Original Article

Association of Clinical Signs of Chorioamnionitis with Histological Chorioamnionitis and Neonatal Outcomes in Women with Premature Rupture of Membranes

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Abstract

Background: Premature rupture of membrane (PROM), especially when preterm or prolonged is associated with an increased risk of chorioamnionitis with its attendant feto-maternal complications. **Aim:** The study was aimed to determine the association of clinical signs of chorioamnionitis with histological chorioamnionitis and neonatal outcomes in women with PROM. **Materials and Methods:** Eligible participants with clinical diagnosis of PROM at gestational age of ≥28 weeks managed between December 2018 and June 2019 were consecutively recruited. Their sociodemographic characteristics, obstetrics history, and evidence of clinical chorioamnionitis using the Gibb's criteria were obtained. Following delivery, chorioamnionitis was histologically confirmed. Primary outcome measure was the proportion of women with PROM and histological chorioamnionitis that were detected clinically. **Results:** Of the 136 participants analyzed, 108 (79.4%) had term PROM, while 28 (20.6%) had preterm PROM (<37 weeks). The prevalence of histological chorioamnionitis was 50.0% compared to 16.2% using clinical indicators of infection. Histological chorioamnionitis was almost two times higher in preterm than term PROM (71.4% vs 38.9%). About two-third (67.6%) of the chorioamnionitis identified histologically were missed using clinical signs of chorioamnionitis. Clinical signs of chorioamnionitis had specificity of 100.0%, but low sensitivity (35.5%) and accuracy of 70.6%. A combination of three symptoms, maternal pyrexia and tachycardia, and fetal tachycardia appears to be the most reliable clinical indicator of chorioamnionitis in women with preterm PROM. There was a significant association between low birth weight, low Apgar score, NICU admission, and the presence of histological chorioamnionitis in women that had PROM. **Conclusion:** Clinical signs of chorioamnionitis have a low sensitivity and are not very accuracy in diagnosing chorioamnionitis in women with PROM.

Keywords: *Chorioamnionitis, preterm labor, preterm rupture of membrane, rupture of membrane*

Introduction

Chorioamnionitis is a histopathologic finding of inflammation of fetal membranes (the amnion and/or chorion) and may extend to the umbilical cord (funisitis).[1,2] Chorioamnionitis occurs when protective mechanisms of the urogenital tract and/or uterus fail during pregnancy as seen in premature rupture of membranes (PROM).

Approximately, 8% to 10% of term pregnancies will experience spontaneous rupture of membranes

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before the onset of uterine activity.[3,4] Preterm PROM complicates 2% to 4% of all singleton and 7% to 20% of twin pregnancies.[3-6] However, Aror*a et al.* reported 7% incidence of preterm PROM in their study.[7] It is the leading identifiable cause of preterm birth and accounts for approximately 18% to 20% of perinatal deaths in the United States.[5,6]

Prolonged PROM refers to PROM lasting more than 24 h and is associated with an increased risk of ascending infection and chorioamnionitis.[3] Fetal complication of chorioamnionitis includes preterm birth and neonatal sepsis with associated chronic lung disease and brain injury and perinatal death.[3,4,8,9] Tsamantioti *et al.* in their study recently reported an increased risk of neurodevelopmental disorders, particularly cerebral palsy, autism, attention deficit, hyperactivity disorders, and intellectual ability in offspring that had in utero exposure to chorioamnionitis.[10]

Maternal complications of chorioamnionitis include endometritis, pelvic infections, and intra-abdominal infections. Maternal chorioamnionitis or other secondary infectious complications may cause thrombosis of pelvic vessels and the potential for pulmonary emboli.[11,12]

