

# Treatment of pregnant women with preterm premature rupture of membranes in prevention of adverse neurological consequences of a child

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Bracha, Lirose

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**UNIVERSITY OF ZAGREB  
SCHOOL OF MEDICINE**

**Lirose Bracha**

**Treatment of pregnant women with preterm  
premature rupture of membranes in the prevention  
of adverse neurological consequences of a child**

**GRADUATE THESIS**



**ZAGREB, 2022**

This graduation paper was made at The Department of Obstetrics and Gynecology under the supervision of Assistant professor Josip Juras, M.D., Ph.D. It was submitted for evaluation in the academic year 2021/2022.

Graduation paper was made at The Department Obstetrics and Gynecology, University Hospital Centre Zagreb.

Mentor: Assist. prof. Josip Juras, M.D., Ph.D.

## **List of Abbreviations**

ACS -Antenatal corticosteroids

ADHD - Attention deficit/hyperactivity disorder

AFI – Amniotic fluid index

BMI – Body mass index

BPD - Bronchopulmonary dysplasia

CNS – Central nervous system

CP – Cerebral palsy

cPVL – cystic periventricular

leukomalacia

CSF – Cerebrospinal fluid

FM – Fetal membranes

GBS – Group B streptococcus

GMH-IVH - Germinal matrix hemorrhage and intraventricular hemorrhage

IGFBP-1 - Insulin-like growth factor binding protein

IL - Interleukin

IMs – Intracellular mediators

IVH – Intraventricular hemorrhage

MMP – Matrix metalloproteinase

NDI – Neurodevelopmental impairment

NEC – Necrotizing enterocolitis

PAMG-1 - placental -microglobulin 1

PHVD - Posthemorrhagic ventricular dilatation

PIVH - Peri-intraventricular hemorrhage

PPROM – Preterm premature rupture of membranes

PROM – Premature rupture of membranes

PTB – Preterm birth

PVHI – Periventricular hemorrhagic infarction

PVL – Periventricular leukomalacia

RDS – Respiratory distress syndrome

ROM – Rupture of membranes

ROP – Retinopathy of prematurity

ROS – Reactive oxygen species

SES – Socio-economic status

TNF – Tumor necrosis factor

WMD - White matter damage

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## Summary

Preterm premature rupture of membranes (PPROM) occurs in 3% of all pregnancies and is responsible for around one-third of all preterm births, resulting in more frequent perinatal morbidity and fetal death. Generally, complications of PPRM increase in frequency and severity as gestational age decreases. PPRM has been linked to several risk factors, including PPRM in a previous pregnancy, maternal cigarette smoking, and importantly urogenital tract infections, leading to chorioamnionitis. The role of infection and inflammation in the development of PPRM and subsequent adverse neurological outcomes on the child, both short-term and long-term, has been demonstrated and established in the scientific literature. It is therefore crucial to correctly diagnose the pregnant woman presenting with signs and symptoms of PPRM and have a satisfying management plan. Expectant care vs intervention, the use of tocolytics, the duration of antimicrobial prophylaxis, the timing of prenatal corticosteroids, the use of magnesium sulfate, and the timing of delivery are all topics of intense research and controversy in the management of PPRM. Studies show that antibiotic administration increases the period of latency and improves certain short-term neurological outcomes, such as lowering the rate of abnormal cerebral ultrasound scans prior to discharge from the hospital, but it has no effect on perinatal mortality, preterm births, or long-term neurological outcomes. Furthermore, an agreement on the best antibiotic treatment regimen, mode of administration, and duration has yet to be reached. Antenatal corticosteroids improve infant survival and lowers substantial short-term morbidity, but long-term neurodevelopmental disability is still a challenge. The use of tocolytics as a preventive measure for neonatal morbidity and mortality is still controversial and research on this approach has not been sufficient. There is evidence that the use of Magnesium sulfate is beneficial in terms of neuroprotection and prevention of adverse neurological outcomes. Ultimately, a universal approach to the management of PPRM has yet to be agreed upon by clinicians. Larger-scale, better quality, and more up to date research is still required in order to find the optimal clinical management protocol.

Keywords: Preterm premature rupture of membranes, antibiotics, corticosteroids, tocolytics, neuroprotection, neurological outcomes



## Sažetak

Prijevremeno prsnuće plodovih ovoja prije termina (PPROM) javlja se u 3% svih trudnoća i odgovorno je za otprilike jednu trećinu svih prijevremenih porođaja, što rezultira češćim perinatalnim morbiditetom i fetalnom smrću. Općenito, komplikacije PPRM-a češće su i teže što je gestacijska dob manja. PPRM je povezan s nekoliko čimbenika rizika, uključujući PPRM u prethodnoj trudnoći, pušenje cigareta majke I, možda najvažnije, infekcije urogenitalnog trakta koje dovode do korioamnionitisa. U znanstvenoj je literaturi dokazana i utvrđena uloga infekcije i upale u nastanku PPRM-a i naknadnih nepovoljnih neuroloških ishoda na dijete, kratkoročnih i dugoročnih. Stoga su ispravni dijagnostički postupak u trudnice sa znakovima i simptomima PPRM-a te zadovoljavajući plan liječenja od velike važnosti. Ekspektativan postupak naspram intervencije, uporaba tokolitika, trajanje antimikrobne profilakse, vrijeme primjene kortikosteroida prenatalno, uporaba magnezijevog sulfata i vrijeme porođaja teme su intenzivnog istraživanja i kontroverzi u skrbi za trudnice s PPRM-om. Istraživanja pokazuju da primjena antibiotika povećava razdoblje latencije i poboljšava određene kratkoročne neurološke ishode, kao što je smanjenje stope abnormalnih cerebralnih ultrazvučnih pretraga prije otpusta iz bolnice, ali nema utjecaja na perinatalnu smrtnost, učestalost prijevremenih porođaja ili dugoročne neurološke ishode djeteta. Nadalje, dogovor o najboljem režimu liječenja antibioticima, načinu primjene i trajanju tek treba postići. Antenatalni kortikosteroidi poboljšavaju preživljavanje novorođenčadi, ali dugoročne posljedice na neurološki razvoj i dalje je izazov. Korištenje tokolitika kao preventivne mjere za smanjenje neonatalnog morbiditeta i mortaliteta još je uvijek kontroveržno i istraživanja o ovom pristupu nisu bila dovoljna za jasan zaključak. Postoje dokazi da uporaba magnezijevog sulfata djeluje neuroprotektivno. U konačnici, kliničari se tek trebaju dogovoriti o univerzalnom pristupu pri PPRM-u. Još uvijek su potrebna veća i kvalitetnija istraživanja kako bi se pronašao optimalni protokol kliničkog odlučivanja.

