Perinatal infections and perinatal outcomes

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ACOG - American College of Obstetricians and Gynecologists

ADHD - Attention deficit hyperactivity disorder

CMV - Cytomegalovirus

CP - Cerebral palsy

HBV - Hepatitis B virus

HIV - Human immunodeficiency virus

HSV - Herpes simplex virus

IUGR - Intrauterine growth restriction

IVH - Intraventricular hemorrhage

GBS - Group B streptococcus (*Streptococcus agalactiae*)

NEC - Necrotizing enterocolitis

NICU - Neonatal intensive care unit

PAMG-1 - Placental alpha microglobulin-1

PPROM - Preterm premature rupture of the membranes

RDS - Respiratory distress syndrome

ROM - Rupture of membranes

STDs - Sexually transmitted diseases

Table of Contents

Abstract

Preterm premature rupture of the membranes (PPROM) is a condition that can lead to maternal, fetal, and neonatal morbidity and mortality. It happens in 3% of pregnancies and is the cause of one-third of the total number of preterm births. An infection has been implicated both as a common underlying cause and a consequence of PPROM.

The challenge in managing PPROM is the need to balance the risk of prematurity with the risk of fetal infection and other complications. The management differs according to the gestational age at PPROM (before limit of viability, 23+0 to 33+6, 34+0 to 36+6) and generally includes either delivery induction or expectant management. Expectant management consists of monitoring, administering corticosteroids, tocolytics, magnesium sulfate, prophylactic antibiotic therapy, and screening for infections.

The period between rupture of membranes (ROM) and delivery is called latency period and it can take hours, days, and even weeks. The main question of this review is the influence of its length on the perinatal outcomes. It seems that long latency generally has a beneficial effect on the primary outcomes. However, a higher rate of chorioamnionitis and funisitis has increased with long latency, and it has a potential for long-term neurological complications.

Keywords: PPROM, length of latency, chorioamnionitis, neurological outcomes.

Sažetak

Prijevremeno prsnuće vodenjaka prije termina (PPROM) stanje je koje može dovesti do pobolijevanja i smrti majke majke, fetusa ili novorođenčeta. Javlja se u 3% trudnoća i uzrok je jedne trećine ukupnog broja prijevremenih porođaja. Infekciju se može pronaći i kao uzrok i kao posljedicu PPROM-a.

Izazov u terapijsko pristupu trudnoći s PPROM-om je potreba da se uravnoteži rizik od nedonošenosti s rizikom od infekcije fetusa i drugih komplikacija. Liječenje se razlikuje ovisno o gestacijskoj dobi kada se dogodi PPROM (prije granice vijabilnosti, 23+0 do 33+6 tjedana gestacije ili 34+0 do 36+6) i općenito uključuje ili indukciju porođaja ili liječenje uz daljnji nastavak trudnoće. Uobičajeno liječenje sastoji se od praćenja, primjene kortikosteroida, tokolitika, magnezijevog sulfata, profilaktičke antibiotske terapije i probira na infekcije.

Razdoblje između rupture membrane i porođaja naziva se razdobljem latencije i može potrajati satima, danima, pa čak i tjednima. Glavno pitanje ovog pregleda je utjecaj njegove duljine na perinatalne ishode. Čini se da duga latencija općenito ima povoljan učinak na primarne ishode. Međutim, viša stopa korioamnionitisa i funisitisa porasla je s dugom latencijom i nosi rizik od nastanka dugoročnih neuroloških komplikacija.

Ključne riječi: PPROM, duljina latencije, korioamnionitis, neurološki ishodi.

Introduction

Perinatal infections are acquired just before delivery, often after rupturing membranes or when the neonate passes through the birth canal. In this period, the neonate is exposed to maternal microflora and some other pathogenic organisms such as group B Streptococcus (GBS), herpes simplex virus (HSV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), cytomegalovirus (CMV), and Candida species (1). Perinatally acquired infections can present just after birth or weeks to months later (e.g., HIV). Usually, early-onset sepsis (<72 hours of life) is a result of perinatal infection and is more frequent with preterm delivery, maternal fever, chorioamnionitis, and prolonged ROM (more than 18 hours) (1,2). Late-onset sepsis (4 to 30 days of life) can also result from perinatally acquired organisms but is more frequently caused by postnatally acquired organisms (3). GBS is the most common cause of perinatal infection and can cause either early-onset sepsis or late-onset sepsis in neonates (4). Preventive actions, such as vaccines, screenings, and some treatments, can be done before and during pregnancy or labor to reduce morbidity and mortality from perinatal infection (5).

