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ORIGINAL ARTICLE

Distribution of cord inflammation in cases with clinical suspicion of chorioamnionitis

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Abstract

Introduction: Identification of acute funisitis, a sign of foetal inflammatory response (FIR), is crucial as their presence is associated with ominous neonatal outcomes. Recommendation on which part of umbilical cord should be sampled to facilitate optimal identification of acute funisitis is limited. Methods: This is a retrospective cross-sectional study over a seven-month duration recruiting all patients with clinical suspicion of chorioamnionitis and/or maternal intrapartum pyrexia. The distribution and the degree of cord inflammation were assessed. The cases were also evaluated for maternal inflammatory response (MIR) and chorionic vasculitis (CV). Results: Of the 191 placentas, 88 (46.1%) had some degree of cord inflammation. Forty-nine (55.7%) had a differential in cord inflammation, with distal cord section (n = 38) demonstrating significant greater inflammation than that of proximal cord section (n = 11) ($p<0.001$). There were 20 cases with phlebitis only and 8 cases demonstrated arteritis only in either proximal or distal cord sections. Increasing magnitude of cord inflammation was significantly associated with increasing severity of MIR and the rate of CV ($p<0.001$). CV was observed in 25 (24.3%) cases showing absence of cord inflammation, while 12 (13.6%) cases with cord FIR demonstrated no CV. Discussion: Inflammatory reaction can occur variably throughout the length of the umbilical cord and chorionic plate vessels, with greater inflammation seen in the distal cord section. We affirm the current Amsterdam recommendation of submitting at least two cross sections of the cord representing proximal and distal sites and two sections from placental parenchyma to facilitate the identification of FIR.

Keywords: Chorioamnionitis, foetal inflammatory response, funisitis, inflammation, maternal inflammatory response, placenta, umbilical cord

INTRODUCTION

Human foetus can deploy a local and systemic inflammatory response following exposure to microorganisms or non-infectious stimuli. Acute funisitis, an acute inflammatory response involving the umbilical cord, is the histological hallmark of foetal inflammatory response (FIR). It serves as a potential surrogate marker to predict intrauterine infection.[1] Microorganisms such as *Escherichia coli*, enterococcus, group B streptococcus (GBS), *Ureaplasma* spp., *Gardnerella vaginalis*, *Candida* spp. and SARS-CoV-2 were among the microorganisms previously reported associated with FIR.[2-4] GBS is reported to have extensive FIR compare to maternal inflammatory response (MIR). Identification of acute funisitis or any degree of umbilical cord vascular inflammation is crucial as their presence is associated with ominous short- and long-term neonatal morbidity such as early-onset neonatal sepsis, intraventricular haemorrhage, bronchopulmonary dysplasia and cerebral palsy.[5,6] Generally, inflammation of the umbilical artery (umbilical arteritis) is associated with an increased rate of perinatal morbidity than umbilical phlebitis alone, which in turn associated with greater morbidity compared to cases without umbilical cord inflammation.

Placental and umbilical cord examination

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are essential in cases with clinical suspicion of chorioamnionitis. Wong *et al*. recommended rapid processing of the umbilical cord ahead of the rest of the other placental sections to allow early detection of FIR.[7] Nonetheless, the recommendation about which part of umbilical cord should be sampled to facilitate optimal identification of acute funisitis remains unascertained. The topographic distribution of cord inflammation is not fully appreciated. In 2001, Kim *et al*. proposed standard sampling procedure taking one section from each third of the umbilical cord[8], while Katzmann *et al*. suggested that at least two cord sections should be taken, one within 5cm of the cord placental insertion site and another at least 10cm distal to the first section.[9] In 2016, a group of placental experts published a standard practice guideline recommending two cross sections of the umbilical cord, one from the fetal end and another approximately 5cm from the placental insertion end.[10]

In the present study, we investigated the distribution and the degree of cord inflammation in cases with clinical suspicion of chorioamnionitis, maternal intrapartum pyrexia and/or premature rupture of membrane (PROM), and whether cord vessel inflammation could occur independent of MIR. The significance of cord inflammation in relation to gestational age, birth weight, placental weight and chorionic vasculitis were also studied.

