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Review

Chorioamnionitis

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Abstract

Chorioamnionitis is a serious complication of the pregnancy. The ascending microbial infection from the vagina to the amniotic cavity, seems to be the main mechanism of causing an intra-amniotic infection. The most common microbes are the E Coli, aerobic and anaerobic streptococcus, anaerobic staphylococcus and the bacteria that are responsible for sexually transmitted diseases. Diagnosis of chorioamnionitis is challenging, as clinical signs and symptoms are not specific. Fever is a dominant clinical feature, followed by maternal and fetal tachycardia, sensitivity to the uterine palpation, odorous vaginal secretion and leukocytosis. Early diagnosis and initiation of treatment with broad spectrum antibiotics are estimated to contribute in preventing significant short – term and long-term consequences, concerning the mother, the fetus and the newborn. This article, based on the systematic citation of contemporary bibliographic references, attempts to briefly review this serious obstetric complication, with particularly regard to the diagnostic and therapeutic approach, the awareness of which can ensure as far as possible the best prognostic outcome for the mother and the fetus – infant as well.

Keywords: Chorioamnionitis, Bacteria, ascending infection, fever, leukocytosis, antibiotics, complications

INTRODUCTION

The time span from conception to the end of the perinatal period is unique. It is estimated that a number of stimuli, events, and infections have long-lasting effects on the embryonic unit, signaling and defining human life. To this end, Perinatal Medicine and Neonatology have made tremendous progress in recent years. Scientific thinking about everything that concerns human reproduction has been developed to such an extent that not only a good result of medical intervention is anticipated, but the best possible one. Problems and challenges, however, continue to arise and there will always be space for improvement. Assuring the quality of perinatal care depends on the application of documented practices and clinical guidelines throughout the woman's life.

The normal implantation of the fetus and the physiological further development of pregnancy, depend mainly on the hormonal preparation of the uterus, the secretory activity of the endometrium and embryo, and the local reduction of the immune response towards the embryo rejection. Pregnancy is a unique state for a woman. It is the only biological phenomenon where the embryo, having half its characteristics "foreign" to the characteristics of the mother, is transplanted into the endometrium without risk of being rejected. The mother needs to adapt to this new condition in order to ensure the proper development of the fetus which, nine months later, will come to life as a perfect human being (Surrey, 2003).

The initial cavity of the fetus is called yolk sac and is bordered by the primary mesoderm downwards and the primary endoderm upwards, which forms the "roof" of the yolk sac. Adequate infiltration of the trophoblast, appears to be very important for the supply of the placenta with a sufficient amount of maternal blood and for the normal progression of pregnancy (Naicker et al, 2003). The trophoblast originally develops across the whole surface

of the fetus. The entire fetus is surrounded by a shell, composed of trophoblast and primary mesoderm, which is called chorion. Fetal membranes, chorion and amnion, are membranes in which the fetus is enclosed thereby forming the fetal follicle. The chorion is the outer envelope of the fetus, grows under the amnion and encircles the umbilical vessels. Amnion is a thin transparent membrane that forms the inner shell (Cunningham et al, 2010).

In this bibliographic review a brief description of chorioamnionitis is attempted, particularly with regard to the pathophysiological mechanisms and the modern diagnostic and therapeutic approach of this serious obstetric complication, the correct knowledge of which can ensure as far as possible the best prognostic outcome for the mother and the fetus – infant as well.

Chorioamnionitis

Chorioamnionitis or intra – amniotic infection is a serious complication of pregnancy, characterized by inflammation of the embryonic membranes. It is estimated to affect about the 3% to 10% of term pregnancies (Braun et al, 2016), posing a serious cause of neonatal sepsis (Taylor and Opel, 2012; Jan et al, 2017). Chorioamnionitis is mainly due to ascending infection of the intrauterine cavity with bacteria coming from the vagina, that are difficult to cultivate using traditional methods (Hagberg et al., 2002; Granger et al., 2018). In cases of preterm births weighing less than 2000 grams, the presence of chorioamnionitis is estimated to be about 50%, often associated with premature rupture of embryonic membranes, or rupture of the membranes just before parturition, concerning though less than 0.5% of cases with embryos weighing less than 1000 grams. In the vast majority of cases (99% or more) the body weight of the embryos is greater than 1000 grams (Weinstein 2003).

