SEVERITY OF PLACENTAL INFLAMMATION IN PRETERM DELIVERIES- A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND

The study was conducted to find the presence of placental inflammation in preterm deliveries and to assess its severity based on histopathological staging.

METHODS

This prospective observational study in preterm deliveries between 25 and 34 weeks of gestational age was conducted from May 2014 to December 2015 in a tertiary care hospital in South India. Placentas were collected during the delivery and histopathological examination was done to check acute placental inflammation. The inflammatory findings in the placental parenchyma and/or membranes were classified as maternal inflammatory response (MIR). The inflammatory findings in the umbilical cord sections were classified as foetal inflammatory response (FIR). As per the layers involved and severity of inflammation, the MIR and FIR were further divided into 3 stages and 2 grades. Based on presence/absence of placental inflammation, study cohort was grouped into two groups. The maternal and neonatal characteristics were compared between the two groups.

RESULTS

Among the 120-placentae studied, 39% (47/120) showed placental inflammation. The placental MIR was present in all forty seven placentas but foetal inflammatory response (FIR) was present only in 19% (23/120). Further staging and grading were done for all placentas with MIR or FIR. So, there were 47 cases in placental inflammation group and 73 cases in no placental inflammation group. The maternal and neonatal characteristics were compared between the two groups. The premature rupture of the membranes and the spontaneous onset of the labour were significantly higher in group with placental inflammation.

CONCLUSIONS

Acute placental inflammation was associated with preterm deliveries and significantly higher in preterms with premature rupture of membranes and spontaneous onset of labour.

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BACKGROUND

Acute Chorioamnionitis (CA) is an important cause of prematurity and generally considered due to intrauterine infection.[1,2] But studies have shown that it can occur in "sterile intraamniotic inflammation" due to cellular stress or injury.[3-5] The term "acute chorioamnionitis" means the inflammation of the foetal membranes, namely, the chorion and the amnion. The term "acute funisitis" refers to the inflammation of the umbilical cord. Redline et al reviewed various placental reactions seen in amniotic fluid infection and developed standardized diagnostic criteria for placental inflammation.[6] As per their report "Amniotic Fluid Infection Nosology Committee" classified the placental inflammation broadly as foetal inflammatory response (FIR) and maternal inflammatory response (MIR). This study was conducted to find out the magnitude of placental inflammation in preterm deliveries and assess its severity based on histopathological staging.

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METHODS

A prospective observational study was conducted in a tertiary care hospital in South India, from May 2014 to December 2015. The objectives were to estimate the severity of placental inflammation in preterm deliveries and its association with maternal and neonatal characteristics. The study was approved by Institute Scientific Advisory and Ethics Committees. The preterm deliveries in the same institute at the gestational age between 25 and 34 weeks were included in the study. The gestational age assessment was based on first trimester ultrasonography (USG). Neonates with major congenital anomalies and multiple pregnancies were excluded from this study. Preterm deliveries that fulfilled study criteria were recruited after getting written informed consent. A sample size of 120 was estimated using open Epi software with an assumed 50%

prevalence of placental inflammation at 5% level of significance.

Placentas were collected during delivery, after complete separation. Then the membranes, cord and placental parenchyma including the maternal and foetal surface were examined in detail. Placenta was stored at room temperature in 10% formalin and was sent to pathology laboratory for histopathology. Five tissue sections - 2 sections of umbilical cord (proximal and distal end), 2 full-thickness sections of placental parenchyma and a section of a membrane roll that included the point of membrane tear or rupture were taken from the formalin fixed placenta. Additional sections were taken from grossly abnormal lesions. All these sections were embedded in the paraffin and blocks were made according to standard Pathology department protocols. Four µm sections were cut from each block and the slides were stained with haematoxylin and eosin (H&E).

All five tissue sections were evaluated for the presence and severity of neutrophilic infiltrates. Parameters like villous vascularity, syncytial knots, endarteritis obliterans, fibrinoid necrosis, cytotrophoblastic proliferation, villous stromal fibrosis were also assessed. The inflammatory findings in the placental parenchyma and/or membranes were classified as maternal inflammatory response (MIR). The inflammatory findings in the umbilical cord sections were classified as foetal inflammatory response (FIR). As per the layers involved and severity of inflammation, MIR & FIR were further divided into 3 stages and 3 grades. Other specific features like peripheral funisitis, acute villitis, acute intervillositis with intervillous abscesses, decidual plasma cells were also noted.

