The impact of fetal inflammatory response syndrome on perinatal outcomes in cases of preterm premature rupture of membranes

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Abstract

Objective: To evaluate the impact of fetal inflammatory response syndrome (FIRS) in the cases of preterm premature rupture of membranes (PPRM).

Methods: The study was designed prospectively. The study was consisted of 40 cases between 26 and 37 weeks gestation diagnosed as PPRM without any obstetric and maternal pathologic findings. All cases were followed-up by hospitalization. Umbilical cord sampling was done for IL-6 levels at the time of delivery. The perinatal outcomes of the cases were recorded after birth.

Results: Forty PPRM cases were followed-up in our study. The mean gestational week of cases at the time of delivery was 33.5±3.19. The mean 1st and 5th minutes Apgar scores of the cases with FIRS were 4.6 and 6.2, respectively. The mean 1st and 5th minutes Apgar scores of the cases without FIRS were 6.9 and 8.3, respectively. There was a statistically significant reverse correlation between IL-6 levels of umbilical cord blood and 1st and 5th minutes Apgar scores in PPRM cases (p<0.01). There was also statistically significant reverse correlation between IL-6 levels of umbilical cord blood and birth weight (p<0.01).

Conclusion: Checking IL-6 level of umbilical cord blood (higher than 11 pg/ml) made it easy to diagnose FIRS. Umbilical cord blood sampling at delivery for IL-6 level is not a prenatally diagnostic test but if we can diagnose FIRS earlier, we have a chance to gain time for preparing newborn against the complications that may develop associated with neonatal sepsis and proinflammatory cytokines.

Key words: Fetal inflammatory response syndrome, preterm premature rupture of membranes, perinatal outcomes.

Fetal inflamatuar yanıt sendromunun preterm erken membran rüptürü olgularının perinatal sonuçları üzerine etkisi

Amaç: Preterm erken membran rüptürü (PEMR) olgularında, fetal inflamatuar yanıt sendromunun (FIRS) perinatal sonuçları üzerine olan etkisini araştırmak.


Bulgular: Çalışmanınzu, PEMR olan 40 olgu klinik gebelik takibe alındı. Olguların ortalama doğum haftası ise 33.5±3.19 idi. FIRS gelişen olgularda ortalama 1. dakika Apgar skorları 4.6 idi; 5. dakika skorları 6.2 bulunuyor. FIRS gelişmeye olgularda 1. dakika Apgar skorları 6.2 iken; 5. dakika skorları 8.3 olarak bulundu. PEMR olgularının, umbilikal kordon kani IL-6 düzeyi ile 1. ve 5. dakika Apgar skorlarına arasında istatistiksel olarak anlamlı ters korelasyon olduğu saptandı (p<0.01). Umbilikal kordon kani IL-6 düzeyi ile olguların doğum tarihi arası istatistiksel olarak anlamlı ters yönde korelasyon olduğu tespit edildi (p<0.01).

Sonuç: Çalışmanınzu, umbilikal kordon kanında baktığımız IL-6 düzeyinin bakımasi (11 pg/ml üzerinde), FIRS tanısının kolaylaştırılması sağlamıştır. Doğumda umbilikal kordan kani IL-6 düzeyi tayini, prenatal bir tanı testi olmasa da FIRS tanısının erken konulması sayesinde, yenidogan döneminde, neonatal sepsis ve proinfiamatuar sitokinleri bağış gelişebilir. Komplikasyonlara karşı da- ha uyuşun daha daha uzunlarının hazırlanılabilmesi için zaman kazanılması sağlayacaktır.

Anahtar sözcükler: Fetal inflamatur yanıt sendromu, preterm erken membran rüptürü, perinatal sonuçlar.
Introduction

Fetal infection and excessive inflammatory cytokine response increases neonatal morbidity. The spreading ways of infection can be ascending (from vagina to cervix and cavity), hematogenous (through placenta), intraabdominal (through oviducts), and iatrogenic (during amniocentesis). Fetal vasculitis is defined as the presence of neutrophiles on the chorion (chorionic vasculitis) and umbilical cord (funisitis-umbilical vasculitis) vessel walls. Fetal vasculitis is one of the most essential components of fetal inflammatory response. Maternal leucocytes may invade umbilical cord by passing from intervillous gap to chorionic surface, and from here passing to amnion and amniotic fluid. Funisitis is associated with endothelium activation which has a key role in multi-organ dysfunction.

Inflammation is the part of immediate, non-specific immune response. Excessive or decreased immune response may cause disease. If immune response is insufficient, infection develops; but if immune response is excessive, then FIRS develops.

