Ultrasonographic approach to diagnosis of fetal inflammatory response syndrome: a tool for at-risk fetuses?

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Preterm parturition is a syndrome that may result from many underlying mechanisms. Infection and inflammation are the prominent ones. Intrauterine infection and inflammation have an effect akin to sepsis, and that is similar to systemic inflammatory response in adults. Indeed, there is evidence to support the association of a fetal inflammatory response syndrome (FIRS) to systemic infection and inflammation. The utilization of invasive procedures for the prenatal diagnosis of FIRS is associated with a risk for complications resulting from the invasive method. The progress in the imaging quality of obstetrical ultrasound and the development of novel methods for functional anatomical assessment of the fetal organs may help to identify, noninvasively, fetuses at risk for FIRS in patients presenting with preterm labor. We review the studies describing advanced sonographic modalities and the imaging findings in the heart, thymus, kidney, adrenal glands, and spleen of these fetuses.

Key words: preterm labor, Tei index, fetal thymus, fetal adrenal gland, splenic vein flow

FIRS and spontaneous preterm parturition

Preterm parturition is a syndrome that may result from many underlying mechanisms. Infection and inflammation are the most prominent ones.[1] Intrauterine infection and inflammation have an effect akin to sepsis, and that is similar to systemic inflammatory response observed in adults.[2] Indeed, there is evidence to support the association of a fetal inflammatory response syndrome (FIRS) to systemic infection and inflammation.[2]

The "fetal inflammatory response syndrome" describes a condition characterized by systemic activation of the fetal immune system accompanied by multiorgan involvement.[2] FIRS was originally reported among patients with preterm labor (PTL) and intact membranes and in those with preterm prelabor rupture of the membranes (PROM).[2-4] The rate of FIRS in pregnancies complicated by preterm parturition is about 39% and increases to 49.3% in fetuses delivered within 1 week from cordocentesis.[2,3] Of interest, FIRS is present in nearly 50% of fetuses with preterm PROM.[2,4]

This syndrome is associated with a microbial invasion of the amniotic cavity (MIAC) and histological chorioamnionitis (among patients with MIAC alone, 17% have FIRS, whereas in those who have MIAC and histological chorioamnionitis, 68% have FIRS).[5] Nevertheless, some fetuses of patients with preterm parturition will have FIRS without the presence of MIAC, whereas, in women with MIAC, not all the fetuses will develop FIRS.

FIRS can be considered the fetal counterpart of the systemic inflammatory response syndrome (SIRS),[2] described in adults.[6] Table 1 compares criteria for the diagnosis of SIRS and FIRS. Since it is not possible to measure fetal vital signs and inflammatory mediators aside the heart rate in utero, the definition of SIRS cannot be applied on the fetus and other diagnostic criteria are needed. Invasive methods such as amniocentesis and cordocentesis were used to establish cutoff values of interleukin-6 (IL-6) to achieve a prenatal diagnosis of fetuses affected by FIRS (a cutoff value of 11 pg/mL was reported). In addition, evidence of umbilical cord inflammation, named funisitis, as well as chorionic vasculitis, is regarded as the histologic counterparts and histopathologic hallmarks of FIRS, allowing a postnatal diagnosis.[2,7]

Funisitis is associated with endothelial activation, and this is a key mechanism in the development of organ damage.[8] The utilization of invasive procedures for the prenatal diagnosis of FIRS is associated with a risk for complications resulting from the invasiveness of the method. The advances in the imaging quality of obstetrical ultrasound and the development of novel methods for functional anatomical assessment of the fetal organs may help today to identify, noninvasively, fetuses at risk for FIRS, in patients presenting with preterm parturition or preterm PROM. In this review, we describe the available sonographic diagnostic modalities for the study of the

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TABLE 1
Comparison between diagnostic criteria for SIRS and FIRS

SIRS[1,2]	Two or more of the following: 1. Changes in temperature >38°C (fever) or <36°C (hypothermia) 2. Heart rate changes >90 bpm (tachycardia) 3. Respiratory rate or $PaCO_2$ changes >20 breaths/min (tachypnea) or $PaCO_2$ <32 mm Hg (hypocapnia) 4. White blood cell count changes >12,000 cells/mm^3 (leukocytosis) or <4000 cells/mm^3 (leukopenia), or more >10% immature (band) cells
FIRS[3,4]	At least one of the following: 1. Fetal plasma interleukin-6 (IL-6) concentration IL-6 >11 pg/mL 2. Histopathologic hallmarks: Histologic chorioamnionitis and funisitis

[1] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74; [2] Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. Crit Care Med 1997;25:1789-95; [3] Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. Am J Obstet Gynecol 1998;179:194-202; [4] Romero R, Gomez R, Ghezzi F, et al. A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. Am J Obstet Gynecol 1998;179:186-93.