Definitions[6]

Placenta
Composed of placental disc (parenchyma), membranes (chorion & amnion) and the umbilical cord (umbilical vein, umbilical artery & Wharton's jelly).

Acute Placental Inflammation
The neutrophil infiltration of placenta.

Maternal Inflammatory Response (MIR)
The inflammatory findings in the placental parenchyma and/or membranes.

Foetal Inflammatory Response (FIR)
The inflammatory findings in the umbilical cord.

Staging
Assess the progress of inflammation based on layers infiltrated by neutrophils.

Grading
Assess the intensity of inflammation at a particular site.

MIR Stage 1 (Early)
Acute subchorionitis or chorionitis - presence of polymorphonuclear neutrophils in subchorionic layer and/or in membrane trophoblast.

MIR Stage 2 (Intermediate)
Acute chorioamnionitis- diffuse patchy infiltration of polymorphonuclear neutrophils in chorion and/or amnion layer.

MIR Stage 3 (Advanced)
Necrotizing chorioamnionitis- polymorphonuclear neutrophils with karyorrhexis, amniocyte necrosis, and/or amnion basement membrane thickening or hypereosinophilia.

MIR Grade 1
Mild to moderate infiltration of neutrophils.

MIR Grade 2
Severe infiltration of neutrophils- subchorionic micro abscesses (confluent polymorphonuclear neutrophils 10 - 20 cells in extent between chorion and decidua) or isolated foci or continuous band.

FIR Stage 1 (Early)
Chorionic vasculitis or umbilical phlebitis- presence of polymorphonuclear neutrophils in chorionic vessels and/or in umbilical vein.

FIR Stage 2 (Intermediate)
Umbilical vasculitis (one or two arteries ± vein) or umbilical pan vasculitis (all vessels) - presence of polymorphonuclear neutrophils in umbilical artery or arteries (±umbilical vein).

FIR Stage 3 (Advanced)
Subacute necrotizing funisitis or concentric umbilical perivasculitis. Presence of polymorphonuclear neutrophils with or without associated debris in concentric bands around one or more umbilical vessels.

FIR Grade 1
Mild to moderate infiltration of neutrophils.

FIR Grade 2 (Severe)
Presence of confluent intramural polymorphonuclear neutrophils in chorionic and/or umbilical vessels with attenuation/degeneration of vascular smooth muscle cells.

Other Specific Features

Peripheral Funisitis
Focal aggregates of polymorphonuclear neutrophils at the umbilical cord surface.

Acute Villitis
Polymorphonuclear neutrophils in villous stroma.

Acute Intervillositis
Patchy diffuse polymorphonuclear neutrophils in intervillous space.

Decidual Plasma Cells
Unequivocal plasma cells in decidua basalis or capsularis.

The baseline maternal and neonatal details were recorded. Maternal details like age, parity, previous preterm delivery, pregnancy induced hypertension, prolonged rupture of membranes (>18 hours), clinical chorioamnionitis (presence of maternal fever and /or foul smelling amniotic fluid and maternal leucocytosis), antenatal steroids, antibiotic use (4 hour prior to delivery), onset of delivery (spontaneous or induced) and mode of delivery were noted. Neonatal details noted were gestational age, sex, birth weight and small for gestational age (birth weight less than 10th percentile on modified Fenton's chart).

Based on histopathological placental inflammation findings, samples were also divided into two groups: No placental inflammation group and placental inflammation group. The maternal and neonatal characteristics were compared between the two groups. Data entry was done in MS Excel and statistical analysis was done using SPSS software (version 22, IBM, New York). Categorical data such as gender, clinical and obstetrical characteristics at the time of delivery were expressed as frequency and percentages. The continuous variables such as birth weight, gestational age, and maternal age were expressed as mean with S.D. The comparison of presence of placental inflammation in relation to clinical and obstetrical characteristics was done using students t test. p values <5% were considered statistically significant.

