

A Study of the Effect of Mifepristone (Antiprogesterone) Followed by Prostaglandin on Uterine Activity and Fetal Heart Rate in Patients Having a Termination of Pregnancy

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Summary. In the 72 h after a single oral dose of 400 mg of the antiprogesterone mifepristone, 12 out of 14 first and one second trimester fetuses had a slight increase in heart rate; 2 fetuses died and one aborted. During the same 72 h, uterine activity increased moderately, and was physiological with no increase in resting pressure. The treatment sensitized the uterus to prostaglandin (PG) about ten-fold. A low, 0.05 mg IM, dose of sulprostone caused the demise of 5 more fetuses and caused the onset of clinical abortion in less than 2 h. After a relatively short hypertonic phase uterine resting pressure fell to normal levels and active contractions occurred leading to expulsion of uterine contents. The plasma level of progesterone (P) remained unaltered after mifepristone treatment, but the levels of estradiol 17 β (E₂) and cortisol increased. The plasma level of mifepristone was 1640 ± 424 ng. ml⁻¹ at 72 h, and the substance was still detectable after one week.

Key words: Fetus – Antiprogesterone – Prostaglandin – Uterine activity

Introduction

Because antiprogesterones like RU 38486 [1] (mifepristone), ZK 98734 and ZK 98299 [6], might one day be used to induce labor or to treat dysfunctional labor we felt that their effects on the fetus should be studied. We therefore made observations on the fetal heart rate, intra-uterine pressure, prostaglandin sensitivity, ultrasound measurements, and maternal plasma concentrations of P, E₂, cortisol and RU 38486 after a single oral dose of 400 mg of the antiprogesterone RU 38486.

Methods

Fourteen first trimester and one second trimester fetuses (mean gestational age 8.8 ± 1.6 (SD) weeks) were studied. The study was approved by Ethics Committee and the patients gave informed consent. Measurement of crown-rump length (CRL) and biparietal diameter were made to confirm the duration of pregnancy (Table 1). The fetal heart rate (FHR) was measured by the ultrasonic Time Motion (TM) method just before and 72 h after a 400 mg oral dose of mifepristone. In ten cases the FHR was checked 1 h after an 0.05 mg IM dose of sulprostone, a prostaglandin E2-derivate. Uterine activity was recorded with a Millar catheter microtransducer and the signal was amplified by an HP-amplifier 8805C. Prostaglandin sensitivity was studied by injecting 0.05 mg of sulprostone except in the first 2 cases, when the dose was 0.5 and 0.25 mg respectively. Plasma levels of P, E2 and cortisol were measured by direct RIAs. Plasma levels of mifepristone were measured by Roussel-Uclaf.

Results

In the 72 h after the administration of mifepristone two out of 15 fetuses died and one aborted (at 33 h). The average FHR in the 12 fetuses alive at 72 h had increased slightly (Table 1, $P < 0.05$). The first two patients, who were respectively given 0.5 and 0.25 mg sulprostone after 72 h, aborted in a very short time and no FHR or intra-uterine pressure (IUP) recordings were made. Five more fetuses died within the 2 h after the mother had been given 0.05 mg of sulprostone IM. The remaining 5 fetuses had low to normal FHR (Table 1).

The amplitude of uterine contractions increased after mifepristone, but the resting uterine pressure remained unchanged. The frequency of contractions decreased (Table 2). 0.05 mg sulprostone at first produced a tonic uterine contraction and after that high amplitude contractions leading to clinical abortion within two h (see Fig. 1). 72 h after a single oral dose of 400 mg mifepristone the plasma level of P was unchanged (Table 3), E2 was slightly elevated ($P < 0.01$), and cortisol highly elevated ($P < 0.001$). At 72 h the RU 38486 concentration was 1640 ± 424 ng. ml⁻¹ ($n = 6$).

In the one patient studied, the plasma level of mifepristone fell from 3096 at 72 h to 352 ng. ml⁻¹ at 168 h (comparable to plasma hHCG-change, from 2500 U. l.⁻¹ to 680 U. l.⁻¹, respectively).

