ORIGINAL RESEARCH

CORRESPONDENCE: A Mini| Email: ayandaninchauke@icloud.com

The prevalence and outcomes of fetal inflammatory response syndrome in women with preterm rupture of membranes

A Mini[1], T Nkwenika[2], G Lindeque[1], S Adam[1]
[1]Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa
[2]Biostatistics unit, South African Medical Research Council, Pretoria, South Africa

ABSTRACT

Background: Preterm birth is a leading cause of neonatal morbidity and mortality worldwide. Approximately 60% are associated with infection. Fetal inflammatory response syndrome (FIRS) occurs in response to maternal or fetal infection and may predispose to adverse outcomes and cerebral palsy.

Objectives: The aim of this study was to determine the latency period in women with PROM and determine the association with FIRS.

Methods: We conducted a prospective cohort study, including women with singleton gestation with PROM between 26-38 weeks in Pretoria, South Africa. Data collection included a demographics, vaginal and urine microcopy and culture and placental histology. ***Results:*** There were 3225 patients seen between 1 August 2021 and 31 July 2022. A total of 217 patients met the criteria to be classified as critical incidents, thus giving an overall critical incidence rate of 6.7%. The median age (interquartile range [IQR]) of the patients who suffered critical incidents was 42 (34 – 54) years. The median (IQR) gravidity and parity were 2(1 – 4) and 2(1 – 3), respectively. Over a third, 37% (n = 80), of these patients were HIV positive. Of the 217 patients who met the critical incidents criteria, 78.3% (n = 170) were admitted with the intention of surgical treatment. Most, 54.4% (n = 118) of those patients were elective admissions. The three most prevalent critical incidents were omission of the procedure (46%, n = 107), followed by death (28%, n = 66) and performance of unplanned surgery (12%, n = 27). Lack of theatre time was the most common reason for procedure omission (46%, n = 49). Other reasons, namely lack of blood products (4%, n = 49), SARS-CoV-2 (Covid-19) positive results (3%, n = 7), new HIV diagnosis (2.5%, n = 6), change of management plan (2.5%, n = 6) and patient not fit for anaesthesia (2.5%, n = 6) were the following prevalent causes of omission of procedures.

The most common avoidable factors were in the category of admin factors (71%, n = 75). The most common reason in this category was inadequate theatre time (46%, n = 49).

Results: Seventy-two women were recruited, sixteen (22.22%) women had a deranged white cell count, 26 (37.14%) had an elevated CRP, 66 (63.77%) had a positive urine culture, and 22 women (51.16%) had a positive culture on high vaginal swab. The mean latency from rupture of membranes to delivery was 246 hours (SD 310), mean birthweight was 2003g (SD 512) and mean 5-minute Apgar score was 8.5 (SD 1.4). Twenty-five (34.7%) women had histological evidence of FIRS. Eighteen (25.35%) neonates had signs of neonatal sepsis. There were 2 (2.8%) neonatal deaths with both placentas showing signs of infection.

Conclusion: Diagnosing fetal infection before birth is only easy in severe cases. Subtle or developing infection is very hard to predict. The inability of this study to correlate risk group with the presence of FIRS emphasizes the need for a high index of suspicion and consider placental examination and follow up of these neonates.

Keywords: fetal inflammatory response syndrome (FIRS), preterm labour, preterm rupture of membranes (PROM), cerebral palsy (CP)

INTRODUCTION

Premature rupture of the membranes (PROM) occurs in 10% of pregnancies and is a risk factor for adverse pregnancy and neonatal outcomes. Preterm PROM (PPROM) is a major complication of pregnancy and accounts for 30% of spontaneous preterm births. The frequency of infection increases over time (latency period), so that when a woman with PPROM eventually goes into labor, microorganisms are detected in 75% of cases.[1-2] Intra-amniotic inflammation is frequently present in women with microorganisms in the amniotic fluid even though, in some cases, sterile inflammation is present. The use of antibiotics in women with PPROM is grounded in the results of multiple randomized clinical trials and meta-analyses.[3] Antimicrobial agents have been shown to prolong the latency period, decrease neonatal infection, and reduce respiratory morbidity, including the need for oxygen and surfactant. Moreover, antibiotic administration also reduces the frequency of clinical chorioamnionitis.[1-3]