Ključne riječi: prijevremeno prsnuće plodovih ovoja prije termina, antibiotici, kortikosteroidi, tokoliza, neuroprotekcija, neurološki ishod

## **1. Introduction**

### **1.1. Preterm premature rupture of membranes**

The term "preterm premature rupture of membranes" refers to PROM that occurs before 37 weeks of pregnancy. (1) Premature rupture of membranes is defined as fetal membrane rupture and amniotic fluid release that occurs more than 1 hour before the commencement of uterine contractions. (2) PPRM is a cause of spontaneous premature birth, similar to preterm labor and cervical insufficiency. Regardless of the gestational age, both term and preterm PROM are associated with a period of latency, which may increase the risk of complications such as perinatal infections and umbilical cord compression, the latter occurs as a result of oligohydramnios. (3) For those reasons, PPRM constitutes an important cause of morbidity and mortality in neonates.

The risk and severity of complications arising from PPRM depend on gestational age, and generally decrease with increasing gestational age. (4) For PROM at term with no associated infection or asphyxia, the neonate's risk of severe adverse outcomes is low. (3) Despite the possibility of complications, birth between 32 and 36 weeks of pregnancy is generally associated with good newborn outcomes, especially if the fetus has demonstrated pulmonary maturity. (3) In contrast, the risk of complications significantly increases with decreasing gestational age. The risk of neonatal complications and morbidities is particularly high with early delivery following preterm PROM at 23 to 30 weeks' gestation. (5) Survival is possible when PROM occurs between 24-weeks to 26-weeks' gestation provided adequate intervention, albeit the morbidities of extreme prematurity are more severe in this group of newborns. (6) With immediate delivery and without medical intervention, neonatal mortality is highly likely when PROM develops before the limit of viability. (7)

### **1.2. Epidemiology**

Approximately 12% of all pregnancies are affected by PROM. (1) PROM occurs in roughly 8% to 10% of term pregnancies (37 weeks or more gestational age) and is usually followed by the start of labor. (3) Preterm births can also be classified by gestational age: about 5% of preterm births occur at less than 28 weeks' gestation (extreme prematurity), 15% at 28–31 weeks' gestation (severe prematurity), 20% at 32–33 weeks' gestation (moderate prematurity), and 60–70% at 34–36 weeks' gestation (moderate prematurity). (8) Preterm PROM is a primary cause

of newborn morbidity and mortality, accounting for roughly 32%-40% of preterm births. (9) The prevalence of PPROM varies, which is due to differences in the populations studied. When it comes to weeks of pregnancy, it affects 0.5 percent of pregnancies before the 27th week, 1% of pregnancies between 27 to 34 weeks' gestation, and 1% of pregnancies between 34 to 37 weeks' gestation. (10) PPROM is one of the most common causes of premature delivery, accounting for 18% to 20% of perinatal fatalities in the United States and 30-40% of preterm deliveries in Oman and Iran. (11) Preterm rupture of membranes is responsible for about 30% of preterm births in Egypt (11), and 26.6% of preterm births in India. (12)

### **1.3. Risk factors**

The occurrence of preterm PROM has been linked to a number of risk factors. Low socioeconomic status, uterine overdistension, second-and third-trimester bleeding, low body mass index (BMI), copper and ascorbic acid nutritional deficiencies, maternal cigarette smoking, cervical conization or cerclage, pulmonary disease in pregnancy, connective tissue disorders (e.g., Ehlers-Danlos syndrome), and preterm labor or symptomatic contractions in the current pregnancy are just a few of them. (3)

Prior PTB, particularly preterm PROM (PPROM), has been linked to PPROM in subsequent pregnancies. (5) The chance of recurrence increases as the index PTB's gestational age decreases. Those who have had a previous delivery near the limit of viability (23–27 weeks) have a 27.1 percent chance of having PTB again. (13) Those who have had PTB owing to PROM in the past have a 3.3-fold higher risk of PTB due to PROM (13.5% vs. 4.1%) and a 13.5-fold higher risk of PPROM before 28 weeks' gestation (1.8% vs. 0.13%) in subsequent pregnancies. (13)

Infections of the urogenital tract have also been connected to preterm PROM. (2) Preterm PROM has been linked to *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* (14), as well as *Ureaplasma urealyticum*, *Sneathia* species, *Escherichia coli*, *Mycoplasma hominis*, *Enterococcus faecalis*, and *Gardnerella vaginalis*. (15) Although vaginal colonization with group B-hemolytic *Streptococcus* (GBS) does not appear to be linked to preterm PROM, cervical colonization appears to be. (16) Preterm PROM and low-birthweight neonates are linked to GBS bacteriuria. (16)

In both nulliparas and multiparas, a short cervical length (25 mm) determined by transvaginal ultrasound and a low maternal BMI (19.8 kg/m<sup>2</sup>) were linked to an elevated risk of later PROM. (3) Mercer et al has also shown that short cervical length is associated with a higher risk of premature birth in women with PPRM. (13) Nulliparas with a 25-mm shorter cervix had a 3.7-fold higher risk, while multiparas had a 3.1-fold higher risk. (9)

Additionally, it has been shown that black race is strongly related to an increased risk of PTB at fewer than 35 weeks of pregnancy due to PPRM, even after adjusting for SES and maternal medical risk variables. (17)

Ultimately, no single risk factor has been associated with all cases of PPRM. (7) In many situations, it is likely that a combination of variables, including a maternal genetic or physiologic predisposition, work together to lead to PPRM. (7)

## **1.4. Pathogenesis**

The development of PPRM is complex and not completely understood. Several mechanisms of disease development have been studied and demonstrated.

