Placenta 97 (2020) 6–17

Contents lists available at ScienceDirect

Placenta

journal homepage: http://www.elsevier.com/locate/placenta

Classics Revisited

Fetal inflammatory response is positively correlated with the progress of inflammation in chorionic plate

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ARTICLE INFO

Keywords:
FIRS
Fetal inflammatory response
Chorionic plate inflammation
Preterm labor
Preterm-PROM

ABSTRACT

Introduction: No information exists about the relationship among the progress of inflammation in chorionic-plate, fetal inflammatory response (FIR), funisitis, amnionitis and early-onset neonatal sepsis (EONS) in patients with either preterm labor or preterm premature rupture of membranes (preterm-PROM). The objective of current study is to examine this issue.

Methods: Study population included 247 singleton preterm gestations (21.6 weeks ≤ gestational age at delivery≤36 weeks) who had either preterm-labor or preterm-PROM with acute placental inflammation. We examined the intensity of FIR, and the frequency of fetal inflammatory response syndrome (FIRS), funisitis, amnionitis and proven or suspected EONS according to the progress of inflammation in chorionic-plate. The intensity of FIR was measured with umbilical cord plasma (UCP)-CRP concentration (ng/ml) at birth, and FIRS was defined as an elevated UCP-CRP concentration (≥200 ng/ml). The progress of inflammation in chorionic-plate was divided with a slight modification from previously reported-criteria as follows: stage-0, inflammation-free chorionic-plate; stage-1, inflammation restricted to subchorionic fibrin (SCF); stage-2, inflammation in the connective tissue (CT) of chorionic-plate without chorionic vasculitis; stage-3, chorionic vasculitis.

Results: 1) Stage-0, stage-1, stage-2 and stage-3 of inflammation in chorionic-plate were present in 36.8% (91/247), 29.6% (73/247), 25.5% (63/247), and 8.1% (20/247) of cases; 2) UCP-CRP concentration at birth was significantly and positively correlated with the progress of inflammation in chorionic-plate (Spearman's rank correlation test, $P < .000001$, $\gamma = 0.391$ and Kruskal-Wallis test, $P < .001$); 3) Moreover, FIRS, funisitis, amnionitis, and EONS were significantly more frequent as a function of the progress of inflammation in chorionic-plate.

Discussion: The intensity of FIR and the frequency of FIRS were positively correlated with the progress of inflammation in chorionic-plate in patients with either PTL or preterm-PROM. This suggests chorionic-plate may be an independent compartment for the analysis of inflammation.

1. Introduction

Ascending intra-uterine infection (AIUI) is a major risk factor for spontaneous preterm birth (i.e., preterm labor and intact membranes [PTL] and preterm premature rupture of membranes [preterm-PROM]) [1–3]. AIUI from the vaginal-cervical canal (stage 1) proceeds through the chorio-decidua (CD) of extra-placental membranes (EPM) (stage 2) to the chorionic vessels (CVs) of chorionic plate or the amnion of EPM (stage 3) ultimately leading to fetal infection (stage 4) [2], inflammation of umbilical cord (UC) and fetal inflammatory response syndrome (FIRS) [1–4]. During the progress of AIUI, acute placental inflammation progresses in each placental compartment (i.e., EPM, chorionic plate, and UC) [3,5,6]. It is well-known that the outside-in migration of maternal neutrophils develops in EPM [7–9] and the amniotrophic migration of fetal neutrophils occurs in UC according to the progress of acute placental inflammation [10–12]. Indeed, our recent studies demonstrated that intra-amniotic inflammatory response (IAIR) and fetal

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https://doi.org/10.1016/j.placenta.2020.05.010
Received 23 December 2019; Received in revised form 11 April 2020; Accepted 25 May 2020
Available online 30 May 2020

Abbreviation list

AIUI	ascending intra-uterine infection
CD	chorio-decidua
CI	confidence interval
CRP	C-reactive proteins
CT	connective tissue
CVs	chorionic vessels
EDTA	ethylene-diaminetetraacetic acid
EONS	early-onset neonatal sepsis
EPM	extra-placental membranes
FGR	fetal growth restriction
FIR	fetal inflammatory response
FIRS	fetal inflammatory response syndrome
GA	gestational age
IAIR	intra-amniotic inflammatory response
IVS	intervillous space
MIR	maternal inflammatory response
OR	odds ratio
Preterm-PROM	preterm premature rupture of membranes
PTL	preterm labor and intact membranes
SCF	subchorionic fibrin
UC	umbilical cord
UCP	umbilical cord plasma
VCAM	vascular cell adhesion molecule

inflammatory response (FIR) increase according to the progress of inflammation in EPM [9] and UC [12] respectively.

Up to now, various classification systems classified acute inflammation in chorionic plate (Table 1) [3,6,13–26]. However, only a few systems included acute inflammation in the full-detailed subdivisions of chorionic plate (i.e., subchorionic fibrin [SCF], connective tissue [CT], and CVs) [20,21,23–26]. It should be noted that Blanc WA et al. [25] and '2015 Amsterdam placental workshop group consensus statement' [24] classified acute inflammation in chorionic plate as two different responses (i.e., maternal inflammatory response [MIR] and FIR) as in the following: 1) Blanc's classification [25]; MIR stage 1 [intervillositis], maternal neutrophils in subchorionic intervillous space (IVS): MIR stage 2 [chorionitis], maternal neutrophils in placental chorion: MIR stage 3 [chorioamnionitis], maternal neutrophils in amnion: FIR stage 1 [marginate], fetal neutrophils in the endothelium of CVs: FIR stage 2 [vasculitis], fetal neutrophils in the walls of CVs: FIR stage 3 [chorionitis], fetal neutrophils in placental chorion: and FIR stage 4 [chorioamnionitis], fetal neutrophils in amnion; and 2) 'Amsterdam staging system' [24]; MIR stage 1 [acute subchorionitis], neutrophils in SCF: MIR stage 2 [acute chorioamnionitis], diffuse patchy neutrophils in fibrous chorion: and FIR stage 1 [chorionic vasculitis], intramural neutrophils in CVs. Unfortunately, we cannot find any data about the relationship between the intensity of FIR and the progress of acute inflammation in the full-detailed subdivisions of chorionic plate in a large study population. Given that the severity of IAIR increases with the progress of acute inflammation in chorionic plate [27], it is plausible that FIR increases as acute inflammation progresses in the full-detailed subdivisions of chorionic plate. Our hypothesis was that the level of FIR, and the rate of FIRS and the surrogate-markers for FIR (i.e., funisitis, amnionitis, and early-onset neonatal sepsis [EONS]) would be positively correlated with the progress of inflammation in chorionic plate. The objective of current study is to examine this issue.