The incidence of chorioamnionitis is not well established. The disease is related to preterm delivery, especially in cases of premature labor following premature rupture of embryonic membranes (Erenberg et al, 2017). In general, endometrial infection is estimated to be responsible for up to 40% of all cases of premature birth worldwide (Challis et al, 2009, Romero et al, 2014, to Imperio et al., 2018). The preterm labor is still a serious public health issue nowadays. Based on the latest data, premature birth is estimated to affect the 5% to 18% of all pregnancies (WHO, 2017) and is the main cause of perinatal morbidity and mortality globally (Goldenberg, 2002).

Pathogenesis

The pathogenesis of the amniotic infection to date has not been precisely defined. Intra-amniotic infection has been noticed among pregnant women born prematurely with intact membranes (Romero et al, 2014; Combs et al, 2015), in pregnant women born after preterm premature rupture of the membranes (Kacerovsky et al, 2012; Romero et al, 2015), pregnant women with incompetency of the internal cervical os (Lee et al, 2008; Oh et al, 2010) or asymptomatic short cervix (Hassan et al, 2006; Romero et al., 2014), as well as among pregnant women with idiopathic vaginal bleeding (Gomez et al., 2005), low lying placenta (Madan et al, 2010) and clinical chorioamnionitis (Romero et al, 2015). Rupture of embryonic membranes is not a prerequisite for the entry of bacteria into the amniotic cavity (Galask et al, 1984). Most of these infections are subclinical and occur in the absence of clinical chorioamnionitis, so their detection is not possible before carrying out an amniotic fluid analysis, in order to detect the responsible bacteria (Romero et al, 2001; Romero et al, 2007).

The most common microbes and pathogenic microorganisms isolated in cases of chorioamnionitis are colobacter, aerobic and anaerobic streptococcus, anaerobic staphylococcus and bacteria that are responsible for sexually transmitted diseases (Table 1).

Table 1. Bacteria and microorganisms responsible for provoking clinical chorioamnionitis (Romero et al, 2015).

• Ureaplasma species
• Gardnerella vaginalis
• Mycoplasma hominis
• Streptococcus agalactiae
• Lactobacillus species
• Bacteroides species
• Acinetobacter species
• Sneathia
• Streptococcus viridans
• Porphyromonas species
• Veillonella species
• Peptostreptococcus species
• Escherichia coli
• Pseudomonas aeruginosa
• Staphylococcus aureus
• Enterococcus species

Genital mycoplasms, and in particular Ureaplasma species (Jacobsson et al, 2009; Oh et al., 2010) and Gardnerella vaginalis (DiGiulio et al, 2010) are the most common microorganisms, isolated in the amniotic cavity of pregnant women suffering from chorioamnionitis. Also, women who have become pregnant carrying intrauterine contraceptive devices, are at a high risk of endemic infection with Candida albicans. The presence of endometrial contraceptive devices is associated with a significant increase in the risk of intra – amniotic infection and placental inflammatory lesions, which encumbers the

normal progression of pregnancy (Kim et al, 2010). However, the multybacterial invasion in the amniotic cavity, is estimated to account for about 30% of cases of clinical chorioamnionitis (DiGiulio et al, 2008). Last but not least, in a recent study, Romero et al. indicated that pathogenic microbes were detected in 61% of patients with clinical chorioamnionitis, while no pathogenic microorganism was detected in 24% of those cases (Romero et al, 2015).