PPROM, a spontaneous rupture of membranes before the onset of uterine contractions and before maturity (<37 weeks of gestation), is an obstetrical condition that can be both caused by an infection and cause an infection (6). PPROM management is a delicate balance between the effort to prolong the pregnancy, to reach a higher gestational age, and complication avoidance, particularly infections. The gestational age guides the management options of this condition, and it is well established that gestational age, both at PPROM and at the time of delivery, is the most crucial factor determining the perinatal outcome (7). It is less clear whether the length of latency (time from PPROM to delivery) itself influences the outcome (8,9), and this review will present the data available on this topic to try and get an answer.

Preterm premature rupture of the membranes (PPROM)

General and epidemiological data

PPROM is defined as spontaneous rupture of membranes, before the onset of uterine contractions, at week 37+0 or less. It should be differentiated from premature rupture of membranes (PROM) which also happens before the onset of uterine contractions but after 37+0 weeks. PPROM affects approximately 3% of pregnancies and is the cause of one-third of the total number of preterm births. Dividing into gestational weeks, it affects 0.5% of pregnancies before the 27th week, 1% of pregnancies from the 27th to 34th week, and 1% of pregnancies between the 34th to 37th week (6,10,11).

An infection has been implicated both as a common underlying cause and a consequence of PPROM and can lead to maternal, fetal, and neonatal morbidity and mortality (6,12,13). In one-third of women with PPROM, the infection can cause intra-amniotic infection (chorioamnionitis), endometritis, and septicemia (14,15). Fetal exposure to the infection and inflammation has been linked with an increased risk for neurodevelopmental impairment, perinatal death, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and sepsis (6,16,17). These complications are also strongly related to prematurity, which is also a complication of PPROM, with or without the presence of infection (18). Other than infection and prematurity, complications of PPROM include abruption placentae, oligohydramnios, cesarean section, low APGAR score, birth weight <2500g, stillbirth, neonatal jaundice, and extended hospitalization of mother and neonates (19).

Risk factors

Although many factors were associated with increased risk for PPROM, its causes are still not fully elucidated (20). Risk factors are related to the mother's socio-behavioral and demographic characteristics and general medical, pharmacological, gynecological, and obstetrical history. The most decisive associated risk factors are BMI<18.5 kg/m^2, low educational level, preexisting and gestational diabetes, nulliparity, multiple pregnancies, previous PPROM or prematurity, and genital tract infections (19,21–24).

Low annual income, smoking, maternal age, high BMI, and the interval between pregnancies (<6 months or >60 months) were found to be related but not independently. This means that some factors might interact with each other, and some of them can be associated, for example, with a low educational level which is a decisive risk factor (19).

Among all these risk factors, the most common is genital tract infection. Epidemiological data that support this statement show that patients with PPROM have pathogenic microorganisms in the amniotic fluid more commonly than those without ruptured membranes. Another piece of evidence shows a higher rate of histologically confirmed chorioamnionitis in PPROM than in other preterm deliveries. Lastly, a woman who suffers from certain lower genital tract infections (particularly bacterial vaginosis) tends to have PPROM significantly more frequently than the ones who do not have it (25).

None of these risk factors are prognostically relevant or reliable, so biochemical risk indicators for developing PPROM are still being searched.

Clinical presentation and diagnostics

Clinical presentation is typical of a sudden gush of copious vaginal fluid, but it should be noted that sometimes it is not presented that way, and a small amount of fluid or just a wetness sensation is reported. If accompanied by fever, abdominal pain, foul-smelling vaginal discharge, and fetal tachycardia, it can suggest an intraamniotic infection (26).