MATERIALS AND METHODS

Study Population

The study was approved by the Human Research Ethical Committee of the Institutional Review Board (1287A/09/2025). A retrospective cross-sectional study considered all consecutive pregnancies delivered in Women's and Children's Hospital, Adelaide for a period of seven months. All cases with a clinical suspicion of intra-amniotic infection (clinical chorioamnionitis), maternal intrapartum pyrexia and/or prolonged rupture of membrane (PROM) with placenta and umbilical cord sent for histopathological evaluations were included in the study. Clinical chorioamnionitis is suspected when intrapartum fever is associated with two other maternal and foetal signs of local or systemic inflammation: foetal tachycardia, fundal tenderness, foul smelling vaginal discharge and maternal leukocytosis.[11] Cases were excluded if there were clinical and/or histological evidence of meconium-related changes in the membrane, as these cases might potentially serve as confounder contributing to cord inflammation.

Clinical data including the maternal and gestational age, existing medical conditions, clinical presentations (preterm delivery and preterm premature rupture of membranes) and neonates' birth weight were recorded. All patients' identities were anonymised and coded accordingly.

Placental Examination

Gross placental examination records such as placental trimmed weight, dimension, umbilical cord length and coiling index were documented. The placenta and umbilical cord were sampled in accordance with the 2016 Amsterdam Placental Workshop Group Consensus guidelines.[10] Briefly, a minimal of four blocks from placenta were taken: one block to include a role of the extraplacental membranes, and two cross sections of umbilical cord, one from the foetal end (uninked, distal section) and another approximately 5cm from the placental insertion end (inked, proximal section); and three other blocks containing full-thickness section of placental parenchyma. All respective histological slides were retrieved and reviewed for foetal and maternal inflammatory responses by two experienced histopathologists, blinded to the original clinical information and histopathological diagnosis.

Foetal inflammatory response (FIR) is at stage 1 when foetal neutrophils are seen involving the umbilical vein (phlebitis) and/or chorionic plate foetal vessels (chorionic vasculitis). Stage 2 is indicated by the inflammation of the umbilical arteries (arteritis), while involvement of Wharton's jelly with necrosis, necrotising funisitis is Stage 3.

Maternal inflammatory response (MIR) is staged according to the location and state of neutrophils. MIR stage 1: maternal neutrophils congregate in the subchorionic intervillous space (subchorionitis) and/or chorion (chorionitis) in the chorionic plate; MIR stage 2: maternal neutrophils in the amnion (chorioamnionitis); MIR stage 3: chorioamnionitis with amnion necrosis and/or neutrophil karyorrhectic debris (necrotising chorioamnionitis).[10,12] Cases with divergent histological interpretations were reassessed together to achieve a consensus.

Statistical Analysis

The following statistical tests were employed as appropriate to compare the differences between

variables: Pearson's chi-square and Fisher exact test for categorical variables, student T-test and Kruskal-Wallis test for continuous variables. All statistical analyses were carried out using the Statistical Package for the Social Science (SPSS) software version 26.0 (PASW Statistics, USA). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Distribution of Cord Inflammation

Of the 191 cases with clinical chorioamnionitis, maternal intrapartum pyrexia and/or PROM, 88 (46.1%) cases had some degree of cord inflammation with the severity of cord inflammation as follows: stage 1 (n = 36/88, 40.9%), stage 2 (n = 47/88, 53.4%) and stage 3 (n = 5/88, 5.7%) (Figure 1). The remaining 103 (53.9%) cases had no histological evidence of cord inflammation. Of the 88 cases with cord inflammation, 77 (87.5%) cases demonstrated a different degree of cord inflammation in the proximal and distal cord sections.

Table 1 highlighted the distribution of acute inflammation in the 77 cases with different degree of cord inflammation in the proximal and distal cord sections. Differential in cord inflammation was referred to cases demonstrating different degree of cord inflammation in either proximal or distal cord section. Briefly, forty-nine (55.7%) of these 88 placentas had a differential in cord inflammation, with distal cord inflammation (n = 38) significantly greater than proximal cord inflammation (n = 11) ($p < 0.001$). Twenty (22.7%) of these 88 placentas had phlebitis in only one cord section, with no significant difference between proximal (n = 6) or distal (n = 14) cord section involvement. Similarly, there were 8 (9.1%) of these 88 cases showing one or two vessel arteritis: one and seven cases involved the proximal and distal cord sections respectively, and their difference was not significant statistically.

