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ORIGINAL ARTICLE

CD47 and CD36 expressions in the placenta of mothers with chorioamnionitis

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Abstract

Introduction: Chorioamnionitis is the inflammation of the placenta and is histologically defined as the presence of neutrophilic infiltration into the chorio-amnion membrane with and without involvement of the umbilical cord. Currently, the inflammatory mediators involved in the eliciting of inflammatory response is still largely under investigation. CD47 and CD36 are pro-inflammatory molecules that are still under investigation. The aim of this study was to determine the expressions of CD47 and CD36 in the placenta of mothers with chorioamnionitis. *Materials and Methods:* This was a cross-sectional study, involving a total of 100 cases that comprised of acute subchorionitis (stage I, n=20), acute chorioamnionitis (stage II, n=20), acute necrotising chorioamnionitis (stage III, n=20) and non-chorioamnionitis placenta as control (n=40). All tissue blocks were retrieved from the archived pathology record over a period of 4 years. CD36 and CD47 immunohistochemistry were performed on all cases and their expression in various cell types on the placenta were analysed. *Results:* CD36 was expressed only on the foetal vascular endothelial cells. Interestingly, CD47 showed positive staining on the neutrophils and its expression was significantly different between maternal inflammatory response stage II chorioamnionitis (n=13/20, $p<0.001$) with stage I and stage III chorioamnionitis. *Discussion:* Our study showed CD47 was expressed in the neutrophils and it was associated with poorer perinatal outcomes and it may have a role in the pathogenesis of chorioamnionitis.

Keywords: CD36, CD47, chorioamnionitis, placenta, immunohistochemistry

INTRODUCTION

Chorioamnionitis is defined by the presence of acute inflammation (neutrophils) within the chorion or amnion (or both) of the extraplacental membranes or chorionic plate (maternal inflammatory response [MIR]), with or without acute inflammation of the umbilical cord vessels and Wharton jelly (foetal inflammatory response [FIR]).[1] The presence of chorioamnionitis is a risk for adverse neonatal and maternal outcomes that can lead to morbidity and mortality.[2] It can be divided into clinical or histological chorioamnionitis depending on the criteria used to diagnose chorioamnionitis. Clinical chorioamnionitis are used to identify pregnant mothers as having chorioamnionitis, and appropriate treatment can be given before histological confirmation. The clinical signs and symptoms of chorioamnionitis include fever, maternal tachycardia, foul smelling vaginal discharge, rupture of membranes and uterine tenderness.[2] However, the clinical diagnosis of chorioamnionitis and blood count are not accurate enough in the diagnosis of chorioamnionitis.[2,3] Studies showed that a proportion of subjects are asymptomatic and can be missed clinically and diagnosed only after birth by histological examination of the placenta.[4,5] Therefore, the identification of reliable markers for early and accurate diagnosis of histological chorioamnionitis is still largely being investigated.

Currently, the inflammatory markers that have been found to be associated with chorioamnionitis include IL-6, IL-8 TNF-α, and MMP-8.[6,7,8,9] However, studies on cell surfaces

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molecules (cluster of differentiation/CD) in cases of chorioamnionitis have been limited.[10]

CD36 is a membrane glycoprotein that is expressed on many type of cells such as adipocytes, phagocytes, hepatocytes, myocytes and certain epithelia.[11] It is known as a scavenger receptor that recognises different type of ligands such as b-amyloid, thrombospondin 1, oxidized phospholipids and lipopolysaccharide, to initiate various pro-inflammatory cascade.[11] In the event of pathogen recognition, CD36 overexpression has been shown to influence the increase of IL-8 secretion in the cells that were exposed to lipopolysaccharide, a cell wall component of gram-negative bacteria.[12] In addition, it recognised b-amyloid and thrombospondin 1 and promoted sterile inflammation through dimerization of Toll-like receptor-4 and Toll-like receptor-6.[13] The role of CD36 in the pathogen recognition and sterile inflammation has been studied in other inflammatory diseases, namely atherosclerosis[14] and Alzheimer's disease[11,15]. In a recent study, they described an increase in CD36 concentration in the amniotic fluid of pregnant mothers with premature rupture of membrane along with intra-amniotic inflammation.[16]

