Review
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The Role of Antibiotic Therapy on the Children's Neurological Outcome in Preterm Premature Rupture of Membranes

Uloga antibiotske terapije u prijevremenom prsnuću plodovih ovoja prije termina, na neurološki ishod djece

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Summary

Preterm premature rupture of membranes (PPROM) occurs in 3% of all pregnancies and is responsible for approximately one-third of all preterm births, causing significant perinatal morbidity and fetal death. In a significant number of PPROM cases an infection is present although it is sometimes difficult to determine clinically. Our knowledge of pathophysiology of intrauterine infection/inflammation and impact of antibiotic therapy on its clinical course is elementary. It is known that intrauterine infection/inflammation is a significant risk factor for developing neurological impairment in children. Prophylactic administration of antibiotics might eradicate infection in women with PPROM and improve neonatal outcomes, on the other hand, it could only increase the period of latency and suppress infection to a subclinical level without eradicating the underlying infection, leaving the fetus in an unfavorable intrauterine environment. Still, the European and the American guidelines recommend routine administration of antibiotic therapy in women presenting with PPROM. Studies have shown that administration of antibiotics increases the period of latency and improves certain short-term neurological outcomes such as reducing the rate of abnormal cerebral ultrasound scan prior to the discharge from hospital, but it does not reduce perinatal mortality, the rate of preterm births and does not have an effect on long-term neurological outcomes. Furthermore, guidelines for antibiotics administration on PPROM are largely based on deficient, low quality and possibly outdated evidence. Optimal regimen and duration of antibiotic therapy are not clear and new studies estimating changes in bacterial resistance and more common clinical use of cephalosporines in the clinical management of PPROM are necessary.

Key words: Preterm premature rupture of membranes (PPROM), antibiotics, chorioamnionitis, neurological outcomes

Sažetak

Prerano prijevremeno prsnuće vodenjaka (PRVP) javlja se u 3% svih trudnoća i odgovorno je za trećinu prijevremenih porođaja, uzrokujući značajni perinatalni morbiditet i smrt fetusa. U značajnom broju slučajeva PRVP-a prisutna je infekcija koja predstavlja klinički dijagnostički problem, a znanje o patofiziologiji intrauterine infekcije/upale, te utjecaju antibiotika na istu je predmet istraživanja. Poznato je

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da je intrauterina infekcija/upala značajan čimbenik rizika za razvoj neuroloških oštećenja u djece. Preventivna primjena antibiotika mogla bi eradicirati infekciju i djelovati pozitivno na ishode djece trudnica s PRVP-om, dok bi, s druge strane, mogla samo produljiti vrijeme latencije, te suprimirati infekciju do subkliničke razine bez eradiciranja infekcije, što ostavlja fetus u nepovoljnom intrauterinom „okolišu". Ipak, europske i američke smjernice preporučuju rutinsku primjenu antibiotika pri PRVP-u. Istraživanja pokazuju kako primjena antibiotika produljuje vrijeme latencije i poboljšava određene kratkoročne neurološke ishode, poput smanjenja učestalosti abnormalnog ultrazvučnog nalaza mozga novorođenčeta pri otpustu iz bolnice, ali ne utječe značajno na perinatalni mortalitet, ne dovodi do smanjenja učestalosti prijevremenih porođaja, te nema utjecaja na dugoročne neurološke posljedice kod djece. Također, smjernice za upotrebu antibiotika kod PRVP-a su u velikoj mjeri bazirane na oskudnim niskokvalitetnim i, moguće, zastarjelim dokazima. Optimalni antibiotski režimi duljine trajanja primjene antibiotika još uvijek nisu ustanovljeni, te su potrebna daljnja istraživanja koja bi uzela u obzir promjenu u bakterijskoj rezistenciji, te učestalije korištenje cefalosporina u kliničkom liječenju PRVP-a.

