Efficacy of the antiprogestin mifepristone (RU 486) prior to prostaglandin termination of pregnancy

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Forty-nine patients undergoing mid-trimester extra-amniotic prostaglandin termination of pregnancy were studied. Twenty patients acted as controls and received the standard hospital regime. Twenty-nine patients received the same regime, but in addition were given a single 200-mg oral dose of the antiprogesterone, mifepristone (RU 486), 24 h prior to prostaglandin infusion. The dose of prostaglandin required and the induction to abortion interval in the mifepristone-pretreatment group was significantly reduced. Complication rates were similar in both groups. Mifepristone is a safe and useful adjuvant therapy in mid-trimester prostaglandin termination.

Key words: mifepristone/extra-amniotic/prostaglandin/termination of pregnancy

Introduction

Mifepristone (RU 486, Roussel Uclaf, Paris) is an antiprogesterone currently undergoing clinical trials (Healy and Fraser, 1985). It is a steroid compound which reversibly binds to the progesterone receptor in target cells but without agonist activity (Philibert et al., 1985). The compound also has an antiglucocorticoid action, but at the small doses required for its antiprogesterone activity, no changes in pulse, blood pressure or serum electrolytes occurred and only transient increases in cortisol and adrenocorticotropic hormone (ACTH) have been observed (Bertagna et al., 1984; Gaillard et al., 1984; Schaison et al., 1985).

There is accumulating experience of its use in first trimester termination of pregnancy (Baulieu and Ulmann, 1986; Elia, 1986). Progesterone blockade has a direct local effect on the endometrium, leading to shedding with detachment of the embryo (Herrmann et al., 1982; Healy et al., 1983) and may have direct inhibitory effects on the corpus luteum (Schaison et al., 1985), the placenta (Das and Catt, 1987) and the pituitary (Collins and Hogden, 1986). A cervical softening effect has been noted and sensitivity to both endogenous and exogenous prostaglandins is increased (Swahn et al., 1985).

The use of mifepristone has been extended into the middle trimester, the aim of the study being to determine whether pretreatment with mifepristone would reduce the induction-to-abortion interval and dose of prostaglandin required to effect second trimester extra-amniotic prostaglandin termination of pregnancy.

Patients and methods

Forty-nine consecutive patients undergoing legal mid-trimester termination were studied. All patients had viable singleton pregnancies between 15 and 20 weeks gestation confirmed by ultrasound. All terminations were being carried out for socio-economic reasons. The first 20 patients acted as a control group. The following 29 consecutive patients were pretreated with 200 mg mifepristone 24 h prior to extra-amniotic infusion of prostaglandin E2 (Prosting E2, Upjohn). The study was approved by the Joint Ethical Committee of the Grampian Health Board and the University of Aberdeen. All patients gave written informed consent. The patient characteristics of age, gestation and parity were similar in both groups (Table I).

In all patients a number 18 Foley catheter was inserted through the cervix into the extra-amniotic space. An escalating regimen of prostaglandin E2 was started at an initial dose of 5 mg in 50 ml diluents at 5 ml/h for 8 h, then increasing through 10, 15, 20, 30, 40 and 50 ml/h to a maximum dose of 60 ml/h if regular contractions had not been established. If necessary, syntocin

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**Table I. Patient characteristics [mean and (SD)]**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 20)</th>
<th>Mifepristone (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.2 (8.5)</td>
<td>21.2 (4.9)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>16.7 (1.3)</td>
<td>17.1 (1.3)</td>
</tr>
<tr>
<td>Parity</td>
<td>12 primigravid (60%)</td>
<td>17 primigravid (59%)</td>
</tr>
<tr>
<td></td>
<td>8 parous (40%)</td>
<td>12 parous (41%)</td>
</tr>
</tbody>
</table>

**Table II. Induction-to-abortion interval and dose of prostaglandin in treated and control patients**

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone treated (n = 29)</th>
<th>Control (n = 20)</th>
<th>Mifepristone treated (n = 29)</th>
<th>Control (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction to abortion interval (h)</td>
<td>9.17</td>
<td>12.17</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Total dose of prostaglandin infused (mg)</td>
<td>4.00–14.17</td>
<td>6.50–22.25</td>
<td>5–30</td>
<td>5–45</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.00,10.7</td>
<td>10.50,13.7</td>
<td>8.14</td>
<td>13.23</td>
</tr>
<tr>
<td>P value Mann Whitney</td>
<td>0.0035</td>
<td></td>
<td>0.0101</td>
<td></td>
</tr>
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</table>
infusion was started 14 h after catheter insertion to expedite the abortion process.

The induction of abortion interval, need for analgesia, dose of prostaglandin required to achieve abortion and frequency of retained placenta were noted in each group.

Results

The results are shown in Table II. The induction-to-abortion interval was significantly reduced from a mean of 12 h 10 min [95% confidence interval (CI), 10 h 30 min to 13 h 50 min] in the control group to 9 h 10 min (95% CI, 8 h to 10 h 10 min) in the group pretreated with mifepristone (P = 0.0035 Mann-Whitney). Secondary to the reduced induction-to-abortion interval, only one patient of the 29, pretreated with mifepristone, required augmentation with syntocin compared with three of the 20 control patients.

The average dose of prostaglandin required was significantly reduced from a mean of 18 mg (95% CI 13, 23) in the control group to a mean of 11 mg (95% CI 8, 14) in the group who received mifepristone (P = 0.0101 Mann-Whitney). Prostaglandin-related side effects of nausea, vomiting and diarrhoea, were less frequent in the mifepristone group. Requirements for analgesia were similar in both groups. All patients in both groups received one i.m. opiate injection. Four controls (20%) and seven study patients (24%) required a second analgesic injection. The incidence of retained placenta was similar in both groups [six of 20 control patients (30%) and eight of 29 pretreated patients (28%)].

Discussion

Prior treatment with mifepristone in mid-trimester termination of pregnancy is advantageous for both the patient and her attendant. The degree of myometrial sensitization to prostaglandin achieved is such that much less exogenous drug is required to induce contractions, reducing the induction to abortion interval and the dose-related side effects of prostaglandin. The absence of pain or bleeding in the 24 h prior to prostaglandin infusion suggests that its effect is achieved mainly by uterine and cervical sensitization to prostaglandin, rather than by placental disruption. Certainly this is supported here by finding (data not shown) no change in serum progesterone, HCG, PAPP-A and SP levels prior to prostaglandin infusion. Recently 'epoestane', an inhibitor of progesterone synthesis, has been shown to have a similar effect, sensitizing the uterus to prostaglandin and reducing the induction-to-abortion interval in mid-trimester prostaglandin termination (Selinger et al., 1987). Following mifepristone pretreatment, no side effects attributable to the drug, other than tiredness and nausea (both symptoms of the underlying condition), were reported. This, along with the expectation that the forthcoming unpleasant experience will be considerably shortened, makes it acceptable to patients. Further placebo-controlled studies are in progress exploring the effect of a 600-mg dose at randomly allocated time intervals prior to prostaglandin infusion, and to assess more critically the reduced side effects experienced by the 'primed' patients.

Mifepristone could eventually be safely administered prior to hospital admission, although current legal advice is that the drug should be administered in hospital.

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References


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