Chapter

Premature Birth, Management, Complications

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Abstract

In recent years an increase in premature births (PB) rate has been noticed, as this pregnancy complication that still remain an important cause of perinatal morbidity and mortality, is multifactorial and prediction is not easy in many cases. There are many bibliographic data supporting the view that PB have also genetic predisposition. The trend of "recurrence" of PB in women as well as its increased frequency in ethnic groups suggests its association with genetic factors, either as such or as an interaction of genes and environment. Immunomodulatory molecules and receptors as well as polymorphisms of various genes and/or single nucleotides (single nucleotide polymorphisms, SNPs) now allow with advanced methods of Molecular Biology the identification of genes and proteins involved in the pathophysiology of PB. From the history of a pregnant woman, the main prognostic factor is a previous history of prematurity, while an ultrasound assessment of the cervix between 18 and 24 weeks is suggested, both in the developed and the developing world. According to the latest data, an effective method of successful prevention of premature birth has not been found. The main interventions suggested for the prevention of premature birth are the cervical cerclage, the use of cervical pessary, the use of progesterone orally, subcutaneously or transvaginally, and for treatment administration of tocolytic medication as an attempt to inhibit childbirth for at least 48 hours to make corticosteroids more effective. Despite the positive results in reducing mortality and morbidity of premature infants, the need for more research in the field of prevention, investigation of the genital code and the mechanism of initiation of preterm birth is important.

Keywords: preterm birth, predisponding factors, complications

1. Introduction

Premature birth defined as the onset of labor before the 37th week of pregnancy and is a clinical symptom that is accompanied by multiple pathogenetic causes. The etiology is multifactorial and complex. It is not a normal premature birth, but a distinct syndrome with specific characteristics [1–5]. Sometimes, the mother, the placenta and the fetus altogether are involved to a different degree. The exact mechanism is not known. Uterine cramps that cause premature birth are coordinated uterine contractions that cause progressive change (elimination and/or dilation) of the cervix before the 37th week of pregnancy. In contrast, premature contractions are rhythmic contractions of the uterus that do not cause a change in the cervix [1–5]. Specifically, in 1948, the World Health Organization (WHO) defined with the term "prematurity" the delivery of a newborn weighing <2500 g. The primary problem that arose was that it characterized a multitude of newborns with heterogeneous fetal development as premature. Therefore, in 1960 Battaglia and Lubchenco used measurements from a large population of newborns to establish the rules of fetal development.

Prematurity based on Birth Weight is divided into "low birth weight" infants <2500 g, "very low birth weight" infants <1500 g (approximately 1–1.5% of live births) and "extremely low birth weight" infants <1000 g (this category includes 0.7% of all live births).

Premature is the newborn that will be born at a gestational age less than the 37th week of pregnancy. Very premature is the newborn which will be born at a gestational age less than 32 weeks of gestation.

Premature birth is subdivided into automatic preterm birth as a consequence of premature contractions with an incidence of 35% of unknown etiology, a corresponding incidence of 25% resulting from premature rupture of membranes and in 25% of cases iatrogenic, as a consequence of medical or obstetric such as maternal hypertension, fetal development pathology and gestational bleeding, while in cases of multiple pregnancy the incidence rate is 15% [6–11].

2. Epidemiology

It contributes a large 75% to the formation of perinatal morbidity and mortality and it is estimated that about 50% of long-term neurological problems are related to prematurity. The incidence is between 10 and 12% over a period of about 15 years (1981–1996) and includes about 467,000 births in United States of America, compared to European developed countries in which the rates of prematurity are lower at 5–6%. Prematurity has gradually increased from 6–13% of all births and it is estimated that 13,000,000 premature babies are born per year worldwide [1–5].

The highest rate of 60% is observed in countries of South Asia and Central Africa while in African Americans it occurs with twice the frequency of 18% compared to Caucasians. It is generally and worldwide accepted that an embryo is viable for more than 20 weeks and in Greece for more than 22 weeks of gestation. Moreover, the implementation of treatment programs for pregnant women with symptoms of threatened preterm delivery, failed to reduce the incidence of preterm birth [12–14]. The lack of progress may be partly related to the increase in the frequency of multiple pregnancies as a result of the widespread use of assisted reproduction methods, but the main cause remains largely unclear. The incidence of prematurity (23rd-24th weeks to <37 weeks) in the US, for single pregnancies is 9.43%, for twins 50.74% and for triplets 91.03%.

It has also been observed that opposed to the Caucasian race, the black race is associated with an increased rate of low birth weight neonates and preterm delivery. There is great heterogeneity within the same racial group, however members of the same race may have different frequency of precocities in different geographical areas. The differences remain even after the control for the social order. The racial difference has not decreased over time. The mother's race is a stronger indicator of precocity than the father's race, although the father's race is also important. The probability that the racial difference is genetically determined is based on data showing different distribution of gestational age in the black and white population. The gestational age distributions for black and non-black women appear to deviate by 1 week, resulting in a mean gestational age of 39 weeks for blacks 37 and 40 weeks for whites [15–20].

Approximately 1/3 of health expenditures in infancy and childhood are due to complications of preterm delivery as 10% of surviving infants have long-term disabilities such as developmental or behavioral problems [12–14]. The Financial Cost in US for health care amounts to 9 billion $/year and the 35% of the expenses is for newborns and 10% for children. Also, the high cost of hospitalization of newborns <1500 g should be emphasized in intensive care units [12–14]. In Germany, out of a total of 50,000 preterm births (BP) and the annual cost are as follows: PB <32 weeks 300 million €, PB ≥ 32 weeks 400 million € and cost for tocolysis 112 million €.

It is estimated that about 85% of neonatal deaths in Western countries are attributed to prematurity and 10% of these neonates will suffer from some form of long-term disability. Of the reported rate of prematurity, 10% of the neonates delivered before the 37th week of pregnancy, about 1.5% before the end of the 32nd week and approximately 0.5% of premature births will take place in the period before the 28th week [12–14]. Premature birth is a potentially very serious problem for newborns and the morbidity and mortality rates are inversely proportional to the maturity of the organic systems, especially the lungs [6, 21].

In particular, in the 22nd week of pregnancy, the temporary survival rate is 40%, respiratory distress syndrome 70%, intra-abdominal bleeding 25%, sepsis 25% and necrotic enterocolitis 8% with a final survival rate of 5% [6, 21]. Some of the following changes are observed between 22nd and 34th week of pregnancy: sepsis 4%, increase of temporary survival to 97% reduction of respiratory distress syndrome to 14%, intra-abdominal bleeding 0%, necrotic 3% with intestinal necrosis final survival 97% [6–11]. The prognosis of newborns improves when the gestation period is prolonged. Recent literature reports indicate the following neonatal survival rates: at 23 weeks 6–9%, at 24 weeks 17–58%, at 25 weeks 35–85%, at 27–28 weeks 90% and at 33 weeks 95%.

3. Risk factors of preterm birth stimulation

Primary risk factors:

- Multiple pregnancies
- History of preterm birth
- History of threatened preterm birth
- Abdominal surgery during pregnancy

- Congenital uterine abnormalities
- History of automatic miscarriages
- History of conical resection
- Cervical removal> 30%
- Polyamnium
- Presence of intense myometrial activity
- Cervical dilation> 2 cm

Secondary risk factors:

- Feverish disease in pregnancy
- Bleeding in the 2nd trimester
- History of acute pyelonephritis
- History of miscarriage in the 2nd trimester
- Smoking more than 10 cigarettes per day

4. Maternal causes and conditions in pregnancy related to preterm birth

4.1 Socio-economic and racial factors

The low socio-economic status of pregnant women related to education, employment or family income and racial, demographic, environmental factors is one of the most common factors associated with the occurrence of preterm birth. Statistically, a causal relationship has been found between the economic situation and the low level of education.

Mothers with a low level of education are more likely to give birth to low birth weight babies and less likely to give birth to large babies. The average birth weight increases with the greater education of the mother. White mothers with 12 years of education, on average, had 82 g heavier babies than mothers with less education, while the corresponding difference for newborns born to black women was 66 g. Mothers with ≥12 years of education had even heavier neonates. The risk of having a very low birth weight neonate has been shown to vary depending on the level of education among white, but not among black women [11, 22–26].

Newborns born from low-educated mothers are less likely to survive. Low-educated mothers have characteristics that are blamed for the birth of low birth weight babies. They are more likely to be young, have less prenatal care, smoke during pregnancy, have a poor diet and have more difficult access to medical care. Also, women in lower social classes have higher levels of stress with elevated catecholamine levels that can lead to increased uterine contractions. Better education of the mother could improve her diet, reduce smoking during pregnancy but also reduce other harmful factors [11, 22–26].

4.2 Maternal age

Maternal age (under 19 or over 35) is associated with an increased incidence of preterm birth [27–30]. However, the risk may not come from age itself but from the factors associated with it. For the young women, it is more usual to suffering of vaginitis than the older women, which may have other health problems, such as fibroids, hypertension and metabolic diseases [15–20]. Also, women with body weight before pregnancy under 50 kg and height below 150 cm, have higher rates of preterm birth. Therefore, chronological age is not an independent factor of gestational age but the increased risks reflect characteristics of the mother's advanced age.

Great importance was given to the premature birth of women over 35 years old due to the growing population of pregnant women with first pregnancies at an older age. However, there are views on the increased risk in those over the age of 30, compared to women aged 20–29. Maybe due to the improvement of perinatal care, the relative risk of preterm delivery in women aged >35 years old, decreased from 1.7% in 1976 to 1% in 1981. Adolescent white women give birth to newborns that are lighter by 149gr, while black women by 99gr, compared to those of mothers aged 20–34 years. Mothers aged 35 years and older give birth to children which are 50gr heavier than those of women 20–34 years [15–20].

Neonatal mortality is also slightly higher in younger and older women.

4.3 Burdened obstetric history

The existence of a burdened obstetric history seems to be directly related to the frequency of preterm birth. Miscarriages, especially in the second trimester, previous preterm births and stillbirths, increase the risk of premature births in subsequent pregnancies. A previous history of low birth weight or preterm birth is one of the most important factors for the next preterm birth. The literature states that the relative risk with a history of preterm birth is 34%, while it is even higher for the third childbirth, although both previous ones were premature. Racial differences have been observed in the relationship between first and second preterm birth, while the previous history of preterm birth is a significant risk factor for premature rupture of membranes.

The number of pregnancies does not seem to affect the likelihood of preterm birth as the results of several studies are contradictory. It is generally accepted that first-born infants weigh less on average compared to their offspring at each gestational age. The explanation for the reported data is not known. It is possible that fetal development is more limited in primiparous pregnant women, due to the anatomy of the muscular walls of the uterus, compared to those with multiple pregnancies [15–20].