Focal infection and inflammation may play a primary or secondary role in the etiology of PPRM, according to histological (evidence of inflammatory processes in close proximity to point of membrane rupture) and microbiological results. (18) Inflammatory mediators are involved in the destruction of the fetal membranes' integrity as well as the activation of uterine contractility. In reaction to a pathogen's invasion, they are created as part of the physiologic maternal defense process. FM thinning and apoptosis are facilitated by reactive oxygen species and intracellular mediators (IMs) such as prostaglandins, cytokines, and proteinases. (19)(20)

It is important to note that the fetal membranes serve as a mechanical and immunological barrier as well as a microbiological barrier. (18) Microbial invasion from the genital tract, activation of the host inflammatory response, collagenolysis-mediated mechanical disruption, and membrane weakening predispose the membranes to PPRM. (21)(22). These are all made possible when the immunological and mechanical aspects of the fetal membranes are compromised.

The structure and collagen content of fetal membranes have also been subject to study to assess the association between differences or deficiencies in certain types of collagen and the

development of PPRM. One study showed that the tensile strength of the chorioamniotic membranes would be reduced if type III collagen (which serves as support inside the extracellular matrix of the membranes) was deficient. (9). Other studies have shown that a decrease in total collagen content of amnions was also seen in patients with PROM at various gestational ages. (4), (9)

PPROM is linked with significant edema and disruption of the collagen network within the compact, fibroblast and spongy layers. (19) MMP-1, MMP-8, and MMP-9 are enzymes that have been linked to the mechanisms of membrane rupture, with several studies providing supportive evidence. (19) (23) (24) Although the exact trigger secreted by chorioamniotic cells to induce MMP-9 expression is unknown, bacterial products and/or pro-inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF-alpha), may act as paracrine or autocrine signals for these metalloproteases in pregnancies complicated by intra-amniotic infection. (21) Mechanical stress also plays a role in the pathogenesis of PPRM. At term, fetal membranes have a weak zone overlying the cervix that demonstrates enhanced collagen remodeling and apoptosis. Preterm FM has a weak region as well but is overall stronger than term FM. (19) A variety of genes associated with apoptosis and MMP activity are induced by stretch pressures, including acute stretch. (25) The separation of the amnion from the choriodecidua happens as part of the FM rupture process. (26) One suggested mechanism for the accelerated degradation rate of FM collagen is that the enzymatic breakdown of a specific collagen molecule creates residual stress in the tissue, which must be transferred to nearby molecules, which may subsequently rupture. (26)

Another pathological process proposed as a contributor to the development of PPRM is oxidative stress. A steady redox balance between reactive oxygen species (ROS) and antioxidants characterizes healthy pregnancy, as it does other physiological states. (27) PPRM-related behavioral risk factors, mainly cigarette smoking, produce a number of ROS, which can disrupt the redox balance, damage the collagen matrix, and deplete antioxidant defenses. (18) Collagen has been identified as a main target for reactive oxygen species (ROS). ROS can activate collagenolytic enzymes such as MMP9, which is suppressed by the antioxidants Superoxide dismutase and N-acetylcysteine (a Glutathione precursor). (28) These reactions are triggered by exposures that have significant biochemical repercussions and can lower the membrane rupture threshold. (18)(27)

## **1.5. Clinical picture and diagnosis**

Patients often describe a "gush" of fluid, while others have a history of small quantities of fluid leaking over time. Urinary leakage is prevalent during pregnancy, especially at the end, and it's easy to confuse it with PROM. Similarly, increased vaginal secretions and perineal dampness (especially in warmer temperatures) may be misinterpreted for amniotic fluid during pregnancy. (1) Patient history is a crucial component in the diagnosis of PPRM. It has a 90% accuracy rate and should not be overlooked. (2)

Examination should be done in such a way that the risk of infection is as low as possible. (29) A sterile speculum should be used to examine the cervix and vagina for patients who are not in active labor. (30) Digital cervical examination should be avoided due to the risk of shortened latency period and subsequent intrauterine infections. (29)

The Nitrazine test can be used to differentiate amniotic fluid from urine and vaginal secretions in the diagnosis of PPRM. (1) The presence of Nitrazine-positive fluid ( $\text{pH} > 6$ ) flowing from the cervix is diagnostic in the setting of questionable clinical history. If the sterile speculum examination is ambiguous, a sterile swab can be used to capture a specimen from the posterior fornix of the vagina. (7)

The ferning test is another diagnostic tool used to differentiate amniotic fluid from other vaginal secretions. If there is contamination with cervical mucous, the ferning test may be falsely positive (generally non-branching arborization). With prolonged leakage and minimal residual fluid, false-negative visual examination, ferning, or Nitrazine testing can occur. (7)

If a diagnosis is suspected but not confirmed clinically, an ultrasound examination should be conducted. (1,7) With ultrasound-guided amnioinfusion of indigo carmine, the diagnosis can be made unambiguously (1 mL in 9 mL of sterile normal saline). The passage of blue fluid through the vaginal canal and onto a perineal pad confirms the diagnosis. (1,7,29) Although this diagnostic method is considered an "unequivocal" diagnostic method for confirmation of membrane rupture, this invasive test carries a higher maternal and fetal risks for trauma, bleeding, infection, and preterm labour. (31)

If pooling is not observed but clinical suspicion still exists, another approach to confirming PPRM with ultrasound is measuring the volume of amniotic fluid. Oligohydramnios (as measured by amniotic fluid index (AFI) of 5 cm, maximum vertical pocket of 2 cm, of

subjective impression) is satisfying evidence of PROM and additional diagnostic tests are not required. (30)

A meta-analysis in 2013 compared the performance of two commercially available tests for the diagnosis of PROM; The AmniSure ® ROM Test (AmniSure ® International LLC, Boston, MA, USA) which is based on the detection of placental -microglobulin 1 (PAMG-1), and the Actim ® Prom Test (Oy Medix Biochemica Ab, Kauniainen, Finland) which is based on the detection of insulin-like growth factor binding protein (IGFBP-1). (32) When the researchers evaluated the sensitivity and diagnostic odds ratio for the IGFBP-1 test between known membrane status vs unknown membrane status at presentation, they discovered that patients with unknown membrane status had lower sensitivity and diagnostic odds ratio than those with known membrane status. This finding has practical relevance because the only clinically relevant population to screen in obstetrical care is women whose membrane status is not clear at the time of presentation. The PAMG-1 test outperformed the IGFBP-1 test in terms of sensitivity, specificity, and diagnostic odds ratio for patients suspected of having ROM but whose membrane status was unknown at the time of entry into the research. (32)

