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Preterm delivery – etiopathogenesis and treatment

Poród przedwczesny – etiopatogeneza i leczenie

ABSTRACT

Preterm delivery is a delivery after 22 and before 37 weeks gestation. The incidence of preterm delivery is very diverse from 5% in European countries to 18% in Africa. The etiopathogenesis of preterm delivery is multifactorial and still not fully understood. The article presents factors related to the increased risk of preterm delivery and possible methods of treatment to prevent the occurrence of preterm delivery. It also present obstetric behavior and treatment including patterns of tocolytic and glucocorticoid treatment taking into account recommendations.

Key words: preterm labour, risk factor, tocolytic therapy, tocolytics

STRESZCZENIE

Poród przedwczesny to zakończenie ciąży po 22., a przed 37. tygodniem ciąży. Częstość występowania porodów przedwczesnych jest bardzo zróżnicowana od 5% w krajach europejskich do 18% w Afryce. Etiopatogeneza przedwczesnego ukończenia ciąży jest wieloczynnikowa i nadal nie w pełni poznana. W pracy omówiono czynniki związane ze wzrostem ryzyka porodu przedwczesnego oraz możliwe metody postępowania w celu zapobiegania występowania porodu przedwczesnego. Przedstawiono postępowanie położnicze i leczenie z uwzględnieniem schematów stosowania leków tokolitycznych oraz glikokortykosteroidów zgodnie z obecnymi rekomendacjami.

Słowa kluczowe: poród przedwczesny, czynniki ryzyka, leczenie tokolityczne, tokolityki

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Introduction

According to the definition of the World Health Organization (WHO), Preterm Birth (PTB) includes any birth occurring after 22 weeks (154 days) of gestation, and before 37 completed weeks (259 days) of gestation (Kalinka, Bitner, 2012; Podsiadło, 2014).

In clinical practice, the classification created by Czajka (Czajka, 1994) seems to be the most important, and it distinguishes:

A. Threatened Preterm Labour includes the early phase of labour that can be stopped. It is characterized by the presence of uterine muscle contraction activity, with no changes in the cervix.
B. Preterm Labour refers to the advanced stage of labour, difficult to be slowed down. It is characterized by a regular and increasing uterine contractile function with simultaneous progressive cervical dilatation.
C. Preterm Birth refers to the birth of a newborn before 37 weeks of gestation.

Another classification considers the week of pregnancy in which preterm labour took place and divides it into:

A. Extremely Preterm Labour – before 28 weeks of gestation.
B. Very Preterm Labour – completed before 32 weeks of gestation.
C. Moderately Preterm Labour – between 33 and 36 weeks of gestation.

The purpose of the article

The aim of the study was to present factors influencing the increased risk of preterm delivery as well as methods of treatment aimed at preventing preterm delivery. In addition, the methods of obstetric and therapeutic management are discussed, including the patterns of tocolytic and glucocorticoid treatment taking into account recommendations.

Epidemiology

Annually, approximately 15 million children are born prematurely. Preterm birth rates vary widely from 5% in European countries to 18% in the sub-Saharan Africa (and largely depend on the world region). The largest percentage, as much as 60% of all preterm births, is recorded in poor parts of the world, such as Africa or the countries of South Asia. Based on data from European countries, the incidence of preterm labours is estimated at 5.5–11.1%. Finland and Ireland are the countries with the least preterm birth rate of 4.3%, while the country with the highest rate is Austria – 8.7%. In Poland, the preterm birth percentage was changing over the last several years from 6.8% recorded in 1996, followed by a slight decrease to 6.3% in 2000, and a further increase in 2012 to 6.8%. Currently, in our country, the rate of preterm labours is 7%. On the other hand, the number of births before 32 weeks of gestation significantly decreased and now they constitute 0.95% of all births (Wielgoś, 2016).

Reasons and risk factors of preterm labour

Preterm delivery is a clinical condition that is affected by many factors. Clinical practice comprises a division of preterm labours based on their reasons, in which the following are distinguished (Kalinka, Bitner, 2012; Podsiadło, 2014).

a) spontaneous uterine contractile function (idiopathic preterm labour) – 29–47% of pregnant women with diagnosed preterm labour;
b) premature rupture of membrane (PROM) – 23–38% of pregnant women;
c) premature termination of pregnancy due to medical indications (iatrogenic preterm labour) – 21–37% of women (Kalinka, Bitner, 2012; Podsiadło, 2014).