Fetal inflammatory response syndrome (FIRS) is a complex pathophysiologic condition associated with systemic inflammation in the fetus and local inflammation in different fetal organs, which may lead to adverse outcomes. Most often, FIRS is caused by an infectious process, such as microbial invasion of the amniotic cavity or amniotic membrane or placenta (chorioamnionitis and funisitis), which can further gain access to the fetal mucosa and induce fetal inflammation.[4] Funisitis and chorionic vasculitis are considered to be the histologic manifestations of the fetal inflammatory response. When funisitis is present, there is an almost 12-fold increased risk for neonatal encephalopathy in term infants.[5] PPROM pregnancies are often complicated by the presence of hostile intra-amniotic conditions such as microbial invasion of the amniotic cavity (MIAC) and intra-amniotic inflammation (IAI). These conditions usually lead to the development of acute histological chorioamnionitis (HCA) followed by the activation of the fetal innate immune system (fetal inflammatory response), characterized by an elevation of inflammatory mediators in fetal blood. This situation results in multisystem involvement and the development of the fetal inflammatory response syndrome (FIRS), which might progress toward multiorgan dysfunction and failure.[5] FIRS results from local inflammation in different fetal organs, including the fetal brain, heart, lungs, skin, hematopoietic system, kidneys, adrenal glands, and thymus,

and it also induces subsequent damage to these organs. FIRS is encountered in women with preterm labour with intact membranes or with PROM.[5] Antimicrobial agents are not effective in eradicating or preventing intra-amniotic inflammation/infection in PPROM.

By activating the innate immune system in an effort to adjust to the inflammatory environment of the uterus, the fetus will struggle to survive. FIRS can lead to adverse neonatal outcomes, including death and multisystem organ damage. Complications of FIRS include fetal heart rate disturbances, changes in diastolic ventricular function, reduction in cardiomyocyte numbers, and patent ductus arteriosus. The most typical impairments of the respiratory system associated with FIRS in preterm infants are respiratory distress syndrome and later bronchopulmonary dysplasia. Other fetal effects include fetal dermatitis, and hepatic inflammation and disturbed lipid metabolism.[6-7]

The brain has a high susceptibility to inflammation and oxidative stress. Given that the brain continues to develop and mature during the third trimester, early postnatal period, and the first few years of life, it is particularly vulnerable to injury during pregnancy and around the time of birth. Isolated deep gray matter injury, white matter injury, periventricular leukomalacia (PVL), and intraventricular hemorrhage (IVH) have been described postnatally following FIRS and appear to confer subsequent high risk for long-term cerebral palsy. Impaired learning, vision, and hearing loss also have been reported in this context. The persisting unchanged prevalence of cerebral palsy (CP) is a major cost driver in obstetric litigation, currently an international crisis in scope and volume leading to cutting of services and discontinuation of practices. CP may be due to antenatal or intrapartum events. [5, 7] However, the difficulty in diagnosing FIRS means that this potential cause may be overlooked, with increasing risk for obstetric litigation.