2. Materials and methods

2.1. Study design

Two hundred forty-seven pregnant women at the Seoul National University Hospital were included in this study. The study population met the following criteria: 1) singleton pregnancy; 2) 21.6 weeks $\leq$ gestational age (GA) at birth$\leq$36 weeks; 3) either PTL (n = 106) or preterm-PROM (n = 141) as causes of preterm birth; and 4) the presence of acute placental inflammation. PTL and preterm-PROM were diagnosed as previously reported [28,29]. At our institution, we routinely obtained UC blood, recommended placental histopathologic examination, and assessed acute placental inflammation in all pregnant women who delivered at preterm. The level of FIR and the rate of FIRS, funisitis, amnionitis and suspected or proven EONS were compared according to the progress of inflammation in chorionic plate. Written informed consent was obtained from all pregnant women included in current study. The Institutional Review Board of Seoul National University Hospital specifically approved this study.

2.2. Clinical chorioamnionitis, acute placental inflammation, and the progress of inflammation in chorionic plate

Clinical chorioamnionitis was diagnosed according to the definition previously described in detail [30]. Placental tissue samples included chorioamniotic membrane roll (i.e., EPM: CD and amnion), chorionic plate and UC for histopathologic evaluation. Those samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections of prepared tissue blocks were stained with hematoxylin and eosin (H & E). Clinical information associated with placental tissue samples was not given to the pathologists. Acute placental inflammation was defined as the presence of acute inflammation in at least one of placental compartments (i.e., CD, amnion, chorionic plate and UC). Acute inflammation in CD, amnion and UC was diagnosed according to the criteria previously reported [22] as follows; 1) chorio-deciduitis was diagnosed in the presence of at least one focus of more than 5 neutrophils in the CD; 2) amnionitis was diagnosed in the presence of at least one focus of more than 5 neutrophils in the amnion; 3) funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly. Inflammation in chorionic plate was diagnosed in the presence of neutrophilic infiltration in SCF, the CT of chorionic plate, or CVs according to the criteria previously published [20]. The progress of inflammation in chorionic plate was slightly modified from previously reported criteria [20] as follows: 1) stage 0, inflammation-free chorionic plate; 2) stage 1, inflammation restricted to SCF; 3) stage 2, inflammation in the CT of chorionic plate without chorionic vasculitis; and 4) stage 3, chorionic vasculitis.

2.3. Fetal inflammatory response (FIR), fetal inflammatory response syndrome (FIRS), and early-onset neonatal sepsis (EONS)

UC blood was collected in ethylene-diaminetetraacetic-acid (EDTA) containing blood collection tubes by venipuncture of the umbilical vein at birth. Samples were then centrifuged and supernatants were stored in polypropylene tubes at −70 °C. Umbilical cord plasma (UCP) CRP concentration (ng/ml) was measured with a commercially available enzyme-linked immunosorbent assay (Immunodiagnostik AG, Bensheim, Germany). The sensitivity of the test was 0.02 ng/ml. Both intra- and inter-assay coefficients of variation were <10%. The level of FIR was determined by UCP CRP concentration (ng/ml) at birth and FIRS was defined as an increased UCP CRP concentration ($\geq$200 ng/ml) at birth [31]. EONS was diagnosed in the presence of a positive blood culture result within 3 days after birth. EONS was suspected in the absence of a positive culture with the use of previously published criteria [32]. Twenty-five newborns were excluded from the assessment of

Table 1
Classification of the progress of inflammation in chorionic plate in various studies.

Study [Reference]	Stage or compartment	Subchorionic space	chorionic plate				EPM or UC	Grade of inflammation in chorionic plate	REMARK
			SCF	Connective tissue	Amnion	CVs			
Dong YLZE et al., 1987 [13]	N/A	N/A	N/A	N/A	N/A	N/A		**Chorionic plate** Grade 1 average of 1–3 leukocytes per HPF Grade 2 4-15 leukocytes per HPF Grade 3 more than 15 leukocytes per HPF	* There is no comment related to the progression of inflammation in the subdivisions of chorionic plate in this system.
Dexter SC et al., 2000 [14]	N/A	N/A	N/A	N/A	N/A	N/A		**Amnion and chorion of the EPM and the chorionic plate:** Grade 1 1- 10 PMNs per HPF Grade 2 11 - 50 PMNs in HPF Grade 3 higher concentrations of PMNs	* The higher grade between inflammation of the amnion/chorion in EPM or in the parenchyma section of chorionic plate was designated as the grade of membrane inflammation.
Torricelli M et al., 2014 [15]	HCA 1 Deciduitis	N/A	N/A		N/A	N/A	**EPM, Decidua** Multiple foci of leukocyte infiltrate limited to the decidua capsularis and associated with areas of necrosis	N/A	* Stage 1 included the inflammation within the EPM only, but not the inflammation of chorionic plate.
	HCA 1 HCA within the membranes	N/A	N/A		N/A	N/A	**and/or** **EPM, Amnion** PMN infiltration <10 per field in 10 nonadjacent 400-power fields		
	HCA 2 Amnionitis without funisitis	N/A	N/A		N/A	N/A	**EPM, Amnion** At least 10 PMNs in 10 nonadjacent 400-power fields		
	HCA 2 Inflammation of the chorionic plate without funisitis	N/A	N/A	**and/or chorionic plate** At least 10 PMNs in 10 nonadjacent 400-power fields	N/A	N/A			* Inflammation in chorionic plate was not classified as inflammation in the subdivision of chorionic plate in detail.
	HCA 3 HCA with funisitis	N/A	N/A	**and/or chorionic plate** At least 10 PMNs in 10 nonadjacent 400-power fields	N/A	N/A	**EPM** HCA1 or 2 **UC, Umbilical vessels** Inflammatory infiltrate in the walls of umbilical vessels and/or in the Warthon's jelly and/		* Inflammation in chorionic plate was not classified as inflammation in the subdivision of chorionic plate in detail. * The diagnosis of HCA 3 should be based on