According to the classification established by Chamberlain (1984), four main categories

of factors: medical, social, environmental, psychogenic factors, predisposing to preterm delivery, are distinguished.

A. Medical factors:
   - obstetric causes requiring labour induction or surgical termination of pregnancy: preterm placental abruption, suspected placental insufficiency, placenta praevia, pregnancy-induced hypertension, intrauterine foetal growth retardation, serological conflict;
   - obstetrical causes leading to spontaneous uterine contractile function: preterm membrane rupture, congenital uterine anomalies, intrauterine infections, cervical incompetence, multiple pregnancies.
B. Social factors: low economic status, poor eating habits, inadequate care during pregnancy or its lack, use of stimulants, age of the woman (under 17 and over 35), multiparity and single marital status.
C. Environmental factors:
   - chemical factors: contact with the environment contaminated with heavy metals, sulphur compounds or fluorine;
   - physical factors: electromagnetic field, all types of radiation, vibrations, as well as noise.
D. Psychogenic factors: mental disorders present in the family, or in the pregnant woman, conflict situations in the family, poor financial situation of the family, stress associated with excess duties, eventful obstetric history, anxiety of the pregnant woman concerning her pregnancy and the child's health status.

Genetic determinants may also be a risk factor for preterm labour, as shown by the results of studies. Porter et al (Kalinka, Bitner, 2012) demonstrated that women who were born at 36 weeks have greater predispositions for preterm labour, and the odds ratio was 1.18. However, in the case of women born before 30 weeks of gestation, this risk increases 2.4 times (Kalinka, Bitner, 2012; Wielgoś, 2016).

Currently, the participation of polymorphisms of genes that are involved in the cascade of processes leading to preterm labour is also considered. Particularly, genes encoding proinflammatory cytokines as well as tumour necrosis factor which regulate the intensification of the inflammatory response, are thoroughly analysed. These proteins are responsible for the synthesis of prostaglandins, as well as reduce the sensitivity of the uterus to progesterone, and thus significantly increase the risk of premature contractile function (Wielgoś, 2016).

Etiopathogenesis of preterm labour

The etiopathogenesis of preterm labour is multifactorial and not fully understood. Roberto Romero et al (Wielgoś, 2016) created the term of *preterm labour syndrome*, which reflects the complex pathogenesis and diversity of risk factors affecting the probability of preterm birth.

Disorders of vaginal biocenosis and intrauterine infections are considered one of the dominant causes of preterm labour. The occurrence of a reproductive tract infection during pregnancy may trigger the arachidonic acid cascade and, as a result, lead to the synthesis of prostaglandins and collagenases. These substances are responsible for the occurrence of uterine contractile function, as well as the maturation and shortening of the cervix. In addition, hydrolysis of collagen may occur in amniotic cells, which may result in membrane rupture (Wielgoś, 2016).

Microorganisms penetrating into the amniotic cavity, cause the development of intraamniotic infection and the onset of foetal inflammatory syndrome. Microorganisms cause the activation of Toll-like Receptors (TLR), which connecting to the ligand lead to the activation of the nuclear factor. As a result of these changes, the mediators of inflammatory response, such as: interleukin (IL) -1, -6, -8, -10, Tumor Necrosis Factor Alpha (TNF-α), are released by macrophages. Cells and inflammatory cytokines present in the amniotic

fluid cause foetal lungs to release a surfactant, which has an inhibitory effect on the inflammatory response, and on the other hand leads to the induction of preterm labour. Studies demonstrate that 12% of women giving premature birth had symptoms of reproductive tract infections (Wielgoś, 2016; Leszczyńska, 2006).

Current research prove that abnormal implantation, and thus disorders of uteroplacental perfusion also affect the increase in the probability of preterm labour. Animal studies confirmed that ischemia of the uterine muscle affects triggering of contractile function. According to another theory, ischemia leads to the release of tissue factors that in turn stimulate haemolytic and thrombotic processes. Extravasated blood and thrombin contained in it affect the production of proteases, which are responsible for cervical dilation, membrane rupture, and initiation of contractile function (Kalinka, Birner, 2012; Wielgoś, 2016; Leszczyńska, 2006).

