

# Preterm birth: multidisciplinary approach PREIS school

*Iu. Davydova*

SI «Institute of Pediatrics, Obstetrics and Gynecology National Academy of Medical Sciences of Ukraine»

In spite of the decades of clinical and basic research, there has not been recognized significant progress in the prevention of premature birth. Different methods has been suggested, such as nutritional supplementation, bed rest, vitamins, antibiotics and medications to stop the uterine contractility have not reduced the rate of preterm birth. The main efforts are being targeted for a strategy to identify the pregnant women at risk for premature birth (target group) and to implement targeted interventions to reduce prematurity [3, 6–9].

The recent clinical achievements in this field, the data of the basic investigations are included into the scheduled educational programs of PREIS school, faculty of this school is being created from the most famous clinicians and scientists of the European Union.

**PREIS – Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine, founded in Florence by EAPM** (European Association of Perinatal Medicine). The multidisciplinary approach for the prevention of the preterm birth and for the diminishing of the negative consequences of the prematurity for mother and child includes the mutual and consistent efforts of the basic scientists, obstetricians, neonatologists, social workers and rehabilitatologists.

In XXI century the preterm birth still remains to be the leading cause of perinatal morbidity and mortality all over the world, with the 70% contribution in neonatal mortality, 50% of long-term neurodevelopmental disabilities. The data of the recent systematic review testified about the 12.9 million preterm births worldwide (9.6% of all births), and 92.3% of them were in Africa, Asia, Latin America, and the Caribbean Region [3, 5, 6, 8, 10].

Within the last two decades, the preterm birth rate in the USA increased 36%, from 9.4% to 12.8%. The main causes revealed by the prominent analysts are: iatrogenic «indicated» preterm births in singleton gestations, preterm delivery in multiple gestations, linked in part with the use of assisted reproductive technologies (ART) [1, 3, 10].

Actually, spontaneous (not iatrogenic, «indicated») preterm labor/delivery is considered to be one of the «great obstetrical syndromes». It means, that several obstetrical disorders with a similar phenotype have peculiarities:

- they are caused by multiple pathologic processes
- they have a long subclinical phase
- they may result from complex gene-environment interactions [3, 7, 9].

**The infant mortality** (death by the age of one year) is the standard indicator of health care of a community or society. The importance and actuality of the preterm birth is strengthened by the evidence that prematurity is the leading cause of infant mortality and severe morbidity.

**The main facts of statistics about the preterm birth are:**

- every five minutes, about 50 preterm babies are born worldwide
- preterm born babies are at increased risk of death and long-term disability (cerebral palsy, autism spectrum disorders and developmental delays) [1, 6, 7].

So, the financial burden of preterm birth to society has been estimated to be \$26 billion per year in the USA alone.

The basic scientists and clinicians reached a consensus that **progesterone** is a key hormone for pregnancy maintenance and its prolongation over 37 weeks. The decline of progesterone action has a strict impact on the onset of parturition, including the fact, that if such a decline occurs in the II gestational trimester, the cervical shortening may occur, and this is the most important factor predisposed to spontaneous preterm delivery.

There is one more consequence of the untimely decline in progesterone action: it has been proposed as a principal mechanism of disease in the «preterm parturition syndrome» [4, 9].

The main progesterone actions are mediated by genomic and nongenomic effects which have been successfully studied in the uterine cervix, myometrium and sperm. It is the matter of the fact that a blockade of progesterone action can lead to the structural cervical changes and cervical ripening. A lot of investigators reported that short cervix detected with transvaginal ultrasound (TVU) is a powerful predictor of preterm birth in women both with singleton and twin gestations [2, 3].

The recent achievements in studies of the molecular basis for progesterone receptor (PR)-mediated control of progesterone responsiveness has led to the hypothesis that in human parturition the functional progesterone withdrawal is mediated by the changes in myometrial PR expression, function, or both of them. Evidently, there are two major subtypes in human PR: PR-A and PR-B [4, 5].

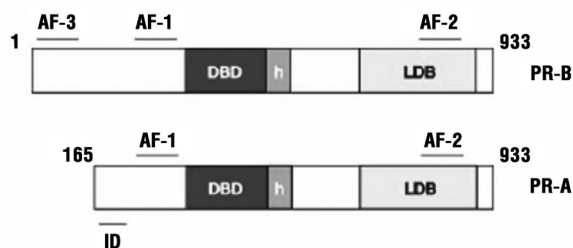
The action of the PR-A is to repress the progesterone activity mediated by PR-B, so the PR-A/PR-B expression ratio is inversely related to the extent of progesterone responsiveness. The onset of term labor depends on a significant increase in the myometrial PR-A/PR-B expression ratio, that may initiate functional progesterone withdrawal. Moreover, functional estrogen activation and functional progesterone withdrawal are linked in the mechanism of preterm birth [4, 5, 7, 9].

Progesterone is absolutely essential for the regulation of normal female reproductive functions during all the reproductive period. The major physiological actions of progesterone are:

- maintenance of early pregnancy
- induction of ovulation
- facilitation of implantation
- lobular-alveolar development in preparation for lactation
- neurobehavioral expression associated with sexual responsiveness
- prevention of bone loss [4, 5].

In order to maintain quiescence of the myometrium throughout first 37 weeks of pregnancy the special mechanisms were developed with their further transformation for labor contractility. The main role in this mechanisms belongs to progesterone (P4) produced by the placenta.