In the diagnosis of FIRS, fetal plasma IL-6 concentration above 11 pg/ml is defined as threshold value in fetal inflammatory response. IL-6 levels higher than 11 pg/ml are associated with neonatal morbidity increase. The diagnosis can be established by CRP analysis in umbilical cord blood sampling. The diagnosis also can be established by white blood cell count in the amniotic fluid. However, evaluating cytokine levels in a single time period does not show sufficient increase secondary to inflammatory response. On that sense, it may remain incapable of revealing the association between inflammatory response and possible neonatal morbidities. In our study, we researched the impact of fetal inflammatory response syndrome on perinatal outcomes in cases of preterm premature rupture of membrane according to the literature.

Method

The study was planned as a prospective research. The cases included to the study were chosen among pregnant women who had premature membrane rupture who referred to Perinatology Clinic of the Department of Obstetrics and Gynecology, Cerrahpaşa Medical Faculty, Istanbul University between January 2009 and July 2011. Forty cases between 26 and 37 weeks gestation diagnosed as preterm premature rupture of membranes without any obstetric and maternal pathologic findings were included to the study. Pregnants who presented maternal (diabetes mellitus, cardiac disease, preeclampsia-eclampsia, ablatio placenta, multiple pregnancy, polyhydramnios, acute pyretic disease) and fetal (severe intrauterine growth retardation, dead fetus, near-fatal fetal anomaly) factors were excluded from the study.

The diagnosis of preterm premature rupture of membrane was established by observing active water break during dry vaginal speculum examination considering the amnensis of the patient. In patients without active water break, the diagnosis was established by making pH analysis via vaginal litmus paper. Additionally, the diagnosis was confirmed in all patients by carrying out single-step immunoassay test. All patients were briefed about the study by informed consents prepared previously. All of the patients were followed-up for vital findings, uterine sensitivity and daily NST by hospitalization. All patients were administered 4 gr/day ampicillin empirically. Totally 2 doses of betamethasone were administrated intramuscularly once in every 12 hours to all pregnants who were below 34 weeks gestation in order to provide fetal lung maturation. When active labor began, fetal distress was detected and chorioamnionitis findings were detected (maternal fever over 38°C, uterine sensitivity, malodorous discharge, maternal tachycardia, fetal tachycardia ‘at and above 160 pulse/minute’, high white blood cell ‘at and above 15,000 leucocyte/microliter’, increased CRP), conservative method was terminated.

In accordance with the obstetric indications, the patients delivered by normal labor, normal labor with induction, and cesarean. Cord blood was taken to dry tube from all patients during labor. Obtained material was centrifuged within maximum 2 hours and serums were kept at -33°C. Serums were processed by IL-6 kit (ELISA DIA Source). IL-6 was shaken at the room temperature and incubated for 2 hours and 15 minutes.

After the delivery, CRP and culture materials (blood culture, culture of gastric aspirates) were taken from
newborns. Neonatal sepsis diagnosis was established with clinical findings (paleness, lethargy, irritability, apnea, respiratory distress, bradycardia, tachycardia, hypotension, vomiting, fever) and/or positive cultures of blood and gastric aspirates. FIRS diagnosis was established when cord blood IL-6 concentration was above 11 pg/milliliter. After delivery, labor information of the patients (maternal age, parity, PRM time, PMR follow-up period, whether induction was performed or not, delivery type, cesarean indication, birth weight, 1st and 5th minutes Apgar scores of the baby, gender of the baby) were recorded. Percentage, mean, standard deviation, and minimum and maximum values were used for definitive analysis. If data were qualitative, chi-square, Fisher’s Chi-Square was used in comparisons. In correlation analysis, Spearman rank correlation was calculated.

**Results**

In our study, 40 patients with PPRM were included into clinical pregnancy follow-up. Mean age of our cases was 312±5.3. While mean gravida of our cases was 2.1±1.3, mean parity was 0.7±0.3. Mean gestational week of our cases at the time when PPRM developed was 32.5±3.3 (minimum: 26.0 - maximum: 36.0). Mean delivery week of our cases was 33.5±3.19 (minimum: 27.0 - maximum: 37.0). Mean follow-up period of our cases was 5.8±2.6 day (minimum: 3.0 - maximum: 15.0). Mean birth weight of our cases was 2184.38±757.8 g (minimum: 400.0 - maximum: 3280.0). Mean 1st minute Apgar score of our cases was 5, while mean 5th minute Apgar score was 7.

There is statistically significant correlation among IL-6, 1st minute Apgar score, 5th minute Apgar score and birth weight (p<0.001). There is statistically significant reverse correlation among IL-6, 1st minute Apgar score, and 5th minute Apgar, respectively 32.0% and 31.0% correlation (respectively; Spearman rho: -0.32, 0.31; p=0.005, p=0.006). Also there is statistically significant reverse correlation between IL-6 and birth weight, which is 41.0% (Spearman rho: -0.41; p=0.003).

