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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 more appropriate intervention conditions in order to protect 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 sonuçlar üzerine olan etkisini araştırmak.

Yöntem: Çalışma prospektif bir araştırma olarak planlandı. Çalışmaya 26.-37. gestasyonel hafta arasındaki obstetrik ve maternal patolojik bulgusu olmayan 40 preterm erken membran rüptürü olan gebe dahil edildi. Bütün hastalar hastaneye yatırılarak takip edildi. Doğumu takiben tüm hastalardan kordon kanı alınarak IL-6 seviyesi çalışıldı. Doğum sonrasında olguların perinatal sonuçları kayıt altına alındı.

Bulgular: Çalışmamızda, PEMR olan 40 olgu klinik gebelik takibine alındı. Olguların ortalama doğum haftası ise 33.5±3.19 idi. FIRS gelişen olguların ortalama 1. dakika Apgar skorları 4.6 iken; 5. dakika Apgar skorları 6.2 bulundu. FIRS gelişmeyen olguların 1. dakika Apgar skorları 6.9 iken; 5. dakika Apgar skorları 8.3 olarak bulundu. PEMR olgularının, umbilikal kordon kanı IL-6 düzeyi ile 1. ve 5. dakika Apgar skorları arasında istatistiksel olarak anlamlı ters korelasyon olduğu saptandı ($p<0.01$). Umbilikal kordon kanı IL-6 düzeyi ile olguların doğum tartıları arasında istatistiksel olarak anlamlı ters yönde korelasyon olduğu tespit edildi ($p<0.01$).

Sonuç: Çalışmamızda, umbilikal kordon kanında baktığımız IL-6 düzeyinin bakılması (11 pg/ml üzeri), FIRS tanısının konulmasını kolaylaştırmıştır. Doğumda umbilikal kord kanında IL-6 düzeyi tayini; prenatal bir tanı testi olmasa da FIRS tanısının erken konulması sayesinde, yenidoğan döneminde, neonatal sepsise ve proinflamatuar sitokinlere bağlı gelişebilecek komplikasyonlara karşı daha uygun müdahale koşullarının hazırlanabilmesi için zaman kazanılmasını sağlayacaktır.

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

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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.[1,2] It is also associated with bad neonatal outcomes such as increased neonatal sepsis, late period bronchopulmonary dysplasia.[3]

Fetal inflammatory response syndrome (FIRS) has short- and long-term impacts on neonatal morbidity. Its short-term impacts are: (1) periventricular leukomalacia (PVL), (2) intraventricular hemorrhage (IVH), (3) fetal sepsis, pneumonia, and (4) necrotizing enterocolitis. In the long-term, it is associated with a number of fetal and neonatal morbidities such as cerebral palsy (CP), and bronchopulmonary dysplasia (BPD).[4] In the beginning, infection appears first, then premature birth risk appears as a result of inflammation. Inflammation is the part of immediate, non-specific natural 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.[5] The diagnosis can be established by CRP analysis in umbilical cord blood sampling.[6] The diagnosis also can be established by white blood cell count in the amniotic fluid.[7] 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 pregnants 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 37weeks 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, polyhydramniosis, 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 anamnesis 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 administrated 4 gr/day ampicilin 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,

Table 1. Evaluation of IL-6, birth weight, and the scores of Apgar 1 and Apgar 5.

		Apgar 1	Apgar 5	Birth weight
IL- 6	Spearman Rho	-0.320**	-0.310*	-0.410*
	p	0.005	0.006	<0.001
	N	40	40	40

*p<0.001

Table 2. Evaluation of the 1st minute and 5th minute Apgar scores according to the presence of FIRS.

FIRS		Apgar 1	Apgar 5
N/A	N	20	20
	Mean	6.9000	8.3500
	Standard deviation	1.77408	.98809
Available	N	20	20
	Mean	4.6000	6.2000
	Standard deviation	2.34857	2.26181
	p	0.002	0.001

hyperventilation, and leukocytosis. There is a misconception that infection or inflammation does not exist in the non-presence of systemic findings (fever, leukocytosis).[13] 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 enables leucocytes 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 syndrome" (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, amniotic 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 outcomes is more important.[1]

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.[8] 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[14] 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).[15,16] This was explained by the increase in IL-6 level.[17] Detecting high level of IL-6, which is a proinflammatory cytokine, in umbilical cord blood was considered as associated with bad perinatal outcomes.[18,19]

In our study, IL-6 levels in umbilical cord blood was found as reverse correlated with 1st and 5th minutes 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 cultures in the follow-up of chorioamnionitis development. Carrying out amniocentesis against the possibility of secret chorioamnionitis is controversial and there is no sufficient experience.[9] 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.[5,6] 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 more appropriate intervention conditions in order to protect newborn against the complications that may develop associated with neonatal sepsis 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 outcomes 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 complications related with this condition such as intraventricular hemorrhage, periventricular leukomalacia and cerebral palsy cannot be prevented only by antibiotic treatment. Animal testings which used anti-inflammatory and chemical agents for the effects of IL-1 and IL-6 widened horizons.[10-12] These treatments can be combined with regimes used to prevent or treat fetal morbidity cause by intrauterine infection and inflammation associated with PPRM.

Conclusion

Prospective and new studies with wider scale are needed in order to understand the etiology of fetal inflammatory response syndrome and to prevent its complications.

Conflicts of Interest: No conflicts declared.

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