Chorioamnionitis may be clinical or subclinical. Chorioamnionitis may be clinical or subclinical. Primary clinical findings include clinical signs, and symptoms of chorioamnionitis include fever, significant maternal tachycardia (>100 beats per minute), fetal tachycardia (>160–180 bpm), purulent or foul-smelling amniotic fluid or vaginal discharge, uterine tenderness, and maternal leukocytosis (total blood leucocyte count >15,000–18,000 cells/uL). When at least two of the aforementioned criteria are present, the risk of neonatal sepsis is increased.[13] Each clinical sign and symptom of chorioamnionitis, however, is by itself of low predictive value.[14] Therefore, histological evaluations of the placenta and membranes are essential for confirmation of diagnosis of chorioamnionitis. Histologic chorioamnionitis occurs in approximately 50–60% of women with preterm PROM.[3,9]

Histologic chorioamnionitis has been shown to be associated with the presence of microbial invasion of the amniotic cavity with its attendant adverse maternal and neonatal outcomes.[15] Early and accurate diagnosis of chorioamnionitis is important, but it is limited by the fact that placental pathology cannot be evaluated before delivery. Recently, the National Institute of Child Health and Human Development (NICHD) expert panel suggested the term "intra-uterine inflammation or infection or both" abbreviated as "Triple I" to replace the term chorioamnionitis.[16]

In low- and middle-income countries including Nigeria, diagnosis of chorioamnionitis and its management are usually based on clinical evidence of infection. However, some authors have reported that clinical signs and symptoms of chorioamnionitis are not always associated with placental evidence of infection.[17,18] This, therefore, suggests that diagnosis of chorioamnionitis based on clinical symptoms and signs may be subjective and may result in over or under treatment, hence the need to assess the sensitivity, specificity, and predictive value of these clinical indicators of infection in diagnosing chorioamnionitis in women with PROM.

Despite the significant maternal and neonatal morbidity and mortality associated with chorioamnionitis, there is a paucity of data and research contribution from resource limited countries that rely majorly on clinical indicators of infection in diagnosing chorioamnionitis in patient with PROM and its subsequent management, hence the need for this study. The findings from this study hopefully may assist in better management of women with PROM in resource limited settings. The study aimed to determine the association of clinical signs of chorioamnionitis with histological chorioamnionitis and neonatal outcomes in women with premature rupture of membranes.

Materials and Methods

A longitudinal prospective study of pregnant women with diagnosis of PROM at gestational age of ≥28 weeks at the two-government owned tertiary health institution in Enugu, south-east Nigeria; the University of Nigeria Teaching Hospital, (UNTH), Ituku- Ozalla, and Enugu State University Teaching Hospital (ESUTH) over a 12-month period from December 1, 2018 to November 30, 2019. Both hospitals serve as referral centers for cases of PROM. Both institutions have well-established Newborn Special Care Unit (NBSCU).

All pregnant women with diagnosis of PROM at ≥28 weeks gestational age were recruited consecutively from the antenatal clinics, accident and emergency unit, and labor wards of both institutions after obtaining their informed consent. A total of 136 participants were recruited in the study. Pregnant women with diabetes mellitus, HIV/AIDS, hematological disorders, and antepartum hemorrhage were excluded from the study.

The diagnosis of PROM was made by recording at least two of the following; pool of liquor in the posterior vaginal fornix or trickling of liquor from the cervical os, positive Nitrazine paper test and microscopic ferning of the fluid on drying and was confirmed using AmnioQuick® Duo plus test.[19]

The sociodemographic data, present and past obstetrics history as well as assessment for clinical evidence of infection (temperature >37.8^{0}C, maternal or fetal tachycardia, uterine tenderness, and foul-smelling vaginal discharge) were done at admission.[13,20] For the purpose of the study, clinical chorioamnionitis was made when maternal temperature was >37.8^{o}C plus any two or more of the following: uterine tenderness, malodourous vaginal discharge, and maternal or fetal tachycardia according to Gibbs criteria.[21] Patients on conservative management were closely monitored in the ward for sign(s) of infection, and all the women were reassessed during labor for signs of infection.