CD47 is an integrin associated protein and its expression is well known as a "don't eat me signal", whereby the CD47 will bind to signal regulatory protein alpha (SIRP-α) on macrophages and prevent phagocytic activity.[17] Apart from that, CD47 expression on neutrophils have been shown to aid in transmigration of the neutrophils and resulted in the accumulation of neutrophils at site of inflammation, in bacterial-induced mouse model.[18,19] So far, previous studies have shown that CD47 and CD36 may potentially involve in both sterile inflammation and bacterial-induced inflammation. We believe these surface markers that are present in the endothelial cells might play a role in pathogenesis of chorioamnionitis. Therefore, the aim of this study was to determine the expressions of CD36 and CD47 in the placenta with histological chorioamnionitis with and without foetal inflammation, and correlate their expressions with the severity of chorioamnionitis and perinatal outcomes.

MATERIALS AND METHODS

Study design and tissue sample

This was a single centre cross-sectional retrospective study using archived formalin-fixed paraffin-embedded (FFPE) placental tissue blocks from Department of Pathology over a period of 5 years. The patients' medical record was retrieved from the integrated laboratory medical system (ILMS) in Hospital Canselor Tuanku Muhriz (HCTM). All cases with the histological diagnosis of acute chorioamnionitis and non-chorioamnionitis (control) placenta were selected. Subjects with foetal anomalies, multiple gestation, maternal hypertension, pre-eclampsia, eclampsia, diabetes mellitus, incomplete placental tissue, unavailable FFPE blocks or insufficient clinicopathological data were excluded from this study.

The relevant clinicopathological data such as maternal age, race, gestational age, parity, histological diagnosis and fetal outcomes were retrieved through the ILMS, Computerised Medical Record system of HCTM (C-hets) and the hardcopy of the patients' medical record. Patients' identity was made anonymous, and each subject was coded accordingly. The placental tissue blocks of all cases including the foetal membrane, a full thickness section and the umbilical cord were retrieved for immunohistochemical study. All cases were re-evaluated histologically for the maternal and foetal inflammatory responses based on the criteria proposed by Redline (2012).

Immunohistochemistry

Formalin fixed, paraffin embedded tissues were sectioned three-micrometre thick and mounted on adhesive glass slides. The glass slides were placed in a 60°C oven overnight for dewaxing. The slides were then pre-treated using the decloaking chamber and immersing the slides in the EnVision™ FLEX Target Retrieval Solution, High pH (Code No. DM828, Dako Agilent, Denmark). Slides were incubated with CD36 or CD47 primary for 30 minutes at room temperature then followed by incubation with EnVision™ FLEX/HRP (Code No. DM822, Dako Agilent, Denmark) for 30 minutes. The slides were incubated with 1X DAB-containing Substrate Working Solution for 5 min for CD36 and 7 min for CD47. The slides were then counterstained with Hematoxylin 2 (REF 7231, ThermoScientific, Waltham, MA, USA) and followed by dehydration in a 60°C oven for 2 hours.

Staining evaluation

The percentage and intensity of CD47 and CD36 staining were evaluated by two observers (either R.A.R and N.A.S or B.S.H and N.A.S) independently. When discordances were

encountered, the slides were then reviewed together, and consensus were agreed upon. The staining for CD47 and CD36 was evaluated by using semi-quantitative method using the following scores. The percentage of positive cells were divided into three categories; <20% (0), 20-70% (1) and 70-100% (2). The staining intensity was scored on a scale of 0-3 whereby, no staining (0), light brown staining (1), moderate intensity of brown staining (2) and strong intensity of brown staining (3). The percentage of positive cells and intensity score were then added to obtain a final score. A score of 0 was regarded as negative, while 1 - 5 as positive.