Diagnosis of PPROM is the same as PROM and is a clinical one. The minimally invasive gold standard for diagnosis traditionally consists of three clinical signs found on sterile speculum examination: pooling of fluid in the posterior vaginal fornix, PH-sensitive paper (Nitrazine test) indicates basic PH and amniotic fluid crystallization (frening) when it is dried on a microscope glass slide (Fren test). If the amniotic fluid is not present, the doctor can ask the patient to press on their fundus, cough, or do a Valsalva to provoke the fluid flow (27). Bimanual screening should be avoided because it increases the risk of intrauterine infection and could shorten latency time, which is especially important with PPROM (28,29).

Each of these three clinical signs has its limitation, and it should be in mind in the evaluation of the diagnosis. One of the limitations is that fluid leakage is a requirement for these tests, and in the absence of fluid, they cannot be performed. Moreover, they lose their accuracy progressively after 1 hour from the rupture and, after 24 hours, are unreliable (30). They also have high rates of false-positive and false-negative results that could lead to inappropriate clinical decisions. Nitrazine test can be false-negative when leaking is not significant or continuous, and other vaginal fluids dilute amniotic fluid. False-positive results of the same test can be due to some vaginal infections (trichomonas, bacterial vaginosis), the presence of alkaline fluids in the vagina (blood, semen, soap), alkaline antiseptics, and alkaline urine pH (proteus infection) (31,32). Fren test can be false-negative with inadequate amniotic fluid or in the presence of heavy vaginal discharge, blood, or

meconium, and false-positive results are connected to fingerprints, semen, or well-estrogenized cervical mucus (32,33).

Diagnosis of oligohydramnios established by Leopold-Pavlik grasping or ultrasound cannot confirm the diagnosis of ruptured membranes simply because it can indicate other problems such as intrauterine growth retardation or congenital abnormalities. Moreover, it may not be present in patients with confirmed PROM (27). According to Robson et al., to have oligohydramnios, a large amount of water needs to be lost rapidly and continuously, considering that the fetus creates fluid replacement all along. In some cases, the presenting part of the fetus can stop the drainage completely or intermittently, and oligohydramnios will not be present (34). With all that said, even though it will not confirm the diagnosis, oligohydramnios may help the clinician to suspect PROM.

Considering the limitations of the gold standard tests and oligohydramnios identification in diagnosing PPROM other tests have been developed for better diagnosis with greater specificity and sensitivity. Biochemical markers present in high concentrations in amniotic fluid compared with normal cervicovaginal discharge were investigated. The most accurate technically advanced test of biological markers is placental alpha microglobulin-1 protein assay (PAMG-1), commercially named AmniSure, which uses immunochromatography technologies (35–37). PAMG-1 is a protein released by the cells of the decidua with a concentration in amniotic fluid that is significantly higher (1000 to 10,000-fold) than the concentration in a normal cervicovaginal discharge. This fact makes it an ideal marker for ruptured membranes, and a trace amount of it can be detected in the vaginal fluid using the AmniSure test (35,38). The detection threshold of this test is 5 ng/mL with a sensitivity of 98-99%, specificity of 88-100%, a positive predictive value of 98-100%, and a negative predictive value of 91-99% (39). This test proved to be rapid, reliable for a wide range of gestational ages (11 to 42 weeks), not affected by the presence of blood or semen and is superior to traditional clinical tests (pooling, ferning, Nitrazine, US) (27,35,40). With all that said, AmniSure may

provide a solution to the clinical challenge of the non-invasive diagnosis of PROM. However, health care practitioners should be mindful of the limitations stated in the manufacturer's instructions and use it as part of a more extensive clinical PROM evaluation together with history, speculum examination, ultrasound findings, etc. (41).

Management and treatment of pregnant women with PPROM

The management of PPROM is one of the most disputed topics in perinatal medicine. The challenge in managing PPROM is the need to balance the risk of prematurity and the risk of fetal infection as well as other complications (placental abruption, cord prolapse/compression) and whether to encourage or postpone labor respectively. Moreover, the management differs according to the gestational age and is divided into management before the limit of viability, which is believed to be around 23 weeks of gestation, and management between 23+0 to 36+6 weeks of gestation (8,9). What makes the decision even more complicated are other factors that need to be considered, except gestational age, when deciding on labor or expectant management: ongoing maternal/fetal infection, presence or absence of labor, fetal presentation, cervical length and position, and whether a suitable level of newborn care is available (42).