(*continued on next page*)

Table 1 (*continued*)

Study [Reference]	Stage or compartment	Subchorionic space	chorionic plate				EPM or UC	Grade of inflammation in chorionic plate	REMARK
			SCF	Connective tissue	Amnion	CVs			
							or in the walls of large vessels of the cord insertion.		the presence of either HCA 1 or HCA 2.
Naeye RL et al., 1971 [16]	Chorionitis	N/A	N/A	**Chorionic plate of placenta** PMNs		N/A		N/A	* Inflammation in chorionic plate was not classified as inflammation in the subdivision of chorionic plate in detail.
	Amnionitis	N/A	N/A		**Amnion** PMNs	N/A			* Inflammation in EPM was not assessed in this system. Instead, amnionitis in chorionic plate was included in the inflammation of chorionic plate.
Hecht JL et al., 2011 [17]	1	**Subchorionic space** Neutrophils	N/A			* Although neutrophilic infiltration into fetal stem vessels in chorionic plate was also noted as present or absent, it was not included in the staging system of inflammation in chorionic plate.		**Chorionic plate** Grade 1: 1–9 neutrophils Grade 2: 10–19neutrophils Grade 3: >20 neutrophils	* Inflammation in SCF and chorionic vasculitis were not assessed in this system.
	2		N/A	**Chorionic plate** Neutrophils					
	3		N/A		**Amnionic epithelium** Neutrophils up to amnionic epithelium				* Inflammation in EPM was not assessed in this system. Instead, amnionitis in chorionic plate was included in the inflammation of chorionic plate.
Sato M et al., 2011 [18]	1 Intervillositis (subchorionic)	**Between the decidua and chorionic plate** Maternal neutrophils	N/A			N/A		N/A	* Inflammation in SCF and chorionic vasculitis were not assessed in this system.
	2 Chorionitis		N/A	**Connective tissues in chorionic plate** Maternal neutrophils		N/A			
	3 Chorioamnionitis		N/A		**Amnion basement**	N/A			* Inflammation in EPM was not assessed in

(*continued on next page*)

Table 1 (*continued*)

Study [Reference]	Stage or compartment	Subchorionic space	chorionic plate				EPM or UC	Grade of inflammation in chorionic plate	REMARK
			SCF	Connective tissue	Amnion	CVs			
					membrane Neutrophils				this system. Instead, amnionitis in chorionic plate was included in the inflammation of chorionic plate.
Wharton KN et al., 2004 [19]	1	N/A	N/A	**Parenchyma (chorionic plate)** 1–10 PMNs	N/A			**Chorionic plate** Grade 1: 1–10 PMNs Grade 2: More than 10 PMNs Grade 3: Severe inflammation	* Inflammation in the parenchyma of chorionic plate was not divided into inflammation in SCF and in connective tissue.
	2	N/A	N/A	**Parenchyma (chorionic plate)** More than 10 PMNs	N/A				
	3	N/A	N/A	**Parenchyma (chorionic plate)** Severe inflammation	N/A				
	4	N/A	N/A	**Parenchyma (chorionic plate)** Severe inflammation	N/A	**Chorionic plate with CVs** severe stem vessel vasculitis (vasculitis was diagnosed if the vessel wall contained PMNs)		N/A	
Salafia CM et al., 1989 [20]	1	N/A	**SCF** 1 focus of at least 5 PMNs		N/A			* Grading system was present in only 'inflammation in SCF'.	
Salafia CM et al., 1997 [21]	2	N/A	**SCF** Multiple foci of at least 5 PMNS		N/A				
	3	N/A		**Connective tissue** few PMNs	N/A			N/A	
	4	N/A	Numerous PMNs in chorionic plate	Numerous PMNs in chorionic plate	N/A	**CVs** Numerous PMNs in chorionic plate, and chorionic vasculitis			
Yoon BH et al., 1995 [22]	1	N/A	**SCF** at least 1 focus of at least 10 neutrophilic collections or diffuse inflammation		N/A			N/A	* This system was modified from 'original Salafia's criteria [20,21]'.
	2	N/A		**Connective tissue**	N/A				

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Table 1 (*continued*)