Ključne riječi: prijeterminsko prijevremeno prsnuće plodovih ovoja (PPROM), antibiotici, korioamnionitis, neurološki ishodi

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Introduction

Preterm premature rupture of the membranes (PPROM) occurs in 3% of all pregnancies and is responsible for approximately one third of all preterm births.[1]

In some countries, the frequency of PPROM is higher, so the frequency of PPROM is 5.3% in Egypt[2], 19.2% in China[3], 7.5% in Uganda[4] and 13.7% in Ethiopia.[5]

It causes significant perinatal morbidity and fetal death and is associated with more than 50% of long-term morbidity including cerebral palsy, chronic lung disease, deafness and blindness and is therefore considered a significant clinical problem.[6] The underlying cause of this condition is thought to be infection.[7] Furthermore, serious infections, such as chorioamnionitis, endometritis and septic shock are the main complications in a third of women with PRVP, and fetal exposure to intrauterine inflammation and chorioamnionitis is associated with neurodevelopmental difficulties, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), sepsis and only treatment in the intensive care unit (ICU). Although more and more premature children survive, they are at an increased risk of developing neurological complications, and in the long term, an even greater challenge is placed before doctors in the treatment of such children.[8] Due to all of the above, the use of antibiotics in PPROM is found in most guidelines and represents the standard treatment for this condition. Nevertheless, numerous antibiotics and their combinations were compared with placebo and with each other, and in a meta-analysis published in 2013, it was concluded that the choice of antibiotic is not clearly defined.[9] In a meta-analysis published in 2020, it was shown that several antibiotics are more effective than placebo in reducing the rate of chorioamnionitis after PPROM, but that none of them is clearly and consistently superior to other antibiotics, and most of them are not superior to placebo for outcomes other than chorioamnionitis.[10] PPROM is one of the most complex problems in perinatal medicine, and the approach to treatment is extremely complex due to several challenges, some of which are as follows: establishing an accurate diagnosis in problematic cases, an expectant approach versus active treatment, the use of tocolytics, the duration of antibiotic prophylaxis, the optimal timing of antenatal corticosteroid administration, a method for determining the infection of the fetus/mother and the time of completion of the pregnancy.

Inflammation, infection, decidual hemorrhage, and placental abruption are strongly associated with PPROM. Proteolytic enzymes and activation of cytokines associated with inflammation play an important role in PPROM, and chorioamnionitis is thought to be present in 26-50% of PPROM.[11] The rates of bacterial colonization of the placental parenchyma in the second trimester are up to 79% in deliveries after 23 weeks of gestation and decreases to 43% after 27 weeks of gestation.[12] Until recently, it was thought that inflammation was always of maternal origin in premature births, but recent studies show that inflammation of fetal origin also plays a significant role.[13]

Risk factors that are questioned with PRVP are low socioeconomic status, low level of education, maternal age and increased or decreased body mass index (BMI) of the mother, PPROM in the medical history, infection of the genital tract, antepartum bleeding and smoking, nulliparity, chronic corticosteroid therapy, drug abuse (cocaine), anemia, twin pregnancies, cervical abnormalities, polyhydramnios, oligohydramnios, acute trauma, and several genetic polymorphisms in genes associated

with inflammation, infection, and collagen degradation.[14]

El-Messidi and Cameron described in their article a number of advantages and disadvantages of different diagnostic tests for determining PPROM.[15]

The aim of the paper is to describe, based on current knowledge, what are the advantages and disadvantages of treatment in cases of PPROM, and what long-term outcomes can be expected for a child born from such pregnancies and with what probability for the said outcome.

Materials and Methods

This is a retrospective, analytical study of the results of research on the association between different approaches in the treatment of pregnant women with PPROM and neurological outcomes in children. Databases were searched: PubMed, Google Scholar, regardless of the language barrier and the time period of the published papers (until 2023). The results of this test include meta-analyses, randomized clinical studies and systematic review papers, as well as recommendations from some of the world's leading gynecological-obstetrical societies. All papers that made logical sense with regard to the topic and keywords of the search were taken into consideration for the analysis, and papers with clear outcomes were selected. Six studies (all randomized clinical trials) were excluded from the research due to non-clearly defined neurological risk analysis, but rather incidental findings without detailed analysis. We assessed bias across studies and outcomes. This research was done in accordance with "Standards for reporting qualitative research: a synthesis of recommendations (SRQR)".[16]

Results

Access to treatment for pregnant women with PPROM before the 24th week of pregnancy

Considering the time when PPROM occurs, we can divide it into PPROM that occurs before the 24th week of pregnancy and is also called previable PPROM, PPROM that occurs between the 24th and 34th week of pregnancy, and late PPROM that occurs from the 34th to the 37th week of pregnancy.