## **2. Neurological outcomes**

The immature brain goes through multiple important stages of CNS development during the perinatal period, and immune system activation during fetal and neonatal life influences vital stages of brain development, with long-term implications for neurological and mental health. (33) The role of inflammation and infection in adverse neurological outcomes has been extensively investigated in an attempt to find a causal relationship between the two. It has been proposed that inflammation can have a priming effect (sensitization or preconditioning) and play a role in both early and late injury, as well as repair and recovery following an insult. (34) Furthermore, in the absence of infection, long-term or intermittent systemic inflammation may be more harmful to the brain than short-term inflammation (such as is seen in infectious diseases). (35) Increased levels of IL-6, IL-8, and IL-1 in the CSF accompany neonatal encephalopathy (36), and elevated levels of these cytokines in the CSF and blood are linked to poor neurological outcomes. (37) Increased levels of various cytokines in the newborn blood at term are also substantially linked to the risk of cerebral palsy. However, it's unclear whether

inflammation is a result or a cause of the encephalopathy and neurodevelopmental complications. (38)

Some clinical studies have provided more clearance on the significance of previous infection in eventual brain injury, such as cerebral palsy. (34) A chart review of children with moderate to severe spastic or dyskinetic cerebral palsy assessed the association between clinical chorioamnionitis and cerebral palsy risk in a case–control study from the Kaiser Permanente Medical Care Program. In term infants, chorioamnionitis or placental infection was linked to a fourfold greater risk of cerebral palsy. (39)

Intraventricular hemorrhage (IVH), periventricular hemorrhagic infarction (PVHI), and periventricular leukomalacia (PVL) are among the neurological complications linked to poor neonatal outcomes. (40) Other neurological outcomes that have been associated with prematurity are Cerebral palsy, and Retinopathy of prematurity. Complications are more likely to occur when the gestational age and birth weight decrease. (41,42) Neurological outcomes can be reviewed from the perspective of short-term and long-term outcomes.

## **2.1. Short term neurological outcomes**

Premature babies are likely to experience short-term adverse clinical consequences as a result of anatomic or functional immaturity during the neonatal period. In the preterm infant, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and brain abnormalities (eg, intraventricular hemorrhage [IVH] and periventricular leukomalacia) are all prevalent short-term consequences, with varying rates of occurrence depending on gestational age and birth weight. (42)

GMH-IVH (germinal matrix hemorrhage and intraventricular hemorrhage) is still an important cause of brain damage in premature babies. (43) GMH-IVH has a deleterious influence on neurodevelopmental outcome due to both direct and indirect effects, including posthemorrhagic ventricular dilatation (PHVD) and white matter damage (WMD). (44) Despite advances in newborn intensive care over the previous few decades, IVH morbidity has not decreased, owing to a considerable increase in premature neonate survival rates. (45) Mild (grades I and II) and severe IVH (grades III and IV) are both linked to a high likelihood of moderate-severe neurodevelopmental damage in survivors. (45,46) Previous research has revealed that inflammatory mediators may contribute to the development of IVH by increasing



cerebral oxygen consumption (47), breaking down brain barriers (48), and activating the immune system. (49) In addition to the impact of inflammatory factors, infection-induced changes in cerebral blood pressure may contribute to the development of IVH. Premature newborns lack a fully developed cerebral blood pressure autoregulation function. (50) A metaanalysis in 2019 studied the relationship between antenatal infection and IVH in preterm infants. Antenatal infection increased the risk of IVH in preterm newborns (OR 2.18, 95 CI 1.58–2.99), according to the findings of 23 cohort studies involving 13605 infants. Antenatal infection raised the risk of both mild (OR 1.95, 95% CI 1.09–3.49) and severe IVH (OR 2.65, 95% CI 1.52–4.61) compared to no infection. The researchers suggested that both histologic and clinical chorioamnionitis increase the risk of developing IVH, and that their emphasis on this etiological factor may be beneficial in the prevention of this common short-term complication. (51) The diagnosis of IVH and associated sequelae is made possible by cranial ultrasonography screening, with up to half of all cases being asymptomatic. (52) Almost all instances of IVH in preterm newborns occur within the first five days of life, (52) with around half of cases in very low birth weight infants happening within the first six hours. (53) For these reasons, the American Academy of Neurology and the Child Neurology Society's Pediatric Committee recommend that routine cranial ultrasound screening be performed between 7 and 14 days of age on all infants born at less than 30 weeks of gestation, or greater than 30 weeks of gestation with any clinical suspicion of IVH, and repeated at 36 to 40 weeks of postmenstrual age. (54)

Periventricular hemorrhagic infarction (PVHI- grade IV IVH previously) is produced by infarction due to poor venous drainage of the medullary veins in the white matter. (55) Doppler ultrasound shows that the circulatory disruption occurs in the subependymal region, where the medullary veins drain into the terminal vein. (43) PVHI can destroy motor and associative white matter axons and evolve into a single or many cysts that can become confluent with the lateral ventricle, depending on the location of the lesion. (52) Cerebral palsy with spastic hemiparesis in about half of the infants or an asymmetric spastic quadriparesis in the majority of infants with bilateral involvement are the clinical manifestations of PVHI. (43) In 2019, a retrospective multicenter observational cohort study on the characteristic sonographic findings of PVHI and their association with neurodevelopmental outcomes suggested that a thorough examination of the sonographic features of PVHI, combining the severity score with lesion size and trigone involvement, can improve the potential for early prognostication of neurodevelopmental outcomes in very preterm infants, particularly gross motor outcome and

cerebral palsy. The researchers concluded that more research is needed to better understand the underlying mechanisms of PVHI so that early intervention strategies, prevention, and family counseling can be developed. (55)

Periventricular leukomalacia (PVL) is a type of cerebral white matter injury that occurs in a specific pattern and includes periventricular localized necrosis with cystic development, as well as more diffuse cerebral white matter injury. (56) PVL, like IVH, has an underlying etiology in the developing cerebral vasculature and cerebrovascular autoregulation system. (50) Preterm newborns are unable to enhance cerebral perfusion to border zone regions of the brain supplied by the immature penetrating cerebral vasculature in response to systemic hypotension. This triggers the hypoxia–ischemia cascade, which results in brain damage, which is amplified by chorioamnionitis. (57) White matter volume loss and ventriculomegaly result from a decrease of premyelinating oligodendrocytes and an increase in hypertrophic astrocytes. (58) White matter alterations may not be visible on the first ultrasound and may not be discovered until a follow-up ultrasound or MRI. At 6 weeks of age, cranial ultrasonography detects PVL in approximately 10% of very low birthweight newborns. (57) Infants diagnosed with PVL are at risk for developing spastic quadriplegia or diplegia, a type of CP that affects the lower extremities more than the upper extremities. (58) A systematic review and meta-analysis in 2019 researched the way PVL and PIVH (peri-intraventricular hemorrhage) affected the incidence of cerebral palsy, sensorineural dysfunction, and developmental scores in preterm newborns. They found that when PVL was the assessed exposure, preterm infants were at increased risk of developing CP in both cystic and non-cystic white matter abnormalities, with higher evidence for cystic PVL. (59)