There is an increased risk of preterm birth compared to the short interval between two pregnancies, but the results are not statistically significant. It is therefore not clear whether there is any relationship between short interval between births and prematurity.

4.4 Previous stillbirths or neonatal deaths

4.4.1 Previous induced abortions

The contribution of abortions to the increased risk of premature birth depends on the type of abortion, the degree of dilation of the cervix, the gestational age and the number of abortions [15–20].

4.4.2 History of infertility

Women who have undergone assisted reproduction therapy in single pregnancies show a prematurity rate of 10–20%. The increase is due to pre-existing reproductive abnormalities, an increased rate of multiple pregnancies, and an increasing number of cesarean sections before the 37th week of pregnancy.

4.5 Various diseases of the mother

Maternal diseases related to pregnancy (e.g. preeclampsia and eclampsia) or unrelated to pregnancy (chronic kidney disease, anemia, chronic hypertension, respiratory failure, etc.) are common causes of premature birth or low birth weight babies. Most of these diseases cause pathology in the placental circulation resulting in problematic fetal development and low body weight. Also the most well-known of the endocrine diseases associated with increased prematurity are diabetes mellitus and hyperthyroidism [20, 31–35].

4.5.1 Smoking and alcohol

Smoking seems to be responsible for an increased rate of prematurity, is associated with placental abruption and perinatal mortality. This effect of smoking is attributed to the increase in anthracylamoglobin and the action of nicotine. Also various toxins also known as Cyanide reduce the levels of vitamin B12 resulting in metabolic disorders. Anthracycline hemoglobin increases from 1.2% to 4.1% and reduces the oxygen available for fetal oxygenation while nicotine increases epinephrine secretion and causes vasoconstriction, further aggravating fetal oxygenation [20, 31–35].

Alcohol abuse, in addition to its association with prematurity, has also been linked to an increased risk of brain damage in premature infants.

4.5.2 Illegal drug use

Marijuana and cocaine have been studied more for their potential effects on preterm birth. There is no serious evidence that marijuana is associated with prematurity. In contrast, cocaine has been studied much more with a wealth of literature linking its use to preterm birth [20, 31–35].

4.5.3 Medical monitoring

Inadequate medical follow-up, as expressed by the late first visit of the pregnant woman and the limited number of visits, has a direct impact on the increase of prematurity. This is confirmed by the increased rate of prematurity in pregnant women, especially in adolescent pregnant women who are not monitored by their personal doctor or midwife, where the system of free medical care applies [20, 31–35].

4.5.4 Surgical diseases during pregnancy

Acute surgical diseases of the abdomen, such as acute appendicitis, are associated with an increased incidence of preterm birth due to the effect of bacterial endotoxins [20, 31–35].

4.5.5 Uterine congenital abnormalities and diseases

Uterine congenital abnormalities characterized as anatomical are responsible for a small percentage of preterm births. The most common occurrences are in the

double uterus, unicorn, duodenum and hypoplastic uterus where the incidence of miscarriage is close to 30% and the risk of premature birth reaches 20% if the pregnancy continues beyond the 20th week of pregnancy. There is also an association with prematurity and fibroids, endometrial adhesions idiopathic myometrial activity [20, 31–35].

4.5.6 Insufficiency of internal cervical os

The uterus and cervix come from the union of M*ü*ller ducts. The cervix is made up of extracellular connective tissue and type I, III and IV collagen fibers. The percentage of smooth muscle fibers is 10–15%. The percentage of muscle and fibrous components ranges from 29% in the inner cervix to 6% in the outer cervix. Other components of the cervix are glycosaminoglycans, proteoglycans, fibronectin and elastin. Before and during labour, the number of ligaments between the collagen fibers decreases, the concentration of hyaluronic acid increases and this leads to elimination and dilation of the cervix and uterine contractions.

Internal cervical insufficiency is a fairly common cause of prematurity. Also a history with conical resection of the cervix is responsible for an increased rate of premature birth which is observed with a frequency of 14% for the first pregnancy and quadruples in subsequent ones [35–40].

4.5.7 Maternal infections

Inflammations of the vagina and cervix caused by anaerobic microbes, Trichomonas, Chlamydia, gonococci and streptococci of group B, usually lead to premature birth, premature rupture of membranes and low birth weight infants. With preventive examinations at the beginning of pregnancy such as vaginal fluid culture and the application of treatment in case of positive results, we achieve the reduction of the possibility for premature birth [35–40].

Subclinical chorioamnionitis can predispose to preterm birth. However, the infection is associated with less than 20% of cases of premature birth without complications. The most common link between infection and premature birth is bacterial vaginosis. Disruption of the nitric acid and prostaglandin balance of the myometrium can cause premature contractions and consequent labor.

The vagina is normally colonized by a variety of microorganisms, many of which are flora, while others are potentially pathogenic. It is not fully known whether the bacterial flora itself acts as a trigger for preterm birth or secondarily becomes active only when the cervix is unable to fulfill its protection against incurable infections. Ascending infection is one of the most important mechanisms that progress to premature birth. The infection can act as a trigger, either in the sense that it is more likely to lead to premature birth when the cervix is open at the end of pregnancy, or when the cervix opens prematurely. The degree of cervical dilation affects the risk of ascending infection.

Infection that occurs with intact embryonic membranes reduces infection by the flora of the vagina and cervix. The incidence of amniotic fluid infection varies depending on gestational age at birth. It is particularly high in very premature fetuses and gradually decreases at 30–34 weeks and remains stable until the end of pregnancy [35–40].

4.5.8 Infection of the lower urinary tract

The essential role of the infection in preterm birth was confirmed by the finding in the amniotic fluid or the dermis and the amniotic fluid of women with

pathogenic microorganisms (Ureoplasma urealiticun, Mycoplasma hominis, *Streptococcus agalactiae*). In particular, the detection rate of the above infectious microorganisms during pregnancy according to the literature is Ureoplasma urealiticun 60%, Trichomonas vaginalis 34%, Mycoplasma hominis20%, Streptococcus agalacticae 5–18% and Gardanerella vaginallis 12% anerobe. Chorioamniosis colonization was twice as much as amniotic fluid. This colonization was more common and inversely proportional to the gestational age and birth weight of the newborn, in women with intact membranes whose labor was spontaneous, compared with women of the same gestational age who gave birth due to medical or obstetric indications other than automatic childbirth. The inverse relationship between positive choriamnia cultures and gestational age was not observed in women giving birth due to medical indications [35–40].

Among women who gave birth up to 30 weeks by spontaneous delivery, choriamnius culture was positive in 73%, compared with 21% of births due to indications. Horiamnius cultures were positive in 83% of mothers with spontaneous onset of labor and in 16% of mothers who gave birth due to indications, in newborns weighing less than 1000 g. An equal number of newborns are born at gestational ages who have proinflammatory cytokines in the amniotic fluid, with negative fluid culture, so that the majority of newborns born under 26 weeks and a significant proportion of those born under 30 weeks have inflammation or inflammation amniotic fluid These findings are mirrored in histological studies of the dermis and amniotic fluid, infiltrated by polymorphonuclear neutrophils in almost all pregnancies of 20–23 weeks, in the majority of those under 26 weeks, and in a significant proportion of those born before 30 weeks [35–40].

The reason for the high frequency of infections - inflammations in the amniotic fluid and chorioamnion is inexplicable in very premature pregnancies under 26 weeks, even under 30 weeks. The flora studies are incomplete from the beginning to the 23rd week of pregnancy, while from the 23rd to the end they show a rather stable vaginal flora [35–40].

The cervix begins to change composition and have maturation elements between 20 and 26 weeks, under the influence of biochemical changes (prostaglandins and interleukin) and uterine contractions. Changes in the cervix increase the exposure to vaginal cervical bacteria of the upper cervix, lower uterus and chorioamnion, resulting in increased amniotic fluid and chorioamnion infection, the most vulnerable barrier between the fetus and the environment.

Most amniotic infections are subclinical, with no maternal fever, uterine tenderness, tachycardia, or foul-smelling amniotic fluid. Very often, however, the mother's infection is not obvious until the infection of the fetus begins. The only fetal sign indicative of amniotic infection is fetal tachycardia, an unstable symptom of systemic neonatal infection. But what makes an amniotic infection fetal and not maternal? The fetus first responds to the infection by responding to the fetal part of the chorioamnion. Proinflammatory cytokines and prostaglandins accumulate in the amniotic fluid. A systemic fetal immune response occurs and produces proinflammatory cytokines and other evidence in the fetal blood [35–40].

Periodontitis has also been studied in women who have low birth weight neonates, resulting from either spontaneous preterm delivery or premature rupture of membranes. It has been found that these mothers have more severe periodontal disease than those who give birth to normal weight babies. It is possible that oral infection with Gram (–) anaerobic microbes fusobacterium nucleutatum, to act periodically, as a chronic factor of hematogenous dispersion of bacteria or bacterial agents (lipopolysaccharides and endotoxins), in the placental unit [35–40].

5. Causes and conditions of embryoplacutic unit related to preterm birth

5.1 Multiple pregnancies

A multiple pregnancy is at greater risk for preterm birth due to the continuous dilation of the uterus and the onset of premature contractions. If the average pregnancy is 280.5 days, in twin pregnancies it is 261 days and in triplets is 247 days [41–44].

5.2 Congenital fetal abnormalities

Increased rate of prematurity due to uterine overstretching is due to polyamine and especially hydramnios. The 1/3 of pregnancies with polyamnios leads to premature birth. The main causes of polyamniosis are congenital abnormalities of the fetus's nervous and digestive systems, intestinal obstruction, septal hernia, Potter's like Syndrome, Skeletal Deformities (Amniotic bands <24 weeks), chromosomal abnormalities, infections. In particular, hydramnios is associated with congenital abnormalities of the fetal nervous system such as aneurysm (due to polydramnios), renal agenesis (due to oligamnius) in combination with pulmonary hypoplasia and endogenous metabolic disorders and some of them are causative factors of preterm birth [45–50].

5.3 Abnormalities of the placenta and umbilicus

Abnormalities in the morphology, implantation and function of the placenta can often lead to premature birth. Placentas with membranous umbilical cord protrusion are at greater risk for premature onset of labor. Also the precursor placenta is an important factor in causing premature birth. It is characteristic that it is more common in premature births than in normal ones. Premature placental abruption has an even higher incidence in preterm birth than in normal.

5.4 Breech fetal presentation

Breech presentation of the fetus in the first trimester of pregnancy has an incidence of 20% compared to all pregnancies and only 2% of this percentage leads to premature birth. However, sciatic projection is associated with increased perinatal mortality as well as placental abnormalities thus increasing the likelihood of preterm delivery.