Pathophysiology

It is generally accepted that the amniotic cavity, based on cultures and molecular microbiological techniques, is totally sterile (Harris and Brown, 1927). Although the vagina of pregnant women has an abundance of bacteria, the cervical mucus plug represents an anatomical and functional barrier, which prevents the microbial infestation of the amniotic cavity (Becher et al, 2009; Hansen et al, 2014). The ascending vaginal infection (Romero et al., 1992), the hematogenous transmission of microbes and the infiltration of the membranes from the systematic circulation or through the placenta (Benedetti et al., 1982), the accidental introduction of microbes and micro-organisms into the amniotic cavity after amniocentecis, transdermal cord blood sampling, or other invasive procedure (Romero et al, 1985; Li Kim Mui et al, 2002) and less frequently the retrograde transmission of the microbes from the peritoneal cavity through the fallopian tubes, represent the four routes of transmission of the responsible bacteria and microorganisms causing chorioamnionitis, into the amniotic cavity (Romero et al, 2006, Romero et al, 2014, Kim et al., 2015).

The ascending bacterial infection from the vagina to the amniotic cavity seems to be the major mechanism for causing intra-amniotic infection. Certain microbes have the ability to enter the amniotic cavity through unerrupted membranes. The endotoxins of these bacteria stimulate the cells of decidua to produce prostaglandins and cytokines, that contribute to the early onset of labor. Thus, microbial invasion into the amniotic cavity causes a local inflammatory response accompanied by a dramatic increase in proinflammatory cytokine concentrations, such as interleukin - 1 (IL - 1), tumor necrosis factor - α (TNF - α), interleukin (IL - 6), interleukin - 8 (IL - 8), as well as a significant increase in the white blood cells count (Sadowsky et al, 2006; Marconi et al, Cobo et al, 2012, Kacerovsky et al, 2014, Romero et al, 2014, Romero et al., 2016).

It is important to note that the evaluation of hematologic disorders during pregnancy, requires the acknowledgment of the changes that normally occur during this period. These physiological changes affect the hematologic markers among pregnant women and make it difficult to recognize pathological conditions. In pregnancy, among other physiological changes, such as anemia, benign thrombocytopenia, increase in coagulation factors, and decreased fibrinolytic activity, the incidence of increased white blood cell counts is frequent, without suggesting inflammation or myeloproliferative disease, but being part of the physiological adaptation of the mother ("normal leukocytosis of pregnancy"). The normal leukocytosis of the pregnancy refers to a "redistribution" phenomenon, where a number of leukocytes that should normally remain attached to the vascular walls detach and circulate freely in the blood stream (Rizack and Rosene - Montella, 2012; Townsley, 2013).

Diagnosis

The diagnosis of chorioamnionitis is not easy, as clinical symptoms and signs are neither specific nor highly specialized (Burke and Chin, 2016). The diagnosis is mainly based on clinical criteria, as sampling amniotic fluid or placenta for culture, is an invasive method and should be avoided. The criteria of clinical chorioamnionitis include fever and two or more of the following: maternal and fetal tachycardia, sensitivity in uterine palpation, odorous vaginal discharge and leucocytosis (Table 2).

Table 2. Diagnosis of chorioamnionitis: the presence of fever and two or more of the above signs or symptoms, are adequate for the diagnosis of clinical chorioamnionitis (Mazaki – Tovi and Vaisbuch, 2016).

- Fever
- Tachycardia of the pregnant woman
- Tachycardia of the fetus
- Painful palpation of the uterus
- Odorous vaginal secretion
- Leucocytocys of the pregnant woman

The individual clinical criteria have variable sensitivity and low specificity and as a result, the accurate diagnosis of the disease is difficult (Tita and Andrews, 2010; Romero et al, 2014; Mazaki - Tovi and Vaisbuch, 2016). Fever is the main feature of chorioamnionitis and its clinical entity, as the hallmark of clinical chorioamnionitis, has been known for centuries (DeLacy, 1989). Fever with or without shivering occurs in 95% - 100% of cases of chorioamnionitis and is a prerequisite for the diagnosis of this serious obstetric complication (Apantaku and Mulik, 2007; Tita and Andrews, 2010). It is also important to note and understand that a not persisting fever does not accompany the disease (Higgins et al, 2016). In cases of choroamnionitis, the measured oral body temperature should be greater than, or equal to 39.0 ° C or 102.2 ° F. If the maternal temperature is greater than 38.0 ° C or 100.4 ° F but less than 39.0 ° C or 102.2 ° F, the body temperature measurement should be repeated after thirty

minutes for confirmation (Tita and Andrews, Avila et al., 2015).