Study [Reference]	Stage or compartment		Subchorionic space	chorionic plate				EPM or UC	Grade of inflammation in chorionic plate	REMARK
				SCF	Connective tissue	Amnion	CVs			
					Diffuse and dense neutrophilic infiltration					
	2		N/A			N/A	**or CVs** Chorionic vasculitis			
Redline RW et al., 2003 [23] Khong TY et al., 2016 [24]	MIR	1 Acute subchorionitis	N/A	**SCF** Patchy-diffuse accumulations of neutrophils		N/A			1, mild–moderate **(amnion, chorionic plate, chorion laevae, and/or SCF):** Not "severe" as defined below 2, severe (**chorion-decidua in EPM and/or under the chorionic plate)**	* There is no comment associated with chorionic plate in MIR stage 3, FIR stage 2 and FIR stage 3. * Inflammation in chorionic plate was classified as both MIR and FIR stages.
		1 Aute chorionitis	N/A			N/A		**and/or EPM, chorionic trophoblast layer** A few scattered neutrophils	Confluent PMN (≥10 x20 cells in extent) between chorion and decidua; ≥3 isolated foci or continuous band	
		1 Aute chorionitis	N/A	**and/or In the lower half of chorionic plate** A few scattered neutrophils	**and/or In the lower half of chorionic plate** A few scattered neutrophils	N/A				
		2 Acute chorioamnionitis	N/A		**Chorionic plate** Diffuse-patchy PMN in fibrous chorion	N/A				
		2 Acute chorioamnionitis	N/A			N/A		**or EPM, chorionic connective tissue and/or amnion** A few scattered neutrophils		
		3 Necrotizing chorioamnio-nitis	N/A			N/A		**EPM, amnion** PMN karyorrhexis, amniocyte necrosis, and/or amnion basement membrane thickening/ hypereosinoph-ilia		
	FIR	1 Chorionic vasculitis	N/A			N/A	**CVs** Neutrophils in the wall of any chorionic plate vessel		1, mild–moderate **(any chorionic or umbilical vessel):** Not "severe" as defined below 2, severe **(Chorionic plate or umbilical vessels)** near confluent neutrophils + attenuation	
		1 Umbilical phlebitis	N/A			N/A		**or UC, umbilical vein** Neutrophils in the wall of vein		
			N/A			N/A				

(*continued on next page*)

Table 1 (*continued*)

Study [Reference]	Stage or compartment		Subchorionic space	chorionic plate				EPM or UC	Grade of inflammation in chorionic plate	REMARK
				SCF	Connective tissue	Amnion	CVs			
		2 Uumbilical vasculitis (one or two arteries ± vein) or umbilical panvasculitis (all vessels)						**UC, umbilical artery or arteries (+/− umbilical vein)** Intramural PMN	± degeneration of vascular smooth muscle cells on the side facing the amniotic cavity	
		3 Necrotizing funisitis or concentric umbilical perivasculitis	N/A			N/A		**UC, umbilical vessels** PMN ± associated debris in concentric bands-rings-halos around one or more umbilical vessels		
Blanc WA et al., 1981 [25] Blanc WA et al., 1959 [26]	MIR	1 Intervillositis (subchorionic)	**Subchorionic intervillous space** Maternal PMNs						N/A	* Inflammation in EPM was not assessed in this system. Instead, amnionitis in chorionic plate was included in the inflammation of chorionic plate. * Inflammation in SCF was not assessed in this system.
		2 Chorionitis		**Placental chorion ("chorionic plate")** Maternal PMNs	**Placental chorion ("chorionic plate")** Maternal PMNs					
		3 Chorioamnionitis				**Amnion** Maternal PMNs				
	FIR	1 Marginate		* FIR begins at about the time maternal polymorphs appear in the chorion ("chorionic plate").			**CVs** Fetal PMNs marginate against that part of the endothelium of the CVs closest to the amnion			
		2 Vasculitis					**CVs** Fetal PMNs invade the vessels wall of chorionic arteries and vein			
		3 Chorionitis			**Placental chorion ("chorionic plate")** Fetal PMNs					
		4 Chorioamnionitis				**Amnion** Fetal PMNs				

EPM, extra-placental membranes; *HCA,* histologic chorio-amnionitis; *CVs*, chorionic vessels; *FIR*, fetal inflammatory response; *MIR*, maternal inflammatory response; *N/A*, not available; *PMNs,* polymorphonuclear leukocytes; *SCF*, subchorionic fibrin; *UC*, umbilical cord.

Table 2
Clinical characteristics and pregnancy outcomes according to the progress of inflammation in chorionic plate.

	Inflammation-free chorionic plate stage 0	Inflammation in chorionic plate			P value
		Inflammation restricted to SCF stage 1	Inflammation in the CT of chorionic plate without chorionic vasculitis stage 2	Chorionic vasculitis stage 3	
	(n = 91) 36.8% (91/247)	(n = 73) 29.6% (73/247)	(n = 63) 25.5% (63/247)	(n = 20) 8.1% (20/247)	
Maternal age, year (mean ± SD)	29.3 ± 4.7	29.5 ± 4.7	29.7 ± 3.8	30.0 ± 3.2	0.545
Nulliparity	51.6% (47/91)	47.9% (35/73)	49.2% (31/63)	20.0% (4/20)	0.080
Clinical chorioamnionitis[k]	1.1% (1/90)	6.9% (5/72)	22.6% (14/62) [a]	30.0% (6/20) [b]	**0.000007**
Preterm-PROM as a cause of preterm delivery	59.3% (54/91)	49.3% (36/73)	57.1% (36/63)	75.0% (15/20)	0.203
Male Newborn	57.1% (52/91)	56.2% (41/73)	50.8% (32/63)	60.0% (12/20)	0.840
Cesarean delivery	27.5% (25/91)	35.6% (26/73)	30.2% (19/63)	25.0% (5/20)	0.663
Median GA at delivery, wks [range]	33.7 [21.7–36.0]	32.6 [21.6–35.9]	30.7 [22.1–35.7] [c]	29.4 [21.9–35.1] [d, e]	< **0.001**
Birth weight, g (mean ± SD)	1981 ± 603	1767 ± 654	1542 ± 602 [f]	1391 ± 643 [g]	< **0.001**
1 min Apgar score of <7	38.5% (35/91)	52.1% (38/73)	68.3% (43/63) [h]	80.0% (16/20) [i]	**0.000217**
5 min Apgar score of <7	24.2% (22/91)	34.2% (25/73)	39.7% (25/63)	55.0% (11/20)	**0.032** [j]