5.5 Premature rupture of membranes

Spontaneous rupture of fetal membranes (s-PROM) before the end of 37 weeks and 1 hour before the onset of labor covers 14.3% in all preterm births. It is distinguished in term Premature Rupture of membranes (t-PROM) which is defined as rupture of membranes after the 37th week of pregnancy and constitutes the majority of cases and in preterm Premature rupture of membranes (p-PROM) which is defined as rupture of membranes before the 37th week of pregnancy has an incidence of 3% and is responsible for 40% of preterm births. Its incidence is 10–15% of pregnancies.

Findings observed are contractions (4 per 20 min or 8 per 60 min) and cervical dilation >2 cm and/or cervical effacement >80%. It is associated with complications related to the outcome of pregnancy and perinatal outcome, increases the chance of premature birth and neonatal morbidity and mortality to 1–2% [45–50].

The incidence rates are 6% - 10% <37 weeks, 1.5% <32 weeks, 0.5% <28 weeks. Often there is no obvious predisposing factor. The main causes of PROM are malnutrition, vaginitis, cervical insufficiency, abnormalities of the uterus. Pregnancy usually precedes the same episode. The diagnosis of PROM is based on the history of the pregnant woman where discharge from the vagina is reported. The differential diagnosis from other conditions (alkaline urine, inflammation) is usually made by direct examination of the cervical spine and by testing the sunflower map.

The complications of PROM, in addition to those of prematurity, include inflammation of the mother and the fetal placenta, as well as umbilical cord prolapse, which implies significant perinatal morbidity and mortality [45–50]. Babies born with symptoms of sepsis are 4 times more likely to have neonatal mortality than those who do not. In addition, there are risks for the mother from the complications of possible chorioamnionitis [45–50].

Diagnosis is not always easy. It seems that taking a good medical history and then examining the woman using a vaginal dilator helps a lot. Moreover, obstetric ultrasound is helpful in diagnosis. Specifically, the presence of amniotic fluid in the posterior vaginal dome is very helpful in the diagnosis. The nitrazine test and the microscopic examination of the amniotic fluid for the typical image of the fern, have a sensitivity of 90% with false positives of 17% and 6%, respectively due to the mixture of urine and blood or cervical mucus, respectively.

6. PROM monitoring

Criteria for diagnosing chorioamnionitis include: fever, tachycardia, fetal tachycardia, odorous vaginal fluids, leukocytosis and uterine tenderness. Vitals are taken every 4–8 hours and the existence of one or a combination of the above findings raises the suspicion of fetal infection. Doppler ultrasound, biophysical profile and fetal heart rate have been used from time to time in various studies to distinguish infected fetuses from non-infected ones and therefore pregnancy can be prolonged without success in distinguishing which fetuses are in risk and which not.

Women should be monitored clinically for signs of chorioamnionitis. Apart from vaginal fluid culture at the time of introduction no other need to be taken on a weekly basis. According to the American College of Obstetricians and Gynecologists, CRP and white blood cell count should be checked twice a week. No daily blood draws are needed for leukocytosis and CRP, due to the low sensitivity. Biophysical and Doppler can be done but have no significant prognostic value [45–50].

6.1 Role of antibiotics

Although different regimens have been used in various studies (penicillins, erythromycin, clindamycin, from 2 doses - 10 days) it seems that the prolongation of pregnancy is stable and the morbidity for mother and newborn is reduced. It is recommended 5–7 days administration of macrolides (erythromycin, azithromycin). Clindamycin is preferred when there is allergy in the first option.

Administration of ceftriaxone, clarithromycin metronidazole β-lactam, appears to significantly extend the time to delivery and the frequency of chorioamnionitis (23 vs. 12 days, p: 0.01, and 50% vs. 67%, p: 0.05, respectively). Finally, there are insufficient data to prove the direct favorable contribution of antibiotics in reducing neonatal morbidity and mortality. Nevertheless the combination of the mentioned antibiotics used as empirical therapy against the

aforementioned germs ureaplasma, mycoplasma, anaerobes and gram negative bacteria according to bibliographic data offered satisfactory results in the early and early rupture of fetal membranes for both the mother and the fetus. Strategy for treating a subclinical possible infection. The administration of clavulanic acid should be avoided due to the possible cause of necrotic enterocolitis in the fetus and in cases of group B streptococci additional antibiotics should be given during delivery. Antibiotics are effective in treating infection without being able to prevent a premature birth.

6.2 Role of steroids

According to the instructions of the American College of Obstetricians and Gynecologists, it is recommended to administer a single dose of steroids in pregnancies <32 weeks with PPROM that do not show signs of infection. Two meta-analyzes conclude that steroids in PPROM significantly reduce Respiratory Difficulty Syndrome, encephalopathy and intra-abdominal bleeding. It does not appear to increase the rate of infection from their administration. A single dose should be given to pregnant women from 24 to 34 weeks. The manifolds are associated with a smaller head size and smaller birth weight [45–50].

6.3 Role of tocolysis

Tocolysis in women with CPR is not recommended because this treatment does not statistically significantly improve perinatal outcome. The administration of tocolysis to women with CPR and contractions to act on steroids and antibiotics remains unclear. Attempting to suppress preterm uterine-related contractions using first-line tocolytic therapy can achieve prolongation of gestational age. Among the administered tocolytics, β-sympathomimetics do not excel in the other categories in terms of their effectiveness and in addition are associated with a negligible rate of side effects. Conservative treatment with β-sympathomimetics or magnesium offers almost nothing in the whole treatment effort. Careful selection of cases is recommended. Hospitalization for 48–72 hours may be needed, but other than that, informing pregnant woman about possible symptoms of chorioamnionitis is necessary (e.g. temperature measurement).

6.4 PROM and cerclage

There are no randomized studies on what should be done in such cases. Some studies show a tendency for chorioamnionitis to start earlier, while others show a prolongation of pregnancy. The risks and benefits of suturing for a short time until steroids work have not been adequately studied [45–50].

6.5 PROM and childbirth

Childbirth should be scheduled between 34th and 40th weeks. If extended beyond this time limit the pregnant woman should be explained the increased chance of choriamnionitis and the reduced chance of respiratory problems from the newborn. In Premature Childbirth the hypoxia is greater compared to that of a full term. Vaginal delivery is recommended at a young gestational age (≤ 25th week). In fetal difficulty many suggest cesarean section. Between 26th and 34th week is no different from the way after 34th week. Vaginal childbirth is the appropriate route of completion of childbirth when there are no abnormal shapes and projections, elements of fetal difficulty, e.g. IUGR [45–50].

Iatrogenic PROM occurs after deliberate medical intervention, when it is estimated that continued pregnancy is at greater risk for the mother and fetus than prematurity.

Complications of the placenta: placental abruption, placenta previa.

Amniotic fluid complications: oligamnium, polyamnion, chorioamnionitis, premature rupture of membranes.

Fetal causes: congenital anomalies, multiple pregnancy, residual development, fetal discomfort.

7. Pathophysiology of preterm labor

Activation of the maternal/fetal hypothalamic–pituitary–adrenal axis (HPA) due to maternal or fetal stress: connection between maternal psychosocial stress and preterm birth - mechanism similar to normal childbirth.

The following factors such as: Stress, Autoimmune mechanisms, PROM, Inflammation, Bleeding, Uterine overdistension, Multiple pregnancies, disorders of axis (pituitary axis), Inflammation, Environmental factors, Social factors, Activation of mechanisms, induction of contractions leading to effacement and dilation of cervix and finally labor [51–56].

Chorioamnionitis or systemic inflammation from systemic or ascending infection: cervical, decidual and fetal membrane's cytokines activation (macrophage activation, production of interleukins IL 1, IL 6, IL 8, cachectin, 5-hydroxytryptheptamine, release of fibronectin in cervical and vaginal secretions).

Bleeding from decidual: three or seven fold risk of prematurity, especially as a result of premature rupture of membranes.

Uterine oversdistension: myometrial stimulation, increased cytokine expression [50–60].

7.1 Preterm labor: the mechanism includes

Activation of the maternal and/or fetal HPA axis (psychological or physical stress).

Inflammatory reaction - local or systemic.

Bleeding from decidual.

Increased uterine stretching (multiple pregnancies, hydramnion).

Cervical insufficiency.

Activation of HPA axis.

An increase of CRH levels (corticosteroids) can cause a raise of PG (Prostaglandin) levels and consequently an increase of the MMPs (metalloproteinases) activity, Activation of metals of protein (MMPs) of the parent substance (MMP-1, −3, −8, −9) leads to degradation of the fibrous tissue, and premature rupture of membranes. Bacterial products and/or profibrous cytokines acting on cervical cells of the uterus may cause a change of MMPs expression. High concentrations MMP-8 of amniotic fluid are associated with PB (before the 32nd week of pregnancy) so induction of uterine contractions (directly or by functional "withdrawal" of progesterone) [50–60].

The angiogenic factor VEGF, expressed in embryonic membranes and perishable, is essentially involved in normal angiogenesis and placentalization - thus ensuring way to normal fetal growth and development - while at the same time modifying its permeability in placenta and amniotic membranes. Daneshmand et al. and Kramer et al. suggest that both the VEGF factor and (VEGF-R1 and VEGF-R2) receptors have reduced expression in hypoxic

conditions and chorioamnionitis, disrupt the smooth functioning of placental abruption and lead to PB. Similarly, Parazoglou et al. proved the correlation among two common VEGF functional gene polymorphisms (−634G/C and 936C/T) with PB [50–60].

In case of preterm labor, CRH levels are ≥ 2 MoM.

Elevated levels of ACTH (Cortical Adrenal Hormone) and CRH can result in raised levels of DHEA (dehydroepiandrosterone) and 16-OH-DHEA-S (dehydroepiandrosterone sulfate) as increased E1 (estrone) – E3 (estradiole). As a result uterine contractions are induced. (Activation through binding in oxytocin receptors, involvement of MLCK (myosin light chain kinase) and calmodulin. Increased E3 in saline is observed in premature labor, 3–4 weeks before delivery.

Inflammatory reaction is mediated through the following cytokine agents:

Cytokines, TNF-α, Il-1, Il-1β, Il-6, Il-8, Il-10, GM-CSF and finally prostagladines increase.

Fetal membranes, trophoblast and the chorionic villi react, in response to inflammation and ischemic lesions of placental unit and cause an increase in cytokines levels in maternal plasma, in the amniotic fluid of women with preterm labor and in cultures of amniotic fluid.

TNF-α is also found in decidual macrophages as well as in chorion villi and trophoblast. The TNF-α factor is found in maperishable cells of perishables, villi and trophoblast, in both the 1st and 3rd trimester of pregnancy. Its allele gene A region −308 of the TNF-α promoter leads to an increase production of it. Roberts et al. reported positive correlation between polymorphism of the TNF-α promoter region (−308 A allele) and the PB and/or premature rupture among African American women [50–60].