Pathogens in the uterus related to the preterm birth are often of low virulence, such as Ureaplasma urealyticum, Chlamydia trachomatis, Mycoplasma hominis, and Trichomonas vaginalis. Unsurprisingly most cases of histological chorioamnionitis are subclinical, and merely 10% have obvious clinical manifestations of infection. [6, 8, 9] Placental pathologic examination is still the gold standard for diagnosing intrauterine inflammation, but it is posteriori and time-consuming.[10] Procedures to detect intrauterine infection at present include amniotic fluid examination via amniocentesis and fetal blood test via cordocentesis. these two methods are however invasive and too risky for general use. [8, 9] Raising maternal white blood cell count (WBC) as an independent indicator to predict intrauterine infection has been studied. It has been demonstrated that increased WBC in maternal circulation is associated with the presence of gross intrauterine infection. With regard to the role of WBC in detecting intrauterine inflammation, however, previous results were inconsistent.[11-12] C-reactive protein (CRP), an acute phase protein secreted by the liver that is part of the non-specific immune mechanisms, have very low levels in normal serum, but is rapidly synthesized in the presence of inflammation within 6-12 hours reaching a peak measurable level at 48-72 hours. If the infection and the inflammation are under control, then the CRP level may rapidly decrease into the normal range. The changes in levels are nonspecific and does not add to the solution in subtle fetal infection. [11-12]

The aim of our study is to determine latency period in women with PROM, i.e. the time from rupture of membranes to delivery of the fetus, and to determine the association and prevalence of FIRS in women with PROM. Such a study has not been conducted in our setting, and may provide clues not only in pathogenic mechanisms, but also in predicting which infants may be at increased risk for developing complications from FIRS.

MATERIAL AND METHODS

We conducted a prospective cohort study at the Obstetric units of Steve Biko Academic Hospital and Kalafong Academic Hospital, Pretoria, South Africa, between 01 October 2018 to 31 August 2019. These are high risk obstetric units in tertiary hospitals. The sample included consecutive women who were admitted for the workup and management of PPROM, between 26 and 37 weeks 6 days gestation. PPROM was suspected on presentation with a history of drainage of liquor and confirmed on vaginal speculum examination and by findings of absent or reduced amniotic fluid on ultrasound examination. Only women with a singleton pregnancy and no known congenital abnormalities were included.

Each woman completed a questionnaire on enrollment in the study to determine demographic and clinical parameters. We collected high vaginal swabs and mid-stream urine specimens for microscopy, culture and sensitivity. Blood specimens were collected on admission, to determine the WCC and CRP levels. An elevated WCC was defined as a serum count above 12.60 x 10^9/L. Elevated CRP levels were defined as serum levels at and above 10mg/L.

The estimated fetal weight was determined by clinical estimation and/or ultrasound using the Hadlock formula[13], and the latency period was calculated from time of PROM to delivery. Following delivery, the placenta was sent for histological examination by a single pathologist who reported on all the specimens. The characteristic feature of acute chorioamnionitis is diffuse infiltration of neutrophils into the chorioamniotic membranes. If the inflammatory process involves the umbilical cord (umbilical vein, umbilical artery, and the Wharton's jelly), this is referred to as funisitis. A swab was taken between the amniotic membranes and sent for microscopy, culture and sensitivity. Neonatal outcomes including Apgar score, neonatal intensive care (NICU) admission, signs of sepsis, and neonatal death were recorded.

Neonatal sepsis was diagnosed in the presence of a positive culture of blood, urine, or cerebrospinal fluid. Suspected neonatal sepsis was diagnosed in the absence of a positive culture when two or more of the following criteria were present: (1) WCC of <5000 cells/mm3; (2) polymorphonuclear leukocyte count of <1800 cells/mm3; and (3) I:T ratio (ratio of bands to total neutrophils) >0.2.

Statistical analysis

Initial analysis including mean and the corresponding standard deviation were given for continuous variables. Frequency counts and proportions together with their associated 95% confidence intervals were given for categorical variables. Chi-square test of association of categorical data was undertaken to determine association between preterm rupture of membranes and the explanatory variables . All statistical analysis was evaluated at 5% level and using STATA 15.

RESULTS

Eighty (80) consecutive women admitted to the obstetric units for the workup and management of PROM were recruited. Eight women were excluded from the study, because they did not fulfill the conditions of the inclusion criteria. The reasons for exclusion were congenital abnormality of the fetus, twin pregnancy, four term pregnancies recruited, woman was transferred to another hospital for further management and women declined hospital treatment and was discharged. Thus, 72 women were included in the study analysis.

