Editorial

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Tinker, tailor, infection, inflammation

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Clinical chorioamnionitis is an entity that is closely associated with pathological intrauterine inflammation. It is also consistently linked to perinatal complications including maternal and early neonatal sepsis, spontaneous preterm delivery (PTD), preterm and premature rupture of membranes (PPROM), intrauterine fetal demise, as well as long-term sequelae such as cerebral palsy and chronic lung disease [1]. To prevent mortality and morbidity in the mother and the offspring, it is important to diagnose clinical chorioamnionitis early and intervene. For clinical chorioamnionitis, recommended intervention is timely delivery as well as antibiotic therapy to the mother and the neonate [2]. Conversely, false diagnosis would result in unnecessary interventions such as pregnancy termination, premature delivery and unnecessary antibiotic exposure as well as in mortality and morbidity due to prematurity. The decision to intervene is often made on the basis of a suspicion supported by clinical signs and symptoms. In an effort to improve the specificity of clinical criteria and decrease unnecessary interventions, a panel of experts invited by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, in 2015, proposed that clinical chorioamnionitis is suspected when maternal oral temperature is $\geq 39.0^{\circ}\text{C}$ or 38.0°C to 38.9°C on two occasions 30 min apart, without a clear source plus any of the following: (1) baseline fetal tachycardia (>160 bpm for 10 min or longer, excluding accelerations, decelerations and periods of marked variability); (2) maternal white blood cell count (WBC) $>15,000$ per mm^3 in the absence of corticosteroids; and (3) purulent fluid from the cervical os [3]. There is concern that the new proposal may lead to missed opportunities to intervene. In one series, 26% of women with intrapartum fever only and who would not have received antibiotics if the above criteria were used, indeed, had confirmed chorioamnionitis by placental histopathology. The rate of combined maternal and neonatal clinical infections, despite antibiotic therapy, was approximately 10% in this population [4]. In another series of women presenting with PPRM and suspected chorioamnionitis, renouncement of fever as an essential increased prediction rate of neonatal sepsis from 17 to 40% [5]. In brief, intervention

based on clinical suspicion may result in under- or over-treatment, and chorioamnionitis must be confirmed by reliable objective methods soon after it is suspected but before delivery.

In this issue of the *Journal of Perinatal Medicine*, Gomez-Lopez et al. [6] evaluated inflammasome activation in the amniotic fluid (AF) collected from women with suspected chorioamnionitis at term. Inflammasomes are cytoplasmic protein complexes, when activated, trigger a cascade of events that culminate in the release of mature and bioactive forms of proinflammatory cytokines, interleukin (IL)-1 β and IL-18. Inflammasome activation, as expected, was prominent in women with intrauterine inflammation as defined by an AF IL-6 concentration ≥ 2.6 ng/mL. In some cases, inflammation was present although AF was sterile. In those cases, the magnitude of fetal and maternal inflammatory response in the placenta and AF was less as compared to those with microbial invasion of the amniotic cavity (MIAC), although no significant difference was observed in AF IL-6 concentration between the two groups.

The traditional view is that intrauterine inflammation is a surrogate for MIAC. Evidence has accumulated that sterile intrauterine inflammation is common [reviewed in ref. [7]]. Sterile inflammation is caused by molecules referred to as damage-associated molecular patterns or alarmins. They act through the same receptors as pathogens. The study by Gomez-Lopez et al. [6] demonstrates that intrauterine inflammation is sterile in some cases of chorioamnionitis presenting intrapartum. This raises several research questions: (1) What are the alarmins that can cause chorioamnionitis during spontaneous term labor? (2) Are these alarmins related to any of common practices used for the management of term labor, e.g. epidural anesthesia? (3) Are there any differences in the short- and long-term outcomes of term chorioamnionitis caused by pathogens vs. alarmins? (4) Is antibiotic therapy relevant to the management of chorioamnionitis caused by alarmins? The answers to the above questions are relevant to clinical practice not only for the management of chorioamnionitis during spontaneous term labor, but also for spontaneous preterm labor, PPRM and cervical incompetence where clinical and subclinical chorioamnionitis caused by pathogens and alarmins also play an important role.

The quest for such knowledge may also lead to a wider use of AF analysis for management of inflammation-mediated pregnancy complications in a clinical setting.

For AF analysis to be clinically relevant in the management of chorioamnionitis, accurate tests with rapid turnaround time are essential. Gram staining of AF or its spun sediment is a rapid but insensitive method to diagnose MIAC [8]. Low AF glucose is a better indicator of MIAC, but is not a good indicator for sterile intrauterine inflammation as demonstrated by Gomez-Lopez et al. [6]. Commercially available point-of-care tests for measurement of AF IL-6 [9, 10] and matrix metalloproteinase-8 (MMP-8) concentrations [11] would aid in the detection of intrauterine inflammation but cannot differentiate sterile from non-sterile.

