A REVIEW ON PPROM (PRETERM PRELABOUR RUPTURE OF MEMBRANES) AND EARLY ONSET NEONATAL SEPSIS AND ROLE OF INFLAMMATORY MARKERS IN DIAGNOSIS OF MATERNAL AND NEONATAL INFECTION

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ABSTRACT

One of the major problems in obstetrics and neonatology till today is the occurrence of preterm births in spite of best possible antenatal care. Many preterm labour are due to PPROM (Prelabour Preterm Rupture of Membranes) where infection plays a major role. The neonatal morbidity and mortality is directly related to maternal infection and early-onset neonatal sepsis. Laboratory evaluation of various inflammatory markers such as TLC (total leucocyte count), ESR (Erythrocyte Sedimentation Rate), CRP (C-Reactive Protein) predict events such as maternal chorioamnionitis, neonatal sepsis with reasonable accuracy and hence are valuable tools in high dependency obstetric (HDU) and neonatal intensive care units (NICU). The following treatise mainly focusses on aetiopathogenesis, clinical features, haematological and biochemical parameters of maternal PPROM and neonatal sepsis. Understanding these factors will definitely prevent adverse maternal outcomes such as postpartum infections and puerperal sepsis and perinatal events such as stillbirth due to intrauterine foetal infection, preterm birth, neonatal sepsis, long term sequele of chronic lung disease and brain injury leading to cerebral palsy and other neurodevelopmental disabilities.

Keywords: PPROM, EONI, Chorioamnionitis, C Reactive Protein, Neonatal sepsis

INTRODUCTION

Millennium Development Goal 4 (MDG4) is one among the eight goals established by the world leaders in 2000 with the aim of eradicating extreme poverty globally [1]. Its aim is to reduce the under 5 y mortality rate to 1/3rd its level in 1990. Although steady progress towards reducing under-five mortality rate has been made in the recent years, millennium development goal 4 is still unlikely to realize due to the difficulty in reducing neonatal mortality. Neonatal mortality now accounts for a greater proportion of global child deaths than in 1990.

Newborns can acquire infections during birth from bacteria which are present in their mother's reproductive tract. The key risk factors for neonatal infection include pre-labor rupture of the membranes (PROM) of the amniotic sac, preterm PROM, and prolonged rupture of membranes. Prelabour rupture of membranes occurs in 10% of all pregnancies. 70% occurs in pregnancies at term. In 2–3.5% preterm, prelabour rupture of membranes (PPROM) is noted and it's the most common antecedent of preterm birth, being present in 30–40% of cases. The three causes of neonatal death associated with PPROM are prematurity, sepsis and pulmonary hypoplasia. Infants born with sepsis have a mortality rate four times higher than those without sepsis [2].

According to the World Health Organization, approximately a million neonatal deaths occur yearly due to neonatal infections [3]. In developed countries the incidence of neonatal sepsis is around 1 to 10 per 1000 live births, however, this rate rises to almost 3 times in developing countries such as India [4].

Prelabour rupture of membranes

PROM refers to a syndrome characterized by rupture of foetal membranes before labour irrespective of gestational age (even at 42 w).

Incidence

Prelabour rupture of membranes occurs in 10% of all pregnancies[1]. 70% occurs in pregnancies at term. In 2–3.5% preterm, prelabour rupture of membranes (PPROM) is noted and it's the most common antecedent of preterm birth, being present in 30–40% of cases.

Preterm prelabour rupture of membranes occurs in 2 to 4% of all singleton pregnancies and 7 to 20% of twin pregnancies. At term with no intervention, 50% of patients with PROM will deliver within 12 h, 70% within 24 h and 95 within 72 h [5]. In patients with preterm PROM, half of them will go into spontaneous labour by 24 to 48 h and 90% within a week.

Etiology of prelabour rupture of membranes

When it occurs at term, PROM is a part of the normal process of parturition and it may happen prior to the onset of contractions or after. This occurs as a result of both apoptosis at the cellular level and rise in activity of collagenase leading to the extracellular matrix of the chorioamnion being dissolved. The shearing effect of contractions further exacerbates this whole process. As the period of gestation decreases however, PROM is more likely to occur due to some underlying pathology [6].