Eight (11.11%) women had a previous history of preterm labour, and 17 (23.6%) women were admitted in preterm labour. Table 1 summarises the population characteristics.

Table 1: Description of study population (n=72)

Characteristic	n (%)
HIV	
HIV negative	54 (75.0)
HIV positive	18 (25.0)
Viral load less than detectable limits	16 (88.9)
White cell count	
Elevated (>12.60 x 109/L)	15 (20.8)
Normal (4-12.6 x 109/L)	15 (77.8)
Reduced (<4 x 109/L)	1 (1.4)
CRP	
Elevated (>10mg/L)	26 (37.1)
Normal (≤10mg/L)	44 (62.9)
Infections at admission	
Urinary tract infection on urine MCS (n=69)	44 (63.4)
Vaginal infection on vaginal swab MCS (n=43)	21 (48.8)
Management of PROM	
Tocolysis	8 (1.1)
Steroids	52 (72.2)
Antibiotics	71 (98.6)
MgSO4 for neuroprotection	2 (2.8)
Labour	
Induced	20 (27.8)
Spontaneous	52 (72.2)
Route of delivery	
NVD	49 (68.1)
Caesarean section	22 (30.6)
Assisted	1 (1.4)
Neonatal outcome	
Mean birth weight (grams)	2003 (range 820 - 3110g)
5-min Apgar <7	4 (5.5)
Neonatal ICU admission	47 (65.3)
Neonatal sepsis	18 (25.4)
Neonatal death	2 (2.8)
Placental infection: swabs (n=28)	5 (17.9)
Placental histology (n=45)	
Infection	25 (55.6)
Funisitis	8 (17.7)
Villitis	3 (6.6)
Stage III Chorioamnionitis	**10 (22.2)**
Deciduitis	3 (6.6)
Macrophages	2 (4.4)
Subchorionitis	5 (11.1)
Suppurative inflammation	2 (4.4)
Mild chorioamnionitis	4 (8.9)
	Mean (Range) (SD)
Age (years)	27.7 (19 - 43) (5.8)
Gestational age (weeks)	31.9 (26 - 37) (2.7)
Estimated fetal weight (grams) at admission	1779.4 (647 - 2990) (582.6)
Latency (hours)	246.4 (4 - 1362) (310.1)
Temperature (ºC)	36.6 (36.0 - 38.8) (0.4)

CRP= c-reactive protein; HIV= human immunodeficiency virus; ICU- intensive care unit; MCS= microscopy, sensitivity and culture; NVD= normal vaginal delivery; PROM= preterm rupture of membranes

Forty-four of 69 women (63.77%) had a positive urine culture on admission. The most common organisms were E. coli, Candida albicans, and Enterococcus. faecalis. Twenty-two of 43 women (51.16%) had a positive culture on high vaginal swab. The most common organisms were Candida albicans, U. urealyticum, and M. hominis. The average maternal temperature was 36.4ºC.

Eight women (11.11%) that presented in active preterm labour received tocolysis. The 64 women who were not tocolysed were either above 34 weeks gestation (n=9), or were not in labour (n=55). One woman (1.39%) did not receive antibiotics in the antenatal period as was admitted in active phase of labour. Two women (2.78%) received magnesium sulphate antenatally for neuroprotection.

Fifty-two women (72.22%) went into spontaneous labour and 20 (27.78%) had induced labour at 34 weeks. Forty-nine women (68.06%) delivered by normal vaginal delivery, 1 (1.39%) had an assisted delivery and 22 (30.56%) delivered via caesarean section. Eighteen of the 22 (81.8%) women had emergency caesarean sections; the indications for the emergency caesarean section included fetal distress (n=8), previous cesarean section (n=7), breech presentation (n=2) and antepartum hemorrhage (n=1).

The mean latency time from rupture of membranes to delivery was 246.4 hours (SD 310). The mean birthweight was 2003g (range 820 - 3110g) and mean 5-minute Apgar score was 8.5 (SD 1.4). Four (5.5%) neonates has a 5-minute Apgar score <7.

