УДК: 615.256.54:615.35:577.175.8

PROSTAGLANDIN INDUCTION OF LABOR

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The role of prostaglandin mechanisms in the implementation of labor, the possibility of induction of labor using prostaglandin's drugs and their modern synthetic analogues presented in this article. The history of the discovery of prostaglandins, their structure, classification types and series, the underlying mechanisms and precursors of endogenous synthesis in the women's body, mechanisms of action, and their main pharmacological side effects, the relevance of applications in modern obstetrics presented in this article.
Key words: **prostaglandin E2, Dinoprostone, prostaglandin F2α, Dinoprost, labor, induction of labor.**

ИНДУКЦИЯ РОДОВ ПРОСТАГЛАНДИНОВЫМИ ПРЕПАРАТАМИ

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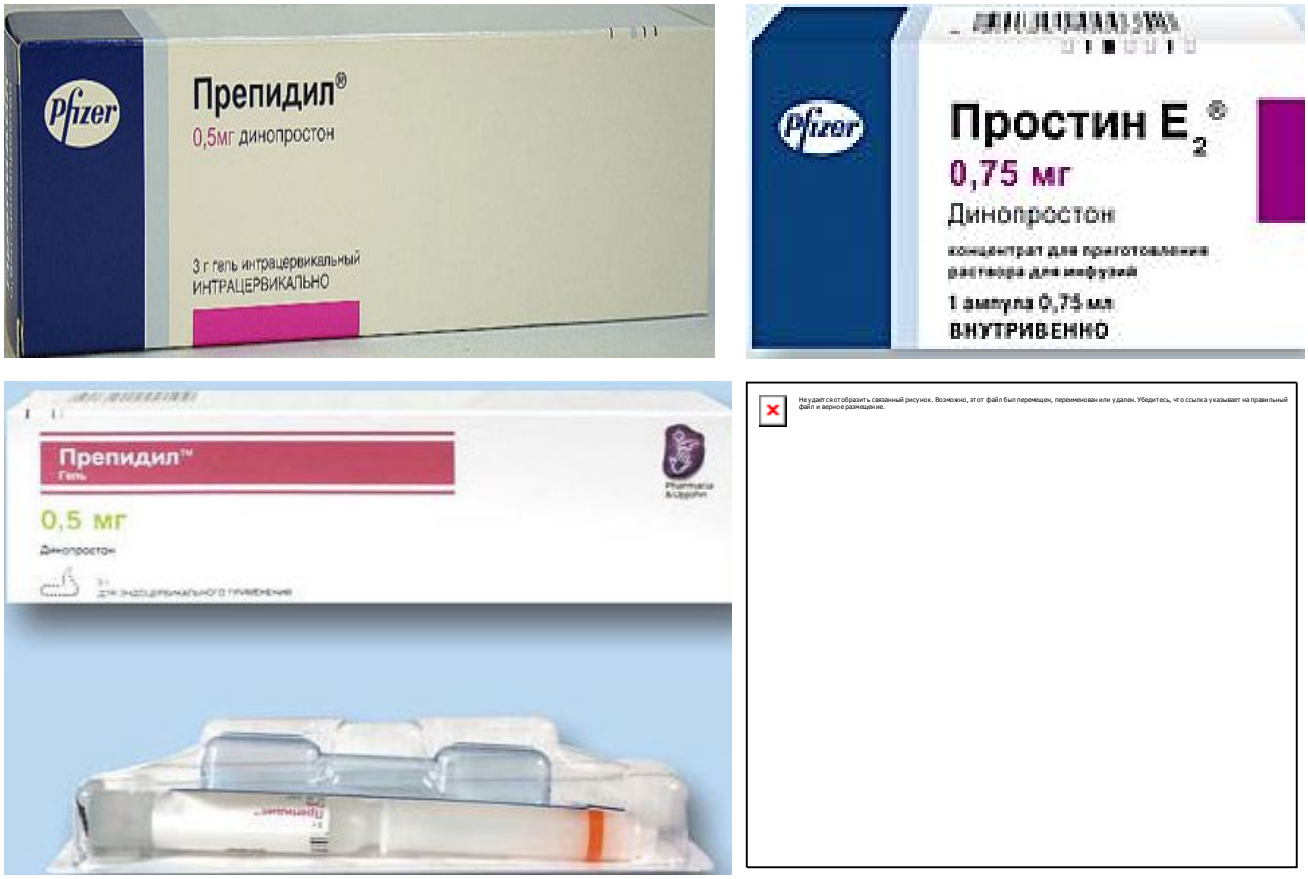
Рассмотрена роль простагландиновых механизмов в реализации родовой деятельности, возможности индукции родов с помощью простагландиновых препаратов и их современных синтетических аналогов. Представлена история открытия простагландинов, их структура, классификация по типам и сериям, основные механизмы и предшественники эндогенного синтеза в организме женщины, механизмы действия, их основные фармакологические и побочные эффекты, актуальность применения в современном акушерстве.
Ключевые слова: простагландин E_2, Динопростон, простагландин $F_{2\alpha}$, Динопрост, родовая деятельность, индукция родов.