Maternal tachycardia (> 100 / min) and fetal tachycardia (> 160 / min) are secondary clinical signs indicative of intra-amniotic infection, which sensitivity and specificity estimated to be 50% - 80% and 40% - 70 %, respectively. Tachycardia of pregnant women in absence of chorioamnionitis, is not uncommon. In these cases, the increase in the mother's heart rate may be due to medication, such as ephedrine or antihistamines, or due to the physiological changes of the cardiovascular system during pregnancy (sinus tachycardia). In any case, however, the combination of maternal and / or fetal tachycardia during pregnancy, suggests a strong probability of intrauterine infection which requires careful evaluation and early initiation of treatment (Tita and Andrews, 2010). Similarly, signs and symptoms of minor sensitivity and specificity in diagnosing intra – amniotic infection, are sensitivity to the palpation of the uterus and odorous vaginal secretion which refer to 4% - 25% of cases of chorioamnionitis, the presence or absence of which are the most of times difficult to be assessed by clinicians (Newton, 1993; Tita and Andrews, 2010).

Leukocytosis of the mother is indicative of the presence of intra-amniotic infection. An increase in white blood cell count is found in approximately 70% - 90% of cases of clinical chorioamnionititis. However, leukocytosis in the absence of other signs or symptoms is of limited value, as it may be caused by several other pathological or non-pathological conditions (Tita and Andrews, 2010). During pregnancy, the white blood cell count and the leukocyte-type values often change. There is usually an increase in the number of white blood cells, mainly due to the increased blood circulation of neutrophile polymorphonuclear cells. The increase in neutrophils starts at the eighth week of the pregnancy and peak values are observed during the second and third trimester of pregnancy. This increase is characterized as "normal" and the number of white blood cells usually ranges from 12,000 / mm^3 to 15,000 / mm^3, although in some studies white blood cell counts up to 29,000 / mm^3 are reported. However, in any case of leukocytosis, especially when it is higher than 18,000 / mm^3, testing should be performed to rule out an underlying infection or other hematologic disease with early onset in pregnancy (Molberg et al., 1994; Tita and Andrews, 2010).

Additionally, other important hematological markers for the diagnosis of an intra-amniotic infection, are the increase in C - reactive protein (CRP) and interleukin - 6 (IL - 6), but their utility has not been documented to date, for the diagnosis or prediction of chorioamnionitis, as part of the routine clinical practice (Tita and Andrews, 2010). In particular, van de Laar et al. analyzing the results of their systematic review in order to determine whether CRP accurately predicts chorioamnionitis and / or neonatal sepsis in women with premature rupture of embryonic membranes, indicated that none of the selected research studies met the criteria for the use of CRP as a prognostic marker in neonatal sepsis and in diagnosis of chorioamnionitis. The authors concluded that current international literature can not support the use of CRP in women with premature rupture of embryonic membranes (van de Laar et al, 2009). Similarly, Trochez - Martinez and colleagues found that there is no clear evidence to support the use of CRP in the early diagnosis of chorioamnionitis and that further scientific research to address the contradictory findings in the diagnostic accuracy of this method is considered necessary and important (Trochez - Martinez et al., 2007).

Amniocentesis and amniotic fluid culture can establish the diagnosis of chorioamnionitis, confirming the presence of pathogenic bacteria into the amniotic fluid. Although it may be regarded as the most reliable test, it has a limited utility though and its value has been questioned, not only because the results are available in up to three days, but because it is an invasive procedure, that should be avoided during pregnancy (Andrews et al, 2008). Furthermore, regarding the recent studies of Romero et al., the diagnosis of chorioamnionitis was questioned, by implementing both cultural and molecular techniques in the amniotic fluid. The authors indicated that in approximately 40% of pregnant women diagnosed with clinical chorioamniotitis, the amniotic fluid culture did not reveal any presence of bacteria and that in about 50% of cases of clinical , the placental histological examination did not come up with acute inflammatory lesions (Romero et al, 2015; Kim et al., 2015).