PROM usually occurs suddenly and unpredictably. Exact causative factor is not known. It is the result of a variety of biochemical and mechanical pathways. Membranes from pregnancies associated with PROM are less elastic than normal chorioamniotic membranes. Studies have found reduced levels of type 3 collagen in membranes which had preterm PROM as opposed to those that didn't [7]. PROM occurs when intrauterine pressure is excessive or when intact membranes are weakened by exogenous factors that destroy the connective tissue framework which imparts tensile strength to membranes.

Positive cultures of the amniotic fluid and placenta have shown that intrauterine infection is quite common in patients with PROM, especially those with PROM far from term. Evidence suggests that infection occurs as a result of colonization of the genital tract with ascending infection which then leads to rise in activity of cytokines enhancing apoptosis of the membranes at the cellular level, protease production, and finally the amniotic membranes extracellular matrix dissolves [6].

Maternal factors

• Preterm prelabour rupture of membranes in a prior pregnancy (recurrence risk is 20-30% compared with 4% in women with a

prior uncomplicated term delivery [8])

- Vaginal bleeding

- Anemia

- Preterm labour

- Low socioeconomic status

- Smoking

- Chronic steroid therapy

- Collagen vascular disorders

- Direct abdominal trauma

Uteroplacental factors

- Polyhydroamnios

- Intra-amniotic infection (chorioamnionitis)

- Placental abruption (may account for 10-15% of preterm PROM)

- Cervical insufficiency

- Multiple bimanual vaginal examinations

Foetal factors

- Multiple pregnancy (7-10% of twin pregnancies)

- Ultimately though, in most cases of PROM, the real may not be known. Multiple factors may act together and cause PROM. The risk of recurrence of preterm PROM is 16 to 32 %, as compared with approximately 4% in women with a prior uncomplicated term delivery [8]. This percentage may be increased if there is evidence of cervical shortening or uterine contractions in the third trimester. However, most cases of PROM occur in otherwise healthy women without identifiable risk factors.

Diagnosis

Accurate and timely diagnosis of PROM is vital to permit the necessary interventions required to prevent maternal and neonatal complications. However, wrongly diagnosing PROM may lead to obstetric interventions that are not necessary such as hospitalization, induction of delivery. Hence it's extremely critical to accurately diagnose PROM for an optimal outcome of pregnancy.

In obstetric practice cases often come with the history of leaking membranes. In some of these cases diagnosis is made without difficulty by seeing the passage of liquor flowing through the external os. But in some other cases, this is not easy, hence other techniques are employed to detect it.

The diagnosis of PROM is largely a clinical one. It is suggested typically when a patient gives a history of watery discharge from the vagina and a speculum examination usually confirms it. Traditionally minimally invasive gold standard diagnosis of rupture of membranes requires documentation of three clinical signs [6]. Firstly, visual pooling of vagina with clear fluid or leakage of fluid from the cervical os. Secondly, alkaline pH of cervicovaginal discharge demonstrated by Nitrazine test (turns yellow to blue). It's however associated with high false positives rates due to associated cervicitis, vaginitis, contamination with blood and semen. It has a sensitivity of 90% and specificity of 16 to 70% [9]. Thirdly, microscopic ferning of cervicovaginal discharge on drying. False-positive results may occur due to fingerprints or contamination with semen and cervical mucus as well as false-negative results due to a technical error (using a dry swab to collect the sample) or contamination with blood. Sensitivity and specificity for the fern test are 51% and 70% [10].

With the possible exception of direct visualization of amniotic fluid spurting from the cervical os, all of these clinical signs have limitations in terms of diagnostic accuracy, and technical ease. If in doubt and the pregnancy is remote from term, amnioinfusion of indigo carmine under ultrasound guidance can be done and the passage of onto a perianal pad of blue fluid is confirmatory.

However, due to its invasive nature, it is not routinely performed [6].

Management

The amniotic membrane functions as a barrier to ascending vaginal infection. Hence, once PROM occurs we should weigh the risk of ascending infection against prematurity and plan delivery. At term with no intervention, 50% of patients with PROM will deliver within 12 h, 70% within 24 h and 95 within 72 h [5].