The RCOG guidelines for the administration of antenatal corticosteroids state that there is evidence of the usefulness of the use of antenatal corticosteroids only after the 23rd week of gestational age, and, even then their use should be considered and an experienced clinician should be consulted. American guidelines (ACOG) refer to the use of antenatal corticosteroids in the middle of the 22nd week of gestational age.[17] Magnesium sulfate for neuroprotection should be administered when labor is expected. If a cerclage is present, and the water breaks during this period, the cerclage is usually left if there are no signs of the onset of labor and infection, but this is a controversial topic because the presence of a foreign body in the cervix can contribute to the development of infection.[18] Amniotic patch, fibrin glue and amnioinfusion have not been proven to be effective methods for PPROM before the 24th week of pregnancy.

Access to treatment for pregnant women with PPROM between 24 and 37 weeks of pregnancy

Before the 34th week of pregnancy, the fetus is still immature, and is at high risk for complications of prematurity, so if there are no signs of placental abruption and/or infection, an expectant approach is recommended.[19] On the contrary, if we notice signs that would confirm the above-mentioned diagnoses, it is necessary to complete the pregnancy, because the condition of the fetus can quickly deteriorate, and no other therapeutic option other than the completion of the pregnancy has proven acceptable.[20] The median latency time in PPROM is 7 days, and it gets shorter as the gestational age increases.[21] During this period, the woman should be hospitalized for signs of infection, abruption of the placenta, compression/prolapse of the umbilical cord and other pathologies for the purpose of early detection and the possibility of rapid response. Possible clinical signs of chorioamnionitis development should be checked every 12 hours. Of course, laboratory findings are also determined, but their reliability is different. The specificity of C-reactive protein (CRP) is 77.1%, and the sensitivity is 68.7%[22], while leukocytosis as a factor in the diagnosis of chorioamnionitis is also doubtful because the sensitivity of leukocytosis is 51%, and the specificity is 65%, and up to 20% of tests are false positive.[22] It should be emphasized that serial testing of leukocyte levels has not been shown to be useful in the absence of clinical signs of infection, especially after corticosteroids have been administered.[23] There are several studies on procalcitonin as a marker of chorioamnionitis, but the results are controversial and not in favor of procalcitonin as a highly sensitive and specific marker.[24-26] Cardiotocographic (CTG) monitoring of the child indicates the presence of tachycardia as a late sign of infection and serves as one of the parameters for establishing the diagnosis of clinical chorioamnionitis. It is necessary to perform a bacteriological smear of the posterior fornix of the

vagina and a complete blood count (FBC) weekly.

Large meta-analyses show that chorioamnionitis is associated with PVL (RR 2.6, 95 % CI 1.7–3.9) and cerebral palsy (RR 1.9, 95 % CI 1.5–2.5)[27,28], and, when obvious chorioamnionitis occurs in these conditions, an experienced clinician should also be consulted in order to prolong the latency period and administer corticosteroids. Current UK and US guidelines[19,29] recommend antibiotics for pregnant women with PPROM. Infection can be both a cause and a consequence of PPROM. The goal and purpose of antibiotic therapy is to reduce the frequency of maternal and fetal infection and thus delay the onset of labor, i.e. prolong the latency period. Reducing the frequency of these infections is important because research shows an association between chorioamnionitis, the duration of the rupture of the fetal membranes and the development of cerebral palsy or neurodevelopmental disorders. A systematic review of 22 placebo-controlled randomized trials involving more than 6800 women evaluated the use of antibiotics before 37 weeks of gestational age.[9] Comparing antibiotic use with placebo/no use, antibiotic use was significantly associated with a reduction in chorioamnionitis (RR 0.66, 95% CI 0.46-0.96), number of neonates born within 48 hours (RR 0.71, 95% CI 0.58-0.87) and seven days (RR 0.79, 95 % CI 0.71-0.89), neonatal infections (RR 0.67, 95 % CI 0.52-0.85), surfactant use (RR 0.83, 95 % CI 0.72-0.96), neonatal oxygen therapy (RR 0.88, 95 % CI 0.81 -0.96), by abnormal brain ultrasound findings at hospital discharge (RR 0.81, 95 % CI 0.68-0.98).