Data analysis

All data were evaluated by either chi-squared test or Fisher's exact test using IBM Statistical Package for the Society Study (SPSS) version 27.0 A p-value <0.05 was considered as statistically significant.

RESULTS

Demographic Data

This study consisted of 60 cases of histologically confirmed chorioamnionitis and 40 controls without chorioamnionitis. Majority of the subjects in the chorioamnionitis group were of the Malay ethnicity (50/60, 83.3%), followed by Chinese (5/60, 8.3%), Indian (1/60, 1.7%) and others (4/60, 6.7%). The age of the mothers ranged from 21-42 years old, with most of them being in the 30-39 age group. Eleven (11/60, 1.7%) cases in the chorioamnionitis group had preterm delivery, while 4/60 cases had intrauterine death. Table 1 summarises the demographic data of the pregnant mothers with and without histological chorioamnionitis in this study.

The association between preterm delivery, stage of maternal and foetal inflammatory response with adverse perinatal and neonatal outcomes

Thirty-seven cases (37/60, 61.7%) of the

TABLE 1: Demographic data of pregnant mothers with and without histological chorioamnionitis

Demographic Details	Chorioamnionitis (n=60) n (%)	Non-chorioamnionitis (Control) (n=40) n (%)	*p* value
Maternal age group (years)			0.828
20-29	24 (40.0)	17 (42.5)	
30-39	34 (56.7)	21 (52.5)	
40-49	2 (3.3)	2 (5.0)	
Ethnicity			0.322
Malay	50 (83.3)	30 (75.0)	
Chinese	5 (8.3)	8 (20.0)	
Indian	1 (1.7)	1 (2.5)	
Others	4 (6.7)	1 (2.5)	
Parity			0.824
1	25 (41.7)	14 (35.0)	
2	15 (25.0)	8 (20.0)	
3	9 (15.0)	9 (22.5)	
4	7 (11.7)	5 (12.5)	
5	3 (5.0)	2 (5.0)	
6	1 (1.7)	2 (5.0)	
Gestational age			0.059
≤28 weeks	6 (10.0)	0	
29-32 weeks	2 (3.3)	0	
33-36 weeks	3 (5)	5 (12.5)	
≥37 weeks	49 (81.7)	35 (87.5)	

mothers with histological chorioamnionitis had foetal inflammatory response (FIR); Stage 1 (18/60, 30%), Stage 2 (13/60, 21.7%) and Stage 3 (6/60, 10%). The maternal inflammatory response (MIR) and FIR were categorised into two groups; stage 1 and stage 2/3. Stage 2/3 was considered high stage of chorioamnionitis, while stage 1 was considered as low stage chorioamnionitis. The neonates of ten cases of high stage chorioamnionitis eventually developed respiratory distress, and 7 cases developed sepsis. Subsequently, we analysed the association of severity of MIR and FIR, and gestational age with the incidence of adverse perinatal and neonatal outcomes such as sepsis, respiratory distress, neonatal intensive care unit (NICU) admission and preterm delivery. High stage MIR and FIR were significantly associated with lung complication and NICU admission ($p < 0.05$). Meanwhile, only a high stage of MIR and preterm birth was associated with sepsis (Table 2).

Expression of CD47 on neutrophils in stage II chorioamnionitis.

The CD47 expression on various types of cells in the placenta were evaluated. Table 3 showed the score of CD47 staining on the placental cells. Foetal vascular endothelial cells (FVEC), umbilical vein endothelial cells (UVEC) umbilical artery endothelial cells (UAEC) were negative for CD47 in all cases of both the chorioamnionitis (0/60) and control (0/40) groups. CD47 staining was observed in the syncytiotrophoblasts and cytotrophoblasts of all cases in both chorioamnionitis and control groups (Table 3 and Fig. 1). Meanwhile, a minority (3/60, 5.0%) of cases with chorioamnionitis showed positive staining in the amnion epithelial cells (AEC), 4/60 (6.7%) cases showed positive staining of the maternal endothelial cells (MEV) and decidual cells (DC). However, the CD47 staining was not statistically significantly correlated with the severity of chorioamnionitis.