A study performed in Zurich University Hospital's obstetrics department claimed that the single most important prenatally accessible risk factor for the development of cystic periventricular leukomalacia (cPVL) is the PPRM-delivery interval. Babies with chorioamnionitis benefit from immediate delivery. Fetal weight gain may mitigate the inflammatory risk of cPVL induced by a prolonged PPRM-delivery delay in the absence of clinical chorioamnionitis. (60)

## **2.2. Long-term neurological outcomes**

There is a high rate of long-term neurodevelopmental impairment (NDI) and chronic health problems among preterm survivors. (41) When examined at 18 to 24 months corrected age, around 15 to 25% of surviving extremely preterm newborns have serious disability (ie, severe NDI), defined as significant cognitive and/or motor impairment (10%-15%); Cerebral palsy (CP) accounts for 6 to 12 percent of the population; Hearing loss that necessitates the use of amplification equipment (1% to 3%); and blindness (1% to 2% of the population). (61)

Multiple mechanisms, including hypoxia and toxic damage by bacterial products, may contribute to neurodevelopmental impairment associated with intraamniotic infection (clinical chorioamnionitis). The majority of research have revealed that intraamniotic infection can cause long-term impairments such as neurodevelopmental delay and cerebral palsy, especially at or near term, but also at extremely preterm gestational ages. (62) Prematurity (78%), intrauterine growth restriction (34%), intrauterine infection (28%), antepartum hemorrhage (27%), and multiple gestation (20%) were the most common clinical factors or pathologies associated with CP in a cohort review of 235 children diagnosed with CP between 1986 and 2003. (63)

A longitudinal observational study assessed the neonatal and neurodevelopmental outcomes of three groups of infants with increasing perinatal inflammatory exposure: no chorioamnionitis, histological chorioamnionitis alone, or histological plus clinical chorioamnionitis. When compared to no chorioamnionitis, histological plus clinical chorioamnionitis was linked to a higher risk of cognitive impairment. When compared to histological plus clinical chorioamnionitis, histological chorioamnionitis was linked with a lower risk of death/neurodevelopmental disability. (64)

In a meta-analysis of the relationship between chorioamnionitis and cerebral palsy, cerebral palsy was linked to both clinical and histologic chorioamnionitis. However, many possible biases, such as discrepancies in definitions between studies, the amount of blinding in establishing exposure status, and whether the study adjusted for relevant confounders, hampered this analysis. (65) A secondary study of data from 1574 babies of patients at high risk for preterm birth (32 weeks) who were recruited in one clinical trial found a link between neurocognitive abnormalities at two years of age and verified neonatal sepsis, but not with clinical chorioamnionitis. (66)

The EPIPAGE-2 research from 2011 is a national cohort study that looked at outcomes and changes in outcomes for infants born between 22 and 34 weeks of pregnancy over 15 years. Between 1997 and 2011, researchers found improvements in survival without neuromotor impairments in each gestational age group in our national population-based cohort of preterm neonates. Even among infants delivered relatively preterm, there was a statistically significant decrease in the likelihood of cerebral palsy, but the risk of developmental delay was considerable. (67)

Preterm birth prevention, antenatal corticosteroid therapy, and delayed umbilical cord clamping have all been suggested to minimize the risk of prematurity, IVH, and PVL, all of which are linked to an increased chance of later developing CP. These measures, however, have not reduced the overall incidence of CP because only a small fraction of CP cases are seen in infants delivered at fewer than 32 weeks of gestation. (58)

### **3. Management**

The approach to the management of PPROM is one of the most controversial subjects in perinatal medicine, as many factors may affect treatment and outcome. (68) After accurately diagnosing PPROM, an assessment of several maternal and fetal conditions should be made. These include gestational age, fetal presentation, and fetal well-being, as well as evidence of intrauterine infection, abruptio placentae, and fetal compromise. (69) The issues under extensive research and debate in relation to the management of PPROM include expectant management versus intervention, use of tocolytics, duration of administration of antibiotic prophylaxis, the timing of administration of antenatal corticosteroids, and timing of delivery. (68) Depending on the factors noted above, the most important decision is whether to induce labor (or perform a cesarean delivery) or to manage the patient expectantly. (68) The management of PPROM can primarily be reviewed in the context of gestational age.

#### **3.1. Treatment of PROM before and at the limit of viability**

Premature rupture of the fetal membranes (PROM) before or at the limit of viability is associated with a relatively poor prognosis, as it has been linked to significant morbidity and mortality. The limit of viability is defined as the earliest stage of fetal maturity at which there is a reasonable chance, but not a high probability, of extrauterine survival, which is roughly before 23 weeks of gestation. (70) Up to 14% of pregnant women who have spontaneous

PROM before or at the limit of viability eventually stop leaking amniotic fluid, owing to the fetal membranes resealing, and the outcomes of this subset of pregnancies are comparable to those of pregnancies without rupture of membranes. (70) Pregnancies complicated by ROM before or at the limit of viability that do not achieve resealing of the membranes progress into a latency period or preterm birth. The majority of pregnancies complicated by PROM before or at the limit of viability deliver shortly after presentation; around half of the patients remain pregnant after the first week of rupture, and the average latency for pregnancies that do not deliver within the first 24 hours is 10 to 14 days. (70,71)

The ideal approach to treatment of pregnancies complicated with previable PPROM is still a matter of debate in the field of obstetrics. Management differs according to patient wishes and expectations, gestational age, fetal and maternal conditions, and can be more or less aggressive depending on desired and expected outcomes and prognosis.