On the contrary, Amory et al. found that homozygotes for the TNF-α allele-863 A gene is significantly increased frequency of PB, chorionicamniotnitis and perinatal morbidity, but this is not associated with an adverse outcome. Il-1 is detected in amniotic fluid, in decidua and trophoblast. The receptor antagonist of IL-1 inhibits the biological effects of IL-1, blocking its receptors. Consequently reduction of IL-1 production and induced from that of prostaglandin production by them endometrial tissue can prevent PB associated with infection Il-1β is found in chorionic villi, decidua, amniotic fluid and placental cultures [50–60]. Elevated levels of Il-6 are usually found in the amniotic fluid, with inflammation. Interleukin-6 (IL-6) is the cytokine expressed more than any other in pregnancy. The finding of extremelly high levels of the specific cytokine in the amniotic fluid pregnant women who presented with some kind of inflammation and its very low concentration in cases of PB "idiopathic" etiology, make it one of the most sensitive and specific PB indicators On the contrary, they were found to be reduced in cases of premature birth. Il-10 is also elevated in amniotic fluid after amniocentesis during the second trimester in pregnancies with IUGR and chorioamnionitis [50–60]. Interleukin-10 (IL-10) is known to be major inhibitory cytokine in the process synthesis of cytokines by both T cells (interferon-γ and IL-2), as well as by monocytes macrophages (TNF-α, IL-6, IL-8, and IL-12) and as therefore plays an important role in achieving the outcome of the pregnancy by securing the maternity tolerance to the allogeneic fetus. In most pregnancies IL-10 is detected in amniotic fluid Its high levels in amniotic fluid of pregnancies complicated with residual embryonic development as well as in cases of pregnant women with clinical symptoms chorioamnionitis associated with dysfunctional for immune activity in pregnancy and in PB [50–60].

Increased levels of interleukin-8 (IL-8) are found in monocytes, in inflammation, in chorioamnionitis and may be used in the future as a prognostic marker of preterm birth. Interleukin-8 (IL-8), a derivative of monocytes; caused by

inflammation, may be used in the future as a PB predictor marker as it has been detected in pregnant women.

Inter twined with chorioamnionitis, and the antigen compatibility (also a derivative of macrocells, which is considered necessary in cellular immune response) is associated with inflammation of the elements of pregnancy.

Bacteria, specially their wall lipoproteins and/or endotoxins can stimulate an increase of IL-1β, TNF-α, IL-8, IL-6, proteases, collagenase, elastase as well as raise of Phospholipase A2 led to PGF2a endothelins and finally increase the myometrial sensitivity to oxytocin [51–56].

7.2 Chorioamnionitis

It is observed in 12% of premature labors with intact membranes. Histological diagnosis of chorioamnionitis is 40% confirmed in the placenta.

It is also known that frequency of choriomnionitis is inversely proportional with gestational age.

8. Preterm labor and genetic background

8.1 Modern molecular biology certifies a premature gene

Quickly developing fields studying human genome (genomic) and protein products (proteomic) may allow the identification of genes and proteins respectively involved in the pathology of PT, making in this way it is possible to develop concrete diagnostic and therapeutic approaches against that. The use of DNA arrays helps to identify the different gene expression and their involvement in childbirth, early or full term.

Reduced expression insulin-dependent factor II (IGF-II), of galgranulin A and B (calgranulin A and B) and of the G-protein-binding receptor (G-protein-coupled receptor) was observed in the myometrium during childbirth - in contrast increased expression of the binding genes protein storage of insulin-dependent IGFs (IGF-binding protein), the binding of the Ca2+/CaM ion protein (Ca2+/CaM binding protein), the C-kinase substrate (kinase C substrate) and the converting enzyme of angiotensin-converting enzyme is noticed. Also, the use of DNA arrays in expression of their cytokine genes fetal membranes of women with endometrial inflammation and who gave birth prematurely, showed hyper-expression in 22 genes and sub-expression in 4 on a total of 90 of genes studied. The IL-1β genes of oncostatin M and the enhancer pre-B-cell enhancing factor factor) were those with the greatest difference expression.

These studies demonstrate the potential for genomic research in the identification of genes involved in the pathophysiology of complex diseases, as in the case of PB.

Although the results of studies with the use DNA arrays may show significant over- or under-expression in a set of genes, that not necessarily related to level changes of their protein expression [50–60].

DNA analysis is based on molecular biology methods, such as:

1. The investigation of the functional variability of the candidate gene.

2. Northern blots analysis.

3. Linkage analysis.

4. Subtractive hybridization.

Mutations and polymorphisms in the cytokine genes seem to be involved in pathogenesis of preterm labor. There is an association between preterm labor and the functional change of a cytokine gene. So, mother's carriers of this mutations, may be can be intensively followed up in the future [51–56].

Proteolytic action of MMPs on fetal membranes and cervical mucus leads to progressive cervical effacement and therefore to PROM.

Bleeding observed in more than 2 trimesters increases the relative risk of PROM 7 times.

According to Salafia et al. [61], in 38% of preterm labors hematoma and/or hemosiderin deposition was detected, instead 0.8% in full-term pregnancies.

According to Gargano et al. [62], in cases of preterm labor, Factor V Leyden & angiotensinogen -6G mutations are associated with an increased relative risk (OR: 4.8) of placental abruption in Caucasians but not in African-American pregnant women.

It is also found increased frequency of PROM in women with increased TF (tissue factor - major cellular mediator of hemostasis).

Uterine overdistension due to multiple pregnancy or polydydramnios are the most common risk factors for preterm labor. Uterine distension leads to oxytocin receptors activation and increase of PG and MLCK.

According to Nemeth et al. [63] fetal membranes rupture stimulate the cytokines, PGs and collagenase production. Warren et al. [64] suggest that cervical incompetence may have a genetic background alleles that control anti-inflammatory mediators, that were found in women with high risk for cervical incompetence. Sanbhag et al. [65] women diagnosed with CIN III are in high risk for preterm labor even have not been cured by cone-biopsy. Congenital cervical incompetence is basically rare [51–56].

In conclusion, preterm labor seems to be a result of the following mechanisms:

1. Factors stimulated the HPA axon activation.

2. Inflammatory response.

3. Decidual bleeding.

4. Uterine overdistension.

Common mechanism– Contraction associated proteins (CAPs) and proteases production.

9. Preterm labor prediction

To predict preterm labor are suggested:

1. Cervical ultrasound evaluation (18–24 Weeks).

   Combination of cervical length and funneling significantly increases the possibility of preterm labor.
   Combination of cervical length and dilatation of internal os, increases the sensitivity, but only 29%.

2. Fetal fibronectin (FFN).

10. Recommendation as routine method in high risk pregnancies

Nowadays, diagnostic view is focused on score systems that combine ultrasound, biochemical and endocrinologic parameters with molecular methods, such as fetal DNA measurement in maternal circulation. Not rarely, among asymptomatic or low risk pregnancies may be can be found high risk pregnancies for preterm labor.

There is a significant statistical correlation between preterm labor and cervical length <20 mm–25 mm [56, 66–69].

11. Controversial aspects for the efficacy of ultrasound examination

Transvaginal cervical length measurement between 18 and 24 weeks is commonly suggested as a reliable index of preterm labor. On the other hand, some studies support that generalized preventive cervical measurement has no sufficient evidence.

The timing of cervical measurement in asymptomatic pregnancies with increased risk for preterm labor (history of preterm labor and history of PROM) seems to significantly affect the estimated risk of preterm labor.

Some other studies propose the combination of cervical length measurement and the detection of fetal fibronectin.

Transvaginal ultrasound confirm the preterm labor diagnosis in high risk pregnancies, especially when was applied in the first trimester.

Regarding the cervical cerclage as a method of preventing preterm labor, we clearly suggest that it should be performed only in women with previous history of preterm labor and if ultrasound examinations indicate cervical incompetence.

12. Biochemical markers of preterm labor

1. Vaginocervical cytokines

2. Vaginocervical and/or proteases

3. Maternal and/or fetal distress index CRH (Corticotropin-releasing hormone) estradiol, estriol (plasma, urine)

4. Fibronectin (vaginocervical)

12.1 Vaginocervical fetal fibronectin (fFN)

Vaginocervical fetal fibronectin (fFN) is a glycoprotein of the extracellular matrix that affects the maintenance of placental adherence to the maternal decidua. Generally, fFN can be found in cervicovaginal fluid early in gestation until 20th week. The detection of fFN after the 20 week may indicate a disruption of the decidual-chorionic interface of the amniotic membrane and is linked with a significant increased risk of preterm labor. Diagnostic tests based on fFN have sensitivity 81.7% and specificity 82.5%.

The absence of FFN is a strong marker that preterm labor is unlikely to occur within the next 7–14 days. So, negative prognostic value in some studies exceeding 99%. The prognostic value of FFN is higher in pregnancies 24–28 weeks, in

comparison with older gestational ages and much stronger for short-term predictions (7–14 days), than in using for the overall outcome [56, 66–69].

13. Preterm labor diagnosis

Painful contractions are observed at regular intervals combined with progressive effacement and dilation of the cervix. However in 50% of cases contractions may not induce premature labor.

14. Pre-symptomatic control for preterm labor

Cervical assessment is necessary to evaluate the risk for preterm labor. Cervical length <15 mm observed in 2% of women in 23th w, in 90% of cases happens labor before 28 weeks.

Cervical length >15 mm implies 4% risk for preterm labor.

Cervical length < 5 mm implies 78% risk for preterm labor.

High Bishop's score increases the risk of preterm labor.

Using the ultrasound cervical length measurement we have to remember that normal average is about 34–40 mm, without bulging of the fetal membranes into the internal os. The major risk factor coming from obstetric history that can be used for the evaluation of preterm risk in the current pregnancy is the previous preterm labor. Avoiding factors as urinary tract infections, vaginal infections, smoking, drug abuse and physically demanding work is also important [56, 66–73].

14.1 Fetal fibronectin measurement

Fetal fibronectin helps to maintain the integrity of the extracellular matrix between chorion villi and basal decidua. It is usually not detected after 20 weeks and until the membranes rupture happens.

If fibronectin was detected, the risk of preterm labor significantly increases.

The presence of fibronectin at 23 weeks implies 60% possibility for labor before 28th week.

15. Preterm neonates and prematurity complications

The prematurity importance is related to the complications that brings both for the newborn survival as well as for the later development. These complications are often unknown and maybe have unclear long-term effects. Medical decisions are normally defined by the possible effects in combination with the available information depending on the gestational age.