Cord Inflammation with Clinicopathological Parameters

Table 2 shows the distribution of cord inflammation and their association with clinicopathological parameters. Mean cord length that was submitted for histopathological examination was 359.5 ± 110.4mm (range: 110 – 750mm). Cord inflammation regardless of distribution is significantly associated with the presence of chorionic vasculitis in the placental section ($p < 0.001$). Of the 88 cases with proximal and/or distal cord section involvement, 68 (77.3%) were term and 20 (22.7%) were preterm (range 23 – 36 weeks' gestational age). Comparing acute inflammation involving proximal and distal cord section, there was no significant difference with respect to the number of cases with preterm delivery. Mean gestational age, birth weight and placental weight were relatively lower/ smaller in the presence of cord inflammation regardless of distribution, although not proven statistically significant ($p > 0.05$).

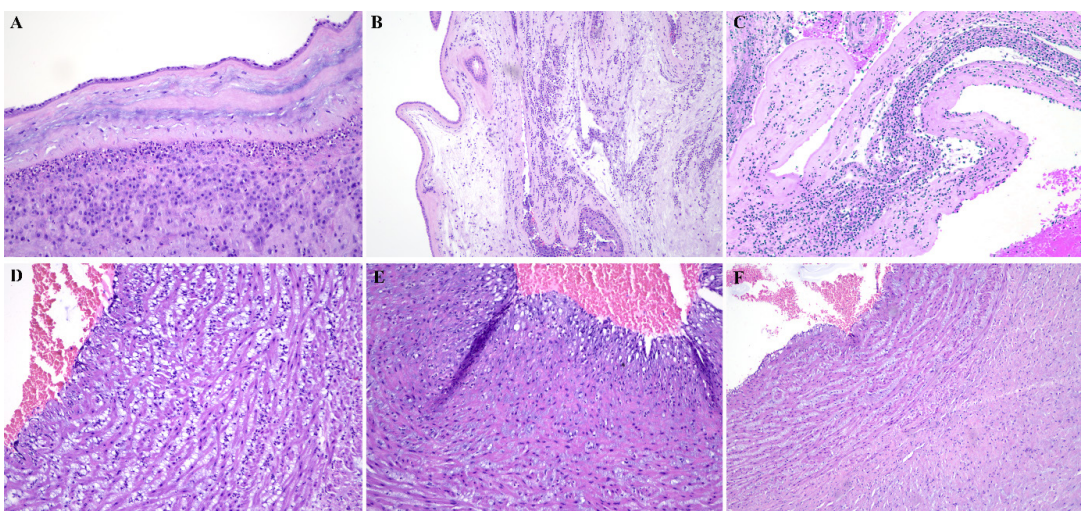

FIG. 1. Staging of maternal inflammatory response (MIR). (A) stage 1 MIR: acute subchorionitis/chorionitis; (B) stage 2 MIR: acute chorioamnionitis; (C) stage 3 MIR: necrotising chorioamnionitis; Staging of foetal inflammatory response (FIR). (D) stage 1 FIR: umbilical phlebitis; (E) stage 2 FIR: umbilical arteritis; (F) Stage 3 FIR: necrotising funisitis

TABLE 1: Distribution of acute inflammation in proximal and distal cord sections

	Proximal (placenta site) n = 191	Distal (fetal site) n = 191	P value
One or both cord sections: one with greater inflammation	11	38	**< 0.001***
Phlebitis in only one cord section	6	14	0.106
Arteritis in only one cord section	1	7	0.067

Cord Inflammation and Maternal Inflammatory Response

Approximately 40% (n = 36) of the 88 cases with proximal and/or distal cord inflammation had only phlebitis (stage 1 cord inflammation). With respect to severity of maternal inflammation (MIR) and its association with foetal inflammation (FIR), 19 (52.8%) of these 36 cases with only phlebitis had early/mild MIR (acute subchorionitis or acute chorionitis). When comparing between proximal and distal cord section involvement, MIR occurred more frequently when distal cord section showed acute inflammation of any stage (n = 81). The degree of FIR was significantly associated with the degree of MIR, with a higher stage of FIR correlated with a greater stage of MIR and vice versa ($p < 0.001$) (Figure 1). Notably, there were no cases of FIR without MIR (Table 3).