Interestingly, we found CD47 staining on the neutrophils (Fig. 2) in 13 cases of the stage II chorioamnionitis (13/20, 65.0%). In contrast, only 1/20 (5.0%) cases in each of the stage I and stage III chorioamnionitis was positive for CD47. This finding is statistically significant ($p < 0.001$).

The association of CD47-expression in neutrophils with adverse perinatal and neonatal outcomes.

We assessed the association of CD47 expression in neutrophils with adverse perinatal and neonatal outcomes. Five of the thirteen (38%) cases with CD47-positive neutrophils had lung complications such as pneumonia, respiratory distress syndrome and transient tachypnea of newborn, while 4/13 (33%) developed sepsis and was admitted to the NICU. The expression of CD47 in neutrophils was statistically significant

TABLE 2: The association of stages of MIR, FIR and gestational age with adverse perinatal and neonatal outcomes

	Preterm delivery			**Lung Complications**			**Sepsis**			**NICU admission**		
	Yes	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**P-value**	**Yes**	**No**	**p-value**
Severity of MIR			0.206			**0.008***			**0.032***			**0.021***
Stage 1	1	19		0	20		0	20		0	20	
Stage 2/3	6	30		10	25		7	28		8	27	
Severity of FIR			0.442			**0.003***			0.108			**0.036***
Stage 0/1	4	35		3	35		3	35		3	35	
Stage 2/3	3	14		7	10		4	13		5	12	
Gestational age			-			0.070			**0.010***			**<0.001***
Preterm <37W	-	-		3	4		3	4		4	3	
Term >37W	-	-		7	41		4	44		4	44	

Maternal inflammatory response (MIR); fetal inflammatory response (FIR)
*p <0.05 is considered as statistically significant

TABLE 3: The expression of CD47 in various types of placental cells

Cell Type	Chorioamnionitis		Non-Chorioamnionitis		p-value
	Negative	Positive	Negative	Positive	
Amnion epithelial cells	57	3	40	0	0.273
Decidual cells	56	4	36	4	0.547
Syncytiotrophoblast	0	60	0	40	NA
Cytotrophoblast	0	60	0	40	NA
Maternal endothelial cells	56	4	40	0	0.148
Foetal vascular endothelial cells	60	0	40	0	NA
Umbilical vein endothelial cells	60	0	40	0	NA
Umbilical artery endothelial cells	60	0	40	0	NA

in lung complications (p = 0.027), sepsis (p = 0.023) and NICU admission (p = 0.037). Table 4 showed the association of CD47 expression in neutrophils with adverse perinatal and neonatal outcomes.

CD36 expression in the placenta with and without chorioamnionitis and its association with adverse perinatal and neonatal outcomes

CD36 was expressed only in the foetal vascular endothelial cells (Figure 3) of both chorioamnionitis (n= 31/56, 55%) and control (n=19/35, 54%) groups, while other cell types in the placenta did not show any expression. The expression of CD36 in FVEC in chorioamnionitis and control groups was not statistically significant (p = 0.92). In addition, there was no association with the adverse perinatal and neonatal outcomes.