Treatment

It is generally estimated that the early diagnosis of chorioamnionitis and the, without delay initiation of treatment with broad spectrum antibiotics, can prevent significantly the short- and long-term consequences on both the mother and the fetus-neonate (Johnson et al., 2014). In any case of diagnosed clinical chorioamnionitis with intact embryonic membranes, the intravenous administration of antibiotics is an absolute indication, but its possible adverse effects on the mother and the embryo should not be ruled out, as well as the significantly increased cost of the healthcare system (Hastings - Tolsma et al., 2013). Studies that have demonstrated the lack of superiority of certain broad spectrum antibiotics, including the combination of ampicillin, gentamicin and clindamycin or piperacillin - tazobactam (Johnson et al, 2014), are currently limited.

The intravenous administration of broad spectrum antibiotics, has an indication among pregnant women diagnosed with chorioamnionitis, as the excessive and uncontroled use of antibiotics in pregnancy is associated with serious fetal and neonatal adverse effects (Bizzarro et al, 2008, ACOG, 2011, Didier et al, 2012). In the case of premature rupture of embryonic membranes,

intravenous antibiotic treatment for two days following oral administration of antibiotics for the next five days, is the basis of the treatment. The continuous use of antibiotics for more than a week, does not seem to have a greater clinical benefit for the affected pregnant women, but appears to be associated with unfavorable effects on the fetus and the newborn (Kenyon et al, 2001; ACOG, 2011).

Recently, Kenyon et al., analyzing the results of their study, revealed that the use of antibiotics following premature rupture of embryonic membranes, significantly reduces the risk of premature labor within seven days of the event, as well as the incidence of chorioamnionitis and neonatal infection (Kenyon et al, 2013). In the case of PPROM after 36 weeks of gestation, a recent randomized study did not detect a reduction in the incidence of septicemia, the need for mechanical ventilation of neonates, or a reduction in endometrial death rates in neonates whose mothers had received antibiotic treatment prenatally, versus those whose mothers had been exposed to placebo (Nabhan et al, 2014).

Moreover, the use of antipyretic drugs and the prenatal administration of corticosteroids, are estimated to be of prime importance in supporting pregnant women with chorioamnionitis. The use of paracetamol is currently considered safe in pregnancy and essential for the treatment of fever among pregnant women. The combination of maternal fever and fetal acidosis is estimated to significantly increase the risk of encephalopathy in the newborn, although there is evidence against the interaction between those two factors (Impey et al, 2008). Maternal fever, even if there is no documented fetal acidosis, is associated with adverse neonatal outcomes, especially encephalopathy, which enhances the role of inflammatory processes in the etiology of neonatal neurological morbidity (Impey et al, 2001). Also, treating fever with antipyretic drugs may be useful in reducing fetal tachycardia, thus avoiding the tendency to terminate the pregnancy by performing a cesarean section, due to a non-reassuring status of the fetus (Tita and Andrews, 2010).

The benefits of prenatal administration of corticosteroids in preterm neonates, have been well established to date. It is also estimated that in pregnant women who have been diagnosed with chorioamnionitis, the administration of steroids may improve the perinatal outcome, significantly reducing the incidence of severe intracranial bleeding and mortality, among preterm infants born before, or at 32 weeks of gestation (Been et al., 2009). A recent survey from Japan, studying the efficacy of prenatal administration of corticosteroids in pregnant women with chorioamnionitis between the 22nd and 34th week of pregnancy, concluded that prenatal administration of corticosteroids was associated with a statistically significant decrease in intracranial hemorrhage and perinatal mortality among preterm neonates with a very low birth weight (> 1500 grams), born of mothers with histologically confirmed chorioamnionitis (Miyazaki et al, 2014).

In addition to this, one year later, the same research team, in its effort to study the long-term effects of prenatal administration of corticosteroids in neonates with very low birth weight, born from mothers with histologically confirmed chorioamnionitis between 22 and 33 weeks of gestation, reported that prenatal steroid therapy is correlated with a statistically significant reduction in neonatal mortality prior to the age of three. On the other hand, there was no statistically significant correlation between prenatal corticosteroid administration and neurodevelopmental problems in children born prematurely, by affected mothers (Miyazaki et al, 2015).