Cord Inflammation and Chorionic Vasculitis

Increasing stage of cord inflammation is significantly associated with the presence of chorionic vasculitis in the placental section ($p < 0.001$). Chorionic vasculitis was observed in 25 cases despite the absence of foetal inflammation in the proximal and/or distal cord section. On the contrary, there were 12 cases (10 in stage 1, 2 in stage 2) with umbilical cord FIR that demonstrated absence of chorionic vasculitis. When comparing the proximal and distal cord sections, chorionic vasculitis was present in 41 and 31 cases with negative FIR in the cord respectively, while 6 (all in stage 1) and 11 (9 in stage 1, 2 in stage 2) cases showed some degree of cord inflammation in proximal and distal cord sections respectively in the absence of chorionic vasculitis (Figure 2).

DISCUSSION

Acute funisitis, a morphologic indicator of FIR, is characterised histologically by the presence of acute inflammation involving the umbilical cord (umbilical vein, umbilical artery and the Wharton's jelly).[1] It serves as a better indicator than MIR in predicting intrauterine infection/inflammation. The timing of FIR however remains unclear, depending on the maturity of the foetal immune system, gestational age, and the virulence of the microorganisms.[13]

Foetal participation in the inflammatory process begins when foetal neutrophils migrate from the foetal circulation and traverse the wall of the umbilical cord vessels to enter the amniotic space upon exposure to intrauterine microorganisms or non-infectious stimuli. It is evidenced histologically as foetal vasculitis. Typically, umbilical vein involvement precedes that of the umbilical arteries, with acute funisitis beginning as umbilical phlebitis, followed by umbilical arteritis, and subsequently progresses to involve Wharton's jelly.[1] The reason behind this phenomenon remains unclear. A few possibilities including differences in blood vessel structure and the velocity of blood flow have been proposed.[14]

Histopathological evaluation of the umbilical cord is crucial to enable identification of FIR, besides sectioning from the placental parenchyma. And hence the need to determine which part of the umbilical cord is the most representative of acute funisitis, and how many sections of the umbilical cord should be submitted to increase sensitivity to efficiently detect FIR. Kim *et al*. in their systematic study reported an inconsistent distribution pattern of inflammation in a given umbilical cord with histological evidence of funisitis. They concluded that acute funisitis is initially present as multiple discrete foci along the umbilical cord, which then merge as the inflammatory process progresses into a more advanced stage.[8] Migration of neutrophils is choreographed by cytokines, chemokines and other chemoattractants in response to concentration gradients of extracellular signals toward the sites of inflammation and infection. This phenomenon is known as chemotaxis.[15] In intraamniotic infection, the entire umbilical cord

TABLE 2: Distribution of Cord Inflammation and their Association with Clinicopathological Parameters

		Both proximal and/or distal cord involvement			Proximal Cord Section Involvement			Distal Cord Section Involvement		
		Yes (n = 88)	**No (n = 103)**	**P value**	**Yes (n = 66)**	**No (n = 125)**	**P value**	**Yes (n = 81)**	**No (n = 110)**	**P value**
Mean gestational age, weeks (SD)		37.4±4.2	37.8±2.4	0.394	37.7±3.7	37.7±3.2	0.998	37.4±4.1	37.8±2.8	0.445
Term delivery	**Yes**	68 (77.3)	73 (70.9)	0.328	51 (76.1)	90 (72.6)	0.730	62 (76.5)	79 (71.8)	0.508
	No	20 (22.7)	30 (29.1)		16 (23.9)	34 (27.4)		19 (23.5)	31 (28.2)	
Mean birth weight, gram (SD)		3044.9±984.3	3353.1±535.8	0.065	3053.9±947.8	3283.9±700.8	0.184	3087.4±963.5	3284.1±651.9	0.244
Mean placental weight, gram (SD)		479.9±117.0	485.2±93.5	0.726	476.6±115.7	486.1±98.6	0.552	481.7±98.2	484.2±113.6	0.871
Chorionic vasculitis	**Yes**	76 (86.4)	25 (24.3)	**< 0.001***	60 (91.0)	41 (32.8)	**< 0.001***	70 (86.4)	31 (28.2)	**< 0.001***
	No	12 (13.6)	78 (75.7)		6 (9.0)	84 (67.2)		11 (13.6)	79 (71.8)	

*Statistically significant

TABLE 3: Association between the distribution and the degree of cord inflammation and maternal inflammatory response

