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Review

Term histologic chorioamnionitis: a heterogeneous condition

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ABSTRACT

A histologic response of histologic chorioamnionitis (HCA) is defined as an intrauterine inflammatory condition characterized by acute granulocyte infiltratration into the fetal–maternal or the fetal tissues. Prevalence of HCA is inversely correlated with gestational age, occurring in 50% of preterm birth and in up to 20% of deliveries at term. Regardless of these standard definitions, understanding HCA is challenging as it reflects a heterogeneous condition. A histologic response of HCA from term placentas often does not correspond to a clinical presentation; in this context, the present review aims to analyze main characteristics of this condition, in particular focusing on mechanisms and birth outcomes.

Contents

Introduction

Histologic chorioamnionitis (HCA) is defined by pathologists as an intrauterine inflammatory condition characterized by acute granulocyte infiltratration into the fetal–maternal (choriodecidual space) or into the fetal tissues (chorioamniotic membranes, amniotic fluid and umbilical cord). HCA is frequently diagnosed in placentas delivered preterm, even in the absence of maternal

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clinical signs. Moreover, recent evidence indicates there is a high prevalence of HCA in women delivering at term. Prevalence of HCA is inversely correlated with gestational age; HCA occurs in more than 50% of cases at preterm birth (PTB) [1], with the highest rate in preterm premature rupture of the membranes (pPROM) and in preterm spontaneous labor [2]. However, the diagnosis of HCA is also made in up to 20% of deliveries at term [3]. Regardless of these standard definitions, understanding HCA is challenging as it reflects a heterogeneous group of risk factors, pathways and presentations [4].

While the relationship between HCA and PTB is well established [5], especially in cases where infective agents have been identified as the primary cause of HCA, increasing reports are indicating that HCA at term is not a rare event [6]. This suggests that placental inflammatory lesions are an inherent part of parturition, potentially representing a physiological response to labor processes, especially in cases where no clinical and subclinical infection related presentations were diagnosed.

Alternatively, other conditions could also be associated with HCA at term. For example, maternal malnutrition, and exposure to endocrine-disrupting chemicals (EDCs; compounds that maybe present in pesticides, plastic food containers and others) have been correlated to chronic inflammation and have been reported as modulators of various immune cell populations [7]; suggesting these events could be directly or indirectly contributing to the placental inflammatory states present in the HCA.

Therefore, in an attempt to better understand term HCA, we reviewed the pathogenetic mechanisms and birth outcomes of this heterogeneous condition.

Epidemiology

The incidence of HCA at term (defined between 37 and 41 weeks of gestation) varies from 20% to 24% and 34% [8]. Several studies report an association between the presence and progress of labor and the risk of intra-amniotic infection, intra-amniotic inflammation and HCA. The association between labor and risk of placental inflammation may be attributed to the so-called ''suction-like'' effect of uterine contractions, which allow vaginal fluid containing a large microbial load to ascend into the uterine cavity [9]. On the contrary, HCA is rare in women at term pregnancy with intact membranes and before onset of labor [10].

Moreover, patients with HCA had significantly higher rates of nulliparity, oxytocin augmentation, regional analgesia, cesarean section or operative vaginal delivery [11]. HCA is also associated with longer duration of labor, PROM, higher gestational age and birth weight at term [6].

Differences between HCA occurring in preterm or at term delivery

Although the physiological mechanisms involved in the initiation of parturition remain unclear, intrauterine inflammation represents a common condition associated with the labor process either at term or preterm [12]. However, significant differences have been reported between the two conditions.

HCA is more common in PTB than at term delivery [12], and is more severe in terms of degree of invasion of gestational tissues. While HCA in PTB is more frequently associated to funisitis, HCA at term presents as chorioamnionitis within fetal membranes, suggesting that inflammatory events at term are more likely to be of maternal than of fetal origin. HCA with funisitis is well known to be a common lesion, associated to severe prematurity, and inversely related to gestational age at birth; its presence increases the risk of proven neonatal sepsis and other long term sequelae, such as cerebral palsy [13]. Conversely, at term, a different scenario was found where HCA was localized to mainly the decidua and chorionic plate rather than amnion and umbilical cord [6,10].

The shift in the rate of HCA from beyond the fetal membranes (HCA2 defied as amnionitis or inflammation of the chorionic plate without funisitis; HCA3 defined as histologic chorioamnionitis with funisitis) in preterm deliveries to within the fetal membranes (HCA1 defined as deciduitis and/or histologic chorioamnionitis within the membranes) in term deliveries, may be due to the feto-placental–maternal immune system that develops a different competence with advancing gestation. When inflammation is detected within the fetal membranes and remains confined to chorion-decidua, the inflammatory process is derived from the maternal compartment, while a fetal response is also activated when inflammation goes beyond the fetal membranes and invades the amniotic cavity and umbilical cord [5].

Infective conditions represent the most frequent causal factors for PPROM and PTB, especially when gestational age is extremely low [14]. Conversely, the rate of microbiologically-proven intraamniotic infection is extremely low in women who deliver at term either not in labor or in early labor [15], suggesting that in most cases HCA may represent a phenomenon that is associated with the inflammatory events driving labor thus representing a physiological response to the labor process, or an inherent part of parturition [3,5].

In this context HCA may reflect the insults of labor in the chorioamniotic membranes, particularly in chorio–decidual interface, which must separate before delivery [3]. These observations are corroborated by the findings that HCA at term is more frequently identified in women with spontaneous onset of labor than in those undergoing elective cesarean section [5]. However, similarly to PTB, it is impossible to determine what fraction of acute inflammatory lesions occurs at the onset of spontaneous labor at term, and what fraction was acquired during the course of spontaneous labor [16].

These observations suggest HCA at term delivery may represent exclusive conditions of labor in terms of etiopathological processes, degree of inflammatory cell invasion into the intrauterine tissues, and different immune competence of the feto-placental unit.

Mechanisms underlying term HCA

The etiology of term HCA has not been studied as comprehensively as that of PTD. It has long been assumed that chorioamnionitis is likely due to infection and that failure to recover microorganisms resulted from inadequate culture techniques. However, accumulating evidence supports the occurrence of inflammation during pregnancy without infection.

The inflammatory pathways and the infectious and non infectious conditions leading to HCA are very similar in preterm and term delivery; however, attention will be placed on the pathogenesis of this condition at term, and the mechanisms will be briefly examined.

Inflammatory pathways underlying HCA

Inflammatory processes may affect intrauterine tissues with different degrees of invasion, allowing for HCA classification by a grade, with the fetal/neonatal acute inflammatory response representing the most severe.

Decidua and/or amnio-chorial space (deciduitis or histologic chorioamnionitis within the membranes) are the first tissues to be afflicted by the inflammatory process activating release of pro-inflammatory cytokines [2]. In this scenario, placenta, fetal membranes, decidua and myometrium represent key tissues activating diverse inflammatory pathways through up-regulation of several molecules including the pro-inflammatory cytokines,