Another theory assumes the effect of excessive stretching of the uterine muscle on the occurrence of premature contractile activity. This is related to the increase in intrauterine pressure, which is relatively constant in physiological pregnancy and is balanced by progesterone or nitric oxide (NO). In the case of multiple pregnancies or polyhydramnios, excessive stretching of the uterus, increased production of prostaglandins (PG) and increased number of oxytocin receptors occurs, which may ultimately lead to premature uterine contractile activity (Kalinka, Birner, 2012; Leszczyńska, 2006).

The responses of the immune system remain important. Pregnancy can be considered a kind of *"transplant"*. Immunologists suggest that obstetric failures, such as miscarriage, premature labour, intrauterine foetal growth retardation, may be caused by an abnormal response of the mother's body to a foreign antigen, which is a foetus. In addition, immune system disorders, such as systemic lupus erythematosus, or an antiphospholipid syndrome predispose to preterm labour. This is because in affected pregnant women, they lead to pathological lesions in the placental vessels, and thus can lead to bleeding and subsequently to a preterm birth of the child. On the basis of research, Arias et al proved that immunological factors can be the cause of as much as 33% of preterm labours (Wielgoś, 2016).

The last mechanism that can contribute to preterm labours is the neurohormonal mechanism. Progesterone is the hormone responsible for the correct course of implantation, |as well as the maintenance of pregnancy, by inhibiting the uterine contractile function and cervical maturation. The most common disorder associated with progesterone deficiencies is luteal phase defect (LDP). Pregnant women with diagnosed LDP who do not take progesterone during pregnancy give birth prematurely in 31.2%. On the other hand, in women receiving progesterone, preterm labour affects 13.7% of cases (Kalinka, Bitner, 2012).

Other hormones involved in the neurohormonal mechanism are corticosteroids. In a physiological pregnancy, foetal corticosteroid levels increase in the perinatal period. However, in the case of excessive exposure to stress, an increase in the concentration of adrenocorticotropic hormones (ACTH) during pregnancy, and thus an increase in 11-β-hydroxylase in the foetal adrenal glands take place. The hydroxylase enzyme causes a production of additional amounts of corticosteroids that affect the production of estriol. It is, in turn, a hormone responsible for the induction of labour with the participation of prostaglandins and oxytocin (Leszczyńska, 2006).

Previous studies have demonstrated that corticoliberins also contributes to the regulation of the duration of pregnancy. Corticoliberin is synthesized both in the hypothalamus and placenta. From the 16th week of pregnancy, its concentration gradually increases and the peak of production is in the perinatal period. Studies show that an increase in its concentration between 16 and 20 weeks of pregnancy increases the probability of preterm labour (Kalinka, Bitner, 2012; Wielgoś, 2016).

Diagnostics

Clinical diagnostic criteria for preterm labour include:

a) gestational age between 22^{+0} and 36^{+6} weeks of gestation;
b) regular contractile activity of the uterine muscle (6 contractions/hour);
c) lesions in the cervix:
   - shortening by 80%;
   - dilation ≥ 2 cm.
d) lower abdominal pain and losing mucus plug (Wielgoś, 2016).

If in a pregnant woman a suspicion of threatening preterm labour occurs, additional tests are included in the diagnostics, such as biochemical preterm labour markers. These substances enable determination of the probability of premature birth (Wielgoś, 2016).

The first marker used in the diagnosis is foetal fibronectin (FFN). This extracellular glycoprotein is produced at the border of the amniotic and temporal bag, i.e. in the maternal-foetal interface. FFN is involved in the formation of connections between the foetal membranes and the uterine mucosa. In physiological conditions high concentrations of foetal fibronectin occur between 10th and 12th weeks of gestation and indicate normal tissue development in the uteroplacental interface, while from the 18th week of gestation its level should decrease below 0.05 µg/ml. Fibronectin should be indeterminable between 22 and 37 weeks of gestation. In this time interval, an increase in FFN concentration above 0.05 µg/ml indicates abnormalities in the maternal-foetal interface, and thus an increased probability of preterm labour. Each result is valid for 7–14 days and may be repeated if necessary (Kalinka, Bitner, 2012; Marszałek, Rychlik, et al, 2014).