Distribution of cord inflammation		Maternal inflammatory response, n (%)				P value
		Stage 0	Stage 1	Stage 2	Stage 3	
Proximal and/distal cord section involvement	**Stage 0**	58 (100.0)	26 (54.2)	18 (22.0)	1 (33.3)	**< 0.001***
	Stage 1	0 (0.0)	19 (39.6)	17 (20.7)	0 (0.0)	
	Stage 2	0 (0.0)	3 (6.3)	43 (52.4)	1 (33.3)	
	Stage 3	0 (0.0)	0 (0.0)	4 (4.9)	1 (33.3)	
Proximal cord section involvement	**Stage 0**	58 (100.0)	37 (77.1)	28 (34.1)	2 (66.7)	**< 0.001***
	Stage 1	0 (0.0)	10 (20.8)	23 (28.0)	0 (0.0)	
	Stage 2	0 (0.0)	1 (2.1)	29 (35.4)	1 (33.3)	
	Stage 3	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	
Distal cord section involvement	**Stage 0**	58 (100.0)	30 (62.5)	21 (25.6)	1 (33.3)	**< 0.001***
	Stage 1	0 (0.0)	15 (31.1)	16 (19.5)	0 (0.0)	
	Stage 2	0 (0.0)	3 (6.3)	41 (50.0)	1 (33.3)	
	Stage 3	0 (0.0)	0 (0.0)	4 (4.9)	1 (33.3)	

is equally exposed to chemoattractant. Although neutrophils originated from the foetal end, it is plausible to believe that neutrophils will migrate and reside at any site of the umbilical cord with the highest concentration of chemoattractant. As a corollary, increasing the numbers of sections from the cord could plausibly increase the odds of detection of clinically relevant umbilical vasculitis.

Various methods of umbilical cord examination have been previously performed with regard to the numbers and distribution of cord sections from prior studies. Kim *et al*. at one extreme submitted 10 cases of umbilical cord with acute funisitis throughout their entire lengths at 1mm intervals, with an average of 334 sections from each cord. The authors recommended taking

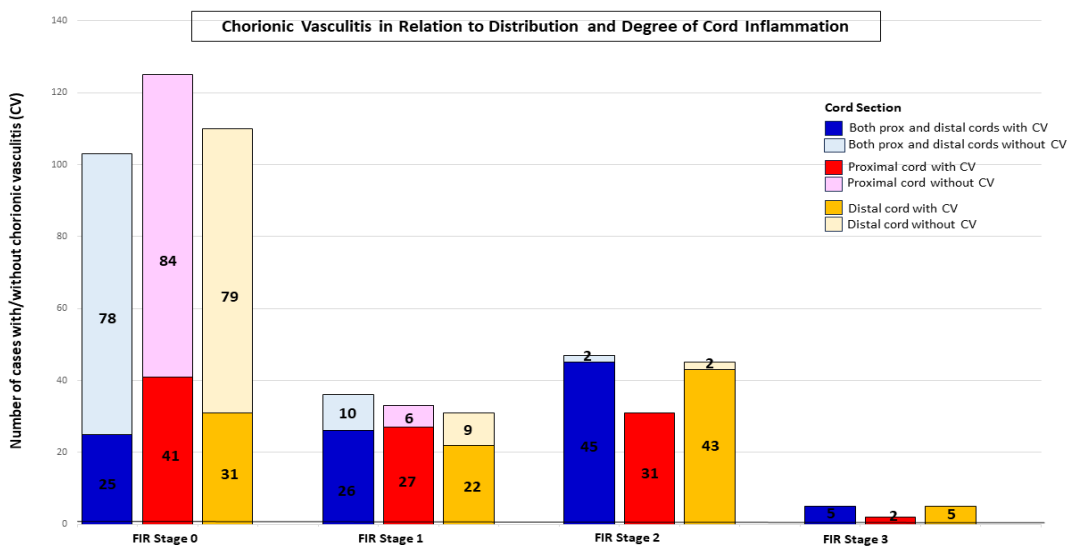

FIG. 2: Number of cases with/without chorionic vasculitis in relation to the distribution (combined proximal and distal, proximal cord section only, distal cord section only) and the degree of cord inflammation (FIR stage 0 – 3), Abbreviations: CV = chorionic vasculitis; FIR = fetal inflammatory response; Prox = proximal

one section from every third of the umbilical cord.[8] Katzmann *et al*. and Dammann *et al*. took sections from both the foetal and placental ends of the cords [9,16], while Hatano *et al*. recommended sampling three cord sections to address the spatial heterogeneity of umbilical cord inflammation.[17] A few other studies submitted sections of the umbilical cord, but the location and numbers of the umbilical cord sections sampled were not specified.[18-20] In the present study, we followed recommendation from consensus guideline[10] and submitted two cross sections of the umbilical cord: one from the fetal end and another approximately 5cm from the placental insertion end.

