PROGINS mutation of progesterone receptors and its role in premature birth – an overview

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Abstract

Premature birth (prior to 37 weeks of gestation) is a big medical and socioeconomic problem. It accounts for 8-12% of the total number of births, and apart from causing increased mortality of newborns, it is also the cause of increased morbidity. Fifteen million babies per year are born preterm. Despite the frequency, consequences and costs of premature delivery, very little has been done for preventing it, especially for preventing extremely premature deliveries (before the 28th gestation week).

Etiology of premature labor is multifactorial, and includes pathophysiology, genetic and environmental factors. Recent scientific research shows that genetic factors, mostly present in the mother’s genome, account for up to 40% of variation in the delivery time.

It is believed that premature birth exhibits the same cascade of events like a normal birth, only it starts sooner. This process is controlled by a series of hormonal effects between the fetus, the placenta and the mother. One of the key signaling pathways in this series is the progesterone signaling pathway.

PROGINS allele is a progesterone receptor gene modification. It is made of three variants: V660L, H770H and alu insertion. Progesterone receptors with PROGINS mutation are less susceptible to progesterone activity, and it seems that the withdrawal of progesterone causes the beginning of birth cascade. Mutation of +331 G/A progesterone receptor is a newly discovered mutation. It is believed that this mutation leads to a PR-A and PR-B receptor quantity disorder before the delivery term.

The aim of this review is to summarize all recent knowledge about PROGINS and +331 G/A mutation of progesterone receptors and to estimate whether this genetic mutation has a value in modulation of risk of preterm birth.

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Introduction

Premature or preterm birth is recognized as a worldwide problem. The percentage of preterm births has not been reduced despite existing research and therapy. It is defined as birth between 22nd and 37th week of gestation, and it is one of the major causes of prenatal mortality and morbidity. Prematurity accounts for 70% of neonatal mortality and 75% of neonatal morbidity (1).

According to gestational age, preterm birth is divided to extremely preterm birth (between 24th and 28th week of gestation), early preterm (between 28th and 34th week of gestation) and late preterm birth (between 34th and 37th week of gestation) (2). The percentage of preterm births varies from 5% of all deliveries in Europe to 18% in South African area (3). There are also variations of the percentage of preterm birth in diverse ethnic groups; for example, the percentage of preterm births is bigger in the population of African Americans than in the population of Caucasians (4,5). In 2010, there were around 15 million preterm births in the world (3,5). In the same period in Croatia, the percentage of preterm births was between 5.19 % and 7.88 % of all births, with a tendency of increasing since 2008 (6).

Etiology and risk factors of preterm delivery

Etiology of preterm birth is heterogenic and is connected to different metabolic pathways in the human body. For almost 50 % of preterm births, the cause is unknown. Preterm birth is divided in three subtypes (2):

- **spontaneous preterm birth** (spontaneous start of labor); 50% of all preterm births, occurring more frequently in the population without any risk factor for preterm birth
- **preterm premature rupture of membranes (PPROM)**: 25% of all preterm births, occurring more often in the African-American population, in most cases as a result of infection
- **iatrogenic preterm birth** before 37 weeks of gestation, due to maternal or fetal medical reasons, or other non-medical reasons that could jeopardize the health of mother and/or fetus (e.g., preeclampsia, placenta previa, placental abruption, multiple gestation, growth restriction of fetus); 25% of all preterm births.

There are many risk factors that relate to preterm birth, as indicated in Table 1. In an ideal situation, risk factors for preterm birth should be identified prior to or during the first trimester of pregnancy and, if possible, that should lead to interventions which would result in term delivery. Some pathways of starting a preterm delivery and related risk factors are presented in Table 2.

Nowadays it is more common to use the term “preterm parturition syndrome” (7), or even “great obstetric syndrome”, because of its multifactorial etiology.

There are four major factors leading to preterm labor (7,8,9,86): 1) Pathological uterine distension; 2) Maternal fetal stress (premature activation of the maternal or fetal hypothalamic-pituitary adrenal axis); 3) Abruption (decidual hemorrhage) and 4) Infection / exaggerated inflammatory response. All these processes could lead to cervical shortening and could start long before obvious signs of preterm birth are shown (10). Also, although they start at different ends of pathophysiology of preterm birth, they end in the same way, by activating choriodecidual reaction, uterine contractility and changes of the cervix. All these changes lead to preterm birth.
It is highly possible that uterine overdistension (caused by multifetal pregnancy, polyhydramnios or any other cause of uterine distension) can cause expression of contraction-associated proteins (CAPs) in the myometrium. Overdistension of the uterus also induces formation of gap junctions, upregulates oxytocin receptors and produces prostaglandins and inflammation cytokines (11). All this can initiate events that could change timing of uterine activation and lead to uterine contractions and cervical dilatation.