CT, connective tissue; *GA*, gestational age; *preterm-PROM*, preterm premature rupture of membranes; *SCF,* subchorionic fibrin; *SD*, standard deviation.
'a' means a significant difference (P < .0001) between stage 0 and stage 2 (Fisher's exact test with Bonferroni's correction).
'b' means a significant difference (P < .001) between stage 0 and stage 3 (Fisher's exact test with Bonferroni's correction).
'c' means a significant difference (P < .00005) between stage 0 and stage 2 (1-way ANOVA with post-hoc Tukey test).
'd' means a significant difference (P < .00005) between stage 0 and stage 3 (1-way ANOVA with post-hoc Tukey test).
'e' means a significant difference (P < .05) between stage 1 and stage 3 (1-way ANOVA with post-hoc Tukey test).
'f' means a significant difference (P < .0005) between stage 0 and stage 2 (1-way ANOVA with post-hoc Tukey test).
'g' means a significant difference (P < .001) between stage 0 and stage 3 (1-way ANOVA with post-hoc Tukey test).
'h' means a significant difference (P < .005) between stage 0 and stage 2 (Fisher's exact test with Bonferroni's correction).
'i' means a significant difference (P < .005) between stage 0 and stage 3 (Fisher's exact test with Bonferroni's correction).
'j', There was no difference in the frequency of '5 min Apgar score of <7' between any of groups by Fisher's exact test with Bonferroni's correction.
'k', Of 247 cases, 244 patients were included in this analysis, because the information about clinical chorioamnionitis in medical record was omitted in 3 patients.

EONS because they died immediately after birth due to extremely prematurity (19 cases) or anomaly (6 cases).

2.4. Statistical analysis

Continuous and categorical variables were compared with the use of Kruskal-Wallis test and Pearson's chi-square test respectively. Multiple comparisons of continuous and categorical variables between the groups according to the progress of inflammation in chorionic plate were performed with 1-way ANOVA with post-hoc Tukey test and Fisher's exact test with Bonferroni's correction respectively. The relationship between FIR and the progress of inflammation in chorionic plate was investigated with the use of Kruskal-Wallis test and Spearman's rank correlation test. We compared the frequency of FIRS, funisitis, amnionitis, and EONS among groups with Pearson's chi-square test. Linear by linear association test was used for the assessment of trend. Logistic regression analysis was utilized to examine the relationship of various independent variables (i.e., the progress of inflammation in chorionic plate) with FIRS controlling for the effect of any other potential confounders. Statistical significance was defined as a $p < .05$.

3. Results

3.1. Clinical characteristics and pregnancy outcomes according to the progress of inflammation in chorionic plate

Table 2 demonstrated clinical characteristics and pregnancy outcomes according to the progress of inflammation in chorionic plate. Stage 0, stage 1, stage 2, and stage 3 were present in 36.8% (91/247), 29.6% (73/247), 25.5% (63/247), and 8.1% (20/247) of study population. There was a significant difference in the rate of clinical chorioamnionitis, 1 min Apgar score <7 and 5 min Apgar score <7, and median GA at delivery and mean birth weight among four groups in spite of there being no difference in other variables (Table 2).

3.2. Intensity of fetal inflammatory response (FIR) according to the progress of inflammation in chorionic plate

Fig. 1 illustrates UCP CRP levels (ng/ml) at delivery with the progress of inflammation in chorionic plate. There was a significant and positive correlation between UCP CRP levels and the progress of inflammation in chorionic plate (Spearman's rank correlation test, $P < .000001$, $\gamma = 0.391$ and Kruskal-Wallis test $P < .001$).