DISCUSSION

CD36 is also known as a fatty acid translocase and is expressed on many types of cells and

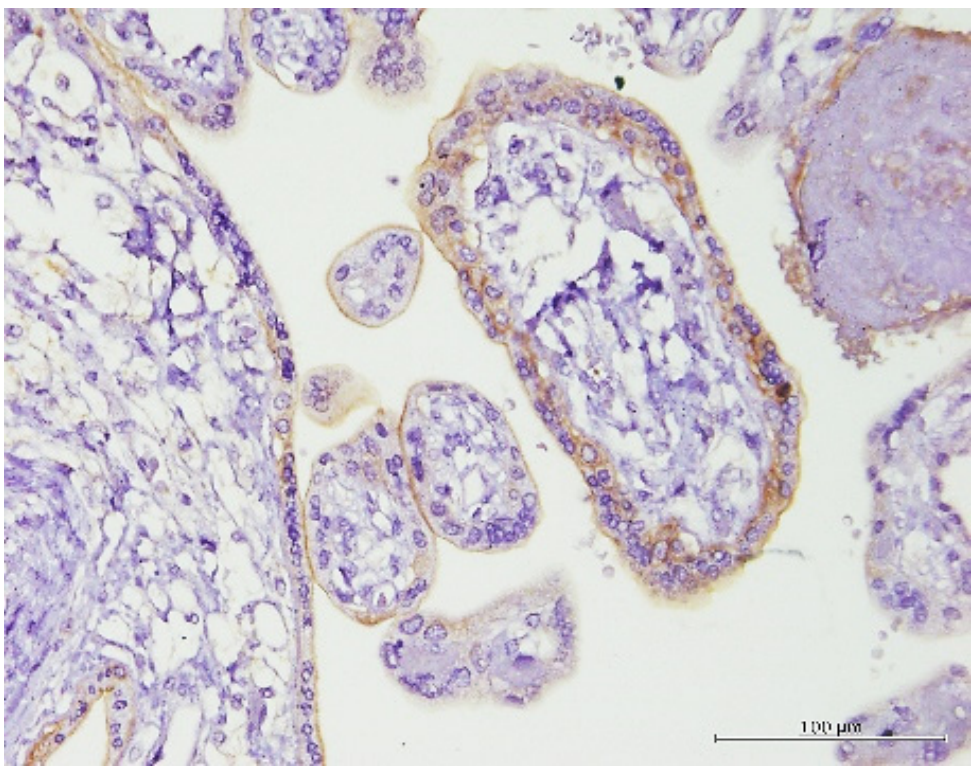

FIG. 1: CD47 expression on the syncytiotrophoblasts and cytotrophoblasts (x40).