**Maternal-fetal stress (premature activation of the maternal or fetal hypothalamic-pituitary adrenal axis)**

In situations of stress, some circumstances disturb normal functions of a person. Maternal stress (infection, multiple pregnancies or psychological stress, such as depression or anxiety) can activate maternal HPA axis and cause preterm birth.

Premature fetal HPA activation, on the other hand, can be the result of stress of uteroplacental vasculopathy. It is more highly correlated with preterm birth than mother's stress (12). The main pathway of this cause seems to be a change in fetal adrenal-placental endocrine cascade, which leads to early rise of maternal CRH (corticotropin-releasing hormone) and estrogen levels. CRH plays a role both in term and preterm birth. Usually it is released by the hypothalamus, but during pregnancy it is released by trophoblast and decidual cells, too (13,14). Increased production of placental CRH stimulates production of ACTH, which further
stimulates production of cortisol. Cortisol inhibits hypothalamic CRH and ACTH, but on the other hand, stimulates CRH from the placenta. CRH also induces production of prostaglandins in the placenta (15). The increase of prostaglandins results in parturition through elevation of proteases in the genital tract (e.g., MMP) and higher myometrial contractility (16). Also, prostaglandins influence the PR-A: PR-B ratio and induce functional progesterone withdrawal (17).

Stress, maternal and/or fetal, can also stimulate steroid-induced immunophilin cochaperone FKBP51 in the decidua. It can also cause functional progesterone withdrawal through inhibition of progesterone receptors (18).

One more pathway of preterm birth caused by activation of fetal HPA axis is the estrogen pathway. Fetal ACTH induces synthesis of DHEA. DHEA in fetal liver is converted to 16-hydroxy-DHEA-S. The placenta converts these precursors to E, E2 and E3, which further activate the myometrium through increase of gap junction formations, oxytocin receptors, activity of prostaglandins and increasing of enzymes responsible for myometrium contractions (e.g., calmodulin) (19,20). All the pathways mentioned above cause contractions of the myometrium and the start of labor.

Infection / exaggerated inflammatory response

It is the only evidence-based and proven cause of preterm birth, which activates different pathways leading to preterm birth. Infection activates a cascade in the immunological response of the mother and leads to preterm birth. Inflammation is a coordinated process, and its role is basically to protect the host. In a normal situation, when the immune system is properly controlled, inflammation is protective. In other cases, it is harmful.

Preterm birth can be caused by both systemic and local genitourinary pathogens. In most cases, the cause can be symptomatic or asymptomatic bacteriuria (21), presence of genital infections (22), periodontal disease (23) and clinical and subclinical chorioamnionitis. The last-mentioned infection is the cause of as much as 50 percent of preterm births before 30 weeks of gestation (24).

Studies have proven that the actual cause of preterm birth is not the infection itself but rather a disorder of maternal immunity (21-24). Pathways of preterm birth in infection start by binding of bacterial ligands to toll-like receptors (TLRs) in placental, decidual, amniochorion and cervical cells. TLRs and local leucocytes activate NFKappaB, which in turn, starts the maternal and/or fetal inflammatory response. Whether TLRs will start the activation of NFKappaB or not, depends on the presence of some intracellular signaling adaptors (e.g., MyD88), coreceptor molecules (e.g., CD 14) and receptor modulators (soluble IL 6 receptor, soluble TNF receptor -1, etc.) (25-27).

Activation of NFKappaB leads to activation of neutrophils, macrophages and various proinflammatory mediators. The most important mediators of this response are TNF and IL 1 Beta. They induce COX-2 expression and production of prostaglandins. TNF also initiates expression of various MMPs in the amnion, chorion, decidua and cervix, and degrade the matrix of cervix and fetal membranes (28,29). TNF alfa can also induce apoptosis in amniotic epithelial cells, which leads to PPROM.

Not just the immune response, but some bacteria themselves (e.g., Pseudomonas, Staphylococcus, Streptococcus) can have a direct role in the pathogenesis of preterm birth. They can produce enzymes that can degrade fetal membranes, as well as phospholipase A2 and endotoxin, which stimulate uterine contractions (30).