However, the management of preterm PROM cases tends to be more challenging. We should start by focusing on confirmation of the diagnosis, assessing accurate gestational age, ensuring fetal wellbeing, fetal presentation, and cervical examination. Studies have shown that as the time since leak increases the risk of developing EONI increases drastically with almost a 5 times more risk noted in cases of leak since 72 h when compared to those since 24 h [11].

Absolute contraindications to conservative management of preterm PROM:

- Intra-amniotic infection (chorioamnionitis)

- Non-reassuring fetal testing

- Active labor

Antenatal glucocorticoids (betamethasone, 12 mg IM once in 24 h × 2 doses or dexamethasone, 6 mg IM once in 12 h × 4 doses) has been proven to decrease the incidence of respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis by approximately 50% [12].

Tocolytic agents may be able to delay delivery by 24 to 28 h, but there is no convincing evidence that they can delay delivery beyond this time period and no consistent evidence that they can improve long-term perinatal morbidity or mortality [12]. It is considered a relative contraindication and should be used only to allow the first course of antenatal corticosteroids to be completed and/or to transfer the patient to a tertiary care center.

Prolonged PROM is a well-documented risk factor for neonatal group B streptococcus sepsis. Unless there is a recently done negative anovaginal culture all patients with preterm PROM should be given prophylactic antibiotics against group B streptococcus. I. V. penicillin 5 million units as a bolus followed up with 2.5 million units 4th hourly is to be given. Those patients that are allergic to penicillin should receive intravenous Cefazolin (2 g then 1 g 8th hourly) [13].

Complications

Complications are generally inversely related to the period of gestation at which PROM occurs. Preterm PROM is associated with a 4-fold increase in perinatal mortality and a 3-fold increase in neonatal morbidity [13].

Neonatal

- Respiratory distress syndrome (10% to 40% preterm PROM, 40% to 70% of neonatal deaths*)*

- *Intraventricular hemorrhage.*

- Neonatal sepsis

- Fetal pulmonary hypoplasia (26% of preterm PROM prior to 22 w)

- Skeletal deformities (12% of preterm PROM)

- Neurodevelopmental delay

- Cord prolapse

- Cord compression (due to severe oligohydramnios in the setting of preterm PROM)

Maternal complications

- Intra-amniotic infection (13% to 60% of women with preterm PROM [6])

- Chorioamnionitis

- Abruption
- Increased cesarean delivery for malpresentation
- Retained placenta
- Puerperal sepsis

Early onset neonatal sepsis

Neonatal sepsis is defined as a systemic infection that occurs in newborns at or before twenty-eight days of life. It is a very important cause of newborn mortality. Those neonates that survive may end up with morbidities such as severe neurological developmental sequelae due to involvement of the central nervous system, hypoxia or septic shock. There's a nearly equal incidence of culture-positive sepsis in both early and late onset groups with the overall incidence being around 1-8 per 1000 live births [14].

Definitions

Early-onset neonatal infection (EONI): It is based on time of onset and has been defined as bacteremia that occurs within 72 h in preterm newborns admitted in the neonatal intensive care unit or within a week in term newborns [15]. Early-onset neonatal infection in preterm newborns has been defined consistently as that which occurs within three days of birth and is caused by vertical transmission of pathogens from the mother during the peripartum period [16].

Late-onset neonatal infection: It is defined as sepsis that occurs in newborns admitted in the neonatal intensive care unit after 3 d and after one week in term infants. It may extend till up to almost 90-120 d of life with pathogens being acquired by both vertical and horizontal transmission [15, 16].

Incidence

Culture positive early-onset neonatal sepsis has an estimated incidence of 0.77 to 1 for every 1,000 live births [17]. Both incidence and mortality rates are noted to rise as the birth weight reduces. Incidence in very low birth weight infants, i.e. birth weight less than 1000 gms is 26 for every 1000 live births. In preterm newborns with birth weight between 1000 to 1500 gms, the incidence is around 8 for every 1000 live births [17].