The correct and appropriate management of pregnant women with chorioamnionitis, depends on the estimated severity of the maternal disease, based on the diagnostic criteria, the response to the treatment, the age of the pregnancy and the clinical evaluation of the fetus. Communication and consultation with a group of neonatalists, in each case, is totally necessary (Higgins et al, 2016). When diagnosing chorioamnionitis, the possibility of induction to delivery has to be taken seriously into account. Regarding the way of parturition, if there is no absolute indication of cesarean section, there is no evidence to support the immediate termination of pregnancy by caesarean section. In most cases, the non reassuring fetal heart rate pattern on CTG, is transient and seems to improve after the administration of antipyretic and antibiotic drugs (Johnson et al, 2014).

In addition, the treatment of chorioamnionitis depends on the stage of pregnancy and to a large extent, on the presence or absence of premature rupture of embryonic membranes (Figure 1). In particular, for gestational ages of less than 26 weeks, where the survival rate of newborns, or the possibility of not developing serious health issues, is extremely low or negligible, it is important to assess the risks of prematurity compared to the risks of the continuation of treatment. Therefore, it is highly important that parents should remain properly informed about all the potential risks that may arise from a postponement of labor, which will not exceed the 27th week after the PPROM event, bearing in mind that the average latency between the rupture of the membranes and delivery, for second-trimester pregnancies, is estimated to be about two weeks. In these cases it is necessary for the pregnant woman to get hospitalized for a thorough evaluation and monitoring of her and her fetus. The conservative treatment in such cases can be justified beyond 23 weeks of pregnancy and only in patients who have been informed, understood and accepted the risks (Moretti and Sibai, 1988; Beckmann et al, 2002; Iatrakis, 2015).

In pregnant women between the 26th and 34th week of the pregnancy and after administration of corticosteroids in order to accelerate the pulmonary