Abruption / decidual hemorrhage

Vaginal bleeding caused by decidual hemorrhage is a risk factor for preterm birth and PPROM. According to one study, vaginal bleeding lasting more than one trimester increases the risk of PPROM seven times (31). PPROM develops after decidual hemorrhage, due to high concentration of decidual tissue factor. It combines with factor VIIa of hemostasis,
and in the end, thrombin is generated. Thrombin binds to decidual protease-activated receptors, which induce expression of proteases (e.g., MMP). Abruption can also be related to an inflammatory reaction without infection. It starts as a result of activation of the immune response by free hemoglobin chains and protease.

**Pathological cervical change**

Most cases of cervical changes prior to term pertain to cervical insufficiency. The changes that cause preterm birth may be the result of a congenital disorder, post-surgical trauma or damage caused by trauma. In most cases, though, cervical shortening is the result of inflammatory or hemorrhagic pathways.

As mentioned above, main changes in preterm birth happen on the placental level. They include effects on the level of prostaglandins (immunology and infection pathways) and the endocrine level (progesterone/estrogen pathway). Recently, new pathways have been identified and they seem to be connected with biological and psychosocial factors. These pathways include, as mentioned above, influence of genetic factors, factors of stress, factors that can be attributed to the mother or to the fetus, conditions which cause mechanical stimuli, and cases of inflammation and infection.

**The role of genes in preterm birth**

Investigations about genetic influence on preterm birth have been common during the last two decades. Studies have shown that the risk of preterm birth is higher in women born prematurely. Women who have had a previous preterm birth are at greater risk to have it again. After the first preterm delivery, the chance of another preterm delivery in the same mother goes up to 30-50% (32). Also, it has been shown that mothers whose sisters, mothers or female cousins have had a preterm birth bear greater risk of having a similar preterm birth themselves (33-34,35). An extensive study, conducted in Sweden in 2010, showed that both maternal and fetal genes are involved in preterm birth (36,37,38). Fetal genetic factors accounted for 13.1% of the variation in gestational age at delivery, while maternal genetic factors accounted for 20.6% (37). In a similar study, estimation of the percent of variation connected to fetal genetic factors ranges from 11% to 35%, while the range for the maternal genetic contribution is 13-20% (39). Another study, by Svensson et al., showed that 25% of variation in preterm birth was explained by maternal genetic effects, 5% by fetal genetic effect, 18% by the environment created by the couple and 52% by unshared environmental effect (40,41). This and other studies showed that paternal genetic influence on preterm birth is minimal (up to 5%) or there is no influence at all. That fact is in discrepancy with two Norwegian studies (42,43). In the same study by Svensson et al. it is shown that fetal genetic effect is higher if preterm birth is induced for medical reasons. Genes can influence different pathways in the body connected with preterm birth. Most of the studies involved gene contribution in immunology and inflammation pathways (32,44). Induction of proinflammatory mediators, especially TNF and its receptors, has been suggested to have a crucial role in activation of labor, both term and preterm (45). Pro-inflammatory and anti-inflammatory cytokines (interleukins) have also been investigated (46,47). There have also been investigations on genetic mutations leading to change of uterine contractility and change of cervical tissue, which leads to cervical shortening and spontaneous preterm birth. They involve genetic mutations in dopamine receptors, OST receptors, progesterone pathway, etc. Recently there have been studies about stress influence and genetic mutations in preterm birth (48).

A big genome-wide association study of a large cohort of women of European ancestry has shown that maternal variants at the EBF1, EEFSEC, AGTR2, WNT4, ADCY5, and RAP2C loci were associated with gestational duration, and that maternal variants at the EBF1, EEFSEC, and AGTR2 loci were associated with preterm birth (49).

In this review, the authors will try to see the influence of specific genetic polymorphisms connected to progesterone pathway that has an
important role in maintenance of pregnancy and changing contractility of the uterus.

The role of progesterone in onset of preterm birth

Progesterone (P4) is one of essential hormones in establishing and maintaining pregnancy. It is a 21-carbon steroid hormone which is mainly produced in the ovaries, placenta, brain and the adrenal glands (50). In early pregnancy, it is produced by corpus luteum whereas from 7th week of pregnancy onwards, its production occurs in the placenta. Progesterone is required for maintenance of pregnancy and one can see its influence on uterus contractility by inhibition of cervical ripening and decreasing of the production of chemokines. Progesterone also prevents apoptosis in fetal membranes in both basal and proinflammatory conditions, and it prevents PPROM and, consequently, preterm birth (51,52).