RESULTS
As per calculated sample size, 120 preterm placentas were collected for the study. The maternal and baseline neonatal details were recorded in these deliveries. Placental inflammation staging in histopathological examination was done and findings were noted. The normal histopathology of placental membrane was present in 61% and normal umbilical cord was present in 81%. (Figure 1-3)

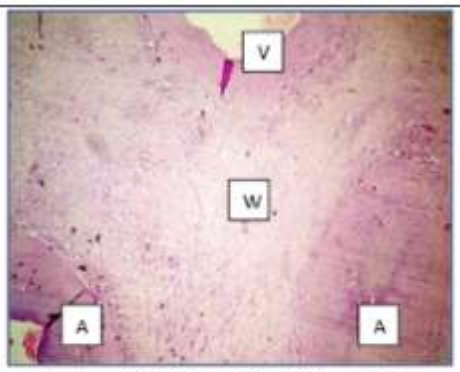

Figure 1. Normal Umbilical Cord Shows 3 Vessels; 2 Arteries (A) and 1 Vein (V) Embedded Within a Myxoid Paucicellular Matrix Called Wharton's Jelly (W). H & E 200 X

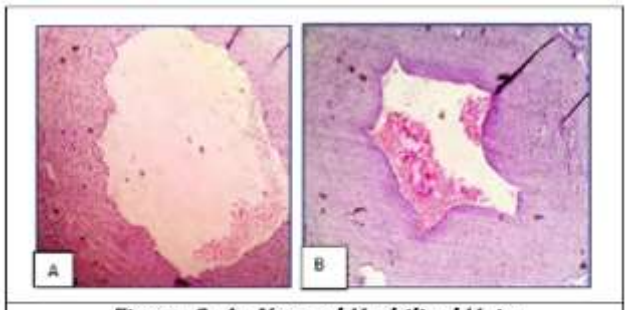

Figure 2. A- Normal Umbilical Vein; Figure 2. B- Normal Umbilical Artery H & E 200 X

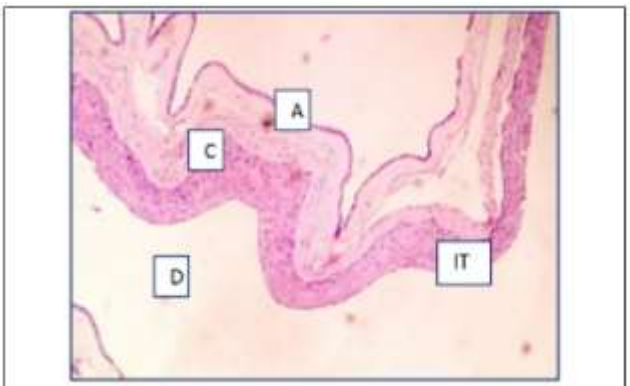

Figure 3. Normal membrane consists of the amnion (A) which is a single layer of cuboidal epithelium; the chorion (C) consisting of a sparsely cellular collagen layer which lies on a layer of intermediate trophoblast cells (IT) deeper to which is the decidual layer (D). H & E 100 x

Out of 120 placentas examined 39% showed placental inflammation. Forty seven preterm placentas had maternal inflammatory response (MIR) and 23 had foetal inflammatory response (FIR) on histopathology. (Figure 4, 5) Further staging and grading of MIR and FIR were done for all placentas with inflammation. (Figure 6-11) Three placentas showed other specific features like acute intervillositis. (Figure 10, 11)