Twenty-eight (38.9%) placental swabs were submitted for evaluation. Five swabs (17.9%) showed evidence of infection with E. faecalis, K. pneumoniae, P. mirabilis, Group B streptococcus, E. cloanae, S. bacillus spp.

Forty-five (62.5%) placentas were submitted for histological assessment. Twenty-five placentas (55.6%) showed signs of infection/FIRS. Ten (40%) women had Stage 3 chorioamnionitis, 8 (32%) had funisitis and 5 (20%) had sub-chorionitis. Table 2 compares women with and without signs of placental infection.

Table 2: Comparison of pregnancies with and without evidence of placental infection based on placental histology

Type of critical incident	Signs of placental infection (FIRS) (n=25) n (%)	No signs of placental infection (n=20) n (%)	p-value
Gestational age			0.614
<34 weeks	18 (72)	13 (65)	
>34 weeks	7 (28)	7 (35)	
HIV			0.651
Negative	19 (76)	14 (70)	
Positive	6 (24)	6 (24)	
CRP elevated	9 (37.5)	7 (36.8)	0.965
WCC elevated	7 (28)	4 (20)	0.849
Antenatal antibiotics	25 (100)	19 (95)	0.44
Latency period	575	460	0.99
Labour			0.236
Induced	7 (28)	9 (45)	
Spontaneous	18 (72)	11 (55)	
5 min Apgar score <7	20 (80)	18 (90)	0.43
Neonatal ICU admission	17 (68)	15 (75)	0.607
Neonatal sepsis	7 (29.1)	5 (25)	0.757

CRP= c-reactive protein; FIRS= fetal inflammatory response syndrome; HIV= human immunodeficiency virus; ICU= intensive care unit; WCC= maternal white cell count.

Forty-seven neonates (65.28%) were admitted to neonatal ICU for low birth weight (n=36) and respiratory distress (n=11). Eighteen neonates had signs of neonatal sepsis (25.35%). Of these, 3 (16.7%) mothers had no evidence of infection on admission, 13 (72.2%) had urinary tract infection, 5 (27.8%) had a vaginal infection, 4 (22.2%) had both urinary tract infection and vaginal infection, 2 (11.1%) had a raised white cell count and 4 (22.2%) had a raised CRP.

There were 2 (2.8%) neonatal deaths in the study population. The placenta of both fetuses showed evidence of FIRS. One neonate was born at 33 weeks with birth weight of 1673g. The 5-minute Apgar score was 2. The other neonate had a caesarean delivery for fetal distress and was born with weight of 1141g and had a 5-minute Apgar score of 7. Their neonatal period was complicated by neonatal sepsis.

Table 3: Comparison of neonates born to mothers with FIRS

Type of critical incident	FIRS + NICU (17)	FIRS + no NICU (6)	p-value
Antenatal			
Latency from PROM to delivery	239	86	0.294
Antibiotics	17 (100)	8 (100)	0.651
HIV			
Negative	13 (76.47)	6 (75)	0.629
Positive	4 (23.53)	2 (25)	
5-minute Apgar score			
< 7	4 (23.53)	0	
≥ 7	13 (76.37)	8 (100)	
Maternal infection			
Positive urine culture	11 (64.71)	5 (62.50)	0.626
Positive vaginal swab	4 (36.36)	2 (50.00)	0.538
Elevated WCC	4 (23.53)	3 (37.50)	0.760
Elevated CRP	6 (37.50)	3 (37.50)	0.668

CRP= c-reactive protein; FIRS= fetal inflammatory response syndrome; HIV= human immunodeficiency virus; NICU= neonatal intensive care unit; PROM= premature rupture of membranes; WCC= white cell count.

From the total of 25 confirmed neonates with FIRS, 17 were admitted to NICU. The results showed that maternal HIV infection had no influence in NICU admission (p=0.651); CRP was not predictive (p=0.668); and there was no relation between NICU admission and maternal urinary tract infection (p=0.626) and vaginal infection (p=538).

