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Isolated acute funisitis in the absence of acute chorioamnionitis: What does it mean?

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ABSTRACT

Objective: Acute funisitis (AF) is most commonly associated with acute chorioamnionitis (AC) and ascending infection. The significance of cases of AF without associated AC or isolated funisitis (IF) is unknown. Our objective was to evaluate clinical and pathologic features of IF and to determine its significance.
Study design: This was a retrospective review of placentas of patients delivering at our institution from 1997 to 2017. Placentas with the diagnosis of IF comprised the study population and placentas without either AF or AC served as controls.
Results: There were 156 cases and 181 controls identified. Maternal age, gestational age, birthweight and mode of delivery were similar in both groups. 132 (84.6%) of cases of IF had meconium, with 62 (47.0%) having meconium only in the membranes, 36 (27.3%) in the membranes and cord and 34 (25.6%) in the membranes and cord with associated myonecrosis. 72 (38.7%) of controls had microscopically identified meconium, with only one (1.4%) showing meconium in the cord. None had myonecrosis ($p < .001$). There was also a significantly higher rate of intrauterine fetal demise (IUFD) in the IF group ($p = .027$). but the rate of suspected Intrauterine growth restriction (IUGR) was significantly greater in the controls ($p = .014$).
Conclusion: IF is highly associated with the presence of meconium discharge and meconium-associated myonecrosis of umbilical vessels. The inflammation in IF may be the result of damage to the muscle fibers of the cord due to meconium but additional studies are necessary to understand the significance of these findings.

1. Introduction

Standardized placental histopathologic examination can greatly contribute to our understanding of the etiology and clinicopathology associated with adverse pregnancy and neonatal outcomes.

A uniform sampling criteria, placental growth descriptors, pathology terminologies and diagnostic criteria have been developed in order to allow us to more consistently and objectively describe placental lesions [1,2]. Acute chorioamnionitis (AC) is the most frequent diagnosis in placental pathology reports [3–5], is considered along with acute funisitis (AF) to be part of the inflammatory response to an ascending, intra-amniotic infection [3,6]. This inflammatory response is characterized by the infiltration of neutrophils and the release of pro-inflammatory cytokines by the mother and the fetus [6].

Intrauterine infection is strongly associated with preterm birth, intrauterine growth restriction (IUGR) and intrauterine fetal demise (IUFD), as well as with preterm rupture of membranes (PROM), cervical insufficiency, neonatal sepsis, neonatal intensive care unit (NICU) admission, and long-term neurodevelopmental injury [3,7–10]. Acute and chronic inflammatory lesions and vascular injury can also be found in up to one quarter of term pregnancies with normal outcome [11–14]. This means that intrauterine infection does not necessarily herald an adverse clinical outcome. A greater understanding of the mechanism of the inflammatory response cascade can lead to a better understanding of adverse pregnancy outcomes and the development of strategies to prevent them.

Meconium in the amniotic fluid and fetal membranes is also well-known to be associated with increased perinatal morbidity and mortality [15,16] as well as poor long-term neurologic outcomes [17]. The presence of meconium-stained amniotic fluid is considered by clinicians to be a sign of fetal distress [18] and necessitates closer fetal surveillance with fetal heart rate monitoring and can lead to expedited delivery [19]. Studies have shown that meconium-staining is associated with increased rates of labor induction, operative delivery, cesarean

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delivery and late- and post-term pregnancy and meconium-aspiration syndrome [18,20,21]. Meconium passage may be a response to an adverse intrauterine environment, but is some cases is clearly physiologic. When intrauterine infection and meconium are both present, it is unclear whether in utero passage of meconium is a fetal response to intraamniotic infection or if the presence of meconium makes for a more hospitable environment for bacteria to thrive and incite an infection, or both [16]. Longstanding meconium maybe associated with meconium-associated myonecrosis of umbilical vascular muscle [15]. Myonecrosis, like AC and AF, has been shown to be associated with adverse clinical outcomes such as IUGR, IUFD, cord complications and placental lesions including fetal thrombosis and chorangiosis [15,16,20].

When histological examination of a placenta demonstrates both AC and AF, it is straightforward that a progressive, infectious process has occurred, specifically an intrauterine infection, or intra-amniotic infection. What is less clear is the clinical significance AF occurring in isolation, in the absence of AC. The objective of this study was to evaluate clinical and pathologic features of cases of isolated AF in order to determine the significance of this finding and determine how it can contribute to our understanding of adverse clinical outcomes.

2. Methods

We searched the surgical pathology database at Weill Cornell Medical Center for third trimester placentas from 1997 to 2017. Placental reports used for data collection were reviewed by a single pathologist (RNB). Placentas with a diagnosis of AF without a diagnosis of AC were identified as cases of isolated funisitis (IF), and placentas without a diagnosis of AF or AC were identified as controls. Clinical features such as gestational age at delivery, mode of delivery, prenatally diagnosed IUGR, presence of IUFD, placental weight and birthweight as well as Apgar scores were recorded. Histopathologic findings were examined and scored as present or absent for all included placentas as follows.

Cord complications were grouped together and included: excessively long cord (≥70 cm), hypercoiling, (defined as a coiling index > 0.3 [22], the presence of true knots, single umbilical artery and velamentous cord insertion. When meconium was noted in the report, it was further characterized as: meconium in the membranes, meconium in the membranes and umbilical cord or meconium in the membranes and umbilical cord with associated umbilical vascular myonecrosis. Lesions of fetal vascular malperfusion (FVM) and lesions of maternal vascular malperfusion (MVM) were also recorded as per Amsterdam criteria [5]. Categorical variables were compared using Chi square analysis, and continuous variables were compared using student t-test.