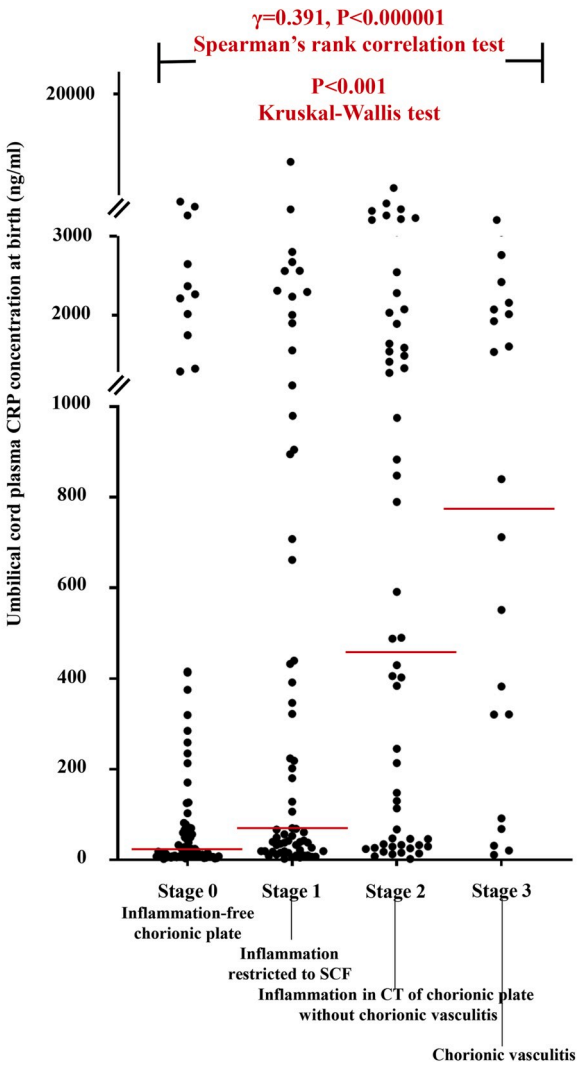

Fig. 1. Positive correlation is shown between the progress of inflammation in chorionic plate and umbilical cord plasma (UCP) CRP concentration at birth (ng/ml). The median value and range of UCP CRP concentrations at birth (ng/ml) in each stage of inflammation in chorionic plate are as in the following: stage 0, 24.4 ng/ml [1.0–5555.0 ng/ml]; stage 1, 63.7 ng/ml [2.2–10897.4 ng/ml]; stage 2, 458.8 ng/ml [1.9–7401.8 ng/ml]; stage 3, 775.8 ng/ml [11.0–3094.9 ng/ml]). Correlation coefficient and P-value of Spearman's rank correlation test are shown in graph. Of 247 cases which met the entry for this study, 222 patients had UCP CRP concentrations at birth; however, 25 patients did not have an UCP CRP concentration at birth because of the limited amount of the remaining UCP.

3.3. Fetal inflammatory response syndrome (FIRS), funisitis, amnionitis, and suspected or proven early onset neonatal syndrome (EONS) according to the progress of inflammation in chorionic plate

Fig. 2 shows a stepwise increase in the rate of FIRS (Fig. 2 A), funisitis (Fig. 2 B), amnionitis (Fig. 2 C) and suspected or proven EONS (Fig. 2 D) as acute inflammation progresses in chorionic plate (each for $P < .01$ in Pearson's chi-square test and $P < .005$ in linear by linear association). Moreover, logistic regression analysis demonstrated the more advanced stage in the progress of inflammation in chorionic plate, the better independent risk factor for FIRS (stage 1, odds ratio [OR] 2.247, 95% confidence interval [CI] 1.071–4.714; stage 2, OR 4.217, 95% CI 1.834–9.692; stage 3, OR 6.653, 95% CI 1.957–22.619) even after the adjustment for potential confounders including GA at delivery (Table 3).

4. Discussion

We found only two studies reporting the contradictory results about the intensity of either FIR or neonatal inflammatory response within 72 h of birth according to the progress of inflammation in the subdivisions of chorionic plate [17,21]. Salafia CM et al. [21] demonstrated there was no significant relationship between increasing stage of acute inflammation in chorionic plate (i.e., mild inflammation restricted to SCF, severe inflammation restriction to SCF, inflammation in CT without chorionic vasculitis, and chorionic vasculitis) and FIR (i.e., IL-1, IL-2R, and IL-6) in preterm gestation (n = 22). On the contrary, Hecht JL et al. [17] demonstrated the intensity of neonatal inflammatory response gauged by various inflammation-related proteins (i.e., IL-1β, IL-6, CCL5, MMPs, and CRP, etc.) within 72 h of birth in extremely low GA preterm newborns (n = 393) elevated with increasing stage of inflammation in chorionic plate (i.e., neutrophils in subchorionic space, neutrophils into chorionic plate, and neutrophils up to amnionic epithelium). However, these two studies had critical weaknesses such as a very small study population (n = 22) [21] and a staging system without chorionic vasculitis in the progress of inflammation in chorionic plate [17]. Our current research is the first study reporting that the levels of FIR, and the rate of FIRS and the surrogate-markers for FIR (i.e., funisitis, amnionitis, and EONS) gradually increase according to the progress of inflammation