The management between 23+0 to 36+6 weeks of gestation

According to the American College of Obstetricians and Gynecologists (ACOG), the general and simplified approach is delivery for all pregnant women with PROM (≥37+0 weeks of gestation). For a woman with PPROM, either expectant management or immediate delivery in a late preterm fetus (34+0 to 36+6 weeks) and expectant management with an early preterm fetus (23+0 to 33+6 weeks) if

the period is long enough to allow a considerable reduction in gestational age-related morbidity (8,43).

Non-reassuring fetal testing, clinical intraamniotic infection, significant placental abruption, and high risk of cord prolapse are indications for prompt delivery for any women with PPROM at any gestational age. Otherwise, gestational age is the most crucial consideration when deciding between delivery and expectant management. However, with all that said, there is no real consensus on the optimal gestational age for delivery (43,44).

Expectant management or immediate delivery in a late preterm fetus (34+0 to 36+6 weeks) should be decided by the patient after both the advantages and disadvantages were presented to her by the gynecologist. Whether to encourage the patient toward one of the options is controversial as some guidelines believe delivery is the better option (42) and postponing the delivery until the term is reached is advocated by other guidelines (44,45).

If expectant management is indicated or chosen, some actions should be made while waiting for delivery: monitoring the mother and the fetus, administration of corticosteroids, tocolytics, magnesium sulfate, and prophylactic antibiotic therapy as well as screening for infections.

PPROM that is managed expectantly usually consists of hospitalization with periodic monitoring (no explicit agreement on the optimal frequency of monitoring). The monitoring is aimed at early detection of infection, placental abruption or umbilical cord compression, assessment of fetal condition, and the need for labor induction. Monitoring also includes ultrasonography for fetal growth assessment and fetal heart rate recording on a regular basis (43). Early diagnosis of intrauterine infection requires a high index of suspicion since early signs may not be easy to detect in preterm pregnancy. Any rise in temperature may imply an intrauterine infection, whereas other clinical signs, such as tachycardia of the patient or her fetus, change in frequency of contractions, and abdominal or fundal

tenderness, have varying specificity and sensitivity for diagnosing an infection in the absence of fever. Leukocyte count and other inflammatory markers have not proven effective and are nonspecific when clinical signs of infection are absent (mainly if antenatal corticosteroids have been administered). Amniocentesis can help in cases of uncertain chorioamnionitis when there is a need to decide between expectant management or delivery, but it is not routinely indicated for screening (42,46).

Administration of corticosteroids shortens the duration of neonatal respiratory support, preventing neonatal death and some complications such as RDS, IVH, and NEC. It is proved beneficial in patients with PPROM between 23+0 and 33+6 weeks of gestation without increasing the incidence of infection both in the patient and her fetus (47,48). It can also be given during expectant management of patients with PPROM at 34+0 to 36+6 weeks of gestation only if they did not get corticosteroids earlier during the pregnancy, there is no sign of infection, and only if the delivery is planned for more than one day after and not more than seven days after the administration of the corticosteroids (43).

The use of tocolytics is controversial in PPROM as it has proved to prolong the latency period but also can increase the risk of developing chorioamnionitis. This was concluded by a meta-analysis of eight studies that dealt with the question of tocolytics efficacy in the setting of PPROM (49). The critical limitation of these trials is that the women were treated with the current standard therapy that includes corticosteroids and prophylactic antibiotics in only two of the trials. Hence, the benefit of tocolytics combined with the current therapy is unclear (43). In practice, tocolytics are given in the setting of PPROM for two main indications: delaying labor for 48 hours to enable administration of corticosteroids when needed and for transporting the patient to a place with a higher level of neonatal care. Contraindication for tocolytics would be a cervical opening of more than 4 cm, signs of uterine infection, or any other signs that indicate prompt delivery. It is also less recommended for patients between 34+0 to 36+6 weeks of gestation (42).

Magnesium sulfate administration for neuroprotection should be considered for women of gestational age between 23+0 and 32+0 when the delivery is imminent, and there are no contraindications (50). It was proved to reduce the risk for cerebral palsy in infants that survived the delivery (51) and proved to have no effect on the latency period (52).