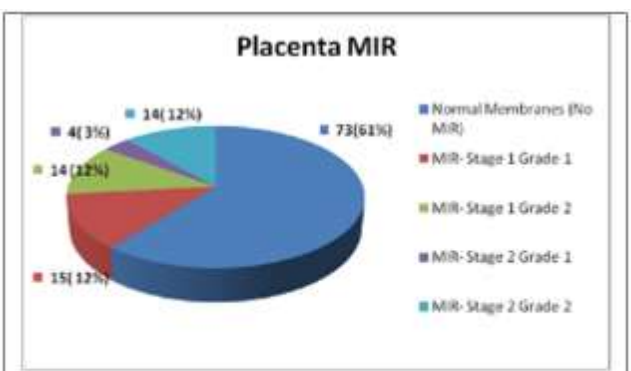

Figure 4. Placental Maternal Inflammatory Response (MIR) in The Study Group

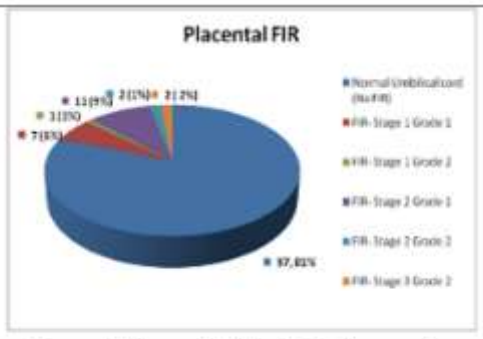

Figure 5. Placental Foetal Inflammatory Response (FIR) in The Study Group

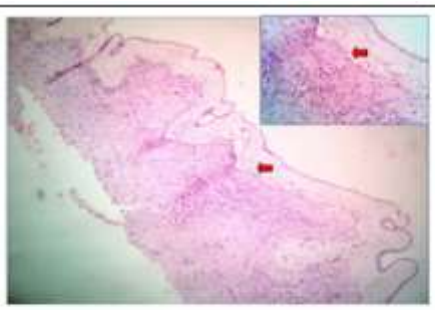

Figure 6. MIR Stage 1 Grade 1- Accumulation of neutrophils in the subchorionic plate fibrin (red arrow). H & E 100 X. Right upper inset shows patchy accumulation of neutrophils in the sub chorionic plate (red arrow). H & E 200 X

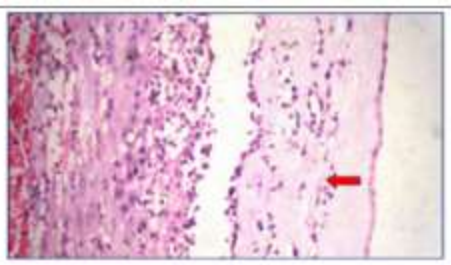

Figure 6. MIR Stage 2 Grade 2 - (Acute Chorioamnionitis)- Scattered Neutrophils in the Chorionic Plate/Membranous Chorionic Connective Tissue (Red Arrow) H & E 200 X

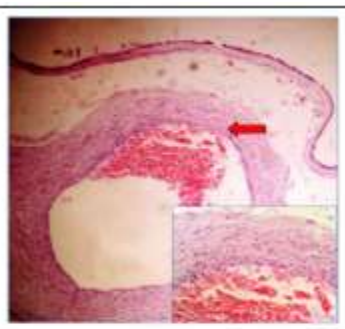

Figure 7. FIR Stage 1 Grade 2 - (Chorionic Vasculitis) Neutrophils in The Wall of Chorionic Plate Vessel (Red Arrow) H & E 100X. Right Inset Shows Higher Magnification of the Area Marked by Red Arrow H & E 200X

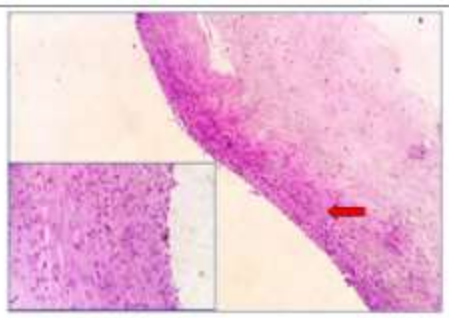

Figure 8. FIR Stage 1 Grade 2 (Umbilical Phlebitis) Neutrophils in the Wall of Umbilical Vein (Red Arrow) H & E 100X. Left Inset Shows Higher Magnification of the Area Marked by Red Arrow H & E 200X

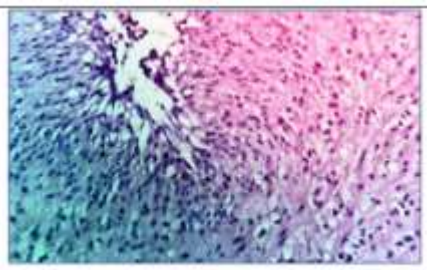

Figure 9. FIR Stage 2 Grade 2 (Umbilical Vasculitis)- Neutrophils in the Wall of Umbilical Artery

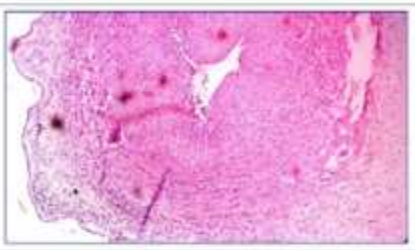

Figure 10. FIR Stage 3 Grade 2 (Necrotizing Funisitis)- Neutrophils Arranged in a Concentric Ring Around One Umbilical Artery. H & E 100X

Based on the presence of placental inflammation the study cohort was classified into two groups (Table 1). The maternal and neonatal baseline characteristics were compared between the two groups. The maternal age and parity were comparable in the two groups. The preterm deliveries with history of previous preterm delivery, premature rupture of membranes or spontaneous onset of labour had higher occurrence of placental inflammation and these were statistically significant.