Most individuals who are stable with PROM before viability and opt to carry their pregnancies to term are not admitted to the hospital and are not given prenatal corticosteroids or tocolytics, but a rectovaginal group B Streptococcus (GBS) culture is collected. (72) As early as 20 weeks of pregnancy, antibiotic prophylaxis may be recommended. (70,72)

Those who are treated as outpatients and reach the limit of viability, typically 23 weeks of gestation, are admitted to the hospital for further treatment. (72) Antenatal corticosteroids and latency antibiotics are primarily administered for fetal maturation when there is a high chance of early delivery. (19,72) Magnesium sulfate for neuroprotection may be recommended once the limit of viability is reached and there's a good chance of delivery. (10,72)

More aggressive intervention at this stage is still controversial and under investigation. Several studies support amnioinfusion for treating PROM before or at the limit of viability, however, this procedure has not been shown to restore adequate amounts of amniotic fluid due to continuous leakage, and its benefit might be more related to the elimination of inflammatory material and bacteria, and inhibition of ascending transcervical infection. (71,73,74)

Over the last two decades, a variety of treatments for sealing both iatrogenic and spontaneously ruptured membranes have been used, including platelet injection with cryoprecipitate ('amniopatch'), gelatin sponges, collagen plugs, and intracervical fibrin sealants. Several studies have provided results on the use of fibrin sealants in small groups of women with preterm PROM. However, these case studies used varied methodologies, enrolled patients at

different gestational ages, and had variable success criteria, making them difficult to compare and pool. (75) One study attempted fibrin adhesion in 26 women with preterm PROM between the ages of 18 and 36 weeks of pregnancy. The pregnancies lasted 3 to 172 days after the sealant was applied, with no evidence of intrauterine infection. The perinatal mortality rate, however, remained high. Unfortunately, because there was no control group in this trial, the technique's efficacy could not be determined. (76)

Quintero presented the first successful amniopatch case in 1999, which involved the intraamniotic injection of platelets and cryoprecipitate. While the exact mechanism of action is unknown, platelet activation at the site of rupture is thought to produce adhesion to damaged areas and the creation of an aggregate. (77) The treatment, while sometimes successful, has been linked to unexpected fetal death and should be considered experimental. (70)

A Cochrane systematic review published in 2016 compared the effects of different sealing procedures used after PPRM with conventional care (no sealant) on maternal and newborn outcomes. The review included two studies involving 141 women. The authors concluded that there was insufficient evidence to evaluate preterm prelabour membrane rupture sealing techniques. This review emphasizes the lack of prospective randomized studies in this field. Future research efforts should focus on conducting randomized trials to test the effect of promising therapies that have only been studied in cohort studies so far, according to the authors. (78)

There is no consensus regarding the management of cervical cerclage in the setting of PPRM. (71,72) One fear is that removing the foreign body will result in an earlier birth; yet, keeping it in place increases the risk of infection, which can lead to premature birth and mother and infant morbidity. (79) One study concluded that the treatment of pPRM in the presence of a cervical cerclage can be tailored to the patient's specific needs, and cerclage removal is not required to prevent infant infections or death. (80)

### **3.2. Treatment of PROM from 24 to 33 weeks of gestation**

In the case of PPRM in the early preterm fetus (ie, <34+0 weeks) and in the absence of obstetric complications, expectant management is thought to benefit the fetus by increasing the gestational age at birth and therefore reducing complications related to prematurity. (68,72,81) This benefit should be carefully weighed against the well-established risks of the latency period

when managing PPROM expectantly, such as maternofetal infection, abruptio placentae, cord prolapse, and intrauterine death. (4,7,81)

Women with a high risk of preterm labor may benefit from prolonged hospitalization in a tertiary center and other preterm labor management options, so it's critical to identify women who will deliver within one week of ROM, especially in the setting of intrauterine infection, placental abruption, or nonreassuring fetal testing. (68,82)

Women with PPROM should have their vital signs, including pulse, blood pressure, respiration rate, and temperature, documented if they are being treated as an inpatient, and clinical symptoms and indicators of infection should also be monitored. (83) To identify clinical infection with chorioamnionitis, the National Institute for Health and Care excellence advises utilizing a combination of clinical examination (pulse, blood pressure, temperature, and symptoms), maternal blood tests (C-reactive protein and white cell count), and cardiotocography to measure fetal heart rate. If the results of the clinical evaluation or any of the tests do not correlate, the patient should be monitored further and the tests should be repeated. (84)

The use of antenatal corticosteroids is standard obstetrical practice for all pregnant patients between 23+0 and 33+6 weeks of gestation who are at an increased risk of preterm delivery within the next seven days, in accordance with nearly all guidelines. (19,72,85) ACS improves neonatal survival and reduces major short-term morbidity at this gestational age, but long-term neurodevelopmental issues remain a concern. (85) One review compared the effects of betamethasone and dexamethasone in the management of preterm birth, and found that when compared to the betamethasone group, dexamethasone reduced the risk of intraventricular hemorrhage (IVH); For RDS and periventricular leukomalacia, there were no statistically significant differences between those who were given dexamethasone or betamethasone. (86)

In Finland, a population-based retrospective cohort study investigated whether antenatal corticosteroid treatment is linked to mental and behavioral issues in children delivered at term (>37 weeks 0 days' gestation) and preterm (37 weeks 0 days' gestation). Attention deficit/hyperactivity disorder (ADHD) or conduct disorder, emotional disorders, social functioning difficulties, and tic disorders were among the disorders studied. The cumulative incidence of mental and behavioral abnormalities was significantly higher among preterm children who were exposed than those who were not (14.6% versus 10.7%), although the hazard ratio did not achieve statistical significance (adjusted HR 1.0, 95 percent CI 0.92-1.09). This

indicates that the short-term benefits of ACS exposure in preterm babies are outweighed by the long-term hazards. (87)

One meta-analysis conducted in 2019 investigated the effects of repeat doses of prenatal corticosteroids and concluded that after an initial course of prenatal corticosteroids, women at continued risk of preterm birth who were given repeat doses had a reduced the likelihood of their baby needing respiratory support after birth and resulted in neonatal benefits. (88) The researchers also showed that there were no differences in neurodevelopment between those who were exposed to repeated prenatal corticosteroids and those who were not, yet found a more significant decrease in birth weight, and suggested that the number of repeat treatment courses should be limited to three at most, and the total dose should be between 24 mg and 48 mg, to provide clinical benefit with the least effect on growth. (85,88)

