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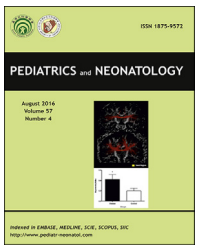

Review Article

Intrauterine inflammation, infection, or both (Triple I): A new concept for chorioamnionitis

Chun-Chih Peng [a,b,c], Jui-Hsing Chang [a,b,c], Hsiang-Yu Lin [d,e], Po-Jen Cheng [f,g], Bai-Horng Su [d,e,*]

[a] Department of Medicine, Mackay Medical College, Taipei, Taiwan
[b] Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan
[c] Mackay Medicine, Nursing and Management College, Taipei, Taiwan
[d] Department of Neonatology, China Medical University Children's Hospital, Taichung, Taiwan
[e] School of Medicine, China Medical University, Taichung, Taiwan
[f] Department of Obstetrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[g] College of Medicine, Chang Gung University, Taoyuan, Taiwan

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Chorioamnionitis is a common cause of preterm birth and may cause adverse neonatal outcomes, including neurodevelopmental sequelae. Chorioamnionitis has been marked to a heterogeneous setting of conditions characterized by infection or inflammation or both, followed by a great variety in clinical practice for mothers and their newborns. Recently, a descriptive term: "intrauterine inflammation or infection or both" abbreviated as "Triple I" has been proposed by a National Institute of Child Health and Human Development expert panel to replace the term chorioamnionitis. It is particularly important to recognize that an isolated maternal fever does not automatically equate to chorioamnionitis. This article will review the current literature on chorioamnionitis, and introduce the concept of Triple I, as well as recommendations for assessment and management of pregnant women and their newborns with a diagnosis of Triple I.

* Corresponding author. Department of Neonatology, China Medical University Children's Hospital, 2, Yuh-Der Road, Taichung, 404, Taiwan. Fax: +886 4 2203 2798.
E-mail address: subh1168@gmail.com (B.-H. Su).

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1. Introduction

Chorioamnionitis is a common cause of preterm birth and may causes adverse neonatal outcomes, including neurodevelopmental sequelae.[1–3] Clinically, chorioamnionitis has been marked to a heterogeneous setting of conditions characterized by infection or inflammation or both, followed by a great variety in clinical practice for mothers and their newborns. Recently, the term "intrauterine inflammation or infection or both" abbreviated as "Triple I" has been suggested by a National Institute of Child Health and Human Development (NICHD) expert panel including maternal and neonatal experts in a workshop to replace the term chorioamnionitis.[4] This article will review the current literature on chorioamnionitis, and introduce the concept of Triple I, as well as recommendations for assessment and management of pregnant women and their newborns with a diagnosis of Triple I.

2. Current understanding of chorioamnionitis

Preterm birth is a major cause of perinatal mortality and long-term morbidity. Chorioamnionitis is a common cause of preterm birth. A recent prospective study of 871 pregnancies found that those with histologic chorioamnionitis, premature delivery occurred nearly twice as often as those without chorioamnionitis.[3] Chorioamnionitis may induce preterm delivery by a maternal inflammatory response.[1,2] Bacterial infection, via the release of endotoxins and exotoxins, stimulates the release of cytokines from the decidua and fetal membranes, which induce uterine contractions and/or rupture of fetal membranes.

According to the presence or absence of clinical signs and laboratory evidence, chorioamnionitis may be categorized as clinical chorioamnionitis and subclinical/histologic chorioamnionitis.[1,2,5–7] Clinical chorioamnionitis is characterized by maternal fever, leukocytosis, maternal and/or fetal tachycardia, uterine tenderness, and preterm rupture of membranes (PROM). Subclinical/histologic chorioamnionitis is asymptomatic and defined by inflammation of the chorion, amnion, and placenta, which is more common than clinical chorioamnionitis.[1,2]

The inflammation of the chorioamnion (histologic chorioamnionitis) and umbilical cord (funisitis) are the manifestations of the maternal and fetal immune responses in condition of intra-amniotic infection.[6,7] Histological and microbiological evidence of inflammation or infection may not always accompany one another. And maternal clinical signs may not be present.

The frequency of histologic chorioamnionitis is higher than that of clinical chorioamnionitis with positive bacterial cultures. The treatment with antibiotics and the difficulty of growing fastidious organisms may lead to negative cultures even in the presence of histological evidence of placental inflammation.[6] Therefore, pathological evaluation of the placenta is essential for definite diagnosis.

Different authors have shown higher positive cultures rates of amniotic fluid in women with preterm labor at earlier gestational ages,[8] higher interleukin (IL)-6 levels in the amniotic fluid in women with spontaneous labor in pregnancies less than 34 weeks,[9] and higher IL-6 levels in cord blood in preterm compared with term newborns born after microbial invasion of the amniotic cavity.[10] The fetal inflammatory response syndrome (FIRS) is a condition characterized by systemic activation of the fetal immune system. FIRS was originally defined as an elevation of the fetal plasma IL-6 concentration in fetuses of mothers with preterm labor and PROM.[11]

PROM refers to rupture of membranes (ROM) prior to the onset of labor but beyond 37 weeks' gestation. ROM prior to 37 weeks' gestation is called preterm PROM (PPROM). PPROM is responsible for one-third of preterm deliveries.[12] Prolonged ROM is any ROM that persists for more than 24 h and prior to the onset of labor; it increases incidence of neonatal sepsis 2–10 times because of the facilitated ascending infection to the uterine cavity, and this risk becomes 4 times higher when ROM is accompanied by chorioamnionitis.[13] The incidence of histological chorioamnionitis increases up to 50% with PPROM[6,7] and is inversely related to gestational age.[14–16]

Histological chorioamnionitis is most commonly associated with intrauterine bacterial infection, and may coexist with umbilical infiltration (funisitis).[17] It is believed that FIRS, as a result of infection pathways and increasing cytokines activate an inflammatory response that potentially lead to fetal vasculitis, congenital anomalies, fetal death, fetal hydrops, spontaneous abortion, preterm labor, or preterm rupture of the membranes.[18,19] Chorioamnionitis has been suggested to affect neonatal outcome adversely by increasing the risk of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, neonatal sepsis, and neurodevelopmental sequelae.[16,20–23]

3. Current management of chorioamnionitis

Chorioamnionitis is an acute condition requiring a high index of suspicion, and the threshold for antibiotics treatment is low in the pregnant woman and their neonates because both are severely affected by the organisms leading to infection.[24] Clinical chorioamnionitis is diagnosed when following clinical signs are present: maternal fever, maternal and/or fetal tachycardia, maternal leukocytosis, uterine tenderness, and foul-smelling or purulent amniotic fluid.[25] However, these subjective findings are generally neither sensitive nor specific.

Maternal fever complicates up to one-third of labors and has diverse causes including infection, epidural anesthesia, and inflammation. Because not every maternal fever is caused by infection, to treat all fevers with antibiotics will result in overtreatment of mothers.[24–26]

Many intrauterine or extrauterine factors may cause maternal fever. Intrauterine infection can result in preterm birth, increased risk of operative delivery, maternal bacteremia and sepsis, postcesarean wound infection, need for hysterectomy, postpartum hemorrhage, admission to intensive care unit, and rarely maternal mortality.[25] However, a clear differentiation between infectious and noninfectious fever during labor is difficult; therefore, intrapartum fever frequently results in evaluation and treatment of neonates for possible sepsis.[27,28]

The clinical signs and laboratory data usually used to diagnose chorioamnionitis have poor predictive value, may be

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