E2 levels, day of menstrual cycle and number of hours that elapsed from the time of ingestion of the drug until performance of the hysteroscopy. Only progesterone levels were significantly higher \( (P < 0.05) \) in the study group (Table II). Analysis of the progesterone levels in the study group revealed that six patients had ovulated early and had high progesterone levels ranging from 21.4 to 64 nmol/l. Excluding these six patients brought the mean of the progesterone levels to 3.2 ± 1.4 nmol/l. To determine if mifepristone caused an additional dilatation of up to 1.5 mm. To achieve a power of 80% and \( P < 0.05 \), we calculated that 30 patients should be recruited for each group (Gahlinger PM & Abramson JH, Version 4.0, 1993–2001). Data were analysed by \( t \)-test where appropriate. A difference of \( P < 0.05 \) was considered to be significant. All values are given as mean ± SD. The degree of cervical dilatation (cervical diameter) before drug administration was compared in the two groups, as was the degree of cervical dilatation after drug administration at the time of hysteroscopy. An analysis of covariance comparison between the two groups was also carried out. The degree of pain in the two groups was also compared. The Spearman correlation test was used to determine the association between the (non-parametric) examiner score and the (parametric) pain scale.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group (n = 28)</th>
<th>Control group (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.2 ± 8.8</td>
<td>31.5 ± 7.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.0 ± 13.2</td>
<td>64.1 ± 14.2</td>
<td>0.95</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 ± 17</td>
<td>164 ± 6</td>
<td>0.56</td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>≥2</td>
<td>12</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>≥2</td>
<td>9</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>12.7 ± 1.5</td>
<td>12.7 ± 1.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Serum E2 level (pmol/l)</td>
<td>262 ± 193</td>
<td>294 ± 402</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum progesterone level (nmol/l)</td>
<td>9.4 ± 14.1</td>
<td>2.1 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Day of menstrual cycle</td>
<td>8.1 ± 5.5</td>
<td>8.8 ± 4.9</td>
<td>0.61</td>
</tr>
<tr>
<td>No. of hours since drug ingestion</td>
<td>30.3 ± 0.5</td>
<td>30.3 ± 0.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Analysis of Hagar measurements and pain assessments after subdivision of the study group into a low progesterone level group versus a high progesterone level group showed no significant differences between the three groups (Table IV).

**Discussion**

In this randomized double-blind placebo-controlled study, we evaluated the efficiency of mifepristone in inducing cervical softening prior to office hysteroscopy in non-pregnant premenopausal women requiring hysteroscopy. We assumed that by comparing the degree of resistance before and after treatment with mifepristone, it would be possible to ascertain if there is any effect of the antiprogestin. We also attempted to determine if mifepristone could modify the pain of the procedure. A VAS was selected as it has been found to be superior to other pain scales (Ohnhaus and Adler, 1975; DeLoach et al., 1998). The examiner also attempted to assess the pain on a subjective scale as well as making a calculated guess as to whether the woman received mifepristone or placebo. Neither the objective VAS nor the subjective examiner assessment could determine who took mifepristone or placebo. These two scales showed very high correlation, indicating that the subjective assessment of the examiner could predict the objective results of the pain scale.

One unexpected finding in this study was that progesterone levels were significantly higher in the women who received...
mifepristone. Although all women were treated in the follicular phase, six patients of the study group ovulated early and had high progesterone levels which increased the mean progesterone level in this group. Nevertheless, we were still unable to show any effect of mifepristone if those women with low progesterone levels and those with elevated progesterone levels were analysed separately (Table IV).

Gupta and Johnson (1990) investigated the role of mifepristone in cervical ripening of non-pregnant women. In their double-blind placebo-controlled trial, they showed that in women undergoing termination of pregnancy and in postmenopausal women undergoing dilation and curettage, the use of 600 mg of mifepristone 48 h prior to the procedure increased the mean pre-operative dilation and decreased the force required to dilate the pregnant and non-pregnant cervix. The limitation of this study was the inability to assess the contribution of the anaesthesia to the cervical softening.