Following delivery, tissue samples were obtained from the placenta (two samples), umbilical cord (one sample), and placental membranes (two samples) and fixed in 10% neutral buffered formalin. The samples were processed and embedded in paraffin at ESUTH Histopathology laboratory by a histopathologist. Sections of tissue blocks were stained with hematoxylin and eosin and examined by two independent histopathologists.

Histological chorioamnionitis was defined by the presence of acute inflammatory changes in any tissue samples (amnion, chorio-decidual, umbilical cord, and chorionic plate) as proposed by Salafia *et al*.[22] All the cases of histologically diagnosed chorioamnionitis were staged and graded according to the Amsterdam consensus criteria.[23]

Histopathologists were blinded to the clinical status of the patient. All the information obtained was recorded in the proforma form designed for the study. Assay of amniotic fluid glucose level, microscopy, and culture were not done.

Women with preterm PROM at less than 34 weeks of gestation were treated with corticosteroids to accelerate the lung maturation (three doses of 8 mg dexamethasone administered intramuscularly 8 h apart) and broad-spectrum antibiotics, whereas no other treatment except antibiotics was initiated after 34 weeks. Conservative management was terminated once should any of the following occurred: ultrasound finding of severe oligohydramnios or gross fetal anomaly, sign of subclinical or overt chorioamnionitis, non-reassuring fetal status and significant abruptio placentae, cord prolapse, patient who entered the active phase of labor, intra-uterine fetal death or vaginal bleeding, and attainment of at least 34 weeks of gestation. Relevant data including the sociodemographic characteristics of the participants were collected using a proforma.

Four research assistants were recruited and trained for the study, two from each of the health institutions. The primary outcome measure was the proportion of women with PROM and clinical indicators of infection that were confirmed histologically. Data collected were coded, entered, and analyzed using statistical package for social sciences (SPSS) computer software version 22.0 for windows. Descriptive statistics which included frequency and percentages were used to summarize categorical variables, while means and standard deviations were obtained for continuous variables. *P*-value <0.05 was considered statistically significant. Ethical approval for the study was obtained from the Health Research Ethics Committees of both study centers with approval number UNTH/CSA/329/VOL 5/08.

Results

Although 148 participants were assessed for eligibility, 136 participants were recruited, while the remaining 12 participants were excluded due to either inadequately collected sample specimens or failure to give consent Figure 1.

Table 1: Sociodemographic characteristics of the participants

Age group	Frequency	Percent
21–25	8	5.9
26–30	54	39.7
31–35	58	42.6
36–40	16	11.8
Tribe		
Igbo	132	97.1
Ikom	4	2.9
Religion		
Christianity	136	100.0
Occupation		
Civil service	34	25.0
Seamstress	16	11.8
Corp member	8	5.9
Trader	58	42.6
Student	8	5.9
Unemployed	6	4.4
Farming	2	1.5
Teaching	4	2.9
Marital status		
Married	134	98.5
Single	2	1.5
Parity		
0	44	32.4
1	26	19.1
2	22	16.2
3	24	17.6
4	20	14.7
Booking		
Booked	78	57.3
Unbooked	58	42.7