Etiology

The organisms that cause early-onset neonatal sepsis are usually found to colonize the genitourinary tract of the mother, leading to subsequent contamination of the vagina, cervix, placenta, and amniotic fluid. The causative pathogen may either ascend after the rupture of amniotic membranes or before onset of labour, leading to an intra-amniotic infection [18].

Thus, the infant may acquire the pathogen either *in utero* or intrapartum. Risk factors for early-onset neonatal sepsis include both maternal and infant factors.

Maternal factors

- Procedures during pregnancy-such as cervical cerclage and amniocentesis
- Prolonged rupture of membranes
- Vaginal colonization with group B streptococcus
- History of a previous infant with GBS infection
- Chorioamnionitis, defined by maternal fever, leukocytosis (>15,000/mm³), maternal tachycardia, uterine tenderness, foul odor of amniotic fluid, and fetal tachycardia at delivery
- Poor or late prenatal care
- Low socioeconomic status of the mother
- Poor maternal nutrition
- Dietary intake of contaminated foods (Listeria monocytogenes contamination of refrigerated foods such as deli meats)
- Maternal substance abuse

Inhaling or swallowing infected liquor amnii by the fetus can lead to sepsis. This explains the high incidence of sepsis in newborns born to mothers with chorioamnionitis. When the membrane have been ruptured for more than eighteen hours, the risk of early-onset neonatal infection rises to 1% and when the mothers have suspected chorioamnionitis the risk is estimated to be around 1 to 4% [19]. Sometimes an infection may occur from the colonization of pathogens causing chorioamnionitis, on the skin and mucosa of the neonate, leading to infection after birth when the integrity of these barriers is lost [19]. Another important risk factor for early-onset neonatal sepsis is the adequate capacity of the immune response of the mother. Studies have shown that when the maternal serum has specific immunoglobulin G antibodies against the capsular polysaccharides of a particular strain of GBS then the neonate also is protected against infection from the same strain of GBS. While those with low maternal titres of immunoglobulins against GBS showed a higher risk [20].

Infant factors

- Prematurity
- Low birth weight
- Congenital anomalies
- Complicated or instrument-assisted delivery
- Low APGAR scores (score of ≤6 at 5 min)

In the preterm neonate the immune system is still immature and there are low levels of immunoglobulin due to reduced transplacental transfer from the mother, leading to increased risk of EONI in preterm neonates [21]. An already reduced barrier functionality of the neonatal skin and mucus membranes in preterm neonates is further compromised in those newborns that require several invasive procedures, such as intravenous cannulation and intubation.

Pathogens

Almost 70% of the cases of early-onset neonatal sepsis in both preterm and term neonates are caused by group B streptococci and E-coli [22].

Additional pathogens:

- Streptococcus viridans
- Streptococcus pneumonia
- Staphylococcus aureus
- Enterococcus species
- Enterobacter species
- Haemophilus influenzae
- Listeria monocytogenes

If term newborns are excluded and only preterm and low birth weight neonates are taken into account, the disease burden caused by gram-negative bacilli, including e-coli becomes higher and makes gram-negative organisms sepsis the most common cause [17]. It should be noted though that although these infections by bacterial can be confirmed by cultures, there are many situations when clinical sepsis in the neonate is treated empirically even if cultures have been negative.

Gram-negative beta-hemolytic streptococci emerged as the key pathogen back in 1960's replacing Staphylococcus aureus as the most important cause [23]. The use of antenatal screening methods and antibiotics during labour have caused a shift in trends, with decreasing rates of GBS caused EONI [24]. A study on a large cohort of preterm neonates found that EONI was still maximally caused by gram-negative pathogens as opposed to gram-positive pathogens or fungal pathogens [25].

Herpes simplex virus, Parechovirus, Enterovirus and other viruses

have also been found to cause EONI and must be differentiated clinically from EONI caused by bacterial pathogens [26].

Although very rare, fungi have also been known to cause EONI with the most likely agent being Candida species especially in very low birth weight infants [27]. Infections with candidial species can also manifest as congenital candidiasis in both term and preterm newborns with clinical manifestations occurring either at birth or within 24 h of birth [28].