The prevalence of umbilical FIR in cases with one or more clinical signs of infection was 46.1% in the present study, comparable with 38% and 36% in previous studies.[21,22] Both the proximal (placental) and distal (foetal) end of umbilical cord sections showed some degree of cord inflammation, with distal cord inflammation significantly greater than that of proximal cord. Our findings are in agreement with Hatano *et al*.[17] On the contrary, Katzmann *et al*. found that there were almost equal amounts of cord inflammation in the umbilical vein between the proximal and distal cord sections.[9] Noteworthy, we observed that 22.7% of the placentas with cord inflammation had phlebitis in only one cord section. Dammann and colleagues identified that as high as 27% of their cases with umbilical vasculitis involved only the foetal end while 6% of these cases involved only the placental end.[16] It is likely that a significant proportion of cases with umbilical vasculitis will be missed if only one cord section (especially from the placental end only) is submitted for histopathological evaluation.

Foetal immune response induces acute inflammation not only affecting the umbilical cord, but also involving the chorionic plate foetal vessels. Chorionic plate vessel involvement is termed chorionic vasculitis and is staged as Stage 1 FIR. This entity however should not be confused with eosinophilic/T cell chorionic vasculitis – a distinct immune-mediated vasculitis that often occurs concurrently with chronic villitis.[23] Increasing stage of umbilical FIR was significantly associated with chorionic vasculitis. Our results concurred with that of Orsaria *et al*. and Katzmann *et al*., who reported that chorionic vasculitis was observed concurrently with acute funisitis, although the prevalence of chorionic vasculitis was somewhat lower (12.4% and 51.0% respectively).[9,24] Notably, acute inflammation of the umbilical cord can be patchy, continuous or multifocal.[8] It is not a surprise to learn that chorionic vasculitis occurs in a proportion of cases in the absence of umbilical phlebitis, and vice versa as demonstrated in the present study. In addition, a "missed" cord or chorionic plate vessel inflammation could be due to the inherent pitfalls in the sampling procedure. In agreement with Khong *et al*.,[10] we suggested at least two sections of placental parenchyma including a section near the cord insertion site should be sampled, to give a better yield of inflammation compared with elsewhere in the placenta.

Concurring with others, MIR had a greater frequency than FIR in cases with clinical signs of infection/ inflammation. MIR was observed in nearly 100% of cases with FIR, whereas FIR occurred in 20 – 70% of cases with MIR.[16,18,20,25] Like FIR, MIR is a maternal host response to chemotactic stimuli present in the amniotic cavity such as microorganisms or any danger signals, in which circulating maternal neutrophils migrate from the decidua to chorion and subsequently amnion.[21] There was no case of FIR without MIR in the present study. Grossman *et al*. showed that isolated funisitis (without the presence of MIR) occurred as a result of meconium-induced myonecrosis in the cord, rather than an ascending infection.[26]

Accumulating evidence reveal that FIR with/without MIR is associated with poor neonatal outcomes such as preterm labour, early neonatal sepsis, bronchopulmonary dysplasia, neuropsychiatric disorders and cerebral palsy.[6,27-31] It is thought to be related to the elevated c-reactive protein or interleukin (IL)-6 levels in the cord blood plasma ($\geq$ 11 pg/ml) following FIR. In addition, studies reported that neonates with umbilical arteritis suffered a higher rate of sepsis than those with only umbilical phlebitis.[14,19] We noticed that cases with FIR were associated with lower birth weight and smaller placentas in the present study, although not proven significant statistically.

Our findings concluded that inflammatory reaction could occur variably throughout the length of the umbilical cord and chorionic plate vessels. In this enriched population, with a clinical suspicion of chorioamnionitis, we confirm submitting at least two cross sections of the cord representing proximal and distal sites and two sections from placental parenchyma including a section from cord insertion site facilitates the identification of FIR. Where there is no clinical

suspicion of clinical chorioamnionitis, the need for additional blocks remains to be determined for that cohort.

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Conflicts of Interest: The authors declare no conflict of interest.

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