DISCUSSION

FIRS is a complex pathophysiologic process associated with significant fetal/neonatal mortality and morbidities.[5] Diagnosing this condition before its consequences develop remains difficult. We found that there was no correlation between the clinical picture of the woman at presentation, markers of inflammation, latency period or neonatal outcomes and the incidence of FIRS.

In 25-40% the placenta in PROM shows evidence of ascending infection (amniotic fluid infection sequence) or vasculopathic problems (hemorrhage or thrombi).[14] Intraamniotic infection has clinical significance for the neonate beyond just causing preterm birth.[5, 7] The fetus may reveal an inflammatory response associated with cytokine release that can cause damage to the developing brain and lungs.[5, 7, 15] FIRS is characterized by circulating cytokines, bacterial toxins and activation of the coagulation cascade, which may predispose to cerebral palsy and other forms of adverse neurological function. The risk is evidenced for cerebral palsy and impaired neurological function when these children reach school age.[15]

Cerebral palsy (CP), has seen a massive increase in litigation for alleged obstetric negligence, despite evidence that CP is largely caused by factors unrelated to obstetrical care.[16] Periventricular leukomalacia (a form of white-matter brain injury characterised by necrosis or coagulation of white matter near the lateral ventricles) and intraventricular haemorrhage, both common features in CP, are associated with prematurity and can occur before the birthing process and irrespective of the care provided by the obstetric team. Similarly, vascular infarcts are known to occur at any stage of neurological development. In many cases, there is a complex interplay of genetic, medical and environmental factors.[17] Routine pathological examination of the placenta in preterm infants could provide clues, not only regarding the cause of preterm labour or PROM, but also

regarding the cause of cerebral palsy.

This would infer that neonates who were found to have histological signs of placental infection would require follow-up to monitor long-term outcome. From the results of this study we can observe that FIRS is difficult to predict. We cannot rely on the woman's presenting clinical picture alone to confirm the diagnosis. Whilst antibiotics may increase the latency period and decrease the incidence of chorioamnionitis, it does not eradicate intrauterine infection.[2-4] We ought to have a high index of suspicion in women who present with preterm rupture of membranes.

It is of the utmost importance to find therapies to treat FIRS or to alleviate its consequences. Strategies that have been considered include IL-1RA, therapeutic hypothermia, regulation of T cells, exendin-4, MgSO4, and exercise.[4] While none of these strategies alone might totally reverse the injuries triggered by FIRS, a combination of these treatments may prevent or attenuate its consequences. Interventions may have to be individualized based on the women's inflammation status at a given point since the efficacy of mid-trimester short-term interventions may depend on the degree of inflammation.[3, 4, 7, 10] Injury to the brain secondary to FIRS may be hard to prevent, and it would be important to examine whether neurorestorative treatments may still improve these injuries after their development

The strength of our study is that we prospectively investigated the prevalence and clinical prediction of FIRS in an unselected cohort of women presenting with PROM, in a pragmatic, resource-restricted setting, with a high HIV prevalence. Standard practice in a busy delivery unit does not always allow for submission of placentas for further histopathological examination. This limitation can be overcome if examination of placentas following PROM is recommended as part of routine practice. A larger study with longitudinal follow up of the offspring of pregnancies affected with FIRS should be considered in future.

CONCLUSION

Preterm birth is a leading cause of neonatal death and disease globally. Up to 15% of these births are caused by preterm rupture of membranes. Our study found no correlation between the clinical presentation or neonatal outcome and FIRS. However, there is an established correlation between FIRS and cerebral palsy, neurological dysfunction and organ dysfunction. Therefore, we recommend that clinicians must have a high index of suspicion when treating women with preterm rupture of membranes, and to consider histopathological examination of the placentas in these pregnancies. We also recommend that the affected children be followed up for signs of cerebral palsy or neurological deficit in their early childhood.