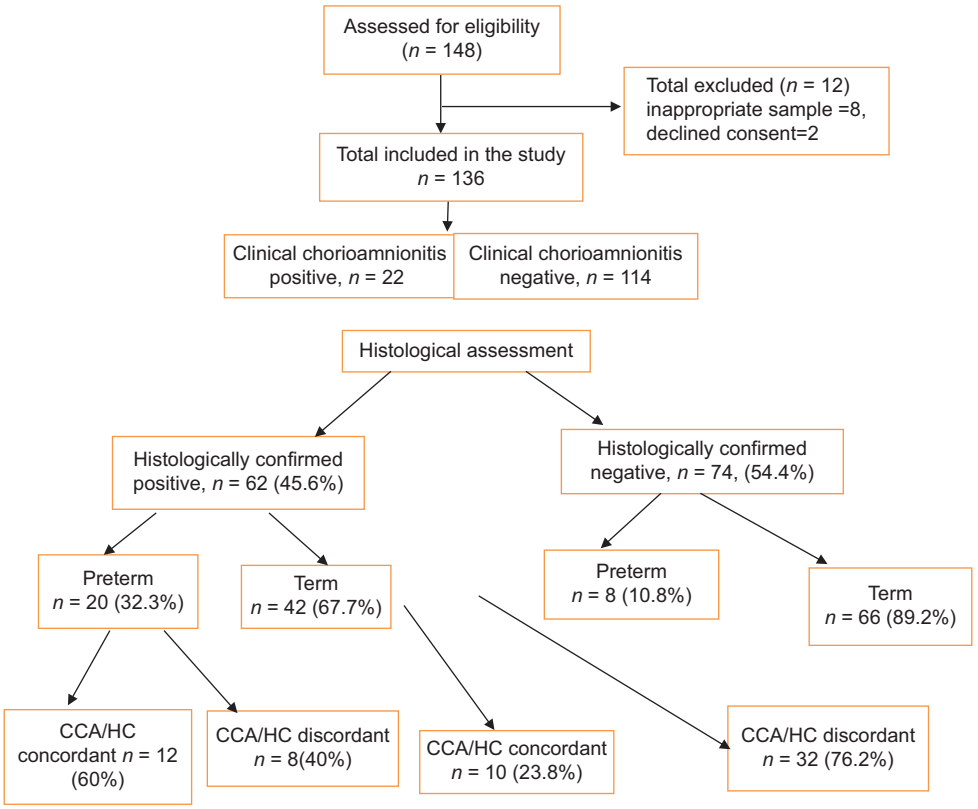

Figure 1: Flow chart showing pattern of recruitment and histological findings, HC = histological chorioamnionitis, CCA = clinical chorioamnionitis, TP = true positive, FP = false positive, TN = true positive, FN = false negative

Table 2: Performances of clinical indicators of infection (at repeat assessment) using Gibbs criteria in relation to gestational age at which PROM occurred, using histological chorioamnionitis as the gold standard.

Test characteristics	Gestational Age <37 weeks	Gestational Age ≥37 weeks
True negative	8	60
True positive	12	10
False negative	8	38
False positive	0	0
Total	28	108
Specificity (%)	100.0	100
Sensitivity (%)	60.0	28.0
NPV (%)	50.0	61.2
PPV (%)	100.0	100
Accuracy (%)	71.4	64.8

Their mean age was 31.2 ± 4.0 years. Majority of them were married (98.5%, *n* = 134/136), Igbos (97.1%, *n* = 132/136), traders (42.6%, *n* = 58/136), and Christians (100%). The majority of them were booked (57.3%, *n* = 78/136). Details are given in Table 1.

The majority of them (*n* = 108, 79.4%) had term PROM (≥37 weeks), while 28 (20.6%) had preterm PROM (<37 weeks). Their mean gestational age at delivery was 38.3 ± 3.5 weeks. The mean duration of PROM was 24.5 ± 30.0 h.

Using the clinical signs of chorioamnionitis, the prevalence of chorioamnionitis was 16.2% (*n* = 22/136), while on histological assessment, the prevalence was 50.0% (*n* = 68/136). Based on Amsterdam consensus criteria, all the histologically diagnosed chorioamnionitis had features of acute placental inflammation (API); the majority (76.7%%) had both maternal inflammatory response (MIR) and fetal inflammatory response (FIR). About 12.8% and 10.5% of them had only MIR and FIR, respectively. Among those that had MIR, the majority of them (50%) were stage 1 (sub-chorionitis), 45% were stage 2 (inflammation of the chorion or chorion and amnion), while the remaining 5% had stage 3 (chorioamnionitis with amnion necrosis). The majority (62.0%) of FIR seen were stage 1 (chorionic vasculitis or umbilical phlebitis), 35.5% was stage 2 (involvement of the umbilical vein and one or more umbilical arteries), while 2.5% was in stage 3 (necrotizing funisitis). About 82.6% of MIR were grade 1(not severe).