AF analysis to assess intrauterine infection and inflammation involves amniocentesis. Serious complications of third trimester amniocentesis that require urgent delivery are rare (<1%) [12, 13], but as with any other procedure, the risks should be carefully weighed against the benefits. This is one of the reasons why amniocentesis has not gained wide popularity to manage suspected chorioamnionitis, because the advantage of incorporating AF analysis in the management of suspected chorioamnionitis has not yet proven to be advantageous over a management based on clinical signs and symptoms alone. The fear of discomfort associated with amniocentesis dissuades some patients to undergo this procedure. Less invasive sampling procedures with minimal risk and coupled with an appropriate biomarker assay are therefore of interest. In this issue of the *Journal*, Oh et al. [14] revisit the concept of utilizing cervical fetal fibronectin (fFN) to predict intrauterine infection and/or inflammation in patients presenting with preterm birth and intact membranes. The investigators evaluated the effect of two threshold values to define a positive fFN test, i.e. >50 and 150 ng/mL, respectively, on the diagnostic performance. A cut-off of 150 ng/mL improved the positive predictive value from 52 to 59% without having a significant effect on the negative predictive value (92%) in a population with a 35% prevalence of intrauterine infection/inflammation. Although fFN >150 ng/mL identified 86% of all women with intrauterine infection and/or inflammation, approximately 40% of women who test positive would have had unnecessary intervention. Such performance is obviously not acceptable to use cervical fFN to diagnose and manage intrauterine infection and/or inflammation. On the other hand, cervical fFN may be useful as a screening test to select patients for amniocentesis to collect AF for analysis for a more definitive diagnosis. Such screening would have decreased the number of amniocentesis

in this population by half but would still achieve a detection rate of 80%. Prospective studies are needed to test the cost and effectiveness of a strategy which combines cervical fFN and amniocentesis to identify women with intrauterine infection and/or inflammation. Obviously, such a strategy is only meaningful if it could be coupled with an intervention known to improve the pregnancy outcomes in women with inflammation and/or infection and presenting with threatened preterm labor and intact membranes. Such a strategy may also be relevant for other high-risk populations, i.e. women with PPROM, although the prospect of obtaining AF by amniocentesis is technically more challenging.

Midtrimester genetic amniocentesis is the most common indication for AF sampling. AF collected for prenatal genetic diagnosis from asymptomatic women has been tested for intrauterine infection and inflammation. In this issue of the *Journal*, Melekoglu et al. [15] provide further evidence that the risk of spontaneous preterm birth is increased in asymptomatic women with intrauterine inflammation as characterized by increased concentrations of a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS) proteases, IL-6 and tumor necrosis factor- α in midtrimester AF collected for prenatal genetic diagnosis. This study was not designed to answer whether pathogens or alarmins play a greater role in the pathogenesis of midtrimester intrauterine inflammation. Although earlier studies suggested that MIAC in midtrimester is up to 13% [16–18], more recent studies utilizing robust microbiologic tests suggest that it is indeed rare, and intrauterine inflammation in midtrimester is often sterile [19, 20]. Detection of midtrimester pathologic inflammation is important if combined with intervention strategies to prevent adverse pregnancy outcomes. One such example is to test midtrimester AF for inflammation to predict the success of short cervix interventions. Kiefer et al. [21] demonstrated that cerclage placement or administration of 17- α hydroxyprogesterone caproate for midtrimester short cervix for PTD prevention benefits those patients with high inflammation. Establishing the AF inflammatory status may allow the physician offer appropriate therapy to women with a short cervix in midtrimester who are at increased risk of PTD. However, reliance on AF for asymptomatic patients will significantly limit our ability to reach that goal because fewer genetic amniocenteses are being performed as the use of non-invasive prenatal screening based on cell-free fetal DNA increases.

Over the past several decades, our understanding of inflammation's role in successful embryo implantation, pregnancy maintenance and delivery has increased significantly. Understanding physiologic inflammation, in turn,

allowed us to identify aberrant and pathological inflammation in the pathophysiology of pregnancy complications such as placental dysfunction, pregnancy-induced hypertension, spontaneous preterm birth, PPRM and cervical incompetence. Despite these major advances, we are limited in our ability to detect and modify intrauterine inflammation for the purpose of avoiding or managing pregnancy complications in a routine clinical setting. This is, in part, due to the lack of accurate tests with short turnaround time and which can differentiate sterile from non-sterile intrauterine inflammation. The latter is crucial to prognosticate and choose appropriate interventions. Lack of noninvasive techniques to study the intrauterine environment is also a limiting factor. Clinical research incorporating the knowledge on intrauterine inflammation to assess the effectiveness and safety of potential interventions is needed.

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