Progesterone produces its physiological effects through progesterone receptors (PGRs). PGRs are expressed in the central nervous system, ovaries, breasts, and the female reproductive tracts, including the vagina, cervix, fallopian tubes and uterine endometrium and myometrium. At term, depending on the species, either withdrawal of P4 by a decrease in hormone levels or alteration of PGR signaling relieves the suppression of inflammation and contraction, which allows the myometrium to start contractions and lead toward labor. Multiple mechanisms, including P4 metabolism, regulation of PGR gene expression, PGR post-translation modifications and PGR co-regulators, which mediate or regulate uterine P4/PGR signaling, have been identified and reviewed (53). One of the hypotheses about preterm birth is that the cascade of events in preterm birth is similar as the events at term birth, with the difference being only that it starts earlier.

Progesterone receptors are members of the group of steroid hormone receptors. They are made of central DNA-binding domain (DBD), N-terminal part with proximal activation function (AF1), distal AF3 in B upstream segment, and nuclear localization signal which is found upstream of LBD. AF1 is ligand-independent, while AF is not. AF1 has an influence on direction of transcription (54). There are two types of progesterone receptors: nuclear and membrane receptors (8). The nuclear PRs function as ligand-activated transcription factors and they influence gene expression. Membrane PRs are on the cell surface; they are related to G-protein coupled receptors and single transmembrane receptors, and they appear to mediate direct non-genomic actions of progesterone (8). Maintenance of pregnancy is mostly regulated through nuclear progesterone receptors, while membrane progesterone receptors are less sensitive to the influence of progesterone. By influencing PRs, progesterone activates a variety of pathways and induces expression of other genes, which leads to activation or deactivation of myometrium. Those pathways include activation of certain CAPs (contraction-associated genes) such as connexin, ion channels (e.g., calcium channels), uterotonin receptor and enzymes that influence synthesis of local prostaglandins (1,55).

Nuclear receptors are coded by the prostaglandin gene located on chromosome 11 (11q22-q23) (56). Two isoforms of nuclear progesterone receptors are most significant for progesterone influence; more specifically, PR-A and PR-B. Both receptors have the same DNA-binding domain, ligand-binding domain and hinge region. The only difference between these two is the fact that there are additional 165 amino acids present in the N-terminus of PR-B (18). There are some other forms of nuclear PRs known, such as PRC, PRM, PRS, PRT etc., but their significance in human birth is irrelevant (55).

PR-B have the function of transcriptional activators of genes involved in maintaining pregnancy, and PR-A repress the activity of PR-B. According to literature, most of the PRs in the myometrium during pregnancy are PR-B, and as the term of delivery comes nearer, the number of PR-A increases (36).

PR isoforms influence the expression of diverse downstream genes through a complex regulatory network which includes the NF-κB, ZEB-microRNAs and UPR pathways, as well as direct transcriptional regulation. They have a
combined influence on activities of downstream effectors. The overall P4/PGR signaling-dependent molecular profiles are modified by activities of PGR isoforms, co-regulators and the ligand availability. P4/PGR signaling mediates and utilizes these interconnected pathways to determine the state of the myometrium throughout pregnancy (53).

Different influences of PR-A and PR-B isoforms are reflected in their influence on expression of proinflammatory and anti-inflammatory genes. PR-A act proinflammatory, by increasing expression of proinflammatory genes for PTGS2, IL8, IL1A and PTX3. On the other hand, PR-B inhibit expression of proinflammatory genes (57).

In mammals, it has been proven that birth starts at the moment of progesterone withdrawal. However, in humans, measurements of the levels of serum progesterone in the blood at the time of birth showed that there was no decline of progesterone level.

At least five pathways of how withdrawals of progesterone influence the start of birth were examined. They include: 1) reduced bioavailability of progesterone, 2) increased cortisol concentration in late pregnancy, which leads to progesterone and cortisol competing for binding to glucocorticoid receptors (58), 3) conversion of progesterone to an inactive form, 4) changes in isoforms of PG receptors (59), 5) changes in progesterone co-regulators (54).

Some studies also include functional estrogen activation (60) and inflammation resulting in NFKappa mediated PR repression (61).

In this short review, the authors have reviewed literature data about changes in isoforms of PG receptors. There is a hypothesis that human parturition involves changes in expression of myometrial nPRs and that change of expression leads to functional progesterone withdrawal and start of birth.