Complications of preterm labor arise from immature systems and organs that are not able to normally function in a ecto-uterine environment. The risk of acute neonatal disease decreases with advancing gestational age demonstrating the fragility of the brain, lungs, immune system, kidneys, skin, eyes and gastrointestinal tract.

15.1 Disorders of preterm neonates

The following are the most important acute and chronic problems faced by premature infants admitted to the Intensive Care Unit. More specifically, these refer

the developmental and mental retardation, cerebral palsy, deafness, blindness, transient dystonia, feeding difficulties and speech delay [70–83].

15.1.1 Disorders of thermoregulation

Premature infants usually present difficulties in thermoregulation due to the immaturity of the homeostatic mechanism of production and elimination. Contributing factors include the large ratio of body surface area/weight, thin and immature skin, immaturity of the autonomic nervous system and incomplete development of sweat glands that can allow increased heat and fluid loss.

15.1.2 Newborn respiratory distress syndrome

Newborn Respiratory Distress Syndrome (NRBS) or hyaline membrane disease is caused due to the deficiency of surfactant factor and is clinically manifested with respiratory distress of varying severity. Its frequency is inversely proportional to gestational age, reaching 80% for premature infants born before 28 weeks. Surfactant factor is produced by pneumocytes type II and reduces cell surface tension by preventing the development of atelectasis at the end of expiration.

In premature infants, in which the surfactant is deficient, cell atelectasis develops and gas exchange is disrupted. Newborns with RDS show respiratory distress immediately after birth or within the first 4 hours, clinically presented by tachypnea, intercostal or subcostal retraction, wheezing, tachycardia and cyanosis.

Diagnosis based on x-ray chest as there are characteristic findings, consisting of an air bronchogram and a reticular appearance that can reach to complete opacity. Treatment is etiological by intratracheally administration of exogenous surfactant factor.

Symptomatic treatment of NRDS is based on oxygen administration and continuous positive airway pressure (CPAP) can be applied with a nasopharyngeal catheter or mechanical ventilation through a tracheal tube [70–83] (**Figures 1-3**).

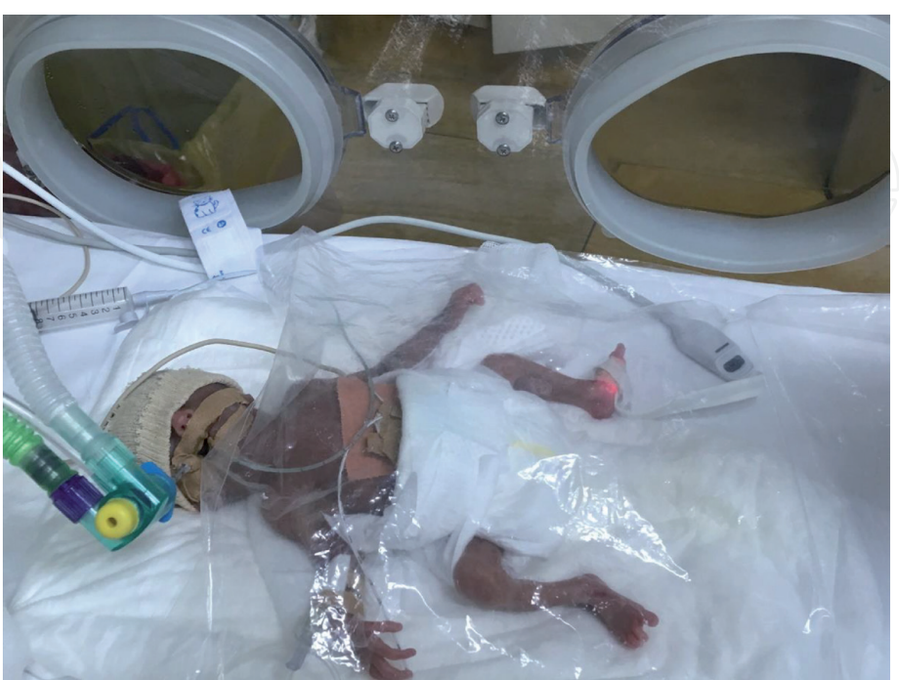

Figure 1.
Intubated neonate.

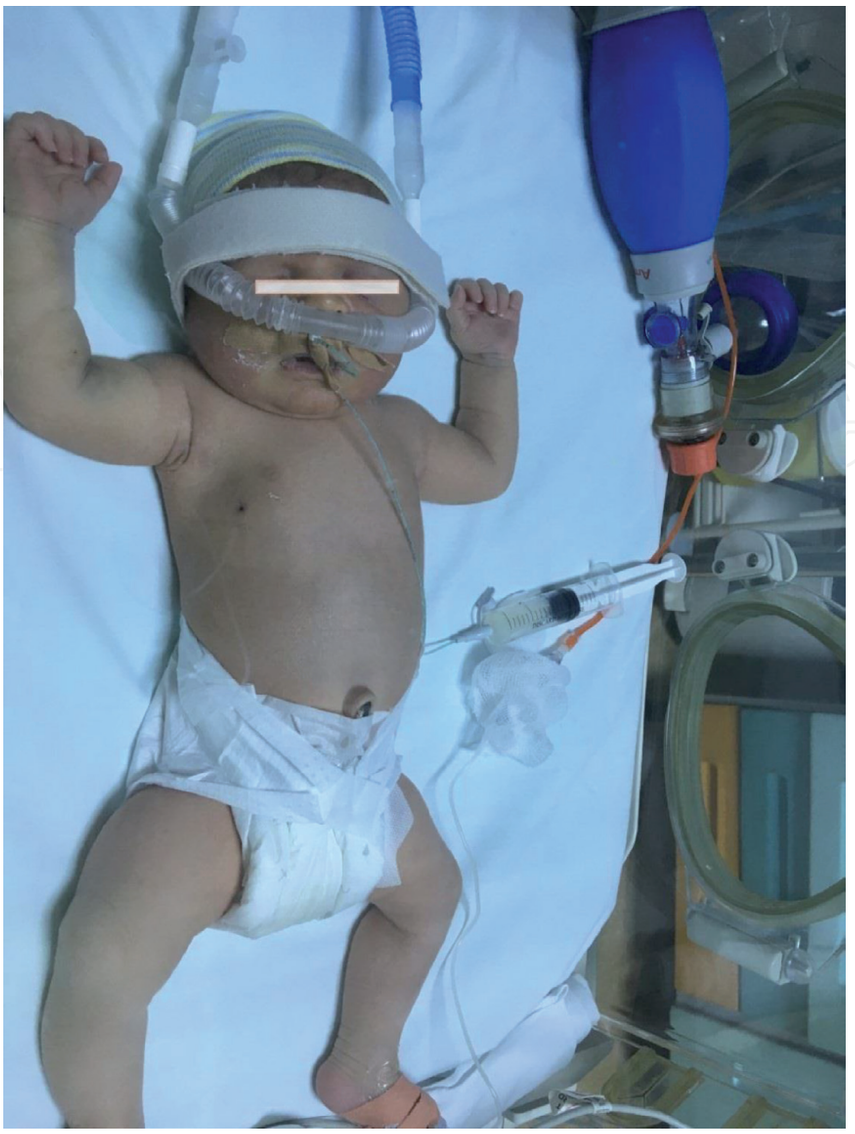

Figure 2.
CPAP in preterm neonate.

15.1.3 Apnea prematurity and bradycardia

In preterm neonates born < 32 weeks of gestation, apnea episodes are common, characterized by periods of stop breathing lasting more than 10–15 seconds, accompanied by cyanosis and bradycardia.

15.1.4 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia or chronic lung disease is the most common lung disease affecting premature neonates. It is characterized by rapid and shallow breathing, dyspnea, shortness of breath, cough, and need for more oxygen. Bronchopulmonary dysplasia may be a temporary condition, but in some children, symptoms persist into adulthood, increasing the risk of developing chronic respiratory disease, such as chronic obstructive pulmonary disease (COPD) [70–83].

15.1.5 Cardiovascular disorders

These symptoms include prolonged capillary refill (>3 seconds), paleness, decreased muscle tone, lethargy, tachycardia followed by bradycardia and persistent

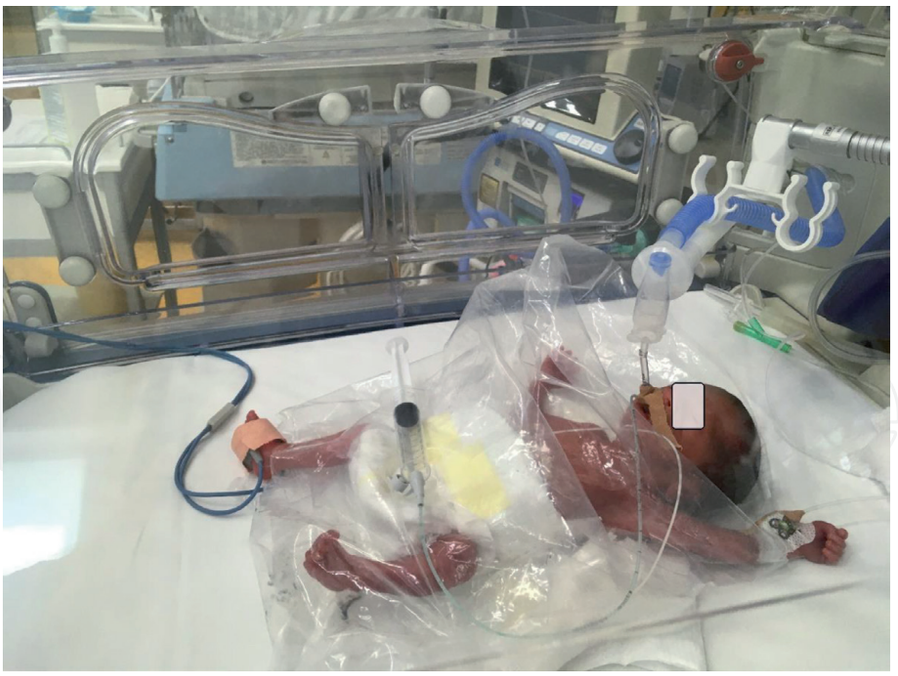

Figure 3.
Preterm neonate,weight 490 gr, 23 W.

respiratory distress, despite oxygen administration and mechanical respiratory support. In some neonates, hypotension appears from the beginning or as a late sign of shock [70–83].

15.1.6 Patent ductus arteriosus (PDA)

The major cardiovascular disorder of premature neonates is the patent ductus arteriosus stay. Its frequency reaches 25% of the total in all preterm infants and exceeds 50% in those born less than 1000 grams.