Screening for infections is also a part of expectant management in patients with PPROM. Screening for GBS is indicated since labor can occur earlier than 36+0 to 37+6 weeks of gestation when the screening is usually done. If the results are positive or unknown and the patient is about to give birth, it should be treated (43). Usually, the prophylactic antibiotic treatment that is administrated to prolong latency (will be discussed next) and the treatment for chorioamnionitis already cover for GBS. In addition, some guidelines suggest screening for bacterial vaginosis and sexually transmitted diseases (STDs) like HIV, syphilis, gonorrhea, and Chlamydia (42).

As infection can be the provoking event that leads to PPROM but also can be caused by and complicate PPROM, prophylactic antibiotics therapy is indicated in expectant management. This approach proved to reduce the rates of infections of both the fetus and the mother, prolong the pregnancy (induce latency), and consequently reduce the gestational age-related short-term morbidities (14,53,54). The use of antibiotics specifically helped to reduce the number of labors within 48 hours and 7 days and rates of chorioamnionitis in the mother (6,14,53). In the neonate, they were found to reduce neonatal morbidities such as INH, NEC, and neonatal infections (sepsis and pneumonia) (6,14) and some markers of neonatal morbidity such as the need to use surfactant, need for oxygen therapy, and abnormal cerebral ultrasound (53). Compared to placebo or no treatment, perinatal mortality rates were not reduced with antibiotics (6,53). Prophylactic antibiotic therapy is indicated in expectant management for a patient in gestational age less than 34+0 weeks (43,53,54). The preferred regimens of prophylactic antibiotics

and the best latency period after regimen administration will be discussed later separately.

The management before 23 weeks of gestation

Gestational age of less than 23–24 weeks is considered pre-viable (43). These weeks define the limit of viability which is the earliest fetal stage of maturity that can have a fair chance of surviving outside the uterine. The exact limit of viability is not yet determined, and there is institutional variability due to different approaches to management and different medical abilities (55). This text will refer to 23 weeks of gestation as the limit of viability.

Rupture of membranes at a pre-viable gestational age necessitates a collaborative and considerable decision-making process between doctors and patients in which the benefits and drawbacks of termination of pregnancy (by immediate delivery) versus expectant management are discussed. This discussion needs to be done in a realistic but compassionate way that considers the beliefs and circumstances of the patient and her partner and includes the most accurate and up-to-date information available (56). In cases the pregnancy is decided not to be terminated, the patient is stable with no infection, and birth is not imminent, the patient can be released from the hospital, and outpatient management with periodic monitoring and testing can be done until viability is reached. The patient needs to be instructed to measure her temperature regularly and how to recognize signs and symptoms of abnormalities that can occur during this period. The patient needs to approach the hospital immediately for any sign of complication such as infection, labor, and placental abruption (43,55). Prophylactic antibiotics therapy can be administrated before viability, at a gestational age of 20 weeks (56). Corticosteroids, tocolytics, and magnesium sulfate are not recommended before viability and are not part of the management at this gestational age (43). Nevertheless, it can be reasonable to give corticosteroids at a gestational age of 22 weeks if the delivery is planned

for the next seven days at the 23rd week and the patient wants an aggressive neonatal treatment after all the risks were presented to her in the consultation by the specialists (42). Cultures for GBS from the rectum and vagina need to be taken, and in case of positive results, GBS prophylaxis is given when viability is reached, and delivery is about to take place (55). When the pregnancy is at the limit of viability, the patient is then hospitalized and managed according to the recommendation of the specific gestational age, the expected time of latency or labor, and the condition of the fetus and the patient (55).

The preferred regimen of prophylactic antibiotics therapy

Part of expectant management for women with PPROM in gestational age between 23+0 to 34+0 weeks is the administration of prophylactic antibiotics therapy. This approach aims to treat the infection that supposedly caused the membrane to rupture or prevent a potential infection that can threaten the mother and the fetus. Infection prevention prolongs the latency period, and this is rational in giving them to women with PPROM with an early preterm fetus that needs more time for better chance to survive (42).