Although the optimal regimen of antibiotic prophylaxis in PPROM has not yet been determined[30], the drugs used according to American guidelines cover most of the major pathogens of the genital tract. Azithromycin/erythromycin is specifically indicated for Ureaplasma, which is one of the main causes of choriamnionitis in PPROM.[31] Ampicillin and amoxicillin are indicated for group B Strep, many aerobic gram-negative bacilli and some anaerobes. Further research is needed to determine the optimal antibiotic regimen taking into account changes in bacterial resistance over time.[32] The extended-spectrum antibiotic regimen proposed by Lee et al. is a combination of ceftriaxone, clarithromycin and metronidazole.[31]

According to the RCOG guidelines[29], magnesium sulfate should be administered for fetal neuroprotection to pregnant women who have started labor or are planning to give birth in the next 24 hours. Meta-analyses of randomized studies have shown that the use of magnesium sulfate during this period reduces the incidence of cerebral palsy (RR 0.69, 95% CI 0.55–0.88) and motor dysfunction in children (RR 0.6, 95 % CI 0.43–0.83).[33] The greatest benefit of using magnesium sulfate refers to the period before the 30th week of gestational age[34], and it should be applied to all pregnant women with PPROM between the 24th week and the 30th week of gestational age who meet the previously mentioned criteria, and the application of magnesium sulfate can be considered in pregnant women between 30 and 34 weeks of gestational age. The neuroprotective effect of magnesium sulfate in women with PPROM was demonstrated in a cohort study.[35] According to ACOG guidelines[19], magnesium sulfate should be administered to all pregnant women between 24 and 32 weeks of gestational age if there are no contraindications and if delivery is expected within the next 24 hours.

It is important to consider the median latency time for a pregnant woman at a certain gestational age, so if PPROM occurred between the 24th and 28th week of gestation, the median latency time is 8-10 days, after that it decreases and in the 31st week of gestation is 5 days.[21] A case-control study showed that women with clinically diagnosed PPROM who have ultrasound-detected reduced amniotic fluid volume are at higher risk for delivery within 7 days of rupture of membranes.[36]

ACOG guidelines recommend the completion of pregnancy in all patients with PPROM with a gestational age ≥ 37 weeks, an expectant approach or an active completion of pregnancy in patients with a gestational age of 34 weeks to 37 weeks, and an expectant approach in those patients with a gestational age <34 weeks.[19] According to the RCOG[29] guidelines, an expectant approach is recommended for all pregnant women with PPROM between 24 and 37 weeks of gestation, unless there are contraindications for such an approach. An active approach i.e. delivery is indicated due to intrauterine infection, placental abruption, high risk of umbilical cord prolapse and uncertain cardiotocographic findings. If the mother and fetus are stable and the gestational age ≥ 34 weeks, it is necessary to present the advantages and disadvantages of an expectant approach and active completion of the pregnancy to the family of the pregnant woman. The optimal timing of intervention varies from clinic to clinic and depends on the balance between the morbidity associated with the immaturity of the newborn and the morbidity associated with prolonged latency time or complications of PPROM, which may be different in different populations. In a meta-analysis published in 2017, Bond et al.[37] compared the expectant approach with the active approach in pregnancies up to the 37th week of gestation. The authors concluded that up to the 37th week of gestational age, in the