It is well established that broad-spectrum antibiotics prolong pregnancy, reduce maternal and neonatal infections, and reduce morbidity associated with gestational age. (72,89,90) One theory proposed that perinatal antibiotic prescriptions could prevent neurological and respiratory disabilities through one of two mechanisms: either extending pregnancy or preventing or eliminating infection, or both. (91)

However, a consensus regarding the ideal regimen, route of administration, and duration of antibiotic treatment has yet to be achieved since several regimens have been demonstrated to be beneficial. (68) Antibiotics have a generic impact, however there may be variances in the actions of different antibiotics in theory. For example, macrolide antibiotics like clindamycin and erythromycin, which diminish bacterial virulence, may be preferable to beta-lactam antibiotics like co-amoxiclav and cephalosporins, which generate endotoxins and prostaglandins, potentially worsening results. (92) In 2013, a systematic review examined the effects of giving antibiotics to women who had preterm rupture of membranes on fetal and neonatal morbidity and mortality, maternal infectious morbidity and mortality, and long-term childhood development. (93) The review included 22 trials with a total of 6872 women and their babies. The review found that compared with placebo/no treatment, there was a significant reduction in the number of newborns with an abnormal cerebral ultrasound before leaving the hospital (RR 0.81, 95% CI 0.68-0.98). Antibiotics were also linked to a statistically significant reduction in chorioamnionitis after preterm rupture of membranes (RR 0.66, 95% CI 0.46-0.96). The researchers concluded that antibiotics prescribed routinely to women with preterm rupture of membranes are linked to prolongation of pregnancy and improvements in a number of short-



term neonatal morbidities, but not to a significant reduction in perinatal mortality. Finally, they stated that despite not having a clear choice of antibiotic treatment, co-amoxiclav should be avoided in women diagnosed with PPROM due to a higher risk of neonatal necrotizing enterocolitis.

The use of erythromycin (with or without co-amoxiclav) was linked to a statistically significant increase in the proportion of children with any level of functional impairment, rising from 38% to 42%. Similarly, erythromycin caused a statistically significant increase in the proportion of children with cerebral palsy, from 1.7 percent to 3.3 percent, and co-amoxiclav caused a statistically significant increase in the proportion of children with cerebral palsy, from 1.9 percent to 3.2 percent. It was suggested that more cerebral palsy-affected children were born to mothers who had taken both antibiotics. In light of these findings, it's critical to be certain that a ruptured membranes diagnosis is correct before prescribing antibiotics. (93,94)

One retrospective study in 2015 claimed that preterm PROM can be caused by anaerobes and genital mycoplasmas, which are not well covered by antibiotics commonly used in clinical practice. (95) The goal of this study was to evaluate the results of PROM treated with commonly prescribed antibiotics vs a novel antibiotic combination that was more effective against these pathogens. They found that in patients with PPROM, a regimen consisting of ceftriaxone, clarithromycin, and metronidazole was associated with a significantly longer latency period and lower rates of spontaneous preterm delivery within 7 days, lower rates of acute histologic chorioamnionitis and funisitis, and lower rates of IVH and CP when compared to a regimen consisting primarily of ampicillin and/or cephalosporins. The findings of this study warrant more research to determine the best antimicrobial strategy and treatment duration in patients with preterm PROM.

A network meta-analysis of randomized controlled trials in 2019 intended to examine the efficacy of various antibiotic regimens on perinatal outcomes and to assess the present evidence's quality. (96) The researchers showed that clindamycin+gentamycin, penicillin, ampicillin/sulbactam+amoxicillin/clavulanic acid, and erythromycin+ampicillin+amoxycillin were found to be superior to placebo/no treatment in avoiding chorioamnionitis, in order of decreasing effect. They claimed that the reported protective effect of certain antibiotics on RDS and IVH can be attributed in part to the prolonging of pregnancy and in part to the prevention of chorioamnionitis, which can predispose to these complications, particularly when accompanied by fetal inflammatory response syndrome. However, they concluded that for

outcomes other than chorioamnionitis, namely short and long-term outcomes on the newborn, most antibiotics are not superior to placebo/no therapy. They stated that the evidence is of poor quality and out of date for some drugs, and routinely used antibiotics, particularly cephalosporins, are underrepresented in randomized controlled studies.

The American College of Obstetricians and Gynecologists recommend a 7-day course of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin during expectant management of women with preterm PROM who are less than 34 0/7 weeks of gestation. (72) In circumstances when erythromycin is not accessible or tolerated, some centers have substituted azithromycin (such as a single oral dose of azithromycin 1 g) for erythromycin, and this substitution is a feasible alternative. (97)

All pregnant women with PPRM between 24 to 33 weeks of gestation should be tested for Group B streptococcus colonization and receive prophylactic treatment, and although there are no well-studied alternatives for women allergic to beta-lactam antibiotics, it may be reasonable to investigate replacing the beta-lactam antibiotic with another medication that is effective against GBS. The intensity of the reported allergic reaction, as well as the antibiotic susceptibility results of the GBS culture, if available, will impact the choice of agent. (98) Daily vaginal tract cultures for GBS were negative in 29/33 patients (88 percent) by day 1, 32/33 patients by day 2, and all 33 patients by day 3 in an observational study of 33 GBS carriers with preterm prelabor rupture of membranes taking penicillin G prophylaxis. (99)

The use of tocolysis in the treatment of PPRM is still debatable. Although delaying birth may allow for prenatal corticosteroids and in utero transfer, as well as a reduction in prematurity-related newborn morbidity, it may raise the risk of newborn morbidity and mortality by prolonging fetal exposure to maternofetal infection. (72) In a secondary analysis of a national, population-based, prospective cohort of preterm newborns recruited in France in 2011, researchers sought to evaluate whether tocolysis administration was linked to better neonatal and obstetric outcomes after PPRM. Their results showed that tocolysis administration was not associated with survival at discharge without significant morbidity or with delivery delayed by 48 hours after PPRM in cases of premature deliveries owing to PPRM, and the rate of histological chorioamnionitis after PPRM is comparable with and without tocolysis. (100)

A 2014 systematic review of randomized trials evaluated pregnancy outcomes of women with