Consequently, Apgar scores and birth weight decrease as IL-6 increases (Table 1). Mean 1st minute Apgar score of FIRS cases was found as 4 while 5th minute Apgar score was 6. These values were 6 and 8, respectively in cases without FIRS. Apgar scores were statistically and significantly lower in cases FIRS compared to cases without FIRS (Table 2).

**Discussion**

Although Systemic inflammatory response syndrome was defined as a local phenomenon in the past, it is a systemic pathology characterized by fever, tachycardia,
hyperventilation, and leukocytosis. There is a miscon-
ception that infection or inflammation does not exist in
the non-presence of systemic findings (fever, leukocy-
tosis).

Now, we know that histological inflammation
and chorioamnionitis are sub-clinical in many cases
during term and preterm labors.

Granulocyte and macrophages have an essential
role in natural immune response. Chemokines are
small peptides or glycoproteins that can be solved and
responsible for communication among cells (IL, INF,
TNF, growth factors and chemokines). Chemokines
enable leukocytes to migrate into inflammation region
(IL-8, IL-10). Cytokines can be in proinflammatory or
anti-inflammatory structure. IL-1, IL-6, TNF-alpha
and IFN-gamma are proinflammatory cytokines; IL-4,
IL-10, IL-11, and IL-13 are anti-inflammatory
cytokines. Systemic inflammatory response emerging
in fetus is called “fetal inflammatory response syn-
drome” (FIRS). It is characterized by proinflammatory
cytokines increased in amniotic fluid and fetal blood
and the presence of fetal vasculitis. There is an
intrauterine infection and an excessive inflammatory
response appears against the infection. Intrauterine
infection affects maternal decidua, myometrium, amni-
otic and chorionic membranes, amnion fluid, cord and
placenta. There are many data stating that these
intraamniotic cytokines are fetal originated. The
impact of fetal inflammatory response on possible out-
comes is more important.

While IL-6 and IL-8 levels are at the highest levels
in umbilical cord blood and postnatal 6th hour, they
gradually decrease and reach the lowest levels at 72nd
hour. So, the time of intrauterine inflammation and the
evaluation time of cytokines during postnatal period
are essential. Regarding with FIRS, target organs
such as hematopoietic system, adrenal glands, kidneys,
lungs, skin, and brain will be affected negatively. It was
shown in the studies performed that there is an
increase in white blood cell count of newborn in the
presence of histological chorioamnionitis and placental
inflammation in the cases of preterm premature rupture
of membrane (above 24 hours).

This was explained by the increase in IL-6 level. Detecting
high level of IL-6, which is a proinflammatory
cytokine, in umbilical cord blood was considered as
associated with bad perinatal outcomes.

In our study, IL-6 levels in umbilical cord blood
was found as reverse correlated with 1st and 5th min-
utes Apgar scores and birth weight. It was observed
that both 1st and 5th minutes Apgar scores, and birth
weight decreased as IL-6 level increased. When the
cases with and without FIRS were compared, Apgar
scores were particularly low in cases with FIRS.

In the follow-up of PPRM cases, serial white blood
cell count and C-reactive protein (CRP) measurements
are used together with basal and weekly vaginal cul-
tures in the follow-up of chorioamnionitis develop-
ment. Carrying out amniocentesis against the possibil-
ity of secret chorioamnionitis is controversial and there
is no sufficient experience. In the limited number of
studies performed, the association of proinflammatory
cytokines (IL-6, IL-8, IL-18) and microbial invasion
of amniotic cavity in PPRM cases. In our study, FIRS
diagnosis was clearly established by means of IL-6 level
(above 11 pg/ml) we checked in umbilical cord blood.

Umbilical cord blood sampling at delivery for IL-
6 level is not a prenatal diagnostic test but if we
can diagnose FIRS earlier, we have a chance to gain
time for preparing more appropriate intervention con-
ditions in order to protect newborn against the compli-
cations that may develop associated with neonatal sep-
sis and proinflammatory cytokines (newborn intense
care unit, antibiotic prophylaxis). By evaluating levels
of other proinflammatory cytokines (such as IL-1,
TNF-alpha) like IL-6, more successful perinatal out-
comes can be obtained in FIRS cases.

The studies performed in recent years make us to
think that fetal inflammatory response syndrome arising
due to proinflammatory cytokines and complica-
tions related with this condition such as intraventricu-
lar hemorrhage, periventricular leukomalacia and cere-
bral palsy cannot be prevented only by antibiotic treat-
ment. Animal testings which used anti-inflammatory
and chemical agents for the effects of IL-1 and IL-6
widened horizons. These treatments can be com-
bined with regimes used to prevent or treat fetal mor-
bidity cause by intrauterine infection and inflammation
associated with PPRM.

Conclusion
Prospective and new studies with wider scale are need-
ed in order to understand the etiology of fetal inflam-
matory response syndrome and to prevent its compli-
cations.
Conflicts of Interest: No conflicts declared.

References