Another indicator used to assess the risk of preterm delivery is the concentration of estriol (E3) in the saliva of a pregnant woman. Estriol is the main estrogen in pregnancy and in about 90% originates from foetal and placental precursors. The estriol concentration gradually increases during the first and second trimester of pregnancy, while in the third trimester it reaches the highest values. The production of this hormone takes place 3–4 weeks before labour. Studies carried out by Hedrian et al demonstrate that the concentration of estriol increases from 0.89 ng/ml determinable in the 30th week of gestation to 2.7 ng/ml at the labour time, with a rapid increase in concentration observed in the 35th week. In addition, it was demonstrated that an increase in estriol value above 2.1 ng/ml in the 30th week of gestation is a predictive factor of preterm labour. However, it should be remembered that estriol is a hormone subject to variations in the diurnal cycle and reaches the highest concentrations at night, therefore it is recommended to conduct the test during the day, 30 minutes after a meal (Semczuk, Krzyżanowski, 2011).

Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) is also a marker used to assess the risk of preterm labour. It is produced by the decidua and regulated by progesterone. The highest concentrations of phIGFBP-1 are observed in the perinatal period as a result of separation of the foetal membranes and the decidua. Values above 30µg/ml determined in cervical secretion may indicate an increased risk of preterm labour within seven days after the performed measurement. Studies demonstrate that an increase in the concentration of phIGFBP-1 correlates with an increased risk of labor (Kalinka, Bitner, 2012; Semczuk, Krzyżanowski, 2011).

Ultrasound (US) transvaginal cervical length measurement is a test used in clinical practice to assess the risk of preterm labour. During the test, the patient should have emptied the urinary bladder. The ultrasound head is placed in the front vaginal vault to obtain a correct sagittal section. During the test, the external and internal orifice of the cervix as well as the mucosa of the canal should be identified. The measurement must be performed between the triangular area of the external orifice and the V-shaped recess of the internal orifice and repeated 2–3 times during the entire ultrasound examination. Studies

demonstrate that shortening of the cervix in the second trimester is a predictive factor of preterm labour. In the group of pregnant women with an increased risk of preterm labour, ultrasound examination of the length of the cervix is recommended every 2 weeks between 14 and 22 weeks of gestation. The probability of preterm birth is inversely correlated with the length of the cervix (Wielgoś, 2016; Wielgoś, Szymusik, 2011).

Other factors that can be used to assess the risk of preterm labour include: assessment of IL-6 in vaginal discharge and IL-8 in cervical secretion; pH assessment in vaginal discharge; a nitrazine test; assessment of prolactin and α-fetoprotein concentration (Semczuk, Krzyżanowski, 2011).

In summary, the diagnosis of preterm labour should include: an accurate family history to assess the risk of preterm labour, monitoring of uterine contractile function, an assessment of infections and invasions in the lower reproductive tract, an assessment of the condition of the cervix including ultrasound and biochemical tests, as well as an assessment of the outflow of amniotic fluid (Semczuk, Krzyżanowski, 2011).

Prophylaxis of preterm labour

The etiopathogenesis of preterm delivery has not yet been fully understood, and moreover, the multiplicity of risk-increasing factors means that there is no effective method to prevent premature birth of a newborn. In the selection of appropriate obstetric procedure, both risk factors and probable pathogenic mechanisms should be considered (Wielgoś, 2016).

One of the factors significantly increasing the possibility of preterm labour includes disorders of vaginal biocenosis and intrauterine infections. Studies demonstrate that the use of antibiotic therapy every 4 months until the conception in women whose history is burdened with preterm labour does not bring the expected results (Wielgoś, 2016). In pregnant women suffering from bacterial vaginosis during gestation, the introduction of clindamycin therapy reduces the probability of late miscarriage, as well as labour before 37 weeks of gestation. However, the risk of labour before 33 weeks of gestation does not decrease despite the treatment (Wielgoś, Szymusik, 2011). In the case of bacterial vaginosis, the use of clindamycin seems to be correct, as it has greater efficacy compared to metronidazole (Wielgoś, 2016). In case the microorganisms colonise the cervix, the endometrium, as well as the decidua, the use of antibiotics in their intravaginal form, is not associated with risk reduction.