3. Results

There were 181 control cases without AF or AC and 156 cases with IF identified from the surgical pathology database during the collection period. The median maternal age of the study population was 33 yrs [30–37], the median gestational age at delivery was 39 wks [range 38–40], the median birthweight was 3270 g [range 2891–3629], and the median placental weight was 450 g [range 378–518]. Maternal age, gestational age at delivery and neonatal gender were similar in both groups (Table 1).

The study groups also had similar rates of cesarean delivery (58.7% in controls and 61.2% in IF, p = .638) and median neonatal birthweight, (Table 2). IUGR was significantly more common in the control group (11.0% vs 3.8%, p = .014) and IUFD was more common in the IF group (4.5% vs 0.6%, p = .027), although these outcomes were not frequent. There was a significant difference between the median placental weights in the two groups as the placentas in the control group weighed significantly less than those in the IF group (441 gms vs 460 gms, p = .034), however the actual difference in the median was small at 19 g and therefore might not be clinically relevant (Table 2).

Table 1
Demographics.

	No funisitis (controls) N = 181	Isolated funisitis N = 156	p-value	CI (95%)
Maternal age (yrs)[a]	34 [31–37]	33 [29–36.75]	.090	-.164–2.224
Gestational age at delivery (weeks)[a]	39 [38–40]	39 [39–40]	.259	-.194–.718
Neonatal gender			0.126	
Male	89 (51.1%)	82 (59.9%)		
Female	85 (48.9%)	55 (40.1%)		

[a] Results presented as median [interquartile range].

There was a significantly increased rate of meconium in the IF group compared to the control group (84.6% vs 38.7%, p = < .001). In both study groups, if meconium was found it was most commonly noted to be in the membranes, however there was significantly more meconium in the cord and myonecrosis in the IF group compared to the control group (27.3% vs 1.4% and 25.6% vs 0%, respectively, p = < .001). Lesions related to MVM and cord complications were more common in the control group, but lesions of FVM were more common in the IF group (Table 3).

4. Discussion

In our study, there was a clear and significant increase in the presence of meconium in cases of IF versus controls. This was particularly true with the presence of meconium in the cord and associated myonecrosis. As such, it may be that IF most commonly occurs as a result of damage to the cord and/or the muscle fibers of the cord from meconium rather than an ascending infection. Damage to the cord from inflammation and/or meconium would explain the increase in the presence of fetal vascular thrombosis or FVM in the study group. This association may also explain the increase in fetal demise in the study group. In our control group, there was a higher rate of IUGR and cord complications, as well as lesions of MVM. This may be due to selection bias in that in our institution, as all placentas are not routinely submitted to pathology, but are submitted when there is a concerning maternal and/or fetal finding. This would result in the control group possibly having an artificially higher rate of abnormal placental lesions and adverse outcomes. In addition, although IUGR can be associated with FVM, the thrombosis in this case is likely relatively acute in onset, a matter of days rather than weeks. As such, there would not be time for this finding to result in growth restriction. With regards to MVM, there is no reason to suspect that this type of lesion, associated with abnormalities in the maternal circulation, would be increased in the study group.

The major strength of this study is the separation of cases of AF in the absence of AC to examine outcomes related to funisitis in isolation, whereas most studies combine these inflammatory lesions of AF and AC together. One weakness is that the sample size is relatively small and therefore some differences between groups may not be able to be identified. Another weakness is that, as previously discussed, our control group may not have been truly representative of a control population, because placentas in pregnancies without concerning clinical findings like abnormal fetal heart monitoring, suspected IUGR etc. are not routinely submitted to pathology.

We hope to perform larger studies to enable us to compare cases of isolated AF with cases that exhibit both AF and AC, as well as with controls. Antepartum and intrapartum clinical indicators that are associated with IF may hopefully be identified and with further study enable a greater understanding of this lesion.

Table 2
Delivery and fetal outcomes.

	No funisitis (controls) N = 181	Isolated funisitis N = 156	p-value	CI (95%)
Mode of delivery			0.638	
Vaginal delivery	74 (41.3%)	57 (38.8%)		
Cesarean delivery	105 (58.7%)	90 (61.2%)		
Fetal outcomes				
IUGR	20 (11.0%)	6 (3.8%)	**.014**	
IUFD	1 (0.6%)	7 (4.5%)	**.027**	
Birthweight (grams)[a]	3205 [2816.5–3607.5]	3410 [3070–3696]	.054	−273.687–2.455
Placental weight – (grams)[a]	441 [370–500]	460 [390–550]	**.034**	−48.819–1.907

[a] Results presented as median [interquartile range].

Table 3
Histopathologic findings.

	No funisitis (controls) N = 181	Isolated funisitis N = 156	p-value
Meconium- any location	70 (38.7%)	132 (84.6%)	< **.001**
Meconium in membranes	69/70 (98.6%)	62/132 (47.0%)	
Meconium in cord	1/70 (1.4%)	36/132 (27.3%)	
Myonecrosis	–	34/132 (25.6%)	
Maternal vascular malperfusion	58 (32.0%)	46 (29.5%)	< **.001**
Fetal vascular malperfusion	19 (10.5%)	20 (12.8%)	**.027**
Cord complications	58 (32.0%)	37 (23.7%)	< **.001**

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2018.12.002.

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