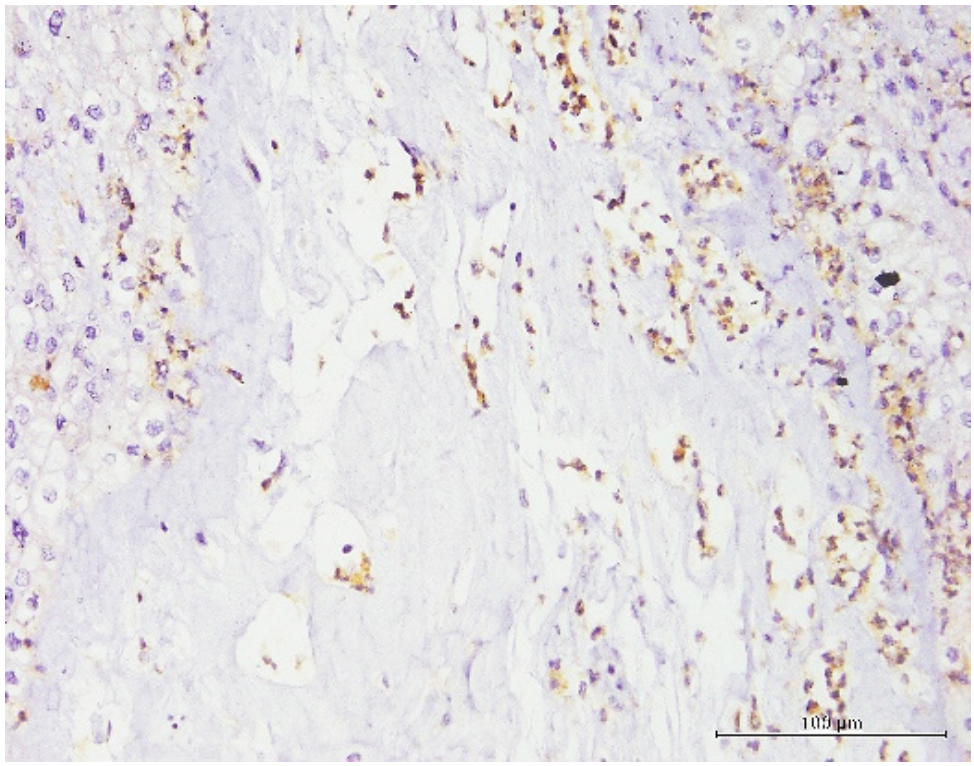

FIG. 2: Expression of CD47 in the neutrophils of stage II chorioamnionitis (x40).

TABLE 4: The association of CD47 expression in neutrophils with adverse perinatal and neonatal outcomes

	CD47 staining on neutrophils				p-value
	Positive		Negative		
	N	(%)	*N*	(%)	
Foetal inflammatory response					
Normal	3	13.6	19	86.4	
Stage 1	5	30	12	70	0.151
Stage 2	5	42	7	58	
Stage 3	0	0	5	100	
Lung complications					
Yes	5	50	5	50	**0.027***
No	8	17.4	38	82.6	
Sepsis					
Yes	4	57	3	43	**0.023***
no	9	18.4	40	81.6	
Birth categories					
Preterm	3	43	4	57	0.188
Term	10	20.4	39	79.6	
NICU admission					
Yes	4	50	4	50	**0.037***
No	9	18.8	39	81.2	

*p <0.05 is considered as statistically significant

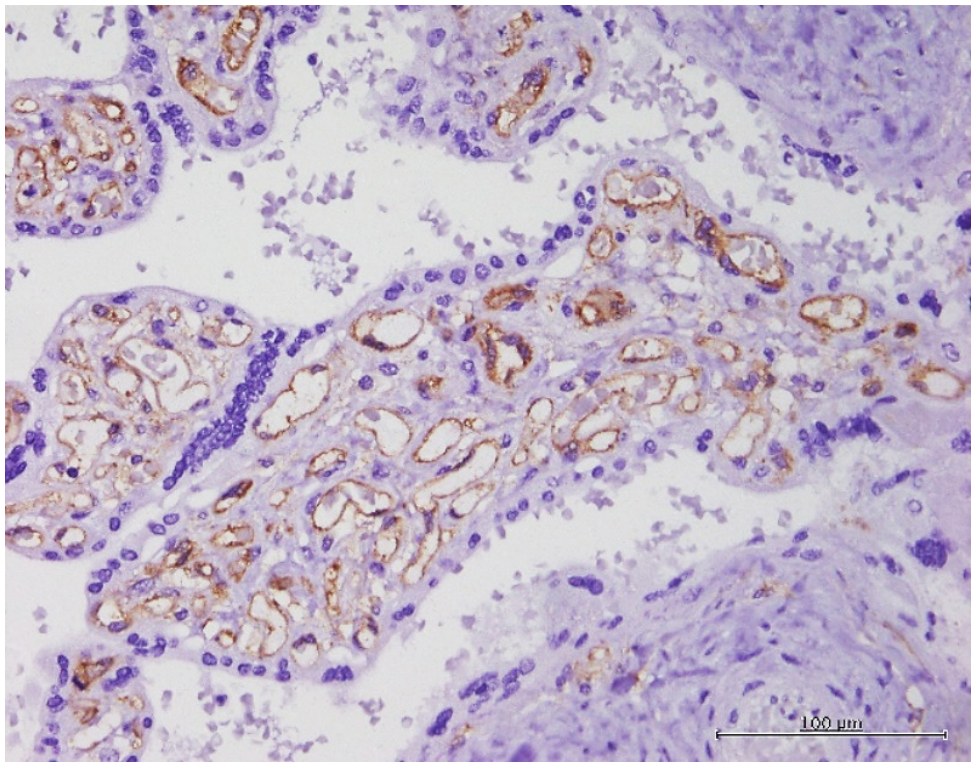

FIG. 3: CD36 expression in the foetal vascular endothelial cells (x40).