In the prophylaxis of preterm labour occurring as a result of genital infections, maintaining the vaginal ecosystem seems to be very important. The main microorganisms of the vaginal ecosystem are lactobacilli, which hinder the development of pathogens. In addition to the use of probiotics of human origin, the diet of pregnant women seem to be important. It should abound in dairy products containing probiotics, as well as garlic or dried fruits, which are a natural source of prebiotics. Both probiotics and prebiotics increase the risk of preterm labour. However, these theories are still at the research phase (Myhre, Brantsæte, et al, 2011; Myhre, Brantsæte, et al, 2013).

Another factor affecting the probability of preterm labour is premature opening and shortening of the cervix. Currently, in the area of prophylaxis, progesterone, cervical cerclage or cervical pessary are used (Wielgoś, 2016; Milanowska-Koloch, 2014).

Progesterone is a hormone that inhibits premature cervical dilation. Studies demonstrate that progesterone administered intravaginally at a dose of 250 mg/week in pregnant women with a cervix shortened below 25 mm reduces the probability of preterm labour before 35 weeks of gestation (Bomba-Opoń, 2012). In the case of women in whom shortening of the cervix below 15 mm occurs, the progesterone application does not reduce the risk of preterm labour. The team of experts of the Polish Society of

Gynecologists and Obstetricians (PTG) recommends the intravaginal administration of progesterone in pregnant women with shortened cervix, or with eventful obstetric history (Bomba-Opoń, 2012). In 2008, the ACOG recommended a prophylactic administration of progesterone in women with obstetric history in the direction of preterm labour. In turn, the Food and Drug Administration (FDA) in 2011 issued recommendations according to which it is recommended to use 17-α-hydroxyprogesterone in women with a history of preterm labour, and the supplementation should start between 16 and 21 weeks of gestation. Prophylactic use of progesterone in multiple pregnancies unfortunately does not bring the expected results (Bomba-Opoń, 2012).

Cervical cerclage is one of the oldest methods of treatment of cervical incompetence and is based on performing McDonald, Shirodkar circular cerclage or abdominal cerclage. This method is performed under general anaesthesia and is associated with the possibility of complications such as premature rupture of membrane, intraoperative cervical injury, intrauterine infection, cerclage slippage from the cervix, as well as bleeding from the reproductive tract. Performing a cervical cerclage with cervix shortening below 25 mm confirmed by an ultrasound examination reduces the percentage of preterm births and thus improves neonatal results. The use of a rescue cerclage, which is performed before 24 weeks of gestation in pregnant women with a dilation of not less than 4 cm, in the absence of contractile activity of the uterine muscle, improves obstetric and neonatal results (Wielgoś, 2016; Milanowska-Koloch, 2014).

The cervical pessary is intended to support the cervix by directing the cervix towards the sacrum and thereby relieving the internal orifice. The cervix is placed in the central opening of the pessary. They are made of flexible silicone. Despite this, women may experience increased discharge and discomfort. Therefore, currently they are not recommended in prophylaxis of preterm labour (Wielgoś, 2016; Milanowska-Koloch, 2014).

Incorrect implantation can also affect the occurrence of preterm labour. This condition may lead to preeclampsia, premature separation of the placenta, or intrauterine foetal growth restriction. These pathologies are indications for iatrogenic preterm termination of pregnancy (Wielgoś, 2016). The introduction of prophylaxis during the development of uteroplacental circulation and spiral artery formation may significantly reduce the risk of the onset of obstetric complications in the second half of pregnancy (Wielgoś, 2016). The introduction of acetylsalicylic acid in pregnant women with an eventful history, as well as anomalies in the uterine arteries, reduces the risk of preeclampsia and, consequently, preterm labour. It is important to include the prophylaxis before 16 weeks of gestation, before the end of formation of the walls of spiral arteries (Bujold, Roberge, et al, 2010). Products with acetylsalicylic acid should be taken in the evening, and the daily dose should be within 50–100 mg. Low molecular weight heparin is a substance that is administered to pregnant women with thrombophilia. Recent studies using heparin together with acetylsalicylic acid as prophylaxis for preeclampsia in pregnant women not suffering from thrombophilia have demonstrated a significant improvement in obstetric outcomes (Wielgoś, 2016).