Clinical presentation

The clinical features of newborns with sepsis vary with gestational age and extent of infection. They usually do not present directly with fever unless they are delivered by a mother with fever herself, in which case they may have fever immediately at birth. The neonates are more likely to present with hypothermia when they have EONI. Systemic hypothermia, though not specific, is an important marker of sepsis in neonates. Other general symptoms are poor feeding, lethargy and excessive crying. General nonspecific signs that may be seen are acidosis and reduced or absent urine output. The most common presenting infection is usually pneumonia, which presents with respiratory symptoms such as grunting, tachypnea, apnea, nasal flaring and intercostal retractions. Manifestation of cardiac involvement includes bradycardia, hypotension, cyanosis, desaturation and poor perfusion. One of the first few signs of a severe life-threatening sepsis in neonates are a subtle difference in the newborns respiratory condition, hypothermia or poor feeding and it's hence vital to pay close attention to these changes.

Preterm infants

Gram-negative bacilli and fungal pathogens cause more severe infections as opposed to gram-positive bacilli. The first few signs are bradycardia, apnea and cyanosis. Lim at al in their studies found that in preterm newborns there was a high incidence of reduced activity also known as lethargy along with increased need for respiratory effort [29]. Preterm neonates have been found to be relatively immunocompromised with reduced ability to form an antibody response and prevent infections especially against T-independent antigens [30].

Term infants

The first signs of EONI usually start to appear within 6 h of life, with most of them being present by 24 h of birth. The most common first presenting symptom is respiratory changes such as grunting, apnea or increased respiratory effort. Sometimes this may be wrongly interpreted as a sign of other conditions such as congenital cardiac disease, transient tachypnea of the newborn, congenital diaphragmatic hernia or pneumothorax. EONI should be considered a differential in all these cases and a chest x ray and arterial blood gas analysis will help in easy differentiation. In neonates presenting with only mild symptoms, they can be kept under observation for 6 to 8 h and started on antibiotics empirically. If the neonate does not improve clinically then blood cultures and further evaluation should be done to ensure that the correct antibiotics are being given. Almost 80 to 90% of the cases of EONI present within 24 to 48 h of birth [19].

While evaluating a neonate suspected to have EONI, a complete review of all the risk factors present during the antenatal period should be performed. This includes details such as the presence of maternal GBS colonization, the period of gestation, prolonged PROM, amniotic infection and history of the previous neonate with GBS infection.

Laboratory investigations

A complete laboratory evaluation of sepsis in a newborn includes a complete blood picture with total leukocyte count and differential counts, a blood culture, urine culture and cerebral spinal fluid culture [19].

Protein biomarkers of infection and inflammation such as procalcitonin and C-reactive protein (CRP) have been used increasingly along with other blood scoring systems to help in the diagnosis of neonates with clinical suspicion of sepsis. Based on the presence or absence of respiratory system symptoms the need for a chest radiograph may arise.

White blood count and differential counts

Total leukocyte counts along with differential counts, absolute counts and ratio of immature and mature neutrophils are routinely used worldwide as screening tools for EONI. However, none of these individually has been proven to be particularly efficacious in accurately identifying neonates with sepsis. A research article by Kun Wang *et al.* stated that neonatal total leucocyte count is not very reliable because secondary to physiological alterations and noninfectious inflammatory conditions there may be increased variability of hematological parameters leading to overdiagnosis and treatment of neonates [31]. A study in 2012 by Hornik *et al.* claiming their large cohort size as one of their key strengths of the study found that not raised but low total leukocyte counts in neonates were associated with EONI [32]. Although high specificities were noted for counts below 5000/mm^3, sensitivity was found to be poor. On the contrary though Champa P*et al.* and Mayuga *et al.* noted that even though total leukocyte count may not have been elevated in all neonates, it was statistically significantly raised in neonates with sepsis proven by culture [33, 34]. Khair KB *et al.* observed that total leukocyte count doesn't have much use clinically for diagnosing EONI due to its wide variability in levels. In their study total leukocyte count was not elevated in every case and showed the sensitivity of 50% and specificity of 91% and hence allowing us to conclude that total leukocyte count is a decent confirmatory parameter but not a diagnostic parameter [35]. Normal values of neutrophil counts depend of the age of the neonate and usually start with a peak at around 12 to 14 h, ranging from 1700 to 14,500/mm^3 [36]. Low neutrophil counts i.e. neutropenia has a much higher specificity for early-onset neonatal sepsis, however, its levels depend on age, method of delivery and height above sea level [37]. The level of absolute neutrophilic count reaches a peak at 12 h after birth with a value of 1100 to 1500cells/mm^3 [37]. On the contrary, the ratio of immature to total leukocyte count is maximal with a value of 0.16 immediately at birth and as age increases after delivery slowly arrives at a nadir of 0.12. One independent value of the ratio of immature to total white cell count more than 0.3 has a very good negative predictive value but not a great positive predictive value [37]. 1539 newborns were studied by Murphy *et al.* and they found that using a combination of a negative blood culture report at 24 h and 2 normal values of immature to total white cell counts value done serially was quite accurate in excluding early-onset neonatal sepsis [38]. Viral infections such as Enterovirus causing EONI usually have either normal total leukocyte counts or a very mild form of leukopenia [39].