Preparation of pregnant women for childbirth, during complicated pregnancy or in presence of associated diseases is extremely relevant and insufficiently developed problem in modern obstetrics. Numerous studies have found that the efficiency of patrimonial activity depends on the degree of readiness of the woman's organism for childbirth [2; 4]. Preparation of a uterus for childbirth is a process of gradual maturing of the enzyme systems producing prostaglandins, accumulation of their precursors and the subsequent strengthened synthesis. The culmination of this process is the induction and self-accelerating process of childbirth. When the patrimonial act begins in the absence of biological readiness for the birth, it is protracted, and in 50% of cases is complicated with abnormalities of labor and untimely amniorrhea. Immaturity of the cervix occurs in one out of five women, each fourth one has the traumatic injuries from unprepared cervix - this is one of the indications for carrying out obstetrical actions.

Starting with 70 years of XX century and in modern obstetrics successfully used numerous drugs and synthetic analogs of prostaglandins E2 (Dinoprostone, Prepidil, Predinil, Prostin E2 Prostenon, Tserviprost / Cerviprost, Medullin, Prostarmon E, Prostin E2, Prepidil-gel / Prepidil, Enzaprost / Enzaprost and others) and F2α (dinoprostu / Dinoprost, Prostin F2, Enzaprost F / Enzaprost F, Minprostin F2, Amoglandin, Panacelan F, Prostaglan, Prostarmon, Prostarmon F, Prostin F2, etc.) (picture 1). In recent years, in the arsenal of obstetricians appeared and tablet form a synthetic analogue of prostaglandin E1 - Misoprostol (Cytotec). Prostaglandins (PREPIDIL-gel ENZAPROST®-F and others) are used in order to achieve optimal biological readiness to childbirth in case of labor complications[1-4; 6-9].



Picture 1. Prostaglandin's drugs.

History of the prostaglandin discovery starts in 1930, when R. Kurzrok found that human semen contains components that cause smooth muscle contraction. Later, similar results were obtained by M.V. Goldblatt in 1933 and U. von Euler in 1936. The last one entered the term "prostaglandins", by identifying them as an active component of seminal fluid [5].

However, the nature of prostaglandins has been established only in 1957, when C. Bergstrom and J. Shevvalyu managed to extract and characterize two substances from the seminal glands of sheep, one of which was called prostaglandin F ($PGF_{2\alpha}$) due to its ability to be dissolved in phosphate buffer, and another one prostaglandin E (PG_{E2}) - dissolving in ether. Finally, Bergstrom and van Dorp in 1964 in a series of biochemical studies found that the precursors of prostaglandins are the C20 polyunsaturated fatty acids, i.e. eicosatrienoic acids, and that various prostaglandins may be formed from one precursor.

Work on prostaglandins have rapidly evolved, and in the years 1972-1976 S. Bergstrom, B. Samuelsson and John. Wayne have got 10 more pure prostaglandins, established their structure and identified their biological properties. For these studies in 1982 scientists were awarded the Nobel Prize [5,6].

Prostaglandin (prostoglandina; anat. prostata prostate gland + glandula gland; syn. prostatoglandin) is a group of biologically active compounds belonging to unsaturated fatty acids produced by cells of various organs and tissues (practically all, except for erythrocytes). In female organism out of pregnancy the main source of prostaglandin is in the uterus endometrium, and during pregnancy prostaglandins are formed in amnion, in decidua tissue and placenta.

The main substrate for prostaglandin synthesis in the human body is - arachidonic acid (20: 4, ω-6) and in a lower extent eicosapentaenoic (20: 5, ω-3) and eicosatrienoic (20: 3, ω-6) fatty acids.

Polyene fatty acids which can serve as substrates for the synthesis of the prostaglandins are part of glycerophospholipid membranes. Under the action of membrane-associated phospholipase A_2 or phospholipase C, the fatty acid is cleaved from glycerophospholipids and goes for the synthesis of prostaglandins.