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heart, thymus, kidney, adrenal glands, and spleen in these fetuses.

What are the consequences of FIRS?

FIRS is associated with a higher risk for short-term perinatal morbidity (respiratory distress syndrome, neonatal sepsis, pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis)[2] and mortality after adjustment for gestational age at delivery, as well as for the development of long-term sequelae such as bronchopulmonary dysplasia and cerebral palsy.[9]

The involvement of FIRS in the pathophysiology of cerebral palsy in preterm neonates was reported by Yoon et al.[10] This group followed a number of 123 children who were delivered preterm (≤35 weeks of gestation from mothers who underwent amniocentesis) until the age of 3 years. The authors found that, after adjustment for gestational age at delivery, the risk of developing cerebral palsy was higher in cases of increased amniotic fluid IL-6 concentrations (odds ratio [OR], 6.4; 95% confidence interval [CI], 1.3-33.0), increased amniotic fluid IL-8 concentrations (OR, 5.9; 95% CI, 1.1-30.7), and funisitis (OR, 5.5; 95% CI, 1.2-24.5). Collectively, these findings suggest that there is a direct link between intrauterine fetal insults such as infection and inflammation, leading to FIRS, and subsequent adverse neonatal outcome and long term sequelae of prematurity.[2,3,11]

How do we diagnose FIRS today?

The diagnosis of FIRS can be achieved antenatally or postnatally. In the first case, the gold standard is represented by invasive procedures such as amniocentesis and cordocentesis,[2,3] whereas the postnatal diagnosis of FIRS is established through histology.[7]

Amniocentesis and cordocentesis allow prenatal diagnosis of intraamniotic infection/inflammation through the measurement of intraamniotic or cord concentrations of cytokines and matrix metalloproteinases (MMPs).[3] Indeed, Kim et al[12] used a rapid bedside test that can be performed in 15 minutes to examine whether the MMP-8 PTD Check (SK Pharma Co, Ltd, Kyunggi-do, Korea) could be valid in the identification of intraamniotic infection and/or inflammation and in the assessment of the likelihood of adverse pregnancy outcomes including short latency such as chorioamnionitis, and significant neonatal morbidity in patients with preterm PROM. They found that patients with a positive MMP-8 PTD Check test result had a significantly higher rate of intraamniotic infection/inflammation (77% [54/70 women] vs 9% [6/71 women]; $P < .001$), proven amniotic fluid infection (33% [23/70 women] vs 3% [2/71 women]; $P < .001$), and adverse outcome than those with a negative MMP-8 PTD Check test result. A positive MMP-8 PTD Check test result had a sensitivity of 90%, a specificity of 80%, a positive predictive value of 77%, and a negative predictive value of 92% in the identification of intraamniotic infection/inflammation, and was an independent predictor of interval to delivery (hazards ratio, 3.7; 95% CI, 2.4-5.9) and significant neonatal morbidity (OR, 3.1; 95% CI, 1.2-7.9).

In an attempt to avoid the complications arising from direct procedures, currently, there is an effort to seek for an indirect approach for those patients who should be considered at risk for the development of FIRS (patients with preterm labor and intact membranes or with preterm prelabor rupture of membranes). To achieve this goal, the approach of monitoring fetal heart rate patterns with non-stress test, fetal well-being with the biophysical profile (BPP), and the evaluation of cervical length is being attempted. Laboratory exams and fetal well-being assessment with BPP are used to diagnose subclinical intraamniotic infection.[13,14] BPP test scores of 6 or less have been demonstrated to correlate with perinatal infection, with high sensitivity and specificity according to some authors.[13,15] However, evidence supporting the BPP as a predictor of infections is lacking and has led to questions about its clinical use for predicting chorioamnionitis and FIRS, especially in cases of PROM. In their study, Muller et al[16] showed that although neonatal sepsis was present in 73.3% of the preterm PROM group, there was an abnormal BPP score in only 26.7% of these cases.

In light of these results, a more specific and targeted sonographic examination may represent a tool to study those