There is not one optimal regimen, as many of them proved to provide the desired results and are better than a placebo (6,53). The regimens are usually composed of several antibiotics to cover a broad spectrum of potential pathogens. One widely accepted regimen that the ACOG also adopted was suggested by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial (14). This seven-day regimen is composed of two days of treatment with parenteral 2-grams ampicillin every 6 hours plus 250-milligrams erythromycin every 6 hours, followed by five days of treatment with oral 250-milligram amoxicillin every 8 hours plus 333-milligram erythromycin every 8 hours (14,57). Based on this regimen, some other alternatives were tested and proved to be as efficient as this one. One of them suggests using 1-gram of oral azithromycin once on

admission instead of 7 days of erythromycin. This regimen proved to have the same latency period, the incidence of infections, and neonatal outcomes (58,59) but is easier to administer, has fewer GI side effects, and is cheaper (42,59) and it was also adopted by the ACOG (43). Some guidelines suggest this regimen as the preferred one (42), but others suggest using it only as an alternative when erythromycin is not available, not tolerated, or contraindicated (57,58).

The rationale for using ampicillin and amoxicillin is mainly to eradicate GBS, if present, but also aerobic gram-negative bacilli and anaerobes are targeted by these drugs (42). Erythromycin and azithromycin cover for Chlamydia to prevent neonatal conjunctivitis and pneumonitis and for Mycoplasma and Ureaplasma, which are essential causes of chorioamnionitis (42,60). Animal studies have demonstrated that genital mycoplasma has a role in the pathogenesis of preterm labor. It might explain why erythromycin and azithromycin may be beneficial in prolonging the latency period and reducing the infection and neonatal morbidity (61).

Another alternative suggests using 875-milligram oral amoxicillin every 12 hours instead of 333 milligrams every 8 hours for both the patient's convenience and minimizing GBS colonization if there is one, but efficacy data for this regimen are lacking (42). In addition, there is evidence that adding parenteral clarithromycin can reduce the intra-amniotic inflammatory response in patients with PPROM (62). A very broad-spectrum alternative consisting of clarithromycin, ceftriaxone, and metronidazole was also suggested and proved beneficial (60). It is important to note that the usage of amoxicillin and clavulanic acid combination relates to higher rates of NEC in neonates and should be avoided (53,54). There is a constant need for more studies to determine regimens for prophylactic antibiotics as the sensitivity and resistance are constantly changing (63).

There are no one well-studied treatment alternatives for women allergic to penicillin, and it may be fair to consider replacing penicillin-containing antibiotics with another agent effective against GBS. The severity of the reported

allergic reaction and antibiotic susceptibility results of the GBS culture, if available, will influence the antibiotic choice (64). If the severity of the allergy is of low risk of developing anaphylaxis, in addition to erythromycin/azithromycin, two days of 1-gram parenteral cefazolin every 8 hours replace the ampicillin, and five days of 500-milligram oral cephalexin every 6 hours replace the amoxicillin. If the risk of anaphylaxis is high and GBS culture is susceptible to clindamycin, in addition to erythromycin/azithromycin, two days of 900-milligrams parenteral clindamycin every 8 hours plus 5-milligram per kilogram parenteral gentamicin every 24 hours followed by five days of oral 300-milligrams of clindamycin is suggested. If there is a high risk for anaphylaxis and GBS culture is resistant to clindamycin or the susceptibility is unknown, in addition to erythromycin/azithromycin, two days of 20-milligram per kilogram vancomycin every 8 hours (maximum single dose of 2-grams) is suggested (42).

Outcomes of PPROM with regard to the length of latency

Gestational age proved to be the most crucial determinant of neonatal outcome with PPROM (7). As reviewed in the previous section, the management of PPROM is gestational age guided, and with an early PPROM, expectant management is indicated to prevent adverse neonatal outcomes related to early gestational age (prematurity). Nevertheless, it is less clear whether the length of latency itself impacts the outcome for the neonate (7,9).

Length of latency is defined as the time from spontaneous ROM to delivery (9). Latency tends to be shorter as the gestational age at PPROM is more advanced and the median latency period with PPROM is about 7 days (65–67). Prolonged latency is defined as latency of more than 7 days (7), and this will be the cutoff in this review.