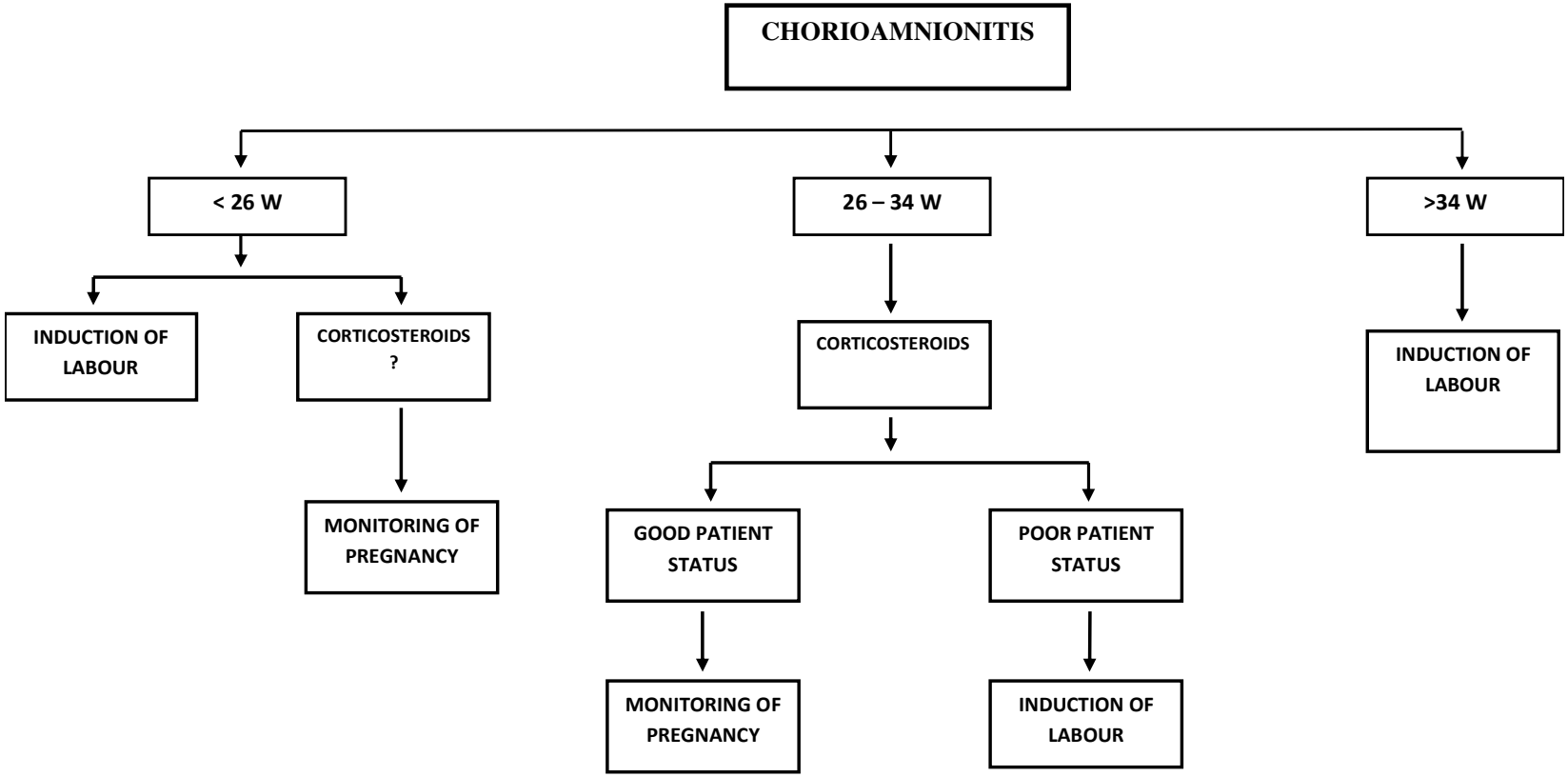

Figure 1. Treatment of chorioamnionitis depending on the gestational age, after Preterm Premature Rupture of Membranes.

maturity of the fetus, the decision for delivery depends on the condition of both the mother and the fetus. The excellent clinical and laboratory parameters of the pregnant woman, in conjunction with the well being of the fetus, allow for waiting. On the other hand, for women who have completed the 34th week of pregnancy, waiting is considered a contraindication and direct induction of labour is the best therapeutic option (Weinstein, 2003; Iatrakis, 2015).

Prognosis

Chorioamnionitis is accompanied by complications involving the mother, the fetus and the neonate (Table 3). Maternal complications include dysfunctional progression of the labour, which often leads to the need for cesarean section and abnormal uterine response to the use of oxytocin and other uterotonics, resulting in an increased rate of bleeding or placental retention after childbirth (Martinelli et al., 2012). Chorioamnionitis is estimated to increase statistically significantly the risk of post partum hemorrhage after both cesarean section and vaginal birth. This probably indicates the deleterious effect of this medical issue on uterine function (Mark et al, 2000). Furthermore, choroamnionitis is associated with statistically significantly increased risk of blood transfusion, septic pelvic thrombophlebitis and pelvic abscess formation (Rouse et al, 2004).

Table 3. Complications of chorioamnionitis.

• **Complications related to the pregnant woman**
- Increased percentage of cesarean section
- Postpartum hemorrhage
- Placenta retention
- Septic pelvic thrombophlevitis
- Pelvic abscess
- Septic shock
- Disseminated Intravascular Coagulation
- Respiratory Distress Syndrome
• **Complications related to the fetus - neonate**
- Premature delivery
- Respiratory Distress Syndrome
- Intraventricular Hemorrhage
- Necrotizing enterocolitis
- Cerebral palsy
- Sepsis
- Pneumonia
- Bronchopulmonary dysplasia
- Intrauterine death

Septic shock, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), and increased maternal mortality are detrimental complications of chorioamnionitis which, fortunately, are rare (Tita and Andrews, 2010).