PDA may be asymptomatic or clinically presented by intense heartbeat, Corrigan pulse, and systolic or continuous murmur. If there is severe left–right escape, it causes pulmonary congestion with difficulty breathing and increased need for oxygen and mechanical respiratory support. Other manifestations include tachycardia, hepatomegaly, heart failure, and recurrent episodes of apnea. The diagnosis is based on chest X-ray which shows pulmonary edema or an increase heart shadow and on clinical examination. Finally, it is confirmed by echocardiogram, heart and large vessels Doppler. Treatment includes fluid restriction and administration of indomethacin or ibuprofen. If conservative treatment does not work then duct surgical ligation is performed [70–83].

15.1.7 Neurological disorders

Central nervous system of preterm neonates is really susceptible specifically in damages caused by labor injuries that can affect the immature intracranial structures, by the capillary bleeding, by coagulation disorders and recurrent hypoxia. It's also worth to mention the perseverance for hypoglycemia and blood pressure fluctuations that reflect in cerebral flow and pressure [70–83].

15.1.8 Neonatal brain hemorrhage

Cerebral bleed is one of the most serious problems of prematurity, as it is the commonest cause of death and disability. Its frequency is inversely proportional to

gestational age and occurs in 50–60% of newborns born less than 1000 grams and in 10–20% of newborns with a birth weight of 1000 to 1500 grams [3].

The frequency has actually decreased in recent years, however, cerebral hemorrhage remain a major complication, as the survival of very preterm infants increases. 90% of brain bleeding occur in the first 3 days of life and starts in the germinal matrix, a group of immature thin-walled capillaries which is located on the head of the caudate nucleus and underneath ventricular ependyma, behind the Monroe foramen.

Size of this area is gradually decreasing, starting from 2.5 mm at 23–24 weeks to 1.4 mm at 32 weeks, and is completely regressed at 34 weeks. The diagnosis of cerebral hemorrhage and its complications based on brain ultrasound [70–83].

15.1.9 Gastrointestinal disorders

Nutrition improvement is particularly essential in the treatment of low birth weight full-term infants as well as in preterm neonates. All preterm infants are at risk due to limited nutrient stores and specific physical and developmental characteristics [70–83].

15.1.10 Necrotizing enterocolitis

The incidence of the disease in extremely preterm infants can reached 10% and the mortality in these children is about 30%. Prematurity is the most important risk factor.

The onset of the disease initiates usually within the first 10 days of life (in 90% of cases), but can range from the 1st day of life until to the 3rd month.

Symptoms in newborns vary and in mild cases recess without important sequel. Abdominal distention and lethargy are early signs of a more serious form of the disease, followed by bilious vomiting, gastrointestinal bleeding and, in severe cases, erythema of the anterior abdominal wall (especially in periumbical region).

The prognosis is actually bad and mortality rate can reach up to 20%. Bowel stenosis and malabsorption syndrome in cases of surgical resection of a large part of the intestine are some long-term complications [70–83].

15.1.11 Hematological disorders

The premature neonate is usually predisposed to hematological disorders due to increased capillary fragility, increased bleeding mood, slow red blood cell production, increased fetal hemoglobin, blood loss due to frequent peripheral blood draws and decreased albumin levels in peripheral blood. These newborns are checked for signs of bleeding at the puncture site, in the gastrointestinal tract and in the respiratory system.

15.1.12 Metabolic disorders

- Hypocalcaemia

- Hypoglycemia

  Hypoglycaemia is defined as a fall in serum glucose below 40mg/dl for preterm and full-term infants.

- Hyperglycemia

  Hyperglycemia is defined as an increase in the plasma glucose value> 130 mg/dl.

Retinopathy of prematurity
It is observed in very premature infants, who have been given oxygen in large concentrations and for a long time. After the recognition of the administered oxygen as a causative factor, the retinopathy of prematurity is now a rare disease. Newborns who are more likely to develop retinopathy are those weighing less than 1,500 grams and those who have been given oxygen in high doses for a prolonged therapy.

- Neonatal jaundice

Jaundice is probably the most common neonatal disorder especially in premature neonates.

15.2 Preterm labor management

Maternal well-being control (infection; bleeding; WB; CRP; Urine and vaginal culture).

Fetal Well-being control (NST, US, Blood pressure, Doppler).

Corticosteroids administration if preterm labor <34 weeks is possible (betamethazone, dexamethazone) result to decrease newborn respiratory distress syndrome (50%), necrotizing enterocolitis and intraventricular hemorrhage.

Corticosteroids are contraindicated in cases of maternal sepsis.

Antibiotics: are not routinely recommended, if maternal infection is absent.

Tocolysis is recommended at least until steroids administration is completed [70–83].

15.2.1 Contraindications of tocolysis

A. Relatives

Severe Vaginal bleeding
Preclamspia
Severe fetal growth restriction

B. Absolute

Fetal death
Fetal anomalies incompatible with life
Chorioamnionitis
Severe fetal distress
Maternal indication for delivery

16. Conclusion

Despite the great progress of neonatology and prenatal medicine, prematurity is a serious factor in neonatal morbidity and mortality. Causative factors leading to prematurity have not yet been completely identified and are a really multifactorial condition. Preterm labor can be caused by a number of many different factors, such as in the case of various infections or diseases of the mother, in the absence of prenatal control, the low socio-economic level. Preterm labor is a traumatic experience and extremely stressful not only for the newborn but for the whole family.

Parents are possessed by feelings of frustration, failure as well as anxiety about the survival and future development of their baby.

The severity of a preterm birth lies in the fact that premature neonates are at greater risk for short-term and long-term complications including normal physical and mental development, disability and congenital disorders.

This is because the newborn is fully developed in the last weeks of pregnancy. That's the reason that medical and obstetric staff should contribute from the beginning of a pregnancy, in the investigation of all the causes of preterm labor in order to apply in clinical routine the appropriate treatment protocols.

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References

[1] Adams MM, Read JA, Rawlings JS, Harlass FB, Sarno AP, Rhodes PH. Preterm delivery among black and white enlisted women in the United States Army. Obstet Gynecol. 1993 Jan;81(1):65-71. PMID: 8416464

[2] Blackmore CA, Savitz DA, Edwards LJ, Harlow SD, Bowes WA Jr.Racial differences in the patterns of preterm delivery in central North Carolina, USA. Paediatr Perinat Epidemiol. 1995 Jul;9(3):281-95. doi: 10.1111/j.1365-3016.1995.tb00144.x. PMID: 7479277

[3] Schieve LA, Handler A Preterm delivery and perinatal death among black and white infants in a Chicago-area perinatal registry. Obstet Gynecol. 1996 Sep;88(3):356-63. doi: 10.1016/0029-7844(96)00203-7. PMID: 8752239

[4] Reynolds HD. Bacterial vaginosis and its implication in preterm labor and premature rupture of membranes. A review of the literature. J Nurse Midwifery. 1991 Sep-Oct;36(5):289-96. doi: 10.1016/0091-2182(91)90043-o. PMID: 1757814 Review.

[5] Newton ER. Preterm labor, preterm premature rupture of membranes, and chorioamnionitis. Clin Perinatol. 2005 Sep;32(3):571-600. doi: 10.1016/j.clp.2005.05.001. PMID: 16085021 Review.

[6] Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, Thornton JG, Crowther CA; PPROMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet. 2016 Jan 30;387(10017):444-52. doi: 10.1016/S0140-6736(15)00724-2. Epub 2015 Nov 10. PMID: 26564381

[7] Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. J. Pediatrics. 2003 Jan;111(1):e61-6. doi: 10.1542/peds.111.1.e61. PMID: 12509596 Free PMC article.

[8] Alexander GR, Tompkins ME, Allen MC, Hulsey TC.Trends and racial differences in birth weight and related survival. Matern Child Health J. 1999 Jun;3(2):71-9. doi: 10.1023/a:1021849209722. PMID: 10892415

[9] Alexander GR, Kogan MD, Himes JH, Mor JM, Goldenberg R Racial differences in birthweight for gestational age and infant mortality in extremely-low-risk US populations. . Paediatr Perinat Epidemiol. 1999 Apr;13(2):205-17. doi: 10.1046/j.1365-3016.1999.00174.x. PMID: 10214610

[10] J. DeFranco EA, Hall ES, Muglia L Racial disparity in previable birth. Am J Obstet Gynecol. 2016 Mar;214(3):394.e1-7. doi: 10.1016/j.ajog.2015.12.034. Epub 2015 Dec 22. PMID: 26721776

[11] Berger TM, Bernet V, El Alama S, Fauchère JC, Hösli I, Irion O, Kind C, Latal B, Nelle M, Pfister RE, Surbek D, Truttmann AC, Wisser J, Zimmermann R. Perinatal care at the limit of viability between 22 and 26 completed weeks of gestation in Switzerland. 2011 revision of the Swiss recommendations. Swiss Med Wkly. 2011 Oct 18;141:w13280. doi: 10.4414/smw.2011.13280. eCollection 2011. PMID: 22009720 Review.

[12] Ananth CV, Friedman AM, Gyamfi-Bannerman C Epidemiology of moderate preterm, late preterm and early term delivery. Clin Perinatol. 2013 Dec;40(4):601-10. doi: 10.1016/j.clp.2013.07.001. Epub 2013 Sep 20. PMID: 24182950

[13] Chapman E, Reveiz L, Illanes E, Bonfill Cosp X. Antibiotic regimens for management of intra-amniotic infection. Cochrane Database Syst Rev. 2014 Dec 19;(12):CD010976. doi: 10.1002/14651858.CD010976.pub2. PMID: 25526426 Review.

[14] Buchanan SL, Crowther CA, Levett KM, Middleton P, Morris J. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database Syst Rev. 2010 Mar 17;(3):CD004735. doi: 10.1002/14651858.CD004735.pub3. PMID: 20238332

[15] Andrews WW, Goldenberg RL; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned from an antibiotic trial in fetal fibronectin positive women. Semin Perinatol. 2003 Jun;27(3):231-8. doi: 10.1016/s0146-0005(03)00006-5. PMID: 12889590 Review.

[16] Sanu O, Lamont RF. Periodontal disease and bacterial vaginosis as genetic and environmental markers for the risk of spontaneous preterm labor and preterm birth. J Matern Fetal Neonatal Med. 2011 Dec;24(12):1476-85. doi: 10.3109/14767058.2010.545930. Epub 2011 Jan 24. PMID: 21261445

[17] Beckmann M, Gardener G. Hospital versus outpatient care for preterm pre-labour rupture of membranes. Aust N Z J Obstet Gynaecol. 2013 Apr;53(2):119-24. doi: 10.1111/ajo.12021. Epub 2012 Dec 6. PMID: 23216409

[18] Faucett AM, Metz TD, DeWitt PE, Gibbs RS Effect of obesity on neonatal outcomes in pregnancies with preterm premature rupture of membranes. Am J Obstet Gynecol. 2016 Feb;214(2):287.e1-287.e5. doi: 10.1016/j.ajog.2015.09.093. Epub 2015 Oct 3. PMID: 26435047

[19] Hernández y Ballinas A, López Farán JA, Gámez Guevara C. Comparison of maternal and perinatal outcomes in the conservative treatment preterm premature membrane rupture between the use of erythromycin and clindamycin. Ginecol Obstet Mex. 2011 Jul;79(7):403-10. PMID: 21966834 Clinical Trial. Spanish.

