

## PHARMACOLOGY AND TOXICOLOGY

# Effect of Mifegin on the Content of Cyclic Nucleotides in the Cervical Myometrium in Full-Term Pregnancy

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Cervical myometrium was examined in 22 pregnant women at 39-41 weeks gestation at risk of labor abnormalities. The patients received mifegin for preparing to labor. A new component in the mechanism of mifegin effect on the uterine cervix in full-term pregnancy was revealed: mifegin elevated the content of cAMP by 50% and almost 2-fold increased the cAMP/cGMP ratio compared to the initial level.

**Key Words:** *cAMP; cGMP; antigestagens; myometrium; labor*

Complications associated with impaired contractile activity of the myometrium during labor remain an important problem of modern obstetrics. The outcome of labor is largely determined by the state of the birth canal at the end of pregnancy. Immaturity of the uterine cervix on the eve of labor often leads to disorders in myometrium contractility, which, in case of inefficiency of drug therapy, often become an indication for urgent abdominal delivery. The incidence of abdominal delivery for labor abnormalities is about 37% [1].

In normal pregnancy the preparation to labor is a spontaneous process [4]. However in some women, particularly in those at risk of labor abnormalities, biological readiness to labor does not develop, which requires special therapy. We propose a protocol of treatment with mifegin (mifepristone, Ru 486) for preparing the uterine cervix to labor. Mifegin is an anti-gestagen blocking the effect of progesterone at the level of receptors and producing a potent effect on the uterine cervix, which is important for normal delivery. The maturation of the uterine cervix is an intricate

cascade of mechanisms including activation of destruction enzymes and changes in the production of extracellular matrix proteins and glycoproteins.

Mifegin improves myometrial contractility [5] by potentiating the effects of endogenous prostaglandins and uterotonics [4] via induction of the synthesis of specific receptors. The drug increases the number of progesterone receptors. However tissue sensitivity to bioactive agents is determined by not only the presence of specific receptors, but also the competence of the target cells (state of second messengers and effector systems) [2]. Cyclic nucleotides and Ca ions are the main intracellular transmitters of the hormonal effects in myouterocytes. The second messenger system in cells is strictly coordinated. For example, accumulation of cAMP leads to blockade of L-type potential-dependent Ca channels, decrease in intracellular Ca content, and, finally, to relaxation of the muscle cell. In turn, cGMP is a component of cGMP-dependent NO-relaxing system of the myometrium. We found no published data on the effect of antigestagens on the content of cyclic nucleotides in the uterine cervix.

Here we investigated the effect of mifegin on the content of cyclic nucleotides in the cytosol of the cervical myometrium at the end of gestation.

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## MATERIALS AND METHODS

Twenty-two pregnant women aged 21-34 years were examined at 39-41 weeks gestation; all women received mifegin for preparing to labor. Biopsy specimens of the cervical myometrium were obtained with a conchotome before and after mifegin therapy. cAMP in the myometrial cytosol fraction was radioimmunoassayed using Amersham kits.

Nineteen examinees were primigravidae and 3 patients were secundigravidae. Sixteen (73%) women had a history of genital diseases, endocrine ovarian dysfunctions, or perinatal loss during previous labor.

The state of the uterine cervix was scored using the Bishop scale before delivery. All examinees were at a high risk of labor abnormalities (birth canal readiness 0-3 points) and were candidates for abdominal delivery.

Mifegin in a single daily dose of 200 mg was given orally for 2 days (interval 24 h). The state of the uterine cervix was repeatedly evaluated 48-72 h after the last dose of the drug and further treatment was carried out if necessary; labor was induced with prostaglandins E1 (Saitotek orally, 200 µg).

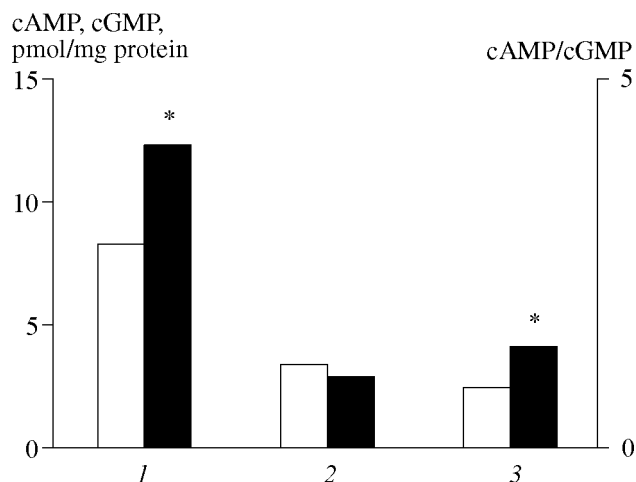
Eleven (50%) women had regular labor activity after preparation; in 4 (18%) programmed labor was planned and amniotomy was carried out for labor stimulation under conditions of biological readiness to labor. In 7 (32%) women the course of labor was complicated by premature rupture of fetal membranes, and in 1 patient labor was stimulated by enzaprost in a standard dose. Seventeen (77%) patients had normal uterine contractility, in 5 (23%) patients uterine inertia was observed. No correction was carried out in 1 case because of acute fetal hypoxia; other women received oxytocin (2.5-5.0 U, i. v. drip infusion) with good results.

Twenty (91%) women had normal delivery and 2 (9%) were subjected to cesarean section because of acute fetal hypoxia.

The significance of differences in the content of cyclic nucleotides was evaluated using Student's *t* test.

## RESULTS

Pretreatment with mifegin according to our protocol was effective in all cases: the state of the uterine cervix according to Bishop score improved by at least 2 points (maximally by 6 points). It should be emphasized that our study was carried out in pregnant patients with zero biological readiness to labor. Hence, it can be expected that in patients with less pron-



**Fig. 1.** Levels of cAMP (1) and cGMP (2) and their ratio (3) in the uterine cervix myometrium in full-term pregnancy in the control (light bars) and during prelabor treatment with mifegin (dark bars). \* $p < 0.05$  compared to the control.

ounced immaturity of the uterine cervix (4-5 points) even minimum doses of mifegin will be effective.

The content of cyclic nucleotides in cervix cytosol changed under the effect of mifegin (Fig. 1): cAMP level increased by 50%, while cGMP level tended to decrease. The dynamics of cyclic nucleotides and their ratio are particularly interesting, because most cell reactions are mediated by combined effects of cAMP and cGMP. After mifegin therapy the cAMP/cGMP ratio in the uterine cervix cytosol increased almost 2-fold, which indicates changed regulation of the tissue adaptation-homeostatic reaction. Increased content of cAMP and the resultant decrease in free calcium level lead to relaxation of the uterine cervix essential for favorable outcome of labor.

Hence, a new component in the mechanism of the effect of mifegin on the uterine cervix in full-term pregnancy was revealed: increase of cAMP content determining relaxation of the muscle tissue.

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