There are several possibilities which could account for the failure of mifepristone to have any effect. In the first place, it is possible that an ineffective dose of mifepristone had been administered. Although the manufacturer recommends administration of 600 mg of mifepristone to be given 36–48 h prior to prostaglandin for pregnancy termination, identical results have been obtained with 200 mg (Christin-Maitre et al., 2000). Furthermore, a small study also showed that 100 mg was effective (Creinin et al., 2001a). These results are not surprising since pharmacokinetic studies in non-pregnant women have shown that there are no significant dose-dependent differences in serum concentrations within the first 48 h following the administration of single doses of mifepristone ranging from 200 to 800 mg. Furthermore, a dose-finding study with administration of mifepristone in doses ranging from 50 to 600 mg showed that all doses above 50 mg produced a significant degree of cervical dilation (Lefebvre et al., 1990). For this reason, the approved dose of mifepristone in cervical dilation in the European label is 200 mg. Thus, it appears unlikely that the dose of mifepristone explains the ineffectiveness.

Another possibility to explain our negative findings is that the hysteroscopy was performed at an inappropriate time after mifepristone. With the exception of the study of Gupta and Johnson (1990), we are unaware of another study which determined the effect of mifepristone on dilation of the non-pregnant cervix. All other studies were conducted in pregnant women. It is not really appropriate to extrapolate observations made in pregnant women to those in the non-pregnant state. Nevertheless, when misoprostol was given by the vaginal route 24, 48 or 72 h following mifepristone (200 mg) to terminate pregnancy, the results were identical (Schaff et al., 2000). Indeed vaginal misoprostol can be given as early as 6–8 h after oral mifepristone with excellent results (Pymar et al., 2001; Fox et al., 2002). On the other hand, the success of pregnancy termination is lower if misoprostol is given by the oral route 6–8 h following mifepristone as compared with when it is given 48 h after the antiprogestin (Creinin et al., 2001b). Moreover, women who received mifepristone 24 h prior to surgical termination of pregnancy had a significantly lower baseline cervical dilation and required greater mechanical force to dilate the cervix than did those who received mifepristone 48 h prior to surgery (Ashok et al., 2000). Lefebvre et al. (1990) observed that cervical dilation in women with pregnancy of 7–12 weeks duration was greater at 48 than at 24 h. Taking these findings as well as the earlier observations of Gupta and Johnson (1990) into consideration, it is conceivable that we would have obtained greater cervical dilation had we performed the hysteroscopy 48 h as opposed to 30 h following mifepristone.

Immunocytochemical analysis of progesterone receptors (PRs) shows that in contrast to the uterus, cervical stroma showed a fairly constant expression of PR at a moderate concentration during the different menstrual cycle phases and after menopause (Snijders et al., 1992). Stjernholm et al. (1996) found a 4-fold decrease in PR in late pregnancy compared with non-pregnant controls. This decrease in PR levels coincided with a decrease in collagen concentration and an increase in collagenase activity and collagen metabolism that permit cervical softening. Despite the decreased PR in the third trimester, mifepristone administration is still able to elicit labour. In the cervix of non-pregnant women, it is possible that the number of PRs is adequate, but the affinity of these PRs may be low compared with those of pregnant woman. Low affinity may thus also be an explanation for the lack of an effect of mifepristone. Another possible difference in the effect of mifepristone in pregnant as compared with non-pregnant women could be the effect of mifepristone in inducing uterine contractions which lead to cervical dilatation in the pregnant state.

The fact that mifepristone was not effective leaves us with the unavoidable conclusion that in contrast to the situation in pregnant women, mifepristone (200 mg) given 30 h prior to hysteroscopy is ineffective in non-pregnant women in producing cervical dilatation. It remains to be determined as to whether this is due to low serum progesterone levels, or
altered numbers or sensitivity of PRs in the cervix of the non-pregnant compared with the pregnant woman. Since cervical dilation increased to the same degree in both placebo- and mifepristone-treated women, the results emphasize the importance of conducting randomized double-blind placebo-controlled studies.

Acknowledgements

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References


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Creinin MD, Schwartz JL, Pymar HC and Schwartz JL (2001b) Efficacy of mifepristone 100 mg in non-pregnant compared with the pregnant woman. Since cervical dilation increased to the same degree in both placebo- and mifepristone-treated women, the results emphasize the importance of conducting randomized double-blind placebo-controlled studies.


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