[20] Wong LF, Holmgren CM, Silver RM, Varner MW, Manuck TA.Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks. Am J Obstet Gynecol. 2015 Feb;212(2):215.e1-9. doi: 10.1016/j.ajog.2014.09.005. Epub 2014 Sep 16. PMID: 25218125 Free PMC article.

[21] Pasquier JC, Claris O, Rabilloud M, Ecochard R, Picaud JC, Moret S, Buch D, Mellier G Intentional early delivery versus expectant management for preterm premature rupture of membranes at 28-32 weeks' gestation: A multicentre randomized controlled trial (MICADO STUDY). Eur J Obstet Gynecol Reprod Biol. 2019 Feb;233:30-37. doi: 10.1016/j.ejogrb.2018.11.024. Epub 2018 Dec 5. PMID: 30553135 Clinical Trial.

[22] Gyamfi-Bannerman C. Late preterm birth: management dilemmas. Obstet Gynecol Clin North Am. 2012 Mar;39(1):35-45. doi: 10.1016/j.ogc.2011.12.005. PMID: 22370106

[23] Fuchs K, Wapner R. Elective cesarean section and induction and their impact on late preterm births. Clin Perinatol. 2006 Dec;33(4):793-801; abstract viii. doi: 10.1016/j.clp.2006.09.010. PMID: 17148005 Review.

[24] Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. Clin Perinatol. 2008 Jun;35(2):325-41, vi. doi: 10.1016/j.clp.2008.03.003. PMID: 18456072 Review.

[25] Wong AE, Grobman WA. Medically indicated--iatrogenic prematurity. Clin Perinatol. 2011 Sep;38(3):423-39. doi: 10.1016/j.clp.2011.06.002. Epub 2011 Jul 23. PMID: 21890017 Review.

[26] Meloni A, Antonelli A, Deiana S, Rocca A, Atzei A, Paoletti AM, Melis GB. Late preterm: obstetric management. J Matern Fetal Neonatal Med. 2010 Oct;23 Suppl 3:113-5. doi: 10.3109/14767058.2010.512137. PMID: 20873975

[27] Carter D. Elective early births put moms and infants at risk. Am J Nurs. 2012 Apr;112(4):19-20. doi: 10.1097/01.NAJ.0000413449.20830.f9. PMID: 22456560

[28] Goldenberg RL, Iams JD, Das A, Mercer BM, Meis PJ, Moawad AH, Miodovnik M, VanDorsten JP, Caritis SN, Thurnau GR, Dombrowski MP, Roberts JM, McNellis D. The Preterm Prediction Study: sequential cervical length and fetal fibronectin testing for the prediction of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 2000 Mar;182(3):636-43. doi: 10.1067/mob.2000.104212. PMID: 10739521

[29] Goldenberg RL, Iams JD, Miodovnik M, Van Dorsten JP, Thurnau G, Bottoms S, Mercer BM, Meis PJ, Moawad AH, Das A, Caritis SN, McNellis D. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1996 Oct;175(4 Pt 1):1047-53. doi: 10.1016/s0002-9378(96)80051-2. PMID: 8885774

[30] Goepfert AR, Goldenberg RL, Andrews WW, Hauth JC, Mercer B, Iams J, Meis P, Moawad A, Thom E, VanDorsten JP, Caritis SN, Thurnau G, Miodovnik M, Dombrowski M, Roberts J, McNellis D; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The Preterm Prediction Study: association between cervical interleukin 6 concentration and spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 2001 Feb;184(3):483-8. doi: 10.1067/mob.2001.109653. PMID: 11228507

[31] Yu H, Wang X, Gao H, You Y, Xing A. Perinatal outcomes of pregnancies complicated by preterm premature rupture of the membranes before 34 weeks of gestation in a tertiary center in China: A retrospective review. Biosci Trends. 2015 Feb;9(1):35-41. doi: 10.5582/bst.2014.01058. PMID: 25787907 Review.

[32] Simhan HN, Canavan TP. Preterm premature rupture of membranes: diagnosis, evaluation and management strategies. BJOG. 2005 Mar;112 Suppl 1:32-7. doi: 10.1111/j.1471-0528.2005.00582.x. PMID: 15715592 Review.

[33] Tsikouras P, Anastasopoulos G, Maroulis V, Bothou A, Chalkidou A, Deuteraiou D, Anthoulaki X, Tsatsaris G, Bourazan AH, Iatrakis G, Zervoudis S, Galazios G, Inagamova LK, Csorba R, Teichmann AT. Comparative Evaluation of Arabin Pessary and Cervical Cerclage for the Prevention of Preterm Labor in Asymptomatic Women with High Risk Factors. Int J Environ Res Public Health. 2018 Apr 18;15(4):791. doi: 10.3390/ijerph15040791. PMID: 29670041

[34] Sieroszewski P, Jasiński A, Perenc M, Banach R, Oszukowski P. The Arabin pessary for the treatment of threatened mid-trimester miscarriage or premature labour and miscarriage: a case series. J Matern Fetal Neonatal Med. 2009 Jun;22(6):469-72. doi:

10.1080/14767050802531748. PMID: 19530009 Clinical Trial.

[35] Barinov SV, Shamina IV, Lazareva OV, Tirskaya YI, Ralko VV, Shkabarnya LL, Dikke GB, Kochev DM, Klementyeva LL. Comparative assessment of arabin pessary, cervical cerclage and medical management for preterm birth prevention in high-risk pregnancies. J Matern Fetal Neonatal Med. 2017 Aug;30(15):1841-1846. doi: 10.1080/14767058.2016.1228054. Epub 2016 Sep 9. PMID: 27550418

[36] Ting YH, Lao TT, Wa Law L, Hui SY, Chor CM, Lau TK, Yeung Leung T. Arabin cerclage pessary in the management of cervical insufficiency. J Matern Fetal Neonatal Med. 2012 Dec;25(12):2693-5. doi: 10.3109/14767058.2012.712559. Epub 2012 Aug 22. PMID: 22871155

[37] Boelig RC, Berghella V. Current options for mechanical prevention of preterm birth. Semin Perinatol. 2017 Dec;41(8):452-460. doi: 10.1053/j.semperi.2017.08.003. Epub 2017 Oct 13. PMID: 29033106 Review.

[38] Saccone G, Ciardulli A, Xodo S, Dugoff L, Ludmir J, Pagani G, Visentin S, Gizzo S, Volpe N, Maruotti GM, Rizzo G, Martinelli P, Berghella V.Cervical Pessary for Preventing Preterm Birth in Singleton Pregnancies With Short Cervical Length: A Systematic Review and Meta-analysis. J Ultrasound Med. 2017 Aug;36(8):1535-1543. doi: 10.7863/ultra.16.08054. Epub 2017 Apr 11. PMID: 28398701

[39] Bonanno C, Wapner RJ. Antenatal corticosteroids in the management of preterm birth: are we back where we started? Obstet Gynecol Clin North Am. 2012 Mar;39(1):47-63. doi: 10.1016/j.ogc.2011.12.006. PMID: 22370107

[40] Briceño-Pérez C, Reyna-Villasmil E, Vigil-De-Gracia P. Antenatal corticosteroid therapy: Historical and scientific basis to improve preterm birth management. . Eur J Obstet Gynecol Reprod Biol. 2019 Mar;234:32-37. doi: 10.1016/j.ejogrb.2018.12.025. Epub 2019 Jan 6. PMID: 30639954 Review.

[41] Fuchs F, Audibert F, Senat MV. Prenatal corticosteroids: short-term and long-term effects of multiple courses. Literature review in 2013. J Gynecol Obstet Biol Reprod (Paris). 2014 Mar;43(3):211-7. doi: 10.1016/j.jgyn.2013.11.015. Epub 2014 Feb 12. PMID: 24529761 Review. French.

[42] Crowther CA, Ashwood P, Andersen CC, Middleton PF, Tran T, Doyle LW, Robinson JS, Harding JE; ASTEROID Study Group.Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. Lancet Child Adolesc Health. 2019 Nov;3(11):769-780. doi: 10.1016/S2352-4642(19)30292-5. Epub 2019 Sep 12. PMID: 31523039 Clinical Trial.

[43] Hong S, Lee SM, Kwak DW, Lee J, Kim SY, Oh JW, Oh S, Park CW, Park JS, Chung JH, Jun JK. Effects of antenatal corticosteroids in twin neonates with late preterm birth (ACTWIN [Antenatal Corticosteroids in TWIN late preterm neonates] trial): study protocol for a randomized controlled trial. BMC Pregnancy Childbirth. 2019 Apr 3;19(1):114. doi: 10.1186/s12884-019-2235-5. PMID: 30943910 Free PMC article.

[44] Hong S, Lee SM, Kwak DW, Lee J, Kim SY, Oh JW, Oh S, Park CW, Park JS, Chung JH, Jun JK. Schmitz T. Prevention of preterm birth complications by antenatal corticosteroid administration. J Gynecol Obstet Biol Reprod (Paris). 2016 Dec;45(10):1399-1417. doi: 10.1016/j.jgyn.2016.09.008. Epub 2016 Oct 21. PMID: 27776846 Review

[45] Mercer B. Antibiotics in the management of PROM and preterm labor. . Obstet Gynecol Clin North Am. 2012 Mar;39(1):65-76. doi: 10.1016/j.ogc.2011.12.007. Epub 2012 Jan 28. PMID: 22370108

[46] Jackson GL, Rawiki P, Sendelbach D, Manning MD, Engle WD. Hospital course and short-term outcomes of term and late preterm neonates following exposure to prolonged rupture of membranes and/or chorioamnionitis. Pediatr Infect Dis J. 2012 Jan;31(1):89-90. doi: 10.1097/INF.0b013e31822fb15d. PMID: 21860336

[47] Hernández y Ballinas A, López Farán JA, Gámez Guevara C. Comparison of maternal and perinatal outcomes in the conservative treatment preterm premature membrane rupture between the use of erythromycin and clindamycin. Ginecol Obstet Mex. 2011 Jul;79(7):403-10. PMID: 21966834 Clinical Trial. Spanish.

