Editorial

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Clinical chorioamnionitis – an ongoing obstetrical conundrum

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The clinical entity of intrapartum fever, the hallmark sign of clinical chorioamnionitis, has been known for centuries [1]. As early as the late 18th century it was precisely defined as any fever arising in consequences of pregnancy or delivery [2]. The grave consequences of this condition were well known to the physicians at that time as attested by the comment of John Leake of the New Westminster Lying-in Hospital in 1772: *"If those diseases which have been found most dangerous and mortal in their effects ought principally to be considered by physicians, none will more deservedly engage their attention than the Childbed Fever, as there is not, perhaps, any malady…"* [3].

The criteria for the diagnosis of clinical chorioamnionitis include fever and two or more of the following: maternal and fetal tachycardia, uterine tenderness, foul smelling amniotic fluid, and maternal leukocytosis [4–13]. These criteria have been used in clinical practice since the early 70s of the previous century. When it comes to management and understanding of the pathophysiology of intrapartum fever and clinical chorioamnionitis, a walk into labor and delivery ward today can be like taking a step back to the 70s. Admittedly, with regard to intrapartum fever, our discipline, which was awarded the wooden spoon by Archie Cochrane for being the least evidence based medical specialty [14], has not done enough yet to restore its reputation.

The association between short- and long-term adverse neonatal outcomes and chorioamnionitis are well established [11, 15–39], with neonatal sepsis and cerebral palsy being the most noteworthy [17, 21]. This issue of the *Journal* shed new light on the ongoing clinical challenge of diagnosis and management of chorioamnionitis at term. Using state-of-the-art methods and unique study and control population, this set of articles [40–44] provides a wealth of novel and important information and can be viewed as the first genuine and comprehensive attempt to decipher the enigma of clinical chorioamnionitis. These articles challenge the diagnosis, the underlying mechanism of disease and indeed, the very definition of clinical chorioamnionitis at term. Precision in diagnosis and taxonomy, as well as the molecular mechanism(s) responsible for this common and important complication may have preventive, diagnostic and therapeutical implications. Similarly important is to avoid over diagnosis which leads to unnecessary, potentially harmful, treatment and interventions. The urgent need to improve the knowledge in this important subject is evident as the human fetus is probably most vulnerable during labor and delivery and that these complications should be regarded as preventable.

The initial report [45] by Romero's group recently published in this Journal challenges the clinical diagnosis of chorioamnionitis at term. Using both cultivation and molecular techniques of amniotic fluid, almost 40% of women clinically diagnosed with chorioamnionitis did not have any evidence of bacteria in the amniotic cavity. Notably, nearly 50% did not have evidence of acute inflammatory lesions of the placenta (i.e. histologic chrioamnionitis [46]).

In the first report [40] of the series of articles published in this special issue of the *Journal*, the authors characterized the intra-amniotic inflammatory response in women with clinical chorioamnionitis at term. Expectably, women with intra-amniotic infection and/or inflammation had significantly higher concentrations of pro- and anti-inflammatory cytokines and chemokines compared to women at term in labor without intra-amniotic inflammation. Yet, although diagnosed with clinical chorioamnionitis, patients without intra-amniotic inflammation had a similar amniotic fluid expression of cytokines/chemokines to normal women in labor at term [40].

The next step was to demonstrate how well the different clinical criteria used for the diagnosis of chorioamnionitis perform in the identification of proven intra-amniotic infection [41]. Not surprisingly, none of the individual clinical signs, or any of their combination, accurately identified patients with intra-amniotic infection or microbial-associated intra-amniotic inflammation. Thus, there is a need for better methods to enhance our precision in the clinical diagnosis of chorioamnionitis at term.

These results lead the authors to focus their interest in the maternal compartment to characterize the plasma cytokine profile [42]. Using cutting edge methods, the authors demonstrate that patients with clinical chorioamnionitis at term have higher maternal plasma concentrations of pyrogenic cytokines than patients in spontaneous labor at term without a fever. However, the absolute concentration of cytokines cannot be used to identify those who have bacteria in the amniotic fluid, suggesting that amniotic fluid assessment is required to identify women with intra-amniotic inflammation.

Next, the authors focused their attention to the fetus [43] and placenta [44]. Characterization of inflammatory status in dyads of maternal-fetal samples revealed that neonates born to mothers with clinical chorioamnionitis at term had higher concentrations of umbilical cord plasma cytokines than those born to mothers without clinical chorioamnionitis. This inflammatory "mirror syndrome" was anticipated. However, less predictable is the finding that even neonates exposed to clinical chorioamnionitis without intra-amniotic inflammation had elevated concentrations of inflammatory cytokines. This suggests that intrapartum fever, *per se*, is associated with an altered fetal immune response. Thus, antibiotics administration, which is the mainstay of treatment in patients with intrapartum fever [9, 47–50], may be too little and too late. The role of other therapeutic strategies such as anti-inflammatory agents should be investigated in this clinical set-up [51, 52].

The conventional wisdom is that histology is the "gold standard" for the diagnosis of chorioamnionitis. Nevertheless, despite the association between histologic chorioamnionitis/funisitis and intra-amniotic infection/fetal inflammatory response syndrome [53–55], the performance indices of histology were surprisingly low [44]. The practical conclusion is that the current pathologic methods have limitations in the identification of the fetus exposed to amniotic cavity infection. One way to look at the placenta is as the "black-box" of the pregnancy. However, in contrast to chorioamnionitis in preterm gestations, in the context of term deliveries, the time interval between the occurrence of clinical chorioamnionitis and the delivery of the placenta may be too short for the placenta to "record" the insult.

The term "*clinical chorioamnionitis*" is an oxymoron. As the name implies, diagnosis of chorioamnionitis is based on histological evaluation of the placenta. However, the prefix "*clinical*" means that the diagnosis should be made well before the delivery of the placenta. The articles in this special issue of the *Journal* bridge the gap and attempt to ease the inherent tension between the "clinical" and the "chorioamnionitis".

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