absence of fetal and maternal complications, an expectant approach has an advantage over an active approach. In a meta-analysis, it was shown that an active versus expectant approach increases the risk for several worse neonatal outcomes such as RDS (RR 1.26, 95% CI 1.05-1.53), the need for mechanical ventilation (RR 1.27, 95% CI 1.02-1.58), treatment in ICU (RR 1.16, 95 % CI 1.08-1.24), neonatal deaths (RR 2.55, 95% CI 1.17-5.56). Also, it was shown that there was no increased risk for neonatal sepsis (RR 0.93, 95 % CI 0.66-1.30), nor fetal death (RR 0.45, 95% CI 0.13-1.57), nor neonatal mortality (RR 1.76, 95% CI 0.89- 3.50), as well as positive blood cultures in newborns (RR 1.24, 95% CI 0.70-2.21). In pregnant women, an active approach to pregnancy management resulted in a reduced rate of chorioamnionitis (RR 0.50, 95% CI 0.26-0.95), shortened duration of hospitalization (1.75 days less, 95% CI -2.45 to -1 ,05), increased cesarean section rate (RR 1.26, 95% CI 1.11-1.44) and higher incidence of endometritis (RR 1.61, 95% CI 1.00-2.59). In a 2018 meta-analysis in which "individual patient data" from 3 studies included in Bond et al. meta-analysis, the expectant approach was compared with the active approach in late PPROM (34-37 weeks of gestational age).[38] The active approach reduced the risk of antepartum hemorrhage and chorioamnionitis in the mother but increased the risk of cesarean section. No significant statistical difference was found between the groups in terms of endometritis rates and the length of hospitalization. Also, the rates of neonatal sepsis, NEC, RDS, and neonatal death were also similar in both approaches.[39] These meta-analyses should be read with caution because more than 50% of patients were included from a single study related to near-term PPROM. Furthermore, the studies included in the meta-analysis were conducted over a period of 9 years. This is a relatively long period in which there was progress in obstetrics and perinatal medicine and improved outcomes for newborns and mothers, so the results should be evaluated from that aspect as well. In that time interval, as now, there was no agreed position on the method and regime of administration of antenatal corticosteroids, tocolysis and antibiotics, which can also affect the results. Finally, it should be taken into account that a certain part of the patients included in the research was under home supervision.

Association of infection/inflammation and neurological outcomes in PPROM

Subclinical infection is present in a large number of preterm births, so theoretically, acute antibiotic use could eradicate the infection, prolong the latency time, and improve neonatal outcomes. On the other hand, antibiotics could suppress the infection, thus prolonging the pregnancy, but leave the fetus in the inflammatory "environment" of the mother. Infection, or inflammation, is often associated with PPROM, especially when it comes to the gestational age of less than 30 weeks, and it is considered that it contributes significantly, directly or indirectly, to high mortality and neurological adverse outcomes in a child affected by this condition.[40] Lower gestational age in PPROM and prolonged latency time are statistically significantly associated with the onset of cerebral palsy.[41] The high risk of neurological consequences and brain injuries in premature children could be directly related to intrauterine inflammation or infection, of course with all the negative consequences that premature birth additionally carries with it.[42] The infection stimulates the activation of the mother's immune system, which leads to an inflammatory response of the fetus mediated by cytokines, which all together leads not only to the development of periventricular leukomalacia and cerebral palsy, but also to other disorders from the spectrum of neurodevelopmental pathology, such as autism and schizophrenia.[42] Pro-inflammatory cytokines can cause direct injury to oligodendrocytes and neurons, indirect injury through the activation of microglial cells that are present in the white matter during brain growth and remodeling. In addition, activated microglial cells produce pro-inflammatory cytokines and free radicals that damage neighboring cells. Also, microglial cells can produce toxic metabolites such as glutamate and quinolinic acid. TNF-α has been shown to be a cytokine that reduces the number of oligodendrocyte progenitor cells causing oligodendrocyte apoptosis. However, some studies do not support the thesis that infection or infection/inflammation is responsible for central nervous system injury.[43] The study by Reiman et al. should be taken into account with caution because there is a relatively small number of participants and a large number of participants who were excluded from the research. Also, the research shows that newborns born prematurely by spontaneous delivery are at a higher risk of developing brain injury (higher frequency of infections) in contrast to newborns who were born by medical intervention (lower frequency of infections). Furthermore, cord inflammation, high levels of IL-6, IL-8, TNF-α, and IL-1β in fetal amniotic fluid and blood are associated with brain white matter damage and cerebral palsy.[44] A systematic review[45] that included 15 studies showed that clinical chorioamnionitis is associated with white matter injury and cerebral palsy (12 studies, RR 1.9, 95% CI 1.5–2.5), while histological chorioamnionitis

is associated with PVL (3 studies, RR 1.6, 95 % CI 1.0-2.5). Infection/inflammation may not directly lead to adverse neurological outcomes by itself, but clinical studies show that it may indirectly cause them. Namely, infection/inflammation can make immature brain tissue more sensitive to hypoxia or ischemia and thus lead to brain damage even with the action of a harmful factor in a smaller amount[46], which certainly shows the complexity of pathophysiological mechanisms in the occurrence of neurological damage.

Short-term neurological outcomes of children of mothers treated with antibiotics for PPROM

A systematic review of 22 studies on the use of antibiotics in pregnant women with PPROM included 6800 women and children.[9] It was shown that the use of antibiotics after PPROM was associated with a statistical decrease in the rate of chorioamnionitis (RR 0.66, 95 % CI 0.46 - 0.96), fewer infants born within 48 hours (RR 0.71, 95 % CI 0.58 - 0.87), and fewer newborns born within 7 days (RR 0.79, 95 % CI 0.71 - 0.89).[9] Neonatal morbidity factors such as neonatal infection (RR 0.67, 95% CI 0.52 - 0.85), surfactant use (RR 0.83, 95 % CI 0.72 - 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 - 0.96) and abnormal brain ultrasound findings at hospital discharge (RR 0.81, 95% CI 0.68 to 0.98) were also reduced. However, there was no statistically significant reduction in perinatal mortality (RR 0.93, 95% CI 0.76–1.14). Also, the mechanism by which the routine use of antibiotics in PPROM leads to improved outcomes is not clear. One of the proposed mechanisms is to prevent ascending infection since most pregnant women with PPROM have negative amniotic fluid cultures. The authors recommend the routine use of antibiotics in pregnant women with PPROM, although the antibiotic of choice is not clearly stated, i.e. it is only recommended that coamoxiclav should be avoided due to the increased risk of neonatal necrotizing enterocolitis (NNE). On the contrary, Gomez et al.[47] concluded that the use of antibiotics (ceftriaxone, clindamycin and erythromycin) rarely eradicates intra-amniotic infection in patients with PPROM, i.e. that more than 83% of PPROM patients in their study with intra-amniotic inflammation or positive amniotic fluid cultures retained the same microbiological and inflammatory status after antibiotic therapy. Despite antibiotic therapy, intra-amniotic inflammation developed in a third of patients who did not have inflammation when admitted to hospital. The authors also state that the use of antibiotics could reduce the fetal inflammatory response syndrome and support this by the reduction in the number of white blood cells in the amniotic fluid in pregnant women with PPROM who have intra-amniotic inflammation and have received antibiotic therapy.[47] Bendon et al. also concluded that there is no statistically significant difference in the rate of histological chorioamnionitis between patients with PPROM who received antibiotic therapy and those who did not.[48] These studies contradict studies showing that antibiotics are effective in eradicating intra-amniotic infection.[49,50] Factors that are problematic in the eradication of infection are the time of initiation of antibiotic therapy, poor bioavailability of antibiotics in amniotic fluid, and the use of the most favorable antibiotic or combination of antibiotics. The most common microbiological causes of chorioamnionitis are *Ureaplasma urealyticum*, *Mycoplasma hominis* and group *B Strep*. It should be kept in mind that the transplacental transfer of erythromycin is only 3% and the concentration in the fetal serum is 0.06 μg/mL, which may be below the minimum inhibitory concentration (MIC) for the mentioned pathogens (MIC for *Ureaplasma* is 0.5–4 mg/mL and for *Mycoplasma*>128 mg/mL).[51] Also, according to the RCOG guidelines, erythromycin is recommended for routine use in premature rupture of water before the due date. Furthermore, it should be kept in mind that even 80% of *Ureaplasma spp.* are resistant to erythromycin.[52] The clinical importance of intra-amniotic infection associated with this microorganism has been highlighted in several studies. When we compare pregnant women with sterile amniotic fluid and those who had a positive culture for *Ureaplasma urealyticum*, pregnant women with a positive culture have a higher concentration of pro-inflammatory cytokines in the amniotic fluid including TNF-α, IL-1β and IL-6, higher concentrations of IL-6 in the blood umbilical cord, higher prevalence of chorioamnionitis, higher risk for premature delivery and poor perinatal outcome.[53] The results of research analyzing the effect of antibiotics on the course of PPROM in terms of treatment and prevention of infection, prolongation of latency time and reduction of neonatal morbidity and morbidity related to gestational age, show a significant prolongation of latency time, but an inconsistent effect on neonatal morbidity and mortality. This can be explained by the fact that extending the latency period does not have such a benefit for the fetus because it is in an unhealthy intrauterine environment. Also, in various studies, antibiotics of different spectrum of action, method and duration of application were used, as well as different approaches in terms of the use and method of administration of corticosteroids and other drugs in

PPROM, which makes it difficult to compare the results of these studies. The routine use of antibiotics in PPROM is a response to an event that is often, but not always, accompanied by infection. The application and choice of antibiotics are not guided by microbiological culture and sensitivity of microbiological agents to antibiotics. The route of administration and duration of antibiotic therapy seem to be unclear. Broad-spectrum antibiotics could make it difficult to establish normal microbiota or even eliminate it, especially those in the intestines, and, on the other hand, support the development of harmful, pathogenic bacteria which can lead to disorders in the development of the immune system in children.[54] In a meta-analysis 20 studies (7169 women) from 2020, Chatzakis et al. compared the difference in outcomes between the use of prophylactic antibiotics with each other and with placebo/no treatment. Regarding short-term neurologic outcomes, ampicillin (RR 0.42, 95% CI 0.20–0.92) and penicillin (RR 0.49, 95% CI 0.25–0.96) were beneficial in reducing the incidence rate of grade 3 and 4 IVH.[30] In the aforementioned meta-analysis, it was concluded that, except for chorioamnionitis, the use of antibiotics improves very few perinatal outcomes comparing the use of antibiotics with placebo/no treatment. The rate of chorioamnionitis is significantly reduced by the use of gentamicin (RR 0.19, 95% CI 0.05–0.83), penicillin (RR 0.31, 95% CI 0.16–0.6), ampicillin + sulbactam + coamoxiclav (RR 0.32, 95 % CI 0.12–0.92), ampicillin (RR 0.52, 95% CI 0.34–0.81) and erythromycin + ampicillin + amoxicillin (RR 0.71, 95% CI 0.55–0.92) compared with placebo/no treatment.[30] None of the antibiotics investigated show consistent and significant utility compared with other antibiotics for improving perinatal outcomes.

This meta-analysis should be interpreted with caution because the number of 7,169 women from 20 studies is still a limiting factor regarding the prevalence and significance of PPROM. Also, as many as 4,826 out of 7,169 women were included from one study. Furthermore, according to the GRADE criteria, the overall quality of evidence for this meta-analysis was rated moderate-low to very low for the primary outcomes, which means that the reliability of the evidence on which the current practice in the approach to PPROM is based is low. Also, erythromycin and ampicillin, which are recommended according to the RCOG guidelines, might be less effective today[29] and the data for these antibiotics may be out of date. On the other hand, very few randomized controlled studies have been conducted on antibiotics, especially cephalosporins, which are quite common in clinical practice today. Generally speaking, in women with PPROM without signs of infection, the use of one antibiotic for a shorter period of time is preferable. Small studies confirm that there is no difference in pregnancy outcomes between the use of prophylactic antibiotics for PPROM for three days compared to seven days.[55] Further, larger studies are needed to confirm this.

Long-term neurological outcomes of children of mothers treated with antibiotics for PPROM

Kenyon et al. conducted a long-term follow-up of children whose mothers had PPROM.[56] Of the 4378 children who were included in the study at birth, the outcomes of 3298 (75%) children were known. Questionnaires were sent to the children's parents at their home addresses containing questions about the frequency of specific health conditions such as cerebral palsy, epilepsy, hydrocephalus and attention deficit hyperactivity disorder (ADHD) and other health outcomes. Most of the data on the children (3171) were obtained through questionnaires, while the rest were collected from the children's family doctors or by contacting the children's parents by phone. Also, the results of national tests conducted at state level at the age of 7 were collected and reading, writing and math skills were analyzed. The results of that study showed that the use of antibiotics had a small impact/effect on children's neurological health and educational achievements compared to children who did not use antibiotics.[56] Namely, there was no difference in the proportion of children with functional disorders at the age of 7 years after the use of erythromycin, with or without coamoxiclav compared to children whose mothers did not receive erythromycin after PPROM (38.3% vs. 40.4%; OR 0.91, 95% CI 0.79–1.05) or after the administration of coamoxiclav with or without erythromycin compared with children whose mothers did not receive erythromycin after PPROM (40.6% vs. 38.1%; OR 1.11, CI 0.96–1.28). Also, the use of antibiotics had no significant impact on behavioral difficulties such as emotional problems, non-specific behavioral disorders, hyperactivity, other problems related to the social environment and prosocial behavior compared to children whose mothers had not received antibiotics after PPROM. Furthermore, antibiotic use had no significant effect on central nervous system (CNS) problems such as cerebral palsy, epilepsy, hydrocephalus and developmental disorders such as ADHD compared to children whose mothers had not received antibiotics after PPROM.[56] It should be emphasized that the research showed that the entire group of children (those whose mothers had received antibiotics and those whose mothers had not)

showed lower educational achievements than the national average, which is in line with the research on the educational achievements of prematurely born children.[57] The results of a weak effect of antibiotics on the neurological outcomes of children at long-term follow-up are in contrast to the expected results of that study. It was expected that the use of antibiotics would have a positive effect and improve the neurological outcomes of children since positive cultures for microbiological agents were found in 32% of women at the time of PPROM onset[58] and in as many as 75% at the time of delivery.[59] The reasons for this are not clear and should be investigated in more detail, primarily in terms of the length of antibiotic administration and the ability of antibiotics to eradicate the infection.

Conclusion

The decision to routinely use antibiotics in pregnant women with PPROM without clinically evident infection is unclear, although current guidelines recommend routine antibiotic use in all women with PPROM. The benefit for short-term outcomes needs to be balanced against the lack of evidence for the long-term consequences of antibiotic use in women with PPROM. Newer studies show that the reliability of the evidence on which current practice is based in the approach to PPROM is low and further research is needed in this area to get a clearer picture of one of the most complex clinical problems in perinatal medicine. Also, recent studies show that routine use of antibiotics has no advantage over placebo for all outcomes except chorioamnionitis. In terms of neurological outcomes, the benefit of antibiotic use has only been demonstrated in reducing the rate of abnormal findings in neonatal brain ultrasound at hospital discharge, while there is no evidence of the benefit of antibiotics on long-term neurological outcomes in children. Also, considering the association between chorioamnionitis and an unwanted neurological outcome, it should be re-investigated whether the antibiotics used in clinical practice today are effective to eradicate chorioamnionitis and prevent unwanted neurological outcomes related to infection/ inflammation, and whether there are alternative antibiotics that do or the solution is in an active approach and completing the pregnancy so that the fetus is not exposed to infection/inflammation.

If we consider that there is no evidence of a beneficial effect of antibiotic use in women with PPROM on long-term neurological and other health outcomes of children, the decision not to prescribe antibiotics to pregnant women without evidence of infection would also be reasonable, especially in developed countries where there are large therapeutic options to support premature newborns. Routine use of antibiotics would be more reasonable in low-income countries where there is no advanced treatment in terms of antenatal corticosteroids, surfactant replacement therapy, and mechanical ventilation. Clinicians should also be careful not to increase the resistance of microorganisms during the routine use of antibiotics.

Pharmaceutical companies are not encouraged to conduct research on the use of antibiotics in PPROM, and, on the other hand, the costs of conducting such research can be prohibitive for academic institutions and health institutions, making it difficult to evaluate different treatment approaches of PPROM. The optimal antibiotic regimen and duration of antibiotic use have not yet been established, and further research is needed in this area.

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