Table 1. Mifepristone and fetal heart rate (FHR)

	Fetal size CRP, mm	14 fetuses, first trimester		
		FHR before RU	FHR 72 h after RU	FHR 1 h after PG
Mean	24	169 (14)	174 ^a (11)	165 (5)
Range	11–32	160–182	157–185/196	140–181
S.E.	2	2	3	7
			2 cases FHR = 0	5 cases FHR = 0
			1 case variable ad 196	
			1 case aborted at 33 h	
		1 fetus, second trimester		
	69	144	153	

CRL = crown-rump length, mm; RU 486 = 400 mg single dose at 0 h; PG = 0.05 mg sulprostone IM; FHR = beats/min. ^a $P < 0.05$

Table 2. Uterine activity after mifepristone 400 mg single dose, first trimester pregnancy

	At 0 h	At 72 h	30 min after PG
AP	4 ± 2	72 ± 6	43 ± 13
RP	15 ± 3	12 ± 2	46 ± 7
F	36 ± 3	15 ± 3	29 ± 8

Mean ± S.E. *n* = 12

AP = active pressure (amplitude), mmHg; RP = resting pressure (tonus), mmHg; F = No of contractions in 15 min; PG = 50 µg sulprostone IM

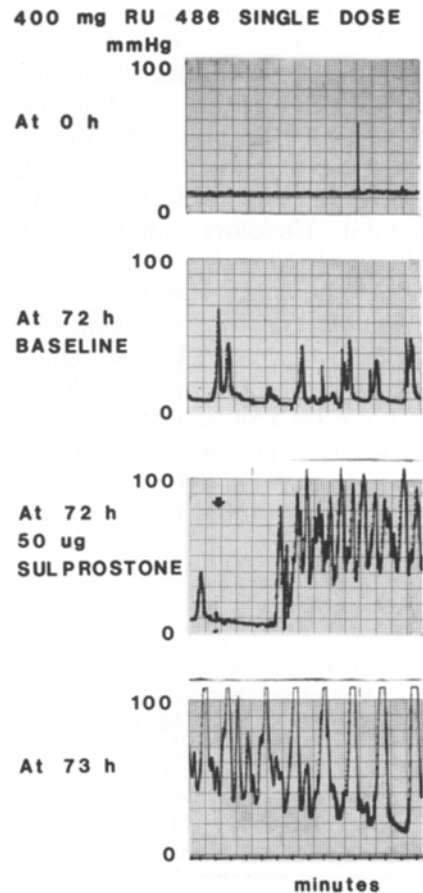


Fig. 1. Intrauterine pressure after a 400 mg oral dose of mifepristone in a patient who was 8 weeks pregnant. Note negligible uterine activity before mifepristone, moderate activity during the 72 h period after the drug. A small, 50 µg dose of the prostaglandin sulprostone caused contracture already 3 min after an IM dose. After 1 h, resting “tone” had returned to normal, but the amplitude of contractions was high at over 100 mmHg with only 8 contractions in 15 min and clinical evidence of onset of the abortion process

Discussion

In spite of the fact that uterine activity was “physiological”, 2 fetuses died during the 72 h after antiprogesterone therapy, and the average FHR increased slightly. A first trimester fetus might tolerate a physiological increase of activity

Table 3. Plasma progesterone (P), estradiol 17 β (E2) and cortisol after 400 mg of mifepristone

	P, nmol/l	E2, nmol/l	Cortisol, nmol/l
At 0 h	63 \pm 5	5 \pm 1	345 \pm 31
At 72 h	66 \pm 5	8 \pm 1 ^a	624 \pm 66 ^b

Mean \pm S.E.; $n = 13$; ^a $P < 0.01$; ^b $P < 0.001$

less well than a normal full-term fetus. In this study, a further "unphysiological" increase of uterine activity with prostaglandin (including temporary increase in resting pressure) caused fetal asphyxia, indicated by large changes in FHR and fetal death.

The increase in the PG-sensitivity of the uterus seen in our study was also seen with luteectomy [5]. If not all the progesterone effect is blocked, complete abortion can be prevented. Luteectomy studies make it clear that progesterone suppression is needed as well as removal of the corpus luteum if an abortion is to occur. Indeed complete abortion only occurs if plasma P levels fall below 5 ng/ml [4]. Therefore, additional PG application is sometimes necessary after mifepristone.

The plasma steroid profile, i.e. unchanged P , increased E2 and cortisol, are in agreement with the findings of earlier studies [3], and the same is true of the concentrations of RU 38486 [7].

Unlike with luteectomy, the abortion process initiated with mifepristone did not involve a fall in blood progesterone level. But uterine activity, caused by the blocking of progesterone receptors [2], was indistinguishable from that caused by luteectomy. Thus, in humans the antiprogesterone effect should not be judged by peripheral blood progesterone concentrations.

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