C-reactive protein

CRP although the most studied acute phase reactant has shown mixed findings in its predictive and diagnostic ability. The CRP levels in a newborn are noted to rise within 6 to 8 h of an infective trigger and usually reach a peak by 24 h [40]. Current evidence states that a rising trend in serial CRP or a measurement after 24 h has a better predictive value with two serial normal CRP levels having a negative predictive value of 99.7%. Several normal levels of CRP are strongly indicative of the absence of sepsis and hence allow us to stop antibiotics [41]. In accordance with a recent study by Boonkasediesha *et al.* found that CRP levels had very high sensitivity, specificity and positive predictive value with a cut off of 1.90 mg/l [42]. Although Alfredo Enguix *et al.* found that procalcitonin was a better predictor than CRP, they still noted a statistically significant association between neonatal CRP levels and neonatal sepsis [43].

Blood cultures

All newborns with clinical suspicion of having early-onset neonatal sepsis should have their blood sent for culture. The amount of blood required for culture is substantially lower in neonates when compared to adults because newborns tend to have a higher concentration of bacteria in their blood as opposed to adults. However, a few studies have shown recently that 25% of the newborns may have low levels of bacteria in their blood with a colony counts as low as<4 Colony forming units/ml and 66% having colony counts of<10 colony forming units/ml [44]. Although traditionally 0.5 ml blood was considered sufficient to detect bacteria in newborns, new evidence claims that 1 ml increases the

diagnosis potential, particularly in those neonates with low levels of bacteremia in their blood [45]. Typically blood is drawn for cultures from peripheral veins, but it may also be procured from a catheter placed in the umbilical artery [46].

Role of C-reactive protein in diagnosis of acute infection

C-reactive protein (CRP) is an acute-phase reactant and an often used biomarker of mild systemic inflammation. Its serum concentrations have been noted to rise in both infectious as well as noninfectious causes of inflammation [47]. It was discovered by Tillet and Francis first in 1930 at Rockefeller University [48]. They were studying the serum of adults with pneumococcal pneumonia when they noted that there was a precipitation reaction between the c polysaccharide pneuomococcal bacterial cell wall and CRP. The unique characteristics of CRP binding has led to the discovery of raised CRP levels in more than 70 inflammatory conditions [49]. A clear understanding of the structure and biochemical nature of CRP is vital to make sure it is used appropriately. CRP is a protein biomarker that is a part of the pentraxin family, which are nonspecific proteins made of 5 subunits of 23-kDa polypeptides arranged in the shape of a cyclic pentamer with each subunit containing 2 sites of binding of calcium and one site for phosphocoline [50].

It is quickly produced and secreted into circulation by the liver. Circulating inflammatory cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor are stimulated by tissue damage or infectious agents. These cytokines, in turn, stimulate the liver hepatocytes to synthesise and secrete acute phase reactants, most importantly CRP [51]. During the acute phase of inflammation the levels of CRP may rise to almost 1000 fold and is considered the most sensitive acute phase reactant. CRP levels start to rise by 4 to 6 h of the beginning of inflammatory process and peak about after 24 to 28 h. It disappears from circulation rapidly after the inflammatory process settles. The extent of rise of CRP in serum depends on the degree of tissue damage. The fetus is able to produce CRP and other acute-phase reactant proteins as early as 4 to 5 w of gestation. Paired mother and infant sampling shows that CRP does not cross the placenta, and although maternal risk factors can exert an effect on the fetus, there is no correlation between maternal and infant CRP levels at birth [52].