Infants born from mothers diagnosed with acute histological chorioamnionitis, are estimated to be at increased risk of major morbidity (respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, congenital septicemia, early pneumonia or bronchopulmonary dysplasia) compared to infants with healthy mothers (Lee et al, 2013). The initiation of premature labor following an intraamniotic infection, accompanied by all the possible consequences of prematurity, is frequent. Recently, Erdemir and his colleagues, indicated that the incidence of histological chorioamnionitis was 47.3% in pregnant women who gave birth before the 32nd week of pregnancy and about double as high (83.3%), among mothers born at a gestational age less than 30 weeks (Erdemir et al , 2013). The results of an old study also suggest that the incidence of histological chorioamnionitis as a cause of premature delivery, is greater in early gestation, ranging from 66% at 20-24 weeks to 16% in women who gave birth at the 34th week of pregnancy (Lahra and Jeffery, 2004).

Fetal exposure to infection (inflammatory reaction syndrome) can lead to intrauterine death and neonatal sepsis. Fetal Inflammatory Reaction Syndrome has been associated with premature labor and increased perinatal mortality, in addition to multiorganic lesions including chronic pulmonary disease and cerebral palsy (Mittendorf et al, 2005; Bashiri et al, 2006; Lee et al. al., 2007). Chorioamnionitis is a risk factor for causing irreversible brain damage in premature neonates. Large multicentre studies have elucidated the important role of chorioamnionitis in modifying brain health, causing long-term effects in neonates (Chau et al, 2014). A recent large multicentre study from Canada concluded that chorioamnionitis is associated with an increased incidence of neurological insults, including severe intraventricular hemorrhage and periventricular leukomalakia, which represent indisputable causes of neurodevelopmental damage among preterm infants (Soraisham et al., 2009).

Fetal exposure to the infected intra-amniotic environment is estimated to significantly increase the risk of neonatal septicemia. In a recent large study involving over 108,000 very low birth weight infants (<1500 grams), that conducted in order to investigate risk factors for septicemia and neonatal mortality, it was determined that the mortality rates among premature infants with a very low birth weight and sepsis of early or late onset, is higher than among the ones with negative cultures (Hornik et al, 2012).

Although there is evidence to support the low correlation between chorioamnionitis and the occurrence of respiratory distress syndrome in preterm infants, bearing in mind that exposure to prenatal inflammation appears to accelerate lung maturity, however, there are several studies which have concluded that there is an increase in the incidence of the respiratory distress syndrome among neonates born prematurely, after intra-amniotic infection of the mother (Jones et al, 2013; McDowell et al., 2016). A recent meta - analysis, investigating the correlation between chorioamnionitis and bronchopulmonary dysplasia in premature neonates, indicated that although chorioamnionitis was estimated to be significantly responsible for causing bronchopulmonary dysplasia, however, it was concluded

that choriomnioniitis can not be considered a determining risk factor for above mentioned disease (Hartling et al, 2012).

CONCLUSIONS

Choriomnionitis is an acute inflammatory disease with significant short-term and long-term clinical consequences, related directly to prematurity. Preterm labor indisputably increases the risk of perinatal and neonatal morbidity and mortality. Significant progress has been made to date, towards the understanding of the pathophysiological mechanisms that are responsible for the maternal and fetal inflammation. There is no sensitive or specific diagnostic, or prognostic test that can accurately diagnose chorioamnionitis. The real causes of intra-amniotic inflammation remain unknown and represent important clinical and scientific challenges, for future clinical and experimental research studies (Kim et al, 2015; Stock et al, 2015).

In the contemporary obstetric clinical practice there is a dichotomy regarding the management of chorioamnionitis. Initiation of prenatal antibiotic treatment to the pregnant woman and the administration of antibiotics in neonates born from mothers diagnosed with clinical chorioamnionitis is recommended, although guidelines for the treatment of neonates exposed to chorioamnionitis, are implemented in only a small percentage of these cases. Future prospective clinical trials are now required, in order to raise awareness about contemporary evidence-based practices for the diagnosis and treatment of chorioamnionitis (Greenberg et al, 2012; Malloy, 2014; Ericson and Laughon, 2015).

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