The main theory is so-called IST (isoform switch theory) (36,62), according to which, as mentioned above, the ratio of PR-A and PR-B is changed in favor of PR-A. PR-A repress PR-B and reduce transcription of pregnancy promoting genes. Increasing level of PR-A at the end of pregnancy occurs because of a change in methylation of PR-A promoter region. That eventually leads to pre-term contractility of the uterus.

Chai et al. wanted to clarify epigenetic mechanisms that contribute to the control of PR isoform expressions in the pregnant human myometrium. They researched the change in methylation of the cPig island in promoter region of PRs and uncovered an epigenetic mechanism for elevated PR-A:PR-B expression ratio in term myometrium during progesterone withdrawal. PR-A promoter loses H3K4me3 selective demethylase JARIDIA, which leads to increased methylation of the PR-A promoter, change of its transcriptional activity and change of PR-A:PR-B ratio (63).

In further investigations, Nadeem et al. identified a mechanism by which P4 action of maintaining the pregnancy has been withdrawn even in the presence of elevated levels of this hormone in circulation. Unliganded PR-A localize to the nucleus, where they paradoxically activate transcription of Cx43 gene through interaction with AP 1 heterodimers (64). Namely, during pregnancy, under the influence of P4, PR-B create a complex with transcriptional repressors and inhibit transcription of Cx43. In labor, as a result of change of PR-A:PR-B ratio, PR-A become unliganded and encourage expression of Cx43.

A similar mechanism can be applicable on other labor-associated genes, such as PTGS2, OXTR, OXN, PTGDS and NFkB2 and some proinflammatory cytokines and matrix proteins. This study has also showed increased level of progesterone metabolized with 20 alpha HSD enzyme, which might be important for the usage of appropriate progesterone for therapy of preterm birth (59).

Beubaker et al. showed that the repressive activity of PR-A and their amount in the myometrium are increased by pro-inflammatory stimulation (65).
Genetic variants of PRs and their influence on preterm birth

Common variant in human PRs is the so-called PROGINS allele. It is present in some frequency in more than 20% of population. PROGINS mutation of progesterone receptors is extensively investigated. One of the research groups, Romano et al. (66), showed that it is characterized by a 320 bp PV/HS-1 Alu insertion in intron G and two-point mutations, V660L in exon 4 (rs1042838 SNP) and H770H (silent substitution) in exon 5 (rs1042839 SNP). The Alu element contains a half estrogen-response element/Sp1-binding site (Alu-ERE/Sp1), which acts as an in-cis intronic enhancer leading to increased transcription of the PROGINS allele in response to 17beta-estradiol. Moreover, Alu insertions in the human genome are frequently methylated. Some data indicate that the PROGINS-Alu does not affect gene transcription due to DNA methylation. However, the Alu element reduces the stability of the PROGINS transcript compared with the CP allele and does not generate splice variants. The amino acid substitution (V600L) in exon 4 leads to differences in PR phosphorylation and degradation in the two PR variants upon ligand binding, likely because of differences in the three-dimensional structures of the two PR variants. Consequently, the PR-L660 (PROGINS) variant displays decreased transactivation activity in a luciferase reporter system and is less efficient in opposing cell proliferation in hamster ovarian cells expressing human PR-A, when compared with the PR-V660 (most common variant).

PROGINS variant of PR is less responsive to progestin compared with the most common PR because of reduced amounts of gene transcript and decreased protein activity (66).

It has been proven that PROGINS allele has its influence, and represents a risk factor in some patients with breast cancer, endometrial cancer and endometriosis. In pregnancy, we see its influence either in decreased effectiveness of PGRs on P4 or through increased risk for conditions associated with preterm birth.

Another SNP that the authors wanted to emphasize is +331 G/A SNP of PR, which is a newly described mutation. Its significance lies in its influence on PR-A/PR-B isoform ratio, more specifically, its ability to change the ratio in favor of PR-A. The possible significance of these mutations could be decreased transcriptional regulation of progesterone target genes, which leads to change of pathways and start of preterm birth.