PPROM who received or did not receive tocolytic therapy (prophylactic or therapeutic). Tocolytic therapy for pregnancies under 34 weeks did not appear to have a meaningful effect on perinatal mortality in women with PPRM as compared to no tocolysis. When compared to no tocolysis, tocolysis was related to a longer overall latency and fewer deliveries within 48 hours and seven days. Furthermore, tocolysis was linked to a greater rate of newborns with an Apgar score of less than seven at five minutes and a higher rate of neonates requiring ventilation. The small number and size of the trials, as well as the fact that patients did not consistently receive antenatal corticosteroids to reduce neonatal morbidity or antibiotics to prolong latency, which differs from current standards of care and may explain the lack of improvement in clinically important outcomes, are all limitations of these findings. (101)

Magnesium sulfate is given to pregnant women prior to delivery as part of conventional clinical protocols for fetal neuroprotection (e.g., pregnancies with a gestation of at least 24 but less than

32 weeks at risk of delivery). (68) Before an early preterm delivery, magnesium sulfate exposure in utero appears to reduce the incidence and severity of cerebral palsy. The mechanism behind magnesium sulfate's neuroprotective effects in preterm newborns is unknown, but it is thought to work by several mechanisms, such as stabilization of cerebral circulation by blood pressure stabilization and normalization of cerebral blood flow; Stabilization of neuronal membranes and blocking of excitatory neurotransmitters, such as glutamate, preventing excitatory injury; Antioxidant actions that protect against oxidative injury, and anti-inflammatory actions provide protection against inflammatory harm. (102,103)

The Cochrane meta-analysis analyzed the effectiveness and safety of magnesium sulfate as a neuroprotective agent when given to women at risk of preterm birth using the best available data. According to their results, the available evidence demonstrated that delivering antenatal magnesium sulfate therapy to women who are at risk of preterm birth significantly improved their unborn baby's chance of survival without cerebral palsy. In the entire exposed population, "any cerebral palsy" was greatly reduced (relative risk [RR] 0.68, 95 percent CI 0.54-0.87). The absolute risk of cerebral palsy was 3.4 percent for fetuses exposed to antenatal magnesium sulphate therapy vs 5% for those who were not, resulting in a 1.6 percent reduction in the absolute risk. (104)

Although maternal magnesium sulfate administration has not been linked to a lower risk of cerebral palsy-causing fetal brain lesions (such as severe intraventricular hemorrhage or cystic

white matter injury), it has been linked to a lower risk of cerebellar hemorrhage in preterm newborns. (105)

Magnesium sulphate should be administered at a dose of 4 g for 20 minutes intravenously, followed by a maintenance dose administered intravenously at a rate of 1 g / h until birth. If birth has not occurred, it is recommended to limit the magnesium sulfate infusion to a maximum of 24 hours, as this was the maximum period of therapy in seminal trials. (105)

### **3.3. Treatment of late preterm PROM (34 to 36 weeks of gestation)**

In patients with PROM between 34 0/7 and 36 6/7 weeks of gestation, the American College of Obstetricians and Gynecologists recommend either expectant management or immediate delivery, both considered an acceptable choice, albeit the balance between benefit and risk, from both maternal and neonatal perspectives, should be carefully considered, and patients should be appropriately informed. (72) A randomized trial of 1,839 women in 2015 compared urgent delivery (within 24 hours of diagnosis) to expectant treatment in patients with PROM between 34 0/7 weeks of pregnancy and 36 6/7 weeks of pregnancy. The researchers found benefits to expectant management. Infants in the immediate delivery group experienced more respiratory distress and required mechanical ventilation, as well as spending more days in intensive care. However, expectant management was associated with a twofold increase in maternal unfavorable outcomes, including bleeding and infection, despite a reduced likelihood of cesarean birth. Therefore, they concluded that if expectant management is indicated, it should include thorough monitoring for signs and symptoms of maternal infection, chorioamnionitis, and antepartum hemorrhage. (106) Individualized care should be provided through joint decision-making, and expectant management should not go longer than 37 0/7 weeks. Antibiotics for latency, as well as tocolytic therapy, are inappropriate in this situation. (68,72)

Betamethasone therapy during the late preterm period, between 34 0/7 and 36 6/7 weeks of pregnancy, lowers respiratory morbidity in neonates. (107) A single dose of corticosteroids should be administered, as recommended by the American College of Obstetricians and Gynecologists, for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of premature birth within 7 days and have not taken prenatal corticosteroids. (108)

According to the American College of Obstetricians and Gynecologists' recommendations, antibiotics for GBS prophylaxis should not be delayed in women who are GBS positive while waiting for labor, and early induction rather than expectant management is indicated. (98)

Most patients will deliver through spontaneous or induced vaginal delivery if there are no contraindications to labor and vaginal birth. (109)

#### **4. Conclusion**

The best way to assess and treat women with term and preterm PROM is still a work in progress. When pregnancy is permitted to develop to a later gestational age, treatment decisions are based on gestational age and a comparison of the relative risks of birth vs the risks (such as infection, abruptio placentae, and umbilical cord accident) of expectant management. Routine antibiotic use in pregnant women with PPROM has no effect on outcomes when compared to placebo, according to recent studies. Although most of today's guidelines recommend routine prophylactic antibiotic use to all pregnant women with PPROM, the decision in case of diagnostically unproven infection and only on the basis of clinical suspicion is still unclear. Regarding neurological results, antibiotics have only been shown to improve the rate of abnormal ultrasounds of the newborn's brain when at discharge from the hospital, with no evidence of antibiotics improving long-term neurological outcomes in children. Tocolytic therapy has no benefit for the baby or the mother in the case of women with PPROM. In fact, it may have detrimental consequences, as it increases the risk of chorioamnionitis. Advances and modifications in obstetric and pediatric treatment have resulted in improved survival and neurological outcomes for extremely preterm infants during the last two decades. Despite these advances, prenatal brain damage remains a major cause of long-term neurodevelopmental impairment. To improve long-term results, more research into novel therapy options addressing various parts of the varied pathways of prenatal brain injury is needed.

## **5. Biography**

Lirose Bracha was born on January 30<sup>th</sup>, 1994. Lirose served in the Israeli Defense Forces (IDF), in the Intelligence unit, between 2012 and 2014. During the years 2016-2022 Lirose studied general medicine in School of Medicine University of Zagreb, Croatia. During the studies Lirose spent three months in Yoseftal Hospital, Eilat as a study experience in the departments of Emergency Medicine, General Surgery, and Gynecology and Obstetrics.

Additionally worked as a Physician's assistant in Yoseftal Hospital's Emergency department.

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