Perinatal outcomes relate both to the mother and the neonate and will be classified as follows: neonatal infectious morbidity, neonatal prematurity morbidity, maternal infectious morbidity, and secondary outcomes. Neonatal infectious morbidity refers to early-onset sepsis, pneumonia, NEC, or infection-related death. Neonatal prematurity morbidity relates to moderate/severe RDS, prematurity-related chronic pulmonary disease, IVH grade 3 and more, periventricular leukomalacia, or prematurity-related death. Maternal infectious morbidity refers to septicemia, endometritis, peritonitis, or infected wound. Secondary outcomes include chorioamnionitis/funisitis (diagnosed clinically or histologically), Apgar score < 7 in five minutes, prolonged stay of the neonate in NICU, and prolonged maternal hospital stay (7,8).

Outcomes of delivery within 7 days versus latency of more than 7 days

For women with PPROM at gestational age 24+0 to 33+6, both neonatal infectious morbidity and prematurity morbidity seem to decrease with latency of more than 7 days compared with any period shorter than that (7–9,67). Frenette et al. also found that longer latency did not show a statistically significant increase in maternal infectious morbidity (8). However, they also found evidence for an increase in the incidence of funisitis and chorioamnionitis with longer latency in the secondary outcomes. Also, a latency period of more than 7 days was found to reduce the time in NICU for the fetus, but a latency of more than 48 hours prolongs the hospital stay for the mother (8). Lorthe et al. found that the rate of fetal and neonatal deaths did not change with the length of latency for these early PPROM cases (9).

Concerning a very long latency period, another study found that latency of more than 28 days is associated with a higher risk of death and morbidity (68). Although the study was conducted on a significant sample and for a period of 15 years, it is

important to note that latencies greater than 28 days are more common in children born after very early PPROM (especially PPROM before 24 weeks), who frequently have the worst outcomes. Moreover, the management was not similar in all the medical centers involved in the study, and it was done between 1997 to 2012, during which protocols were changed (9). All this makes this finding weaker, and there is still a need to determine the length limit for the benefit of a long latency (7).

For women with PPROM at gestational age 34+0 to 36+6, in general, both neonatal infectious morbidity and prematurity morbidity seem to decrease with increased latency period (8,67). Nevertheless, according to Nayot et al., there is a specific increase in the incidence of NEC and a longer NICU stay for the neonate with a latency period longer than 72 hours in these late PPROM cases (67). For secondary outcomes, Frenette et al. found that chorioamnionitis rate increased with latency longer than 24 hours, and funisitis rate increased with latency longer than 48 hours. Moreover, maternal hospital stay was much longer after a latency of more than 48 hours (8).

With all that said about the effect of the latency period on the outcomes, Manuck et al. found the degree of prematurity to be more powerfully correlated with perinatal morbidity than the length of the latency period (7).

Long-term outcomes of a long latency period

Longer latencies were associated with an increased risk of infections such as funisitis and chorioamnionitis in both gestational age groups. Despite this, the increased rates of funisitis and chorioamnionitis did not result in significant immediate neonatal morbidity (8). With that said, long-term outcomes with the potential increase in inflammation after PPROM with long latency is important to relate. Evidence shows that neurological complications can develop because of

intrauterine exposure to inflammation that can alter the development of the brain and its function (7,9,69). This influence may not have an immediate apparent result, as neurological deficits are more evident later in life. A prospective cohort study done in 2007 found no difference in the rate of neurological disorders among infants born after PPROM with a latency period of less than 48 hours and more than 48 hours (70) but without any reference to chorioamnionitis. Freud et al. performed a retrospective cohort analysis to evaluate the association of chorioamnionitis to increased neurological morbidity up to 18 years of age. They found that only cerebral palsy (CP) had a significant and independent association with chorioamnionitis (71). However, another recent retrospective cohort study by Tsamantioti et al. found an increased risk of not only CP but also neurodevelopmental disorders such as autism, attention deficit hyperactivity disorder (ADHD), and intellectual disability (69). This correlates with other studies that also found this association but explained these results as a prematurity consequence (72,73). Tamantioti et al. managed to prove a marked increase in the risk for these adverse neurologic outcomes even among term births (69). If, in fact, inflammation such as chorioamnionitis has this effect on neurological development, the increase in the rate of inflammation with long latency should be part of the assessment while evaluating its benefit.