Obstetric procedures and treatment

The main goal of therapeutic procedure in preterm labour is to minimize the mortality and morbidity of newborns born prematurely. Research proves that spontaneous uterine contractile function precedes about 40–45% of preterm labours. The introduction of tocolysis intended to suppress the contractile function and delay preterm labour is of significant importance for the newborn (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013). It enables implementation of the following activities:

a) providing the woman with a place in the tertiary referral hospital;

Table 1. Contraindications to the introduction of tocolysis (Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Maternal contraindications	Foetal contraindications
■ severe hypertension ■ bleeding from the reproductive tract ■ heart disease with impaired cardiovascular function ■ medical and obstetric contraindications ■ bad tolerance of medication used for tocolysis	■ cervical dilation to 4–5 cm ■ shortening of the cervix ■ gestational age over 34 weeks ■ intraamniotic infection ■ intrauterine foetal death ■ lethal defects in the foetus ■ foetal life-threatening symptoms: hypoxia, intrauterine growth restriction

Table 2. Characteristics of medications used in tololysis (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Medication	Description
Calcium antagonists – nifedipine	■ shows great effectiveness ■ only oral form ■ higher safety of use compared to β-mimetics ■ cannot be combined with β-mimetics and magnesium sulphate
B-mimetics – fenoterol	■ shows great effectiveness ■ intravenous form ■ numerous contraindications considering health condition of the pregnant woman ■ need for intensive monitoring of the pregnant woman and the foetus ■ occurrence of side effects in both the mother and the foetus ■ they must not be combined with calcium antagonists, as vascular complications may occur
COX inhibitor – indometacin	■ is effective and despite this it is rarely used ■ it can only be administered before 32 weeks of gestation ■ requires intensive monitoring of well-being of the foetus (AFI assessment, Doppler flow study)
Oxytocin antagonist – atosiban	■ shows great effectiveness as well as safety of use from 24 weeks of gestation ■ form of intravenous infusion ■ no contraindications related to the mother ■ slight side effects of use ■ this medication can be combined with magnesium sulphate administered for neuroprotective purposes ■ high cost of treatment

b) administration of corticosteroids to accelerate foetal lung development;
c) administration of magnesium sulphate before 32 weeks of gestation, in order to reduce the risk of cerebral palsy;
d) application of antibiotic therapy as prophylaxis of infection with group B streptococci (GBS).

Acute tocolysis should be introduced from the lower limit of neonatal survival to 34^{+6} weeks of gestation and be conducted for 48 to 72 hours. Extending the therapy does not seem to be justified because it does not reduce the prevalence of preterm birth. Contraindications to the referral for tocolysis are presented in Table 1 (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Nowadays, medications such as calcium channel blockers, β-mimetics, cyclooxygenase (COX) inhibitors, oxytocin receptor antagonists are recommended for the treatment of preterm labour (Table 2). In Poland, the most commonly introduced medications include fenoterol as a representative of β-mimetics or nifedipine, which is a calcium receptor antagonist (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Nifedipine has an inhibitory effect on the inflow of Ca^{2+} ions to the inside of smooth muscle cells, which results in their relaxation. There are two oral dosage regimens:

1. Administration of 6 × 10 mg or 4 × 10 mg within 20 minutes, after 4 hours 6 × 20 mg for 48 hours, and subsequently 3 × 10 mg.
2. Administration of the initial dose equal to 20 mg, then 10–20 mg every 6 to 8 hours for 48 hours.

During the administration of tokolysis according to the above regimen, it is necessary to monitor the health condition of the mother: blood pressure, heart rate and temperature, as well as the well-being of the foetus. Nifedipine reaches maximum concentrations in the blood within 15–90 minutes after administration. The above medication cannot be combined with β-mimetics and administered sublingually (Poniedziałek-Czajkowska, Mierzyński, et al, 2013; Czajka, 2008).

The use of β-mimetics allows the postponement of preterm labour, however, it causes many adverse reactions both in the mother and in the foetus. Side effects result from non-selective stimulation of all receptors that induce muscle relaxation. In a pregnant woman, they can lead to: tachycardia, dyspnea, palpitations, an increase in blood glucose concentration above 180 mg/dl or a decrease in potassium concentration below 2.5 mEq/l. Therefore, β-mimetics are contraindicated in women with heart disease, diabetes and hyperthyroidism. The introduction of tocolysis is recommended between the 22 and 37 weeks of gestation for 48 hours under the conditions of continuous monitoring of the health condition of the mother and the child. The dosage regimen includes the administration of fenoterol by intravenous infusion from 1 mg to ¾ mg per minute, and the initial dose should equal 3.5 mg/minute. After termination of the uterine contractile function, the minimum effective dose is set (Poniedziałek-Czajkowska, Mierzyński, et al, 2013; Czajka, 2008).