More than two-thirds (*n* = 46/68, 67.6%) of the chorioamnionitis identified histologically were missed using clinical signs. However, all the cases that had clinical indicator of infection were confirmed to have histological chorioamnionitis. The prevalence of histological chorioamnionitis was almost two times

Table 3: Relationship between histologic chorioamnionitis and neonatal outcome measures

Neonatal variables	Histological chorioamnionitis *n*=68 (%)	No histological chorioamnionitis *n*=68 (%)	Relative risk (RR)	95% confidence interval (CI)	*P*
Birth weight					
<2.5 kg	22 (73.3)	8 (26.7)	4.07	1.67–9.91	0.002
≥2.5 kg	46 (43)	60 (56.6)			
APGAR Score					
≤6	18 (81.8)	4 (18.2)	5.76	1.88–18.09	<0.003
≥7	50 (43.9)	64 (56.1)			
NBICU Admission					
Yes	40 (83.3)	8	10.7	4.41–25.9	0.001
No	28	60			

higher among participants that had preterm than term PROM (71.4%, *n* = 20/28 v 44.4%%, *n* = 48/108).

Clinical prediction of chorioamnionitis using the criteria proposed by Gibbs had specificity of 100%, sensitivity of 35.5%, and accuracy of 70.6%. Its negative predictive value and positive predictive value were 64.9 and 100%, respectively.

However, sub-analysis of the data showed that clinical prediction of chorioamnionitis appears to be more sensitive and accurate in preterm PROM compared to term PROM. From the study, the sensitivity and accuracy when used in preterm PROM were 60% and 71.4%, respectively, compared to sensitivity of 28.0% and 64.8% in term PROM. Interestingly, its specificity in preterm and term PROM remained 100%. This is shown in Table 2.

Interestingly, the combination of elevated temperature (>37.8°c), maternal and fetal tachycardia had the highest sensitivity (17.9%) with specificity of 100% and accuracy (64.4%) in diagnosing chorioamnionitis.

The study showed a significant association between low birth weight, low Apgar score and NICU admission, and the presence of histological chorioamnionitis in women that had PROM. Women that had low birth weight babies were four times more likely to have histological chorioamnionitis compared to women that had normal birth weight babies (RR =4.07, 95% CI 1.67–9.91, *P* = 0.002). Also, women that delivered babies with Apgar score of 6 and below were almost six times more likely to have histological chorioamnionitis than those with babies of normal weight (RR =5.76, 95% CI 1.89–18.09. *P* =0.003). Also, women that delivered babies that were admitted into the NICU were almost eleven times more likely to have associated histological chorioamnionitis (RR =10.7, 95% CI 4.41–25.9, *P* = 0.001). The details are given in Table 3.

Discussion

The prevalence of histological chorioamnionitis among women with PROM from the study was 50%. This is lower than 53.4% earlier reported in a multicenter study in Nigeria.[24] Notably, the prevalence of histological chorioamnionitis was almost times higher in women that had preterm than term PROM (71.4% v 44.4%). This may be attributed to the usual delay in delivery to allow for lung maturity in women at gestational age less than 34 weeks. Studies have shown that prolonged PROM significantly increased the risk of development of chorioamnionitis.[13]

About two-thirds (67.6%) of the chorioamnionitis identified histologically were missed using clinical signs of infection. The study showed that clinical signs of chorioamnionitis either individually or in combination cannot accurately predict the presence of histological chorioamnionitis both in term and preterm deliveries. This finding is similar to that earlier reported by some authors.[25,26] Histologic chorioamnionitis identifies subclinical as well as clinical chorioamnionitis making overall histologic diagnosis about three times as frequent as clinical chorioamnionitis.[26] Romero *et al.* and Aziz *et al.* