REVIEWS

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Current Principles of the Diagnosis
and Treatment of Preterm Delivery

Współczesne zasady diagnostyki i leczenia porodu przedwczesnego

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Abstract

Preterm delivery is one of the main causes of infant mortality in developed countries, and infants who survive require long-term rehabilitation. Therefore it is important to understand the causes of preterm delivery and perform an adequate and early selection of women at risk. This enables surrounding them with intensive supervision and education guided towards prevention and early detection of symptoms of preterm contractions. According to current knowledge, effective prophylaxis of preterm delivery is connected with screening and treatment of asymptomatic bacteriuria in all pregnant women, progestogen administration, and screening for and treatment of asymptomatic bacterial vaginosis in the group at high risk. In the group at high risk, additional actions are necessary: fibronectin marker in cervical-vaginal smear, regular ultrasonographic evaluation of cervix length, and, in case of its shortening, the use of cervical cerclage and examination for the presence of autoantibodies. Treatment of the threat of preterm delivery consists of assuring the patient's peace and using drugs to restrain contractions. Inefficiency of such treatment is connected with the necessity of administering glucocorticosteroids and determining a way of labor termination that will guarantee maximum protection of the fetus (**Adv Clin Exp Med 2007, 16, 1, 155–164**).

Key words: pretern birth, diagnosis, treatment.

Streszczenie

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According to the World Health Organization definition, delivery between the 23rd and full 37th gestational week is treated as preterm, i.e. 21 days before the expected date of delivery. In Poland, preterm deliveries, as in other European countries, accounts for 7% of all births [1]. There are approximately 30,000 premature births per year. Of this group, according to the Central Statistical Office (GUS), about 5500 infants are born before 31 weeks of pregnancy.

During the last few years an increase in the number of preterm deliveries has been observed. this is connected with more effective treatment of miscarriage based on progestogen substitution, the

application of tocolytic drugs, and more precise surgery of uterine malfunctions. Another reason is the rising number of multiple pregnancies, which is a consequence of a more widespread use of assisted reproductive techniques and induction of ovulation. This is reflected in the fact that multiple pregnancies constitute about 9% of all preterm deliveries. The increase in the number of preterm deliveries is assisted by a decrease in infant mortality, which is connected with the rapid development of intensive neonatal care. This means that nowadays the mortality of infants born in modern medical centers after 32 weeks of pregnancy is minimal, and the accepted limit of survival is delivery in the 24th week of pregnancy. It should be remembered that, together with the increase in the survival rate of prematures from less and less advanced pregnancies, the frequency of chronic complications, e.g. retinopathy, sensorial neural deafness, pulmonary bronchial dysplasia, and neurological dysfunction resulting in physical and mental disorders, is also increasing.

Despite such huge progress, preterm delivery remains the main cause for infant death in developed countries, and is responsible for 75% of all such deaths. The high perinatal mortality and the distant effects of prematurity (individual, social, and financial) indicate how important it is to understand the pathogenesis, develop diagnostics, and provide treatment of preterm delivery.

The Pathogenesis of Preterm Delivery

During the last few years, significant progress in understanding the biochemical basis of preterm delivery has been made. According to the present state of knowledge, preterm contractile action of the uterus is a result of mutual local reactions between fetal membranes, the decidua, and uterine muscle. The most important of these are interleukin, prostaglandin, endotelin, and the synthesis of other paracrine proinflammatory mediators which, similarly to term delivery, cause uterine contractions, cervix dilatation, and weakening of the fetal membranes, leading to their rupture. The cascade of such reactions is induced by pathological factors derived from the mother and the fetus. The factor with the greatest influence on preterm uterine contraction by the activation of the above cascade are infections. Bacterial endotoxins and proteolytic enzymes (collagenase, elastase) acting upon decidual amnion and fetal membrane cells cause increased interleukin production, especially of IL-1, IL-6, and IL-8, and of TNF-α. Evidence of this is their increased values found in the amni-

otic fluid of patients with intrauterine infection in the course of preterm delivery. These cytokines, especially IL-6, stimulate prostaglandin synthesis by the activation of cyclooxygenase, leading to increases in its level in the amnion, chorion, decidua, and then in the myometrium itself. Goldberg et al. demonstrated the occurrence of bacterial infection of amniotic fluid and/or fetal membranes in 80% of women who gave birth before the 30th week of pregnancy. Infection was found only in 30% of cases of full-term pregnancy [2].

Infections recognized as factors that may cause preterm contractions are mainly vaginal and urinary tract infections. The transplacental way and iatrogenic factors are definitely less common causes. Among vaginal infections, the most significant microorganisms are *Gardnerella vaginalis* and *Bacteriodes spp.* that cause bacterial vaginosis. According to a study by Hay et al. carried out on a group of almost 800 women, pregnancies of patients with bacterial vaginosis were marked by a higher percentage of preterm delivery (16%) in comparison with women with proper vaginal flora [3]. Nowadays, more attention is also being paid to intracellular microbes, such as *Ureaplasma urealyticum*, *Mycroplasma hominis*, and *Chlamydia trachomatis*. Confirmed infection by these microbes at 20 weeks of pregnancy is connected with an increased risk of preterm delivery [4].

The influence of the above pathogens on the course of pregnancy is an individual issue, connected with a balance disorder between these pathogens and protective factors limiting infection. In the vagina it is the presence of lactic acid bacillus, the number of which increases during pregnancy, and in cervical mucus lactoferrin, lysozyme, and immunoglobulins. The protective barrier in case of the amniotic fluid are non-specific immunity factors: cytokine inhibitors (urinary tripsin inhibitor, interleukin IL-1 activity inhibitor), lysozyme, transferrin, peroxidase, and specific immunity factors, i.e. the immunoglobulins. This keeps the total risk of preterm delivery due to bacterial vaginal infection to only about 2%. In women without relevant obstetrics history and without symptoms, screening for vaginal infections has low specificity and little predictive value and should not be used as a routine procedure. However, such screening is strongly recommended in patients with past preterm labor because treatment of vaginal infection decreases the risk of miscarriage in this group of women [5]. Urinary tract infection, which is the most common pregnancy complication, has a significant impact on preterm delivery. According to the results of a meta-analysis by Romero et al., silent bacteriuria is connected with a twofold increase in the risk of

delivering a low-birth-weight infant [6]. Other causes of preterm delivery are: cervical incompetence, uterine myomas, uterine malformation, as well as frequent surgery performed for it. The most common cause is cervical incompetence, which is cervix effacement and dilation that was not preceded by uterine contractile activity. According to various sources it is responsible for 15–20% of all preterm births. The influence of uterine myomas on the course of labor is dependent on their number, location, and size. Population studies have shown that the presence of uterine myomas is responsible for 40–60% of pregnancy failures. Uterine malformation makes term delivery impossible, according to various authors, in 60–80% of cases. Corrective surgery, especially hysteroscopic uterine septum removal, results in a term delivery increase by 50%. In spite of such good results, it should be remembered that pregnancies after uterine plastic surgery are connected with a 10–20% risk of preterm delivery.

The main immunological causes of preterm childbirth are antiphospholipid syndrome and systemic lupus erythematosus. They are characterized by the presence of autoantibodies, the most clinically significant being lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). A common feature of these syndromes is improper implantation, trophoblast development disorder, and thrombotic changes in placenta vessels, which may lead to miscarriage at any stage of embryo development. Permanent positive results of autoantibody tests have been demonstrated in 15% of patients with recurrent miscarriages and preterm deliveries.

Delivery before the 37th week of pregnancy may be a result of planned medical treatment due to obstetric indications such as, among others, serious pre-eclamptic stage, eclampsia, intrauterine fetus growth retardation, executed serologic incompatibility in the Rh system, intrauterine infections, and hemorrhage during pregnancy. Nowadays about 20–30% of preterm births are iatrogenic in character [7].

Among the fetal factors connected with preterm delivery are the already mentioned intrauterine fetus growth retardation, congenital infections (acronym STORCH), and congenital defects, especially with accompanying polyhydramnio.

The Risk Factors of Preterm Delivery

Age

In case of primigravidae without exposed obstetric history, frequent preterm birth is found in the groups of women younger than 16 and older than 35. Pregnancy after 30 is at a twofold and after 35 at a six-fold greater risk.

Social Factors

Low economic status and, consequently, low educational level, improper diet, low BMI index (< 19), poor living conditions, and difficult access to prenatal care are reasons for frequent preterm deliveries in this group of women. Mental stress, long and onerous commuting, and hard physical work are other risk factors. A separate group at risk is single women who live alone.

Stimulants

Smoking cigarettes during gestation has negative effects both on the mother and the fetus. It leads to increased risk of premature rupture of membranes, preterm placental detachment, intrauterine fetus growth retardation, low birth weight, and increased perinatal mortality [8]. Drug and alcohol abuse are also conducive to preterm delivery. These factors are frequently connected with low social status.

Preterm Labor in Medical History

It has been shown that one previous preterm delivery causes a threefold and two preterm deliveries a six-fold increase in the risk of this complication in the next gestation. Therefore, a detailed diagnosis of patients who have had preterm births in the past is very important to eliminate possible causes or risk factors for this complication before the next gestation.

Multiple Pregnancy

Preterm delivery is more often found in cases of multiple pregnancy, especially monoamniotic, and the risk of its occurrence rises together with the fetus number. The average time of twin pregnancy is 36 weeks, triplet pregnancy 33 weeks, and quadruplet pregnancy 31 weeks. This is caused by excessive uterine muscle distention and inductive increased prostaglandin production, among other things.

Diseases During Pregnancy

The following diseases during pregnancy predispose to preterm delivery: hypertension, hyperthyroidism, heart diseases and malfunctions, drug addiction, gestational cholestasis, with hemoglobi-

nanemia below 9 g%, diabetes, past uterine surgery, and surgery during pregnancy.

Preterm Delivery Prophylaxis

The bedrock of effective preterm delivery prophylaxis is an early selection of women belonging to the risk group. This enables providing these women with intensive supervision, education guided towards early detection of preterm delivery symptoms, and avoidance of established risk factors. Therapeutic action connected with preterm delivery encompasses: antibiotic therapy of infection, progestogen substitution, prophylactic cervical cerclage, heparin and acetylsalicylic acid therapy in the event of autoimmunological abnormality, uterine defect correction during the prenatal period.

Antibiotic Therapy

Despite the connection between vaginal infection and the frequent occurrence of preterm delivery, the effectiveness of using antibiotics in the prophylaxis of preterm uterine contractions still causes a great deal of controversy. Many studies assessing the treatment of bacterial vaginosis affirmed in 20% of pregnant women. Research carried out by the National Institute of Child Health and Human Development on a group of 1953 pregnant women compared the effectiveness of metronidazol oral therapy and placebo therapy in reducing preterm deliveries in patients with recognized silent bacterial vaginosis [9]. The patients belonged to a group at low risk and the infection was recognized between the 16th and 24th weeks of pregnancy. In the group of women treated with metronidazol, preterm delivery occurred in 12.2% of cases and in the group where placebo was used in 12.5% of cases. No difference in terms of birth weight of the preterm infants was found in the two groups. In turn, a study by Ugwumadu et al. on a group of 494 pregnant women with silent bacterial vaginosis showed a statistically significant decrease in premature labor in patients treated orally with clindamycin (300 mg two times a day for 5 days) in comparison with placebo [10]. This may be connected with the fact that clindamycin removes often coexisting intracellular microorganism infection such as *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Chlamydia trachomatis*.

According to the above research, administering antibiotics to patients from a low-risk group for preterm delivery is questionable. In women who have had a previous preterm birth, the situation is different. In accordance with many randomized studies contained in McDonald's et al. meta-analysis, the treatment of bacterial vaginosis leads to a statistically significant decrease in the frequency of another preterm delivery in this group of pregnant women and is therefore recommended [5].

There are no doubts in the case of randomized studies assessing antibiotic treatment of pregnant women with silent bacteriuria. It was ascertained that preterm deliveries as well as the number of low birth-weight infants number were reduced by more than 40% [11]. Because of its simplicity and high prognostic value, monthly urine analysis is one of the basic prophylactic examinations for pregnant women. Recurrent infections, in turn, are indications for carrying out diagnostics for malformation of the patient's urinary system.

Progesterone

The use of natural progesterone metabolites (17α-hydroxyprogesterone) in the prophylaxis and treatment of miscarriage and preterm birth is common. It is believed that progesterone restrains the occurrence of preterm uterine contractions by decreasing its sensitivity to the effects of oxytocine, decreasing prostaglandin synthesis, and increasing the number of beta-adrenergic receptors. The last effect may explain the observed synergic action of progesterone and beta-agonists.

The results of a multicenter randomized study by Meis et al. showed that weekly intramuscular injection of a caproate of 17α-hydroxyprogesterone in pregnancies with a high risk of preterm birth leads to a decrease in the frequency of labor between 37 and 32 weeks of pregnancy in comparison with placebo. A statistically significant reduction of necrotizing enterocolitis, intracranial hemorrhage, and respiratory failure in infants of women receiving a caproate of 17α-hydroxyprogesterone was demonstrated [12].

More and more reports, such as the DaFonesca et al. study, show that an advantageous way of applying progesterone is transvaginally [13]. In this study, prophylactic use of progesterone intravaginally in a dose of 100 mg was evaluated. A decline in the frequency of births between 37 and 34 weeks of pregnancy was shown as well as a decrease in uterine contractions compared with a group in which placebo was used.

The Diagnosis of Preterm Delivery

For effective therapy, it is essential to diagnose the risk of preterm delivery as soon as possible.

Therefore, uterine contraction assessment and cervix evaluation are necessary. Nowadays, biochemical markers are considered auxiliary.

Uterine Contraction Assessment

An easy way to monitor uterine contractions is marking the number of perceptible contractions. Up to 10 contractions per day are normal in physiological pregnancy. Equipment monitoring of uterine contraction activity consists of external tocography. In women with known risk of preterm delivery, the FDA allows its use even in domestic conditions, although such action has not been proved to be better than regular obstetric care in decreasing the frequency of preterm delivery. Irregular contractile activity shown in the tocographic record, without accompanying cervix changes, does not indicate an active labor period. It might be the result of Braxton-Hicks contractions which appear after 24 weeks of gestation and are painfully perceptible by pregnant women. In 75% of such cases, delivery does not ensue within 48 hours, 25% of cases finish with term delivery, and uterine contractile activity is significantly restrained without treatment in 50% of cases [14]. In the course of normal delivery, the frequency of contractions recorded by external tocography should not exceed one contraction per hour in weeks 22–23 and four contractions per hour in weeks 33–34 of pregnancy [15]. Therefore, recognition of more than four uterine contractions per hour at any time before the 37th week of pregnancy or more than two contractions per hour with simultaneous cervix effacement and dilation is treated as a criterion of the initiation of preterm contractile activity.

Cervix Evaluation

Cervix evaluation is essential for diagnosing preterm delivery as it specifies the progression of labor and therefore determines therapeutic possibilities. It consists of gynecological examination with evaluation of its location relative to the genital tract, its consistency, dilation, amniotic sac evaluation, and the progress of the presenting part of the fetus. Unfortunately, a result of gynecological screening showing, for example, cervix effacement or dilation is only determined retrospectively in 4% of patients at low risk and 12–20% with numerous risk factors where preterm delivery occurred. Therefore, ultrasound measurement of cervix length with transvaginal head is recommended. Examinations of pregnant women with suspicion of preterm delivery carried out between the 23rd and 33rd week of pregnancy showed that

cervix length measurement using transvaginal head facilitates the selection of pregnant women with a greater risk of miscarriage [16]. A cervix length of 25 mm is regarded as the border line in the identification of women with a high risk of preterm delivery [17]. In twin pregnancies it has been reported that a cervix length below 35 mm measured at 24–26 week of pregnancy is a factor of increased risk of delivery before the 34th week. Clinical practice shows that pharmacological intervention is effective only when the cervix dilation is up to 2 cm in a primigravida and up to 3 cm in a multigravida.

Biochemical Markers of Threat of Preterm Delivery

The most recognized biochemical markers of a threat of preterm delivery are fetal fibronectin, interleukin 6, and corticotropin-releasing hormone. Fetal fibronectin is a glycoprotein occurring in fetal membranes and the decidua. It is physiologically recognized in cervical-vaginal discharge up to 20 weeks of pregnancy. After this period its presence is a symptom of violating the adjacency of fetal membranes to the decidua and is connected with increased risk of preterm delivery. According to studies by Honest, fibronectin is the best marker for preterm labor within one week in patients with contractions that have no confirmed cervix dilation [18, 19]. The greatest clinical significance of this study is its negative predictive value: only 1% of women who lack fibronectin in their cervical-vaginal discharge and have an ultrasound-confirmed cervix length above 30 mm have preterm deliveries within two weeks [20].

The results of a meta-analysis of more than 20 studies assessing test specificity and sensitivity of fibronectin as a marker in predicting preterm birth are presented in Table 1 [21]. The high negative and positive predictive values of fibronectin in the cervical-vaginal discharge enables a more specific identification of pregnant women with a real risk of preterm delivery and thereby allows therapeutic treatment based on these results, including even decisions about steroid administration. Fibronectin marking as a screening examination is not recommended in women without symptoms of preterm delivery.

The demonstration of interleukins in amniotic fluid and cervical discharge led to studies aimed at determining their usefulness as markers of interdecidual infections in the course of preterm delivery. Romero et al. showed that interleukin 6 concentration in cervical discharge correlates with its concentration in amniotic fluid obtained by amniocentesis [22]. It has been shown that tests determining

Table 1. Metaanalysis results considering sensitivity and specificity of fibronectin determination in prediction of preterm delivery

Tabela 1. Wyniki metaanalizy określające czułość i specyficzność testu na oznaczenie fibrynoektyny w przewidywaniu porodu przedwczesnego

Outcome (Wynik)	Sensitivity (Czułość) %	Specyficity (Specyficzność) %
Delivery < 37th week of gestation (Poród < 37. tygodnia)	52	85
Delivery < 34th week of gestation (Poród < 34. tygodnia)	53	89
Delivery in 1 week (Poród w ciągu 1 tygodnia)	71	89
Delivery in 2 weeks (Poród w ciągu 2 tygodni)	67	89
Delivery in 3 weeks (Poród w ciągu 3 tygodni)	59	92

interleukin 6 in the cervical discharge have high sensitivity and specificity to the onset of interdecidual infection and in predicting the threat of preterm delivery [23, 24].

Various publications have reported an increase in corticotropin-releasing hormone (CRH) in the serum of pregnant women with uterine contractions leading to preterm delivery [25]. It was shown that CRH release is connected with stress caused by illness of the mother or fetus. CRH release causes not only ACTH and adrenal hormones release, but is also responsible for stimulation of prostaglandin production in amnion, chorion, and decidual cells and in this way causes preterm contractions. Further studies are required to determine the clinical usefulness of CRH marking in the serum of patients with the risk of preterm delivery.

Treatment

The treatment of preterm delivery requires evaluation of the current obstetric situation. Medical history, pregnancy history, gynecological examination, and cardiotocography should be analyzed. Additional exams to be carried out are blood cell count, electrolytes, kidney and liver function tests, vagina and cervix canal culture, urine test, and obstetric ultrasonography. The results of these examinations enable choosing the appropriate mode of treatment, estimating the chances of success, and determining the benefit/risk ratio. The possible ways of proceeding are: early *in utero* transport to a higher-level center with a neonatal intensive care unit, tocolytic therapy implementation, antibiotic treatment implementation, cervical cerclage insertion, corticosteroid administration, determining the way of pregnancy termination.

In addition, the treatment of preterm delivery includes assurance of a relaxing atmosphere, staying in bed on the left side, and avoiding sexual intercourse and the use of stimulants.

Tocolytic Therapy

Drugs with tocolytic activity are beta-2 mimetics, oxytocin receptor antagonists, calcium channel blockers, magnesium sulfate, and cyclooxygense blockers. The indications to administer tocolytic therapy are four uterine contractions within one hour or two contractions with progressive cervical change. The contraindications to implementing tocolytics are fetal infection, fetal necrosis, and, usually, delivery after 34 completed weeks of pregnancy. According to several studies, the effectiveness of tocolytic drugs lasts from 48 hours to 7 days. This time should be used to administer steroids and to transfer the patient to a higher-level medical center. According to the current Royal College of Obstetricians and Gynaecologists guidelines, first-line tocolytics should be an oxytocin antagonist (atosiban) or a calcium channel blocker (nifedipine) [26].

Calcium Channel Blockers

Nifedipine is the most commonly used and the best studied channel blocker for tocolysis. According to King's meta-analysis comprising more than 1000 women from 12 randomized trials, calcium channel blockers reduced the number of preterm deliveries within seven days of starting

treatment and before 34 weeks of pregnancy. In comparison with β-mimetics, they produced less adverse drug reactions in pregnant women and less frequent neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and neonatal jaundice. There was no difference in neonatal outcome determined by birth weight, admission to a neonatal intensive care unit, or perinatal mortality [27]. The most common maternal side-effects due to nifedipine are headache, dizziness, flushing, and edema.

Oxytocin Receptor Antagonist

Atosiban, a synthetic oxytocin analogue, is a competitive antagonist of the oxytocin receptor. In a randomized, double-blind trial comprising 247 pregnant women, Mountquin et al. compared the safety and efficacy of atosiban and ritodrine. The study revealed no statistical difference in the number of women receiving atosiban or ritodrine who did not deliver after 48 hours or 7 days. However, atosiban was better tolerated and had fewer maternal and fetal adverse effects [28]. The Worldwide Atosiban versus Beta-agonists Study Group also found no difference in efficacy of atosiban and β-sympathomimetics. The reported side-effects of atosiban were nausea (13%), headache (10%), dizziness (3%), and injection-site reactions. Maternal cardiovascular side-effects appeared in 4% of women receiving atosiban compared with 84% receiving β-mimetics. Fetal side-effect were also minimal: no fetal tachycardia was reported with atosiban compared with 17% for β-sympathomimetics [29]. The Atosiban PTL-098 Study Group revealed that the drug can be administered subcutaneously in a chronic manner as a continuation of effective treatment of threatened preterm delivery and that its administration until 36 weeks of gestation is associated with a significant delay in delivery [30].

Beta-2 Agonists

Beta-2 agonist tocolytics (fenoterol, orciprenaline, salbutamol, terbutaline, ritodrine) are compounds that restrain uterine contractions and have been often applied in the last few years. Alpha-blockers show similar effectiveness, but they are not used so commonly. Of the beta-2 agonists, only ritordine is registered by the FDA (Food and Drug Administration) and, along with terbutaline, is the most frequently used drug of this group in the USA. These preparations are characterized by many contraindications, such as heart disease, aortic coarctation, glaucoma, pheochromocytoma, and thyroid hyperfunction of the pregnant woman.

Serious side effects of the therapy are arrhythmia, cardial ischemia, myocardial ischemia, hypotomia, pulmonary edema, hypokalemia, hyperglycemia, ketoacidosis, and increased renin, aldosterone, and vasopressin levels with water retention in the body. As far as fetal side effects as concerned, potential adverse drug reactions are arrhythmia, ventricular septal hypertrophy, heart failure, pulmonary edema, and intraventricular hemorrhage [31].

These drugs find application only in the short-term restraint of contraction due to the fact that they are subject to tachyphylaxis, resulting in significant loss of effectiveness as early as after 48 hours of therapy. According to the results of randomized studies, beta agonists lead to a significant decrease in preterm births in the first and second day of intravenous therapy. Their long-term oral application, despite the described decrease in uterine contractions, does not lead to significant extension of pregnancy [7]. The above-mentioned contraindications, adverse drug reactions, and tachyphylaxis make the use of this group of tocolytics as first-line preterm delivery therapy strongly controversial.

Magnesium Sulfate

In literature on the subject there are large discrepancies in the evaluation of the tocolytic effectiveness of magnesium sulfate. In the US it is a first-line therapy tocolytic, while most European associations do not recommend its application due to the lack of evidence of its effectiveness. This position is based on an analysis of 17 randomized studies on 2284 women in which no statistically significant reduction in preterm delivery between 24 hours, 48 hours, and 7 days was found when applying magnesium sulfate [32].

There are serious adverse therapy reactions, such as apnea, cardiac arrest, and diuresis restraint. Nowadays a source of controversy is a potential neuroprotective effect of magnesium sulfate on the fetus. This is connected with assumptions that its intravenous administration prior to labor reduce the occurrence of childhood cerebral palsy. The Magnesium and Neurologic Endpoints Trial Study showed that the incidence the magnesium concentration in the umbilical cord blood increases the frequency of neurological complications and infant death [33]. However, in a randomized study by Crowther et al. in which magnesium sulfate was applied at a maximum dose of 28 g prior to the 30th week of pregnancy, a significant decrease in the frequency of motion dysfunction in the second year of the child's life was demonstrated [34].

Cyclooxygenase Inhibitors

The function of cyclooxygenase inhibitors, such as aspirin, indomethacin, naproxen, and ibuprofen, consists of restraining prostaglandin synthesis. They are effective in postponing preterm birth and, in comparison with beta agonists, are well tolerated by pregnant women. However, their use is significantly restricted due to serious side effects on the fetus, such as necrotizing enteritis, intracranial hemorrhage, kidney ischemia, and preterm Botall's duct closure. Botall's duct closure poses a threat especially in the last 2–4 weeks prior to term delivery and therefore application of prostaglandin synthesis inhibitors during this period is absolutely contraindicated. The rules of safe indomethacin application include: therapy duration up to 48 hours, applying a maximum of 200 mg/daily, and use only until the 30th–32nd weeks of pregnancy. Taking into consideration the above recommendations, indomethacin may be used as a second-line drug in restraining contractions [35]. Because of the decrease in the amount of amniotic fluid during indomethacin therapy observed for many years, its application as a first-line tocolytic in treating the threat of preterm delivery in pregnancies complicated by polyhydramnio is considered.

Nitric Oxide Donors

Duckitt and Thornton's study on nitric oxide as tocolytics in treating the threat of preterm delivery did not show their effectiveness in practice [36].

The Function of Antibiotic Therapy in Treating Preterm Delivery

Reports on the implementation of antibiotic therapy in restraining already started preterm uterine contractions are contradictory. In a study with a double-blind sample comprising 205 women exposed to tocolysis due to the threat of preterm delivery, erythromycinum, ampicillin, or placebo was used [37]. In the group of women that took antibiotics, a prolongation of pregnancy by approximately 16 days was demonstrated. In turn, in Pięta-Dolińska's et al. study comprising 1049 pregnant hospitalized due to the threat of preterm delivery, statistically significant differences between groups with and without antibiotic treatment were not found [38].