After separation from phospholipid, the arachidonic acid enters the cytosol, where it further converts through cyclooxygenase transformation path. 1st stage synthesis is catalyzed by cyclooxygenase (PGH_2-synthase), it contains inclusion of four oxygen atoms in arachidonic acid and the formation of the five-membered ring. The result is an unstable compound called PGG_2. After that occurs the hydroperoxide recovery in 15th carbon atom to a hydroxyl group by the action of peroxidase with formation of PGH_2.

Further conversion of PGH_2 are specific for each cell type, such as PGH_2 SMC cells can be restored by the action of PGE-synthase forming PGE_2. $PGF_{2\alpha}$ is synthesized from PGE_2 by the enzyme PGE_2-9- ketoreductase (main activity of the enzyme is in the liver and brain, as well as in the placenta).

Prostaglandin synthesis can take place in one cell, which has a full range of necessary enzymes or through the paracellular synthesis - the conversion of arachidonic acid is carried out in a cell of one type (donor) and then intermediate transferres to the second cell (acceptor) for the complete transformation to a biologically active substance. Transport occurs by fatty acid-binding protein (FABP).

Depending on the structure of the loop and nature of the side chains of prostaglandins are classified into several types, designated by letters A, B, C, D, E, F, H, I, J. Inside each type of prostaglandins are divided into 1st, 2nd and 3rd series depending on the number of double bonds in the side chains of the molecule, designated index: E_2, F_2, D_1, H_2, etc.

The mechanism of prostaglandin action is based on interactions with cytoplasmic receptors (in an autocrine or paracrine mechanism), some are able to induce the transfer of cations through biological membranes, altering the physiological state of the cell. Thus, PGE_2 receptor has four subtypes: EP-1, EP-2, EP-3 and EP-4 respectively localized in the brain, smooth muscle,

macrophages and platelets, and kidneys. $PGF_{2\alpha}$ receptors for FP are located in the uterus, respiratory tract smooth muscle. In addition PGE_2 and $PGF_{2\alpha}$ have a blocking effect on β-adrenergic receptors.

$PGF_{2\alpha}$ action is directed on the activation of phospholipase C leading to phosphoinositide hydrolysis and intracellular Ca^{2+} mobilization. Besides, $PGF_{2\alpha}$ induces Ca^{2+} entering the cell from the extracellular space. Increasing the level of Ca^{2+} in the cell stimulates muscle contraction, which is important for the maintenance of uterine contractions during childbirth. PGE_2 participates in the process of cervical dilatation during labor.

Inactivation of prostaglandins occurs by oxidation of the hydroxyl group in position 15 to keto groups and further reduction of the double bond in position 13. Then, the oxidation of the side chains occurs. The final products are dicarboxylic acids, which are excreted with urine.

The main interest is PGE_2 and $PGF_{2\alpha}$, due to the fact that they take part in the basic process of pregnancy or childbirth, in medicine they are used in the form of synthetic analogues. These drugs are the ones which affect the tone of the uterus, they are the same as uterine medicines or uterotonics, a subgroup of myometrium stimulators, remedies for causing rhythmic uterus contractions.

Dinoprost is an analogue of prostaglandin F2α. It has a strong stimulating effect on the myometrium. Intravenous or intrauterine application causes rhythmic contractions of the myometrium and the expansion of the cervix during pregnancy. The highest sensitivity of the uterus to Dinoprost is observed in the III trimester.

Product: solution for injection.

This active ingredient is contained in the following drugs: Ensaprost-F, Prostin $F_{2\alpha}$, Amogladin, Panacelan F, Prostaglan, Prostarmon, Prostarmon F, Minprostin $F_{2\alpha}$.

Indications for intravenous applications is achievement of optimal biological readiness for delivery and induction of labor of pregnant women with a tendency to overcarrying of pregnancy, with immune conflict pregnancy, with diabetes, with the aggravation of preeclampsia, chronic placental insufficiency, fetal death, premature rupture of water in the absence of biological preparedness for childbirth, to prepare for the birth in pregnant women with a uterine scar under constant monitoring.

Application: for induction the intravenous infusion is carried during at least 30 minutes at a concentration of 15 ug / ml at a rate of 2.5 ug / min. If adequate uterine muscle response is not achieved, the speed can be increased for 2.5 ug / min more every hour until desired effect is reached, as the maximum - 20 ug / min. In case of uterine hypertonus (with fetal bradycardia or without) infusion is discontinued. If within 12-24 hours of dinoprost application no effect is observed, its use is terminated.

Contraindications: acute inflammatory diseases of the pelvic organs, active heart disease, lung, kidney and liver, increased sensitivity to Dinoprost, caesarean section or extensive surgery on the uterus in history, a high degree of imbalance between the mother's pelvis and fetal head, difficult and / or traumatic labor history, six or more full-term pregnancies in the history, bleeding from the genital organs of unknown etiology in history, fetal position anomalies, prior fetal distress.

Side effects when applying for induction of labor: increased uterine contractility with bradycardia of fetus or without it. Nausea, vomiting, diarrhea, hypertension, tachycardia, ventricular fibrillation, bradycardia, anaphylactoid reactions, bronchospasm, uterine rupture, perforation of the uterine cervix is also possible [8; 9].

Dinoprostone is a prostaglandin E_2 drug. It has a stimulating effect on the contractile activity and tone of the myometrium, causing rhythmic contractions of the uterus during any period of pregnancy.

Forms of production: vaginal gel, concentrate for infusion solution preparation.

This active ingredient is a component of the following drugs: Prepidil gel, Prosti E_2, Cerviprost, Enzaprost E, Medulin, Predilin, Prostarmon E.

Indications are similar to those of the Dinoprost.

Application: endocervical 0.5 mg of the drug is introduced immediately below the level of the internal os. After the procedure the patient must lie down for 10-15 minutes on the back. Vaginally 1 mg gel is injected into the posterior vaginal fornix. If necessary, after 6 hours the second dose of the gel can be introduced - 2.1 mg.

Contraindications: identical to those of Dinoprost.

Side effects are similar to those of Dinoprost, but also noted the local reactions in the form of tissue irritation, erythema at the site of intravenous introduction. Special attention is deserved for potentiation effect of oxytocin on Dinoprostone [8; 9].

In the D. O. Ott Research Institute of Obstetrics and Gynecology in Saint Petersburg research on the effectiveness of prostaglandin uterotonic was carried out, during which very satisfactory results were obtained.

So, to prepare the cervix for childbirth PREPIDIL gel (PP-gel) was used in 142 pregnant women. The results showed that 76 (50.3%) of 142 women with unripe cervix under the influence of PP-gel were getting more mature. In 46.5% of subjects were developed regular contractions after the application of PP-gel. In 38.5% of pregnant women on the following day after the application of the PP-gel has been reached successful labor induction [1].

To prepare 44 pregnant women for childbirth combined technique of PP-gel and infusion β-agonists (ginipral, brikanil, partusisten in 500 ml of 5% glucose solution or isotonic NaCl) was used. Induction of labor was effective using this method after one session in 48.8% of pregnant

women, and in 81.4% of patients in the group with a preliminary period. When GHG were applied topically, no side effects were noted that are typical for these medicines during parenteral use (nausea, vomiting, flushing of the face, diarrhea). Preparing to childbirth with the technique described above helped to reduce the duration of labor in primiparous for 23%, multiparous for 45% and the frequency of poor progress in labor rose in 2 times.

In order to induce a birth with untimely discharge of amniotic fluid for the treatment of poor progress in labor Prostin E_2 drug was used in 53 patients. Drug was given intravenously driply in 400 ml of physiological solution at a rate of 6-8 drops / min. The latent period of Prostin E_2 action was 15-30 minutes. Only 6 (11.5%) women in labor while intravenous use of Prostin E_2 led to side effects - nausea, local redness of the skin around the vein where the drug was introduced.

The duration of labor in primiparous receiving Prostin E_2, before applying was 5,9 ± 1,07 h., Multiparous was 5,4 ± 1,2 h. After applying Prostin in primiparous births finished in 6,2 ± 0, 7 hr., and the total duration of labor was 11,2 ± 1,6 h. In multiparous total duration of labor was 8,9 ± 0,7 h [1].

Intravenous drip usage of Prostin E_2 led to a reduction of surgeries to 8.9% compared with the group of women in childbirth where conventional labor induction (24.6%) drugs were used.

The use of $PGF_{2\alpha}$ drugs was shown only in the active phase of labor (to avoid the development of hypertonicity of the uterus). For the treatment of poor progress in labor Prostin $F_{2\alpha}$ was used in 25 women in labor with disclosure of uterine os 3-4 cm at the time of infusion [1].

The general duration of delivery in primiparous was 10 h. 20 min. ± 1 h. 06 min., in multiparous – 9 h. 04 min. ± 1 h. 03 min. In 1 case of childbirth was finished with transaction of imposing of output obstetric nippers of indications from mother (a miopiya of high degree). In total 25 children in a satisfactory condition were born. Not anyone of newborns was noted with the asphyxia phenomena [1].

Thus, medications of prostaglandins E_2 and $F_{2\alpha}$ in the form of gels and infusion therapy is highly effective for cervical preparation for childbirth, induction of labor, for the induction of labor in fixed-term reasons, to prevent overcarrying pregnancy.

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