A 2003 study by Mikko J. Loukovaara found that there was no evidence to support that there is a decrease in the rate of perinatal complications when highly sensitive CRP levels were used for following up on women with PPROM as opposed to normal CRP [53].

A 1998 study by Yoon *et al.* observed that total leucocyte count in amniotic fluid is a better diagnostic predictor of clinical chorioamnionitis and neonatal morbidity than CRP and maternal total leucocyte count in women with PPROM [54].

An early study done by Fisk *et al.* had concluded that a significant correlation was noted between a raised CRP level and chorioamnionitis but they observed that due to overlap between both infected and non-infected cases the use of CRP as a diagnostic test is limited. They suggested the use of higher CRP cut-offs for single measurement to increase specificity but acknowledge that serial measurement of CRP level more than 20 mg/l (190.5 nmol/l) had high predictive value [55].

A systemic review of 8 studies by Trochez-Martinez *et al.* showed that there was no evidence to support the usage of CRP for early diagnosis of maternal chorioamnionitis after prelabour rupture of membranes. Although a link was noted between raised CRP levels and chorioamnionitis, using commonly accepted CRP limits may be misleading. If a single measurement is to be used, a higher cut off level of 30 mg/l (285.7 nmol/l) is more appropriate. For serial CRP measurements, a level of 20 mg/l (190.5 nmol/l) or above is seen to correlate with infection [56].

A recent study in 2016 by Stephen *et al.* found that the 95th centile of CRP and PPROM had a positive predictive value of 90% with a false positive rate of 1%. However, sensitivity was found to be very low at 15% hence limiting its use clinically for detection and rendering it a poor predictor of microbial invasion of the amniotic cavity and histological chorioamnionitis [57].

Rafli Van De Laar *et al.* who conducted a systemic review of 5 studies, were of the opinion that predicting and preventing clinical chorioamnionitis and neonatal sepsis is more relevant than histological chorioamnionitis in women and neonates with no signs of infection. They found that there was no evidence in literature to support using CRP as a predictor for clinical chorioamnionitis or early-onset neonatal sepsis but could also not arrive at the conclusion that CRP is not effective in predicting neonatal sepsis [57]. Popowski *et al.*, did a study which showed that elevated CRP (≥ 5 mg/l i.e., 47.6 nmol/l) was significantly associated with EONI with a sensitivity of 94% and a specificity of 48% [58]. Lee SY *et al.* found that maternal serum CRP is an independent predictor of early-onset neonatal sepsis in women with PROM with a serum level of less than 8 mg/l (i.e., 76.2 nmol/l) having a good negative predictive value [59]. Jeon *et al.* noted that maternal CRP was significantly higher in neonatal sepsis group than in control with a maternal CRP (cutoff value>1.22 mg/d i.e., 11.6 nmol/l) having sensitivity of 71% and specificity of 84% for predicting neonatal sepsis [60].

Summary

Maternal chorioamnionitis and early neonatal sepsis are common succeeding events in the setting of prolonged prelabour preterm rupture of membranes. Though maternal infection can be diagnosed by clinical signs such as pyrexia, microbiological culture of amniotic fluid aspirate and histological examination of placenta and umbilical cord, important time may be lost in waiting for these results and worst prognosis would have already set in. Screening the mother for inflammatory markers mentioned in the review such as, maternal leucocyte count, erythrocyte sedimentation rate and acute phase reactant protein, mainly C-Reactive protein will aid the managing obstetrician to suspect and estimate the severity of infection and to institute interventions such as antibiotic prophylaxis, steroid therapy for foetal lung maturity and to deliver the baby in an appropriate time. These markers also prove beneficial even for a neonatologist to screen the babies for early onset neonatal sepsis and to administer appropriate measures to minimize the adverse neonatal outcomes.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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