The action of nonsteroidal anti-inflammatory drugs (NSAIDs) is based on the inhibition of cyclooxygenase (COX), which is involved in the synthesis of prostaglandin G_2. The main representative of COX inhibitors is indometacin. Restrictions in its use during preterm labours result from its unfavourable effect on the condition of the newborn due to the blockage of constitutive COX (COX-1) in foetal tissues. This medication cannot be administered after 32 weeks of gestation. According to the regimen, the initial dose is 50 mg administered orally or rectally; the maintenance dose is 25-50 mg administered every 6 hours, while the daily dose cannot exceed 200 mg. Pharmacotherapy cannot last longer than 48 hours. Both before the treatment, and after 48 and 72 hours an ultrasound examination should be performed to assess the AFI (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Oxytocin receptor antagonists, whose representative is atosiban, effectively inhibit the uterine contractile function, as well as do not show significant adverse reactions. However, it does not affect the improvement of obstetric outcomes. Pharmacotherapy can be introduced between 24 and 33 weeks of gestation and cannot exceed 48 hours. The total acceptable dose is 330 mg. Initially, 6.75 mg is injected intravenously, after which a continuous infusion with a flow of 18 mg/hour is recommended for 3 hours, and then the flow is reduced to 6 mg/hour for 45 minutes (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Antibiotic therapy used in the case of threatening preterm labour is aimed at reducing perinatal infection of the newborn with group B streptococci in the case of confirmed infection in the mother. In addition, the ACOG recommends the introduction of appropriate antibiotics in such cases as: PROM, bacterial vaginosis or intrauterine infection (Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Preterm labour always has to take place in highly specialized centres that are able to ensure the safety of the woman giving birth, as well as neonatal care to newborn babies born prematurely.

Steroid therapy and neuroprotection

In pregnant women with threatening preterm labour, the administration of glucocorticosteroids is a vital element of a therapeutic procedure. The introduction of the treatment will significantly reduce the probability of a infant respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and also reduces perinatal mortality. According to the PTG guidelines, pharmacotherapy should be introduced in case of any threatening preterm labour between24+0 and 34^{+6} weeks of gestation, with no contraindications. In addition, it is possible to repeat the therapy (the so-called rescue cycle of steroid therapy) in pregnant women, whose first treatment took place before 26 or 32 weeks of pregnancy with the probable completion of pregnancy within 7 days. There are two dosage regimens:

1. Betamethasone – 12 mg every 24 hours in 2 doses administered intramuscularly.
2. Dexamethasone – 6 mg every 12 hours in 4 doses administered intramuscularly (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

Preterm labour, as well as preterm birth are associated with an increased risk of neurological complications in the newborn. Nowadays, the use of magnesium sulphate ($MgSO_4$) as a medication showing tocolytic activity is minimal. However, the results of the studies demonstrate that it has a protective effect on the central nervous system of a premature baby, and thus significantly reduces the occurrence of infantile cerebral palsy and reduces the probability of motor deficits. The pharmacotherapy regimen assumes the intravenous administration of the initial dose in the form of 4 g of $MgSO_4$ for 20 to 30 minutes, and then the administration of 1 g/hour in the form of intravenous infusion as a maintenance dose for up to 24 hours. Labour should never be delayed to administer magnesium sulphate therapy when any maternal or foetal indications to complete pregnancy are present (Wielgoś, 2016; Poniedziałek-Czajkowska, Mierzyński, et al, 2013).

In summary, despite the extensive knowledge on aetiology, diagnosis, prevention and treatment, the problem of premature delivery remains valid and not fully explained. Currently, the main focus is on the elimination of risk factors for preterm delivery, with the use of methods to prevent pregnant women presenting the first symptoms of preterm delivery. Tocolithic treatment is limited to short-term therapy in order to carry out a steroid therapy cycle, as well as providing proper care to both mother and child.

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