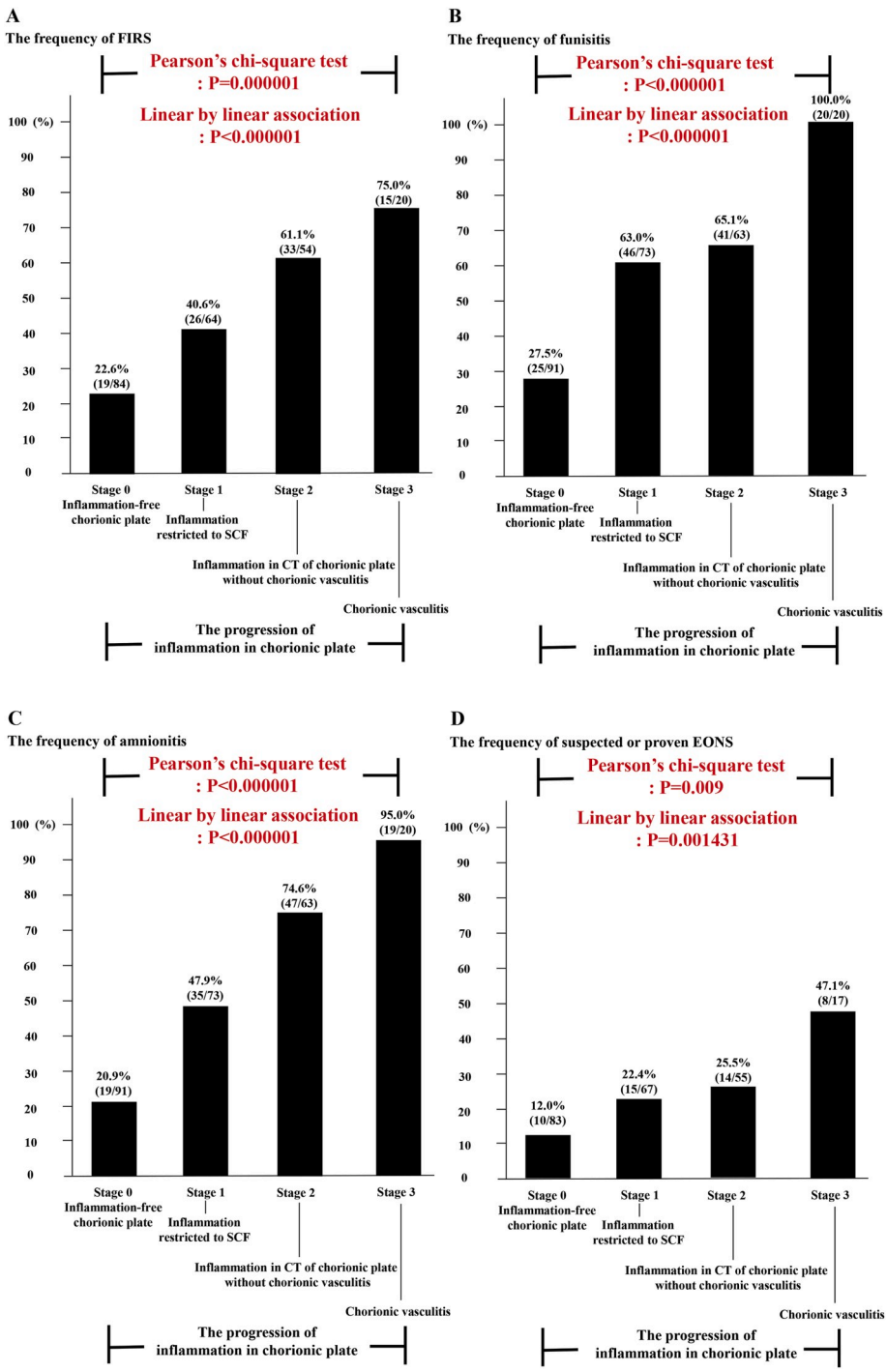

Fig. 2. The frequency of fetal inflammatory response syndrome (FIRS) [A], funisitis [B], amnionitis [C], and suspected or proven early-onset neonatal sepsis (EONS) [D] according to the progress of inflammation in chorionic plate. Frequency and P-values are shown in graph. Positive correlation is shown between the progress of inflammation in chorionic plate and the frequency of each parameter (i.e., [A], FIRS; [B], funisitis; [C], amnionitis; and [D], suspected or proven EONS). Twenty-five neonates were excluded from the analysis in the evaluation of suspected or proven EONS because they died shortly after delivery as a result of extremely prematurity (n = 19) or anomaly (n = 6) and thus could not be evaluated with respect to the presence or absence of EONS. Of 247 cases which met the entry for this study, 222 patients had UCP CRP concentrations at birth; however, 25 patients did not have an UCP CRP concentration at birth and a subsequent information about FIRS because of the limited amount of the remaining UCP.

in the full-detailed subdivisions of chorionic plate including chorionic vasculitis in a large study population (n = 247).

Why is there little information about the intensity of FIR in the progress of inflammation in the full-detailed subdivisions of chorionic plate? The progress of acute inflammation in chorionic plate has been denigrated by the well-known route of EPM and UC during AIUI as in the following reasons; (1) previous study pointed out inflammation in chorionic plate had the higher sensitivity but the much lower specificity for the detection of intra-amniotic infection than inflammation in EPM due to the greater blood flow and availability of neutrophils from the IVS to the chorionic plate [5]; and (2) the pathophysiology of neutrophil infiltration is not well-understood in the progress of acute inflammation in chorionic plate due to both maternal and fetal neutrophil infiltration into chorionic plate [33], while pure maternal neutrophils infiltrates in EPM and pure fetal neutrophils infiltrates in UC in the context of acute placental inflammation. Indeed, 'Amsterdam staging system' divided acute inflammation in chorionic plate into two different inflammatory responses (i.e., MIR [i.e., stage 1, neutrophils in SCF; and stage 2, diffuse patchy neutrophils in fibrous chorion (the CT of chorionic plate)] and FIR [i.e., stage 1, intramural neutrophils in CVs]) [24].

It should be noted that there is a discrepancy in the sequence of 'chorionitis' and 'chorionic vasculitis' in the progress of acute inflammation in chorionic plate between Blanc's classification and 'Amsterdam staging system' [24,25]. Blanc's classification regarded 'chorionitis' (i.e., FIR stage 3, defined as the presence of fetal neutrophils in placental chorion) as a more advanced stage than 'chorionic

Table 3
Relationship of various independent variables with fetal inflammatory response syndrome (FIRS) by overall logistic regression analysis.

	Odds ratio	95% CI	*P value*
Stage-1[a] of inflammation in chorionic plate	2.247	1.071–4.714	0.032
Stage-2[b] of inflammation in chorionic plate	4.217	1.834–9.692	0.000702
Stage-3[c] of inflammation in chorionic plate	6.653	1.957–22.619	0.002405
GA at delivery	0.960	0.781–1.180	NS
Preterm-PROM as a cause of spontaneous preterm delivery	1.691	0.892–3.206	NS
Clinical chorioamnionitis	1.879	0.582–6.070	NS
Cesarean section	1.244	0.650–2.383	NS
Birth weight	1.000	0.999–1.001	NS
5 min Apgar score < 7	2.241	0.977–5.144	NS

CI, confidence interval; *GA,* gestational age; *NS*, not significant; *preterm-PROM*, preterm premature rupture of membranes; *SCF*, subchorionic fibrin; *CT*, connective tissue.

[a] Inflammation restricted to SCF.

[b] Inflammation in the CT of chorionic plate without chorionic vasculitis.

[c] Chorionic vasculitis.

vasculitis' (i.e., FIR stage 2) in the context of FIR [25] while 'Amsterdam staging system' considered FIR, 'chorionic vasculitis' (i.e., FIR stage 1) as a more progressed inflammation than MIR, 'chorionitis' (i.e., MIR stage 2) [24]. However, given that FIR is more intense in 'chorionic vasculitis' than in 'inflammation in the CT of chorionic plate' in our current study, chorionic vasculitis is likely to be a more advanced stage than 'inflammation in the CT of chorionic plate' in the progress of inflammation in chorionic plate.