Characteristics	No Placental Inflammation (N=73)	Placental Inflammation (N=47)	p Value
Maternal Characteristics			
Maternal age (yrs.) *	24.9 (4.1)	25.4 (3.8)	0.50
Primi para †	42 (57.5)	24 (54.2)	0.48
Previous preterm delivery †	04 (5.5)	09 (19.1)	0.019 ‡
Preeclampsia / PIH †	17 (23.3)	04 (8.5)	0.04 ‡

IUGR †	33 (45)	08 (17)	0.001 ‡
pPROM †	22 (30)	30 (63.7)	0.0001 ‡
Clinical chorioamnionitis †	04 (5.5)	05 (10.6)	0.29
Spontaneous labour †	50 (68.5)	45 (95.7)	0.0001 ‡
Caesarean Section †	25 (34)	05 (10.6)	0.004 ‡
Antenatal Steroids †	52 (71)	36 (76.6)	0.51
Antibiotics †	28 (38.4)	16 (34)	0.63
Neonatal Characteristics			
Mean GA (wks.) *	32 (1.4)	31 (2.0)	0.86
25-27 wks. †	02 (2.7)	02 (4.3)	0.3
28-31 wks. †	11 (15.1)	12 (25.5)	
32-34 wks. †	60 (82.2)	33 (70.2)	
Male †	35 (48)	27 (57.4)	0.31
Birth Weight (gms) *	1720 (400)	1655 (440)	0.38
SGA †	33 (45)	11 (23.4)	0.03 ‡

Table 1. Comparison of Maternal and Neonatal Characteristics and Placental Inflammation

Abbreviations

PIH, pregnancy induced hypertension; IUGR, intra uterine growth retardation; pPROM, prolonged premature rupture of membranes; SGA, small for gestational age.

* Mean (SD) and p value from ANOVA test.

†Number (percentage) and p value from chi- square test.

‡ p value <0.05 & statistically significant.

Preeclampsia, Pregnancy induced hypertension (PIH), Intrauterine Growth Restriction (IUGR), Caesarean Section and Small for Gestational age (SGA) were significantly higher in No placental inflammation group. The mean gestational age, birth weight and gender distribution were comparable between the two groups. The two placentae with stage 3 grade 2 foetal inflammatory response (FIR) had prolonged rupture of membranes (>72 Hours).

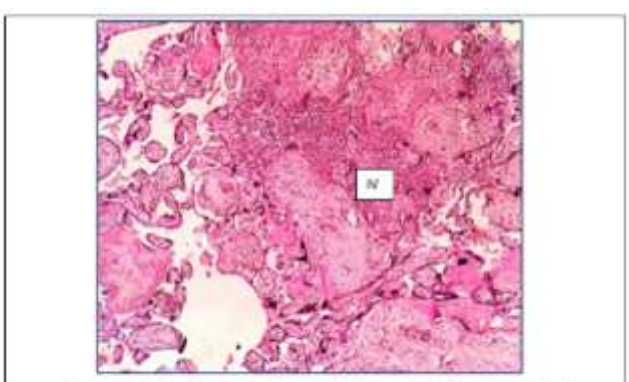

Figure 11. Acute Intervillositis- Neutrophils within The Intervillous (IV) Space. H & E 100X

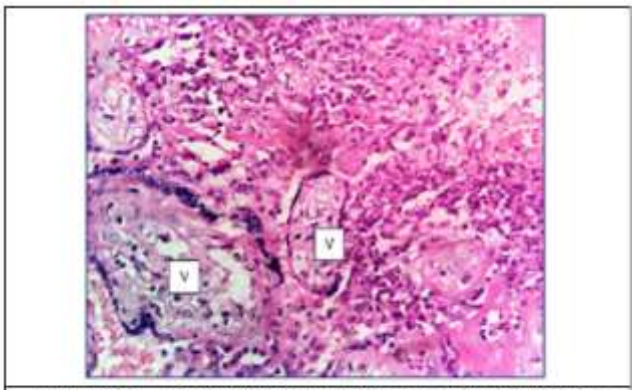

Figure 12. Acute Intervillositis- Neutrophils Seen in The Space Between Villi (V). H & E 200X