Cervical Cerclage

Preventive and therapeutic use of cervical cerclage is a subject of numerous studies. According to Drakeley's et al. meta-analysis of six studies carried out on a total of 2175 pregnant women, cervical cerclage did not significantly surpasses the effectiveness of preservation treatment (such as a bed regime) in terms of total miscarriage risk and the risk of miscarriage before the 24th week and also in terms of perinatal infant mortality [39]. However, it seems that preservation cervical cerclage reduces the frequency of preterm delivery before the 33rd week in the group of women with a high risk of miscarriage (minimum after three miscarriages in the second term of pregnancy). It should be remembered that only women whose cervix shortening and extension were not preceded by contractions should be qualified for such surgical intervention. In many European countries, pessaries are used interchangeably with cervical cerclage. According to many studies, both methods achieve similar effectiveness.

Stimulation of Fetus Lung Maturation

Glucocorticosteroid application is the only procedure in treating preterm delivery with proven impact on increasing infant survival. Indications for its use are a threat of preterm delivery between the 24th and 34th weeks of pregnancy and threat of preterm delivery after 34 weeks in cases where fetus lung immaturity is revealed (L/S, lamellar bodies, etc.). The optimal corticosteroid effect starts 24 hours after application and lasts for seven days. Nevertheless, their use considerably reduces the risk of respiratory failure syndrome, intraventricular hemorrhage, and perinatal infant mortality even if less than 24 hours passes between administration and delivery. Long-term premature rupture of membranes without accompanying amnion infection is not a contraindication to glucocorticosteroid use. The most frequently used drugs are betamethasone and dexamethasone at a dose of 12 mg every 24 hours for two days. Potential adverse corticosteroid reactions are pulmonary edema (especially in combination with beta agonists) and an increase in glycemia in patients with diabetes.

Intra-amniotic surfactant administration is a clinically tested method of preventing respiratory distress syndrome. Lisawa et al. used transamniotic surfactant administration on 15 patients between 24–32 weeks of pregnancy two hours before the due time of delivery. Right before injection, aminophylline was administered in order to stimulate the fetus's respiratory movements. Surfactant was applied intra-amniotically under ultrasonographic control in the area of fetus's mouth and nose. After delivery, no symptoms of serious asphyxia were found in any infant (aver-

age weight: 1207 g). Radiological symptoms of hyaline membrane syndrome were seen in only two cases. It was not necessary to administer surfactant after labor in any case [40]. Qualification of the place of this therapy in the prophylaxis of infant respiratory failure requires further research covering a larger group of pregnant women.

Glucocorticosteroids are the most effective and, according to 20 years of observations, the safest drugs administered to pregnant women to stimulate fetal lung maturation. At present, evidence of the safety and effectiveness of such methods as TRH or intra-amniotic surfactant administration are not sufficient to recommended them in routine practice.

Methods of Pregnancy Termination

Preterm delivery poses a threat of injury, hypoxia, and infection and therefore the choice of the method of pregnancy termination is very important. Cesarean section is advisable in cases of incorrect fetal position (longitudinal pelvic position, transversal position), premature detachment of the placenta, placenta praevia, threat of intrauterine fetal asphyxia, lack of birth progress, decidual infection syndrome, and in extremely low infant birth weight between the 25th and 31st weeks of pregnancy. When deciding about natural childbirth, continuous KTG monitoring is recommended in the first stage together with reactions on muddled uterine contractile activity and contractions which are too strong. The aim of the second stage of preterm delivery is to get the fetus out gently. It is essential to anaesthetize the pelvis base and vulval nerves, application of 2 IU of oxytocin in 20 ml of 5% glucose solution with an infusion pump with a speed of 2 ml per hour for the optimization of uterine contractile activity, early wide perineum incision, head delivery on the fenestrated speculum, and avoiding use of vacuum. It is allowed to use forceps for prematures. Omphalotomy should follow only after termination of umbilical cord pulsation. In the third delivery stage, an accurate control of afterbirth and curettage of the uterine cavity is necessary.

References

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