We reaffirmed a positive correlation between FIR and the progress of inflammation in chorionic plate through the relationship between surrogate-markers (i.e., funisitis, amnionitis, and EONS) for FIR and the progress of inflammation in chorionic plate. We selected funisitis, amnionitis and EONS as surrogate-markers for FIR based on the previous results [7,12,34,35] as follows: (1) It is well-known that funisitis is the histologic hallmark of FIRS [34,35]; (2) The presence of amnionitis in MIR was an indicator for a more severe FIR [7], and the frequency of amnionitis gradually increased according to the progress of funisitis [12]; and (3) There is a substantial body of evidence about an elevated FIR as an independent risk factor for EONS [4,31,34]. Notably, our current study demonstrated a positive relationship between an increase in the rate of surrogate-markers for FIR (i.e., funisitis, amnionitis and EONS) and the progress of inflammation in chorionic plate (Fig. 2). These findings reaffirmed a positive correlation between FIR and the progress of inflammation in chorionic plate.

FIR can be seen in cases with inflammation in the CT of chorionic plate but without chorionic vasculitis. Our explanations for this finding are as follows. Firstly, inflammation in the CT of chorionic plate was included in both MIR and FIR stages in Blanc's classification (Table 1) [25], and moreover, the genotype of neutrophils infiltrated into the amnion of chorionic plate was reported to be the mixture of maternal and fetal genotypes [33]. Therefore, one can expect that FIR can develop in the context of inflammation in the CT and amnion of chorionic plate but not CVs. Indeed, FIRS was present in 61.1% of cases with inflammation in the CT of chorionic plate but without chorionic vasculitis in our current study (Fig. 1 A). Secondly, vascular cell adhesion molecule (VCAM) in the endothelial cells of umbilical vessels was reported to be expressed in cases with histologic chorioamnionitis but without inflammation in umbilical vessels [36], and moreover, elevated circulating VCAM is known to be increased concurrently with pro-inflammatory cytokines in various inflammatory disorders [37,38]. Therefore, there is a good chance that FIR can develop even in the context of histologic chorioamnionitis (i.e., inflammation in the CT of chorionic plate) but without fetal vasculitis (i.e., chorionic vasculitis). An additional explanation for the presence of FIR in the absence of chorionic vasculitis but presence of inflammation in the chorionic plate is that the ascending inflammation triggers a MIR and a FIR but the progression of fetal neutrophils (as opposed to maternal neutrophils) traversing the UC does not reach the CVs till later in the disease.

Major strengths of the study are: (1) our current study compared FIR according to the progress of acute inflammation in the full-detailed subdivisions of chorionic plate in a large number of preterm gestations with acute placental inflammation (n = 247); and (2) we included either PTL or preterm-PROM but not maternal-fetal indication (i.e., fetal growth restriction [FGR]) as causes of preterm delivery for the assessment of FIR only in the context of AIUI, because animal chronic hypoxemia model without infection caused elevated FIR as well as mildly FGR [39,40] and previous human studies reported a positive relationship between FIR and FGR [41,42]. Therefore, we could exclude a major source of bias leading to an increased FIR shown in cases with FGR but without AIUI.

Our data firstly demonstrated FIR, FIRS and the surrogate-markers for FIR (i.e., funisitis, amnionitis, and EONS) increased according to the progress of inflammation in chorionic plate (i.e., inflammation restricted to SCF, inflammation in the CT of chorionic plate without chorionic vasculitis, and chorionic vasculitis). These continuous and stepwise increases in the level of FIR and the frequency of FIRS and surrogate markers for FIR (i.e., funisitis, amnionitis, and EONS) suggest the progressive sequence from MIR (i.e., MIR [i.e., stage 1, neutrophils in SCF; and stage 2, diffuse patchy neutrophils in fibrous chorion (the CT of chorionic plate)]) to FIR (i.e., FIR [i.e., stage 1, intramural neutrophils in CVs]) within chorionic plate in 'Amsterdam staging system' during the progress of AIUI [24]. Moreover, given the our previous study reporting that the intensity of IAIR increases with the progress of inflammation in chorionic plate [27], we may suggest that chorionic plate has the full-detailed subdivisions as a continuum (i.e., SCF, the CT of chorionic plate, and CVs) for the analysis of acute inflammation, and is an independent compartment in the staging system of AIUI in addition to EPM and UC.

Amnionitis and inflammation in the CT of chorionic plate are classified as the same MIR stage 2 in the 'Amsterdam staging system' [24] while amnionitis and chorionic vasculitis have been regarded as the same stage in the conventional pathway of AIUI [2]. However, up to now, there is a paucity of data about the comparisons of IAIR and FIR between amnionitis and inflammation in the CT of chorionic plate, and between amnionitis and chorionic vasculitis. Moreover, a further refinement to the current study would be to see the relationship of the MIR and FIR in the chorionic plate by seeing which stage of the MIR (i.e., the infiltration of the maternal neutrophils into either SCF or the CT of chorionic plate) develops when the fetal neutrophils first appear in the CVs (i.e., the infiltration of the fetal neutrophils into CVs without contamination of the maternal neutrophils in CVs). These kinds of investigations will help us understand the progress of AIUI, and provide the evidence for the pathophysiologic classification of acute placental inflammation based on the intensity of inflammatory responses in the context of each involved compartment of acute placental inflammation.

Author contributions

Guarantor of integrity of entire study: C·W·P.; study concepts/study design: all authors; data acquisition or data analysis/interpretation: all authors; manuscript drafting or manuscript revision for important intellectual content: all authors; approval of final version of submitted manuscript: all authors; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors; literature research: J.W·O., C·W·P.; statistical analysis: J.W·O., C·W·P.; manuscript editing: all authors.

Declaration of competing interest

All authors have declared that no competing interests exist.

Acknowledgements

This study was supported by the grant no. 03-2015-0220 from the Seoul National University Hospital Research Fund (Republic of Korea).

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