There several mechanisms which describe the way progesterone prevents myometrial contractility during pregnancy. The manifestation of the effect is realized by the increasing of the resting potential and prevention of electrical coupling between myometrial cells. **The progesterone significantly decreases the uptake of extracellular calcium that is needed for myometrial contraction by downregulating expression of genes that encode several subunits of voltage-dependent calcium channels.** Within gestational period the adrenergic system is involved in



**Figure 1. Structure of progesterone receptor (PR) variants**

myometrial quietening. The animal models proved that progesterone increased transcription of  $\beta$ -adrenergic receptors in myometrium and resulted in increased sensitivity to adrenergic agents. Progesterone effectively influences on the proinflammatory response pathways (cytokine cascade) and expression of so-called «contractile» genes. The circulating levels of P4 and expression of the progesterone receptors (PR) in myometrium remain elevated throughout pregnancy in humans (Fig. 1). All the data obtained in basic studies testified about the prominent role of P4 decline in the increased uterine contractility and in term and preterm labor development [4, 5, 7, 9, 10].

The development of the obstetric and perinatal disorders depend on the implantation phase and the proper progesterone concentration during early pregnancy is crucial for pregnant and fetus. Within the time of implantation a number of progesterone dependent proteins are produced. Immunohistochemical analysis has revealed these progesterone dependent proteins only in the epithelial component [4, 5, 7].

We have to describe these progesterone dependent proteins : progesterone – associated endometrial protein (PEP), insulin growth factor binding protein 2 (IGFBP2) or protein 14, crystalloglobulin, integrins and glycoproteins or type 1 mucins. Just now the physiological role of these proteins is not fully understood. So, protein 14 has immunodepressive effect thereby facilitating embryo implantation. Moreover, type 1 mucins may inhibit implantation at the maternal cell surface. Uteroglobin is another progesterone regulated protein produced by the endometrial gland [4, 7].

There was a long history of the progestogens (both natural and synthetic) implementation for the prevention of preterm birth. The first significant success was obtained in 2007, when Fonseca et al, (Fetal Medicine Foundation of the United Kingdom), reported the 44% reduction of the rate of spontaneous preterm birth before the 34 weeks of gestation after the administration of vaginal progesterone in women with a cervical length less than 15 mm [1, 3, 10].

The administration of vaginal progesterone is based on its biologic effects on the cervix, myometrium, and chorioamniotic membranes and was proposed for the prevention of preterm birth in women with a sonographic short cervix in the second gestational trimester. DeFranco et al conducted a randomized clinical trial of vaginal progesterone in women with a history of preterm birth and short length of the cervix measured by transvaginal ultrasound [5, 10].

The modern overall randomized clinical trial (Hassan et al) indicated that vaginal progesterone implemented in women with a cervical length of 10–20 mm, resulted in the significant reduction of preterm birth at 28, 33 and 35 gestational weeks. The reduction of early preterm birth (28–32 weeks) is considered as the most serious result, which was associated with a significant 61% reduction in the rate of respiratory distress syndrome (RDS). There were represented several publications concerning vaginal progesterone utilization in women at high risk group of spontaneous preterm birth, which proved the efficacy of this approach for pregnant with a short cervix [8–10].

The main target of the vaginal application of progesterone is to reduce early preterm births (< 32 weeks), which are associated with a highest rate of neonatal complications and neurologic disability in future life. In spite of late preterm births represent 70% of all preterm births and they have a significantly lower rate of complications (especially RDS), they are still a challenge for health care system [10].

The vaginal progesterone (micronizing progesterone, Utrogestan, Besin's Healthcare, France) is widely used in the clinic of high risk pregnancy in the State Institution «Institute of Pediatrics, Obstetrics and Gynecology National Academy of Medical Sciences of Ukraine» for the following target groups:

1. Women with the history of preterm birth.
2. Women with short cervix and singleton pregnancy evaluated by transvaginal ultrasound.
3. Women with clinical and ultrasound signs of threatened abortion.
4. Women with severe somatic pathology with planned or urgent surgeries, including oncology diseases treatment or repair of congenital heart diseases.
5. Women with proved endothelial dysfunction, habitual abortions, antiphospholipid syndrome or inherited thrombophilia.

The multidisciplinary approach allowed not only to prolong the pregnancy in the majority of cases up to 35–39 weeks, but to reduce the post-surgery iatrogenic risks of miscarriage or preterm birth.

### Сведения об авторе

Давыдова Юлия Владимировна – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8; тел.: (044) 483-16-70

### REFERENCES.

1. Barri P.N., Coroleu B., Clua E., Tur R. Prevention of prematurity by single embryo transfer. *J Perinat Med* 2011;39:237–40.
2. Beck S., Wojdyla D., Say L., et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull. World Health Organ* 2010;88:31–8.
3. Di Renzo G.C. The great obstetrical syndromes. *J Matern Fetal Neonatal Med* 2009;22:633–5.
4. Mesiano S., Chan E.C., Fitter J.T., Kwek K., Yeo G., Smith R. Progesterone withdrawal and estrogen activation in human parturition are coordinated by progesterone receptor A expression in the myometrium. *J Clin Endocrinol Metab* 2002;87:2924–30.
5. Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. *J Soc Gynecol Investig.* 2004 May;11(4):193–202. Review.
6. Goldenberg R.L., Culhane J.F., Iams J.D., Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
7. Renthall N.E., Williams K.C., Montalbano A.P. Chen C.C., Gao L., Mendelson C.R. Molecular Regulation of Parturition: A Myometrial Perspective. *Cold Spring Harb Perspect Med.* 2015 Sep 3;5(11).
8. Romero R. Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. *Ultrasound Obstet Gynecol* 2007;30: 675–86.
9. Romero R., Espinoza J., Kusanovic J.P., et al. The preterm parturition syndrome. *BJOG* 2006;113 (Suppl): 17–42.
10. Romero R., Nicolaides K., Conde-Agudelo A., et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012;206: 124.e1–19.

Статья поступила в редакцию 18.11.2015