Discussion

The length of the latency period is less correlated to perinatal morbidity than the degree of prematurity (7), and any finding on the latency period is Inevitably influenced by the gestational age.

Higher levels of neonatal infectious morbidity did not appear to increase with longer latency periods, a consistent finding in several studies that examined the latency period factor (8,74,75). No immediate negative effect of prolonged latency that

could exceed the positive effect of the maturation of the fetus was found (9). It was especially evident in the group of early PPROM (24+0 to 33+6 weeks of gestation), in which the need for latency is not questionable. In the later PPROM group, the benefit of latency is less clear as there are more latency-related complications, according to some of the studies, and fewer complications related to prematurity in these gestational ages (67).

The secondary outcomes in both groups of gestational ages showed an increase in the incidence of chorioamnionitis and funisitis (8). It did not present as an increase in the primary infectious outcomes of the fetus or the mother and is sometimes only a subclinical complication (7,8,67). The effect of this inflammatory process on the fetus seems to appear in the long term, as a connection to adverse neurological outcomes is evident (69,71). The type of adverse neurological outcomes is not identical between studies, but CP seems to have the strongest connection in most studies.

This connection of long latency with potential neurological complications and its less favorable results in the late PPROM group can explain why management protocols for gestational ages between 34+0 to 36+6 suggest both expectant management and delivery induction as options. The decision to delay birth could be viewed as a cost-benefit analysis between the lower morbidity associated with preterm birth and the increased risk of neurological impairment associated with the development of funisitis and chorioamnionitis.

One of the limitations of this review is that the diagnosis of chorioamnionitis is evaluated the same with no regards to the way of diagnosis (clinical or histological), as this variable was not available in most studies (8). This variable may influence the results since the level of inflammation is different in these two entities.

Another limitation of this review is the inherent problem with the assumption that the short and long latency groups are equivalent, and that shorter latency is not caused by any factor that can affect maternal or neonatal morbidity. But in fact,

latency tends to shorten when PPROM is a consequence of preterm labor connected with comorbidities that can influence maternal and neonatal outcomes such as placental issues, infections, Intrauterine growth restriction (IUGR), or preeclampsia (67). Taking this into account, it can provide another explanation for the favorable results of the longer latency group.

On the other hand, the understanding that latency groups are inherently different strengthens the finding that late PPROM is not positively affected by a longer latency period. This is because shorter latencies have better outcomes even though it may relate to comorbidities and despite the advantage of higher gestational age with longer latency (67).

Another strength of this review is the reference to the latency period with regard to the gestational age at PPROM and not at delivery. The existing evidence on the effects of the latency period on perinatal outcomes is sometimes difficult to interpret because studies frequently analyze the latency period according to the gestational age at delivery instead of gestational age at PPROM (8). When considering gestational age at PPROM, the effect of the length of latency period can be better interpreted and practically be used as opposed to gestational age at delivery.

Conclusion

This review found the long latency period to be more beneficial than the short latency period for most of the primary outcomes, especially for the early PPROM group. It is consistent with the management protocols for each PPROM age group and correlated with the gestational age and maturity of the fetus. However, long latency has an increased rate of chorioamnionitis and funisitis, which is related to possible neurological complications in the long term.

With results that show benefit from a long latency period, there is a place to investigate more and try to figure out the optimal length for each gestational age (if there is one) and to set a limit where the latency becomes more hazardous than beneficial. There is also a need to make an additional study about the length of latency that considers the type of chorioamnionitis (histologic or clinical) in order to understand whether there are differences in the long-term outcomes.

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Biography

Noy Aviv was born to Lili and Shmuel on April 28th, 1992, in Tel Aviv, Israel. From 2010 to 2013, Noy served in the Israeli Defense Forces (IDF) medical forces, first as a medic and later as a commander officer of a combat medic course. During 2016-2022, Noy studied medicine at the School of Medicine University of Zagreb, Croatia. During her studies, Noy spent two weeks at SHIBA hospital as a study experience in the departments of Internal medicine. Also, in her 2nd year, she got the dean's award due to her grades.