TABLE 5: CD36 expression in the foetal vascular endothelial cells and its association with adverse perinatal and neonatal outcomes

	CD36 expression in FVEC				P-value
	Positive		Negative		
	N	(%)	*N*	(%)	
Chorioamnionitis					
Yes	31	55	25	45	0.920
No	19	54.2	16	45.8	
Foetal Inflammatory Response					
No FIR	30	53.6	26	46.4	
Stage 1	10	58.8	7	41.2	0.897
Stage 2	6	50	6	50	
Stage 3	4	66.7	2	33.3	
Lung complications					
Yes	5	41.7	7	58.3	0.254
No	45	59.2	31	40.8	
Sepsis					
Yes	3	37.5	5	62.5	0.247
No	47	58.6	33	41.4	
Birth Category					
Preterm	5	41.7	7	58.3	0.276
Term	45	58.4	32	41.6	
NICU admission					
Yes	5	45.5	6	54.5	0.416
No	45	58.4	32	41.6	

FVEC: Foetal vascular endothelial cells

is involved in several cellular functions. As a pro-inflammatory molecule, CD36 interacts with TLR4, TLR6, NLRP3 inflammasome and results in the production of IL-1β.[13,20] Expression of IL-1β has been shown to be involved in neutrophil accumulation in the chorio-decidua area of the placenta as well as in the production of inflammatory mediators in the amniotic fluid.[21] Furthermore, IL-1β was reported to be involved in preterm labour due to intrauterine infection.[22] Hence, CD36 as a regulator of IL-1β production may act as an upstream mediator in the inflammation of the placenta.

However, our study demonstrated that the expression of CD36 was observed only on the foetal vascular endothelial cells, and it did not have any significance correlation with chorioamnionitis and the control group. This might be due to the role of CD36 as a fatty acid translocase that increases the uptake of long chain fatty acid[23] and studies have shown its mRNA expression is highly expressed in placenta of mothers with obesity.[24,25]

Intriguingly, we found that the neutrophils in MIR stage II chorioamnionitis significantly expressed CD47 compared to stage I and stage III chorioamnionitis. MIR Stage II chorioamnionitis is the infiltration of neutrophils at the subchorionic area into the chorion and amnion areas.[1] CD47 expression has previously been shown to be involved in transmigration of neutrophils across epithelial and endothelium layers.[19] Study showed in chronic inflammation of the intestine, neutrophil expressed CD47 interacts with CD18/CD11b to regulate neutrophil transepithelial migration.[18] We postulate that the high expression of CD47 in MIR stage II chorioamnionitis might have a role in the pathogenesis of chorioamnionitis in facilitating the transmigration of neutrophils.

Furthermore, this study showed CD47 expression in the neutrophils was significantly associated with sepsis and lung complications in the neonates. As expected, higher stage of MIR and FIR associated chorioamnionitis were significantly associated with lung complications and NICU admission in the neonates. Our study is limited by a small number of cases. Thus, a study with a larger sample size is warranted to further validate this finding.

CONCLUSION

CD47 expression was observed in all cases of both chorioamnionitis and control groups in the syncytiotrophoblasts and cytotrophoblasts. Of note, CD47 was expressed in the neutrophils. CD36 was mainly expressed in the foetal vascular endothelial cells. Expression of CD47 on neutrophils suggest a possible role in transmigration of neutrophils to the site of inflammation in cases of chorioamnionitis. Further studies with larger sample size should be conducted in order to validate this finding. Nonetheless, this study showed the CD47 expression in neutrophils may be associated with poorer perinatal outcomes and it may have a role in the pathogenesis of chorioamnionitis.

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

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