[48] Ovalle A, Romero R, Gómez R, Martínez MA, Nien JK, Ferrand P, Aspillaga C, Figueroa J. Antibiotic administration to patients with preterm labor and intact membranes: is there a beneficial effect in patients with endocervical inflammation? . J Matern Fetal Neonatal Med. 2006 Aug;19(8):453-64. doi: 10.1080/14767050600852668. PMID: 16966109 Clinical Trial.

[49] Newton ER. Preterm labor, preterm premature rupture of membranes, and chorioamnionitis. Clin Perinatol. 2005 Sep;32(3):571-600. doi: 10.1016/j.clp.2005.05.001. PMID: 16085021 Review.

[50] Singh K, Mercer B. Antibiotics after preterm premature rupture of the membranes. Clin Obstet Gynecol. 2011 Jun;54(2):344-50. doi: 10.1097/GRF.0b013e318217ec5d. PMID: 21508705

[51] Mothers' experiences of parenting and everyday life of children born at 23 weeks of gestation - a qualitative descriptive study. Väliaho A, Lehtonen L, Axelin A, Korja R. BMC Pediatr. 2021 Jan 23;21(1):48. doi: 10.1186/s12887-020-02478-y. PMID: 33485315 Free PMC article.

[52] An Initiative to Reduce Preterm Infants Pre-discharge Growth Failure Through Time-specific Feeding Volume Increase. Chu SS, White HO, Rindone SL, Tripp SA, Rhein LM. Pediatr Qual Saf. 2020 Dec 28;6(1):e366. doi: 10.1097/pq9.0000000000000366. eCollection 2021 Jan-Feb. PMID: 33403313

[53] Ozkur M, Dogulu F, Ozkur A, Gokmen B, Inaloz SS, Aynacioglu AS. Association of the Gln27Glu polymorphism of the beta-2-adrenergic receptor with preterm labor. Int J Gynaecol Obstet. 2002 Jun;77(3):209-15. doi: 10.1016/s0020-7292(02)00035-8. PMID: 12065131

[54] Landau R. Genetic contributions to labor pain and progress. Clin Perinatol. 2013 Sep;40(3):575-87. doi: 10.1016/j.clp.2013.05.014. Epub 2013 Jun 27. PMID: 23972758 Review.

[55] Landau R, Liu SK, Blouin JL, Carvalho B. The effect of OPRM1 and COMT genotypes on the analgesic response to intravenous fentanyl labor analgesia. Anesth Analg. 2013 Feb;116(2):386-91. doi: 10.1213/ANE.0b013e318273f2c7. Epub 2013 Jan 9. PMID: 23302985

[56] Song Z, Du B, Wang K, Shi X. Effects of OPRM1 A118G polymorphism on epidural analgesia with fentanyl during labor: a meta-analysis. Genet Test Mol Biomarkers. 2013 Oct;17(10):743-9. doi: 10.1089/gtmb.2013.0282. Epub 2013 Aug 2. PMID: 23909491 Review.

[57] Hannah C Glass, Andrew T Costarino, Stephen A Stayer, Claire M

Brett, Franklyn Cladis, Peter J Davis Outcomes for extremely premature infants PMID: 25988638 PMCID: PMC4438860

[58] Salverda HH, Oldenburger NJ, Rijken M, Pauws SC, Dargaville PA, Te Pas AB. The effect of automated oxygen control on clinical outcomes in preterm infants: a pre- and post-implementation cohort study. Eur J Pediatr. 2021 Feb 23. doi: 10.1007/s00431-021-03982-8. Online ahead of print. PMID: 33619593

[59] Early protein intake predicts functional connectivity and neurocognition in preterm born children. Duerden EG, Thompson B, Poppe T, Alsweiler J, Gamble G, Jiang Y, Leung M, Tottman AC, Wouldes T, Miller SP, Harding JE; PIANO study group. Sci Rep. 2021 Feb 18;11(1):4085. doi: 10.1038/s41598-021-83125-z. PMID: 33602973 Free PMC article.

[60] Precordial ECG Amplitudes in the Days After Birth: Electrocardiographic Changes During Transition from Fetal to Neonatal Circulation. Hvidemose SO, Pærregaard MM, Pihl CA, Pietersen AH, Iversen KK, Bundgaard H, Christensen AH. Pediatr Cardiol. 2021 Jan 28. doi: 10.1007/s00246-021-02547-8. Online ahead of print. PMID: 33507333

[61] Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. Am J Obstet Gynecol. 1995 Oct;173(4):1049-57. doi: 10.1016/0002-9378(95)91325-4. PMID: 7485292

[62] Gargano JW, Holzman CB, Senagore PK, Reuss ML, Pathak DR, Friderici KH, Jernigan K, Fisher R. Polymorphisms in thrombophilia and renin-angiotensin system pathways, preterm delivery, and evidence of placental hemorrhage. Am J Obstet Gynecol. 2009 Sep;201(3):317.e1-9. doi: 10.1016/j.ajog.2009.05.060. PMID: 19733287

[63] Nemeth E, Millar LK, Bryant-Greenwood G. Fetal membrane distention: II. Differentially expressed genes regulated by acute distention in vitro. Am J Obstet Gynecol. 2000 Jan;182(1 Pt 1):60-7. doi: 10.1016/s0002-9378(00)70491-1. PMID: 10649157

[64] Genetics of the cervix in relation to preterm birth. Warren JE, Silver RM. Semin Perinatol. 2009 Oct;33(5):308-11. doi: 10.1053/j.semperi.2009.06.003. PMID: 19796727 Review

[65] Shanbhag S, Clark H, Timmaraju V, Bhattacharya S, Cruickshank M. Pregnancy outcome after treatment for cervical intraepithelial neoplasia. Obstet Gynecol. 2009 Oct;114(4):727-735. doi: 10.1097/AOG.0b013e3181b5cba3. PMID: 19888028

[66] Pettersson FD, Grönbladh A, Nyberg F, Sundström-Poromaa I, Åkerud H. The A118G single-nucleotide polymorphism of human μ-opioid receptor gene and use of labor analgesia. Reprod Sci. 2012 Sep;19(9):962-7. doi: 10.1177/1933719112438970. Epub 2012 Apr 23. PMID: 22527985

[67] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL; European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. European Association of Perinatal Medicine. Neonatology. 2013;103(4):353-68. doi: 10.1159/000349928. Epub 2013 May 31. PMID: 23736015

[68] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Halliday HL; European consensus

guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update. European Association of Perinatal Medicine. Neonatology. 2010 Jun;97(4):402-17. doi: 10.1159/000297773. Epub 2010 Jun 10. PMID: 20551710

[69] Sweet D, Bevilacqua G, Carnielli V, Greisen G, Plavka R, Saugstad OD, Simeoni U, Speer CP, Valls-I-Soler A, Halliday H; European consensus guidelines on the management of neonatal respiratory distress syndrome. Working Group on Prematurity of the World Association of Perinatal Medicine; European Association of Perinatal Medicine. J Perinat Med. 2007;35(3):175-86. doi: 10.1515/JPM.2007.048. PMID: 17480144

[70] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA, Halliday HL European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. . Neonatology. 2019;115(4):432-450. doi: 10.1159/000499361. Epub 2019 Apr 11. PMID: 30974433 Free PMC article.

[71] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GH, Halliday HL. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. Neonatology. 2017;111(2):107-125. doi: 10.1159/000448985. Epub 2016 Sep 21. PMID: 27649091

[72] Rodriguez RJ. Management of respiratory distress syndrome: an update. Respir Care. 2003 Mar;48(3):279-86; discussion 286-7. PMID: 12667277 Review.

[73] Low JA, Wood SL, Killen HL, Pater EA, Karchmar EJ. Intrapartum asphyxia in the preterm fetus less than 2000 gm. Am J Obstet Gynecol. 1990 Feb;162(2):378-82. doi: 10.1016/0002-9378(90)90390-s. PMID: 2309819

[74] Low JA, Pickersgill H, Killen H, Derrick EJ. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol. 2001 Mar;184(4):724-30. doi: 10.1067/mob.2001.111720. PMID: 11262479

[75] Low JA, Pancham SR, Piercy WN, Worthington D, Karchmar J. Intrapartum fetal asphyxia: clinical characteristics, diagnosis, and significance in relation to pattern of development. Am J Obstet Gynecol. 1977 Dec 15;129(8):857-72. doi: 10.1016/0002-9378(77)90519-1. PMID: 22248

[76] Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the preterm fetus. Am J Obstet Gynecol. 1995 Mar;172(3):805-10. doi: 10.1016/0002-9378(95)90003-9. PMID: 7892868

[77] Low JA. Intrapartum fetal asphyxia: definition, diagnosis, and classification. Am J Obstet Gynecol. 1997 May;176(5):957-9. doi: 10.1016/s0002-9378(97)70385-5. PMID: 9166151 Review.

[78] Low JA. The relationship of asphyxia in the mature fetus to long-term neurologic function. Clin Obstet Gynecol. 1993 Mar;36(1):82-90. doi: 10.1097/00003081-199303000-00011. PMID: 8435949 Review.Anesth Analg 1994 May;78(5):912-7. doi: 10.1213/00000539-199405000-00013.

[79] S H Rolbin, M M Cohen, C M Levinton, E N Kelly, D Farine. The premature infant: anesthesia for cesarean delivery PMID: 8160989 DOI: 10.1213/00000539-199405000-00013

[80] Nwafor MI, Aniebue UU, Nwankwo TO, Onyeka TC, Okafor VU. Perinatal outcome of preterm cesarean section in a resource-limited centre: a comparison between general anaesthesia and subarachnoid block. Niger J Clin Pract. 2014 Sep-Oct;17(5):613-8. doi: 10.4103/1119-3077.141428. PMID: 25244273

[81] Levy BT, Dawson JD, Toth PP, Bowdler N. Predictors of neonatal resuscitation, low Apgar scores, and umbilical artery pH among growth-restricted neonates. Obstet Gynecol. 1998 Jun;91(6):909-16. doi: 10.1016/s0029-7844(98)00094-5. PMID: 9610995

[82] Ong BY, Cohen MM, Palahniuk RJ. Anesthesia for cesarean section--effects on neonates. Anesth Analg. 1989 Mar;68(3):270-5. PMID: 2919765

[83] Burguet A, Pez O, Debaene B, Untersteller M, Bettinger G, Kayemba-Kays S, Thiriez G, Bouthet MF, Sanyas P, Menget A, Mulin B, Maillet R, Boisselier P, Pierre F, Gouyon JB. Very preterm birth: is maternal anesthesia a risk factor for neonatal intubation in the delivery room?. Arch Pediatr. 2009 Dec;16(12):1547-53. doi: 10.1016/j.arcped.2009.09.011. Epub 2009 Oct 23. PMID: 19854034 French.