REFERENCES

1. *Kemp MW. Preterm birth, intrauterine infection, and fetal inflammation. Front. Immunol. (2014); 5: 574.*
2. *Dars S, Malik S, Samreen I, Kazi RA. Maternal morbidity and perinatal outcome in preterm premature rupture of membranes before 37 weeks gestation. Pak J Med Sci. (2014); 626-629.*
3. *Lee JH, Romero R, Kim SM, Chaemsaithong P, and Yoon BH. A new antibiotic regimen treats and prevents intra-amniotic inflammation/infection in patients with preterm PROM. J Matern Fetal Neonatal Med (2016); 29(17): 2727–2737.*
4. *Xiong Y, Wintermark P. Therapeutic interventions for fetal inflammatory response syndrome (FIRS). Seminars in Fetal and Neonatal Medicine (2011); Available online.*
5. *Musilova I, Andrys C, Drahosova M, Zednikova B, Hornychova H, Pliskova L, Zemlickova H, Jacobsson B, Kacerovsky M. Late preterm prelabor rupture of fetal membranes: fetal inflammatory response and neonatal outcome. Pediatric RESEARCH (2018); 83(3): 630-637.*
6. *Madsen-Bouterse SA, Romero R, Tarca AL, Kusanovic JP, Espinoza J, Kim CJ, Kim JS, Edwin SS, Gomez R, Draghici S. The Transcriptome of the Fetal Inflammatory Response Syndrome. Am J Reprod Immunol. (2010); 63(1): 73–92.*
7. *Gotsh F, Romero R, Kusanivic JP; Mazaki-Tovi S, Pineles B; Erez O, Espinoza J; Hassan S. The Fetal Inflammatory Response Syndrome. Clinical Obstetrics and Gynecology (2007); 50(3): 652-683.*
8. *Kacerovsky M, Pavlovsky M, Tosner J. Preterm premature rupture of the membranes and genital mycoplasmas. Acta Medica (Hradec Kralove) (2009); 52: 117–20.*
9. *Capoccia R, Greub G, Baud D. Ureaplasma urealyticum, mycoplasma hominis and adverse pregnancy outcomes. Curr Opin Infect Dis (2013); 26: 231–40.*
10. *Oh J-W, Park C-W, Moon KC, Park JS, Jun JK. The relationship among the progression of inflammation in umbilical cord, fetal inflammatory response, early-onset neonatal sepsis, and chorioamnionitis. PLoS ONE (2019); 14(11): e0225328.*
11. *Li K, Yu H, Wang X, Liu X. Predictive value of procalcitonin or c-reactive protein for subclinical intrauterine infection in patients with premature rupture of membranes (PROM). Journal of Prenatal Medicine (2016); 10(3-4): 23-28.*
12. *Ferguson KK, McElrath TF, Chen YH, et al. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. Am J Reprod Immunol. (2014); 72(3): 326-336.*
13. *Monier I, Ego A, Benachi A, Ancel PY, Goffinet F, Zeitlin J. Comparison of the Hadlock and INTERGROWTH formulas for calculating estimated fetal weight in a preterm population in France. Am J Obstet Gynecol (2018); 219: 476.e1-12.*
14. *Erez O. Preterm Birth. Published online. IntechOpen (2013). Available online at https://www.intechopen.com/books/preterm-birth/placenta-in-preterm-birth.*
15. *Armstrong-Wells J, Donnelly M, Post MD, Manco-Johnson MJ, Winn VD, Sébire G. Inflammatory predictors of neurologic disability after preterm premature rupture of membranes. Am J Obstet Gynecol. 2015 Feb; 212(2): 212. e1–212.e9. doi: 10.1016/j.ajog.2014.09.016*
16. *Tuffnell D. Medicolegal issues in obstetrics. Obstetrics, Gynaecology & Reproductive Medicine (2019); 29(1): 12-14.*
17. *MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. American Journal of Obstetrics and Gynecology (2015); 213(6): 779-788.*