Several studies have tried to show whether there is an influence of these four SNPs on modulation of preterm birth. Results are biased. Some studies (Diaz Cueto et al., 2008; Guoyang et al., 2008; Kurtz et al., 2001; Oliveira et al., 2011) (67,68,69,70) did not find any connection between polymorphism of PGR and risk of preterm birth. On the other hand, some studies (Langmia et al., 2015; Ehn et al., 2007; Tiwari et al., 2014; Mann et al., 2013) (71,72,73,74) have found that mutations of PGRs have a significant influence on modulation of preterm birth. There is a possibility that either mutation in the mother’s or in fetal PGR genes leads to a difference and, consequently, preterm birth. Ehn at al. found that mutation in both fetal and maternal PRGs contributes to greater possibility of preterm birth. In addition, it has been proven that these mutations of PGR receptors differently influence preterm birth depending on race. This influence is bigger in the African-American population. Other studies have only confirmed that women with these mutations have a greater risk of preterm birth.

Progesterone as therapy for prevention of preterm birth

Supplement of progesterone as prevention of preterm birth appears to be effective, but it has to be kept in mind that it is not an ideal medicine. Usage of progesterone as therapy for prevention of preterm birth depends on various factors. First of all, it is important to use the appropriate type of progesterone and to choose appropriate patients. It is also important to use a proper dose, route of delivery and plasma concentration (76,77). The pathway leading to preterm birth is also of importance (78,79).
Studies have shown that clinical efficacy and safety of progesterone therapy can also be altered due to gene polymorphisms of PGRs (75). That fact is especially important in the African-American population, where genetic mutations of PGRs occur more often, and lead to resistance to progesterone therapy.

There are two major preparations of progesterone used in premature birth therapy/prophylaxis: hydroxyprogesterone caproate, a synthetic progesterone usually used in 250 mg dosage once a week, given as an intramuscular injection; and natural/micronized progesterone in a dosage of 100 mg per day, given vaginally.

There is also a rare application of progesterone as vaginal gel in a dosage of 90-200 mg.

Most common usage of progesterone preparations as prophylaxis of preterm birth starts from 16-20 weeks and lasts until the 36th week of gestation.

Several meta-analyses and studies have been made about the efficiency of progesterone treatment in preterm birth.

### Table 3. Recommendations for progesterone supplementation to prevent preterm birth (85).

<table>
<thead>
<tr>
<th>Progesterone preparation</th>
<th>Dosage and route of administration</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Hydroxyprogesterone caproate a 250 mg</td>
<td>250 mg intramuscularly once a week from between 16th and 20th week of gestation until the 36th week of gestation</td>
<td>Singleton pregnancy, prior spontaneous singleton preterm birth, normal cervix length. Singleton pregnancy, prior spontaneous preterm birth of twins, normal cervix length. Twins, prior preterm birth.</td>
</tr>
<tr>
<td>Micronized progesterone vaginal gel/vaginal tablet</td>
<td>90 mg /100 mg per day, vaginally</td>
<td>Singleton pregnancy, prior spontaneous preterm birth of twins, short cervix &lt; 20 mm.</td>
</tr>
<tr>
<td>Progesterone suppository</td>
<td>90-200 mg per day, vaginally, from the moment of diagnosis until the 36th week of gestation</td>
<td>Singleton pregnancy, prior spontaneous preterm birth of twins, short cervix &lt; 20 mm.</td>
</tr>
</tbody>
</table>
Dodd et al. conducted a meta-analysis of usage of progesterone for prevention of preterm birth in singleton pregnant women with high risk for preterm birth. Usage of progesterone made the risk for preterm birth in their current pregnancies lower. (80)

Meis et al. researched the usage of 17 hydroxyprogesterone caproate in women who had a documented preterm singleton birth in their obstetric anamnesis. Therapy started between 16th and 20th week of gestation and was used until the 36th week. Prophylaxis reduced the risk of preterm birth in their current pregnancy. (81)

Da Fonseca et al. analyzed the use of progesterone vaginal suppository between 24th and 34th week of gestation. Therapy was given to singleton pregnant women with risk factors in their anamneses. Risk of preterm birth in their current pregnancies was reduced with prophylaxis. (82)

Contrary to those findings, OPPTIMUM trial, led by Norman et al., showed that vaginal progesterone therapy did not reduce fetal and neonatal mortality and morbidity in preterm birth, or preterm birth itself. (83)

PROGRESS study, led by Crowther et al., also did not find any reduction in mortality or morbidity of fetuses or mothers related to preterm birth (84).

**Conclusion**

In conclusion, usage of progesterone in prophylaxis of preterm birth is still indicated and used worldwide. The most important thing is to choose the right candidates with the right risk factors for preterm birth. Recommendations for usage of progesterone for prevention of preterm birth are given in Table 3 (85).

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