DISCUSSION

This study showed that 38% of the preterms had acute placental inflammation, out of which more than half cases showed foetal inflammatory response (FIR). This is in line with results of the previous studies.[7,8] The histological staging and grading were done for placental inflammation and the observations/findings were comparable with that of the previous reports.[5] But the mean gestational age of the study group was 32 (SD ±1.7) weeks which was slightly higher as compared to the study by Lahra et al where the mean gestational age was 27.1 (SD ±1.6) weeks.[7]

When preterm deliveries with Placental inflammation v/s No placental inflammation were compared, we found that premature rupture of membranes was significantly associated with placental inflammation. The most frequent pathway for intrauterine infection was found to be ascending microbial invasion and its association with preterm rupture of membranes as reported in various studies.[4,9] Studies have shown that the onset of labour in women with preterm premature rupture of the membranes is associated with a subclinical intraamniotic infection.[10]

In the present study, preterms with spontaneous onset of labour had significant placental inflammation when compared to those with induced labour. Romero et al shows that amniotic cavity microbial invasion was higher in women with spontaneous labour at term (17% vs. 1.5%).[11] Park H S et al also showed that after adjusting for various confounders like parity, gestational age at delivery, total duration of labour, the interval from rupture of membranes to delivery and the mode of delivery; histologic chorioamnionitis was significantly more frequent in women who delivered after the spontaneous onset of labour than in those who underwent induction of labour (24.3% vs. 13.1%).[12]

The main indication of induced labour and Caesarean Section in our cohort was severe Preeclampsia and Intrauterine Growth Restriction (IUGR). This could explain significant higher occurrence of Small for Gestational age (SGA), Intrauterine Growth Restriction (IUGR), Caesarean Section and Preeclampsia in No placental inflammation group.

The strength of this study is that standard histopathological criteria[6] are used for staging and grading of placental inflammation.

CONCLUSION

The acute placental inflammation was found to be associated with the preterm deliveries and this was observed significantly in preterm with premature rupture of membranes and spontaneous onset of labour. Placental inflammation a complex process may be infective or non infective in origin. It however leads to preterm deliveries and its associated complication. PPROM though significantly associated with preterm deliveries is either the cause or the effect of placental inflammation.

REFERENCES

[1] Blanc WA. Amniotic infection syndrome; pathogenesis, morphology, and significance in circumnatal mortality. Clin Obstet Gynecol 1959;2:705-734.

[2] Russel P. Inflammatory lesions of the human placenta. I. Clinical significance of acute chorioamnionitis. Am J Diagn Gynecol Obstet 1979;1(2):127-137.

[3] Romero R, Miranda J, Chaiworapongsa T, et al. Prevalence and clinical significance of sterile intra-amniotic inflammation in patients with preterm labor and intact membranes. Am J Reprod Immunol 2014;72(5):458-474.

[4] Romero R, Miranda J, Chaemsaithong P, et al. Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes. J Matern Foetal Neonatal Med 2015;28(12):1394-1409.

[5] Kim CJ, Romero R, Chaemsaithong P, et al. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol 2015;213(4 Suppl):S29-52.

[6] Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2003;6(5):435-448.

[7] Lahra MM, Beeby PJ, Jeffery HE. Maternal versus foetal inflammation and respiratory distress syndrome: a 10-year hospital cohort study. Arch Dis Child Foetal Neonatal Ed 2009;94(1):F13-1F6.

[8] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, foetal involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. Am J Obstet Gynecol 2009;201(6):587.e1-8.

[9] Prendergast M, May C, Broughton S, et al. Chorioamnionitis, lung function and bronchopulmonary dysplasia in prematurely born infants. Arch Dis Child Foetal Neonatal Ed 2011;96(4):F270-F274.

[10] Romero R, Quintero R, Oyarzun E, et al. Intraamniotic infection and the onset of labor in preterm premature rupture of the membranes. Am J Obstet Gynecol 1988;159(3):661-666.

[11] Romero R, Nores J, Mazor M, et al. Microbial invasion of the amniotic cavity during term labor. Prevalence and clinical significance. J Reprod Med 1993;38(7):543-548.

[12] Park HS, Romero R, Lee SM, et al. Histologic chorioamnionitis is more common after spontaneous labor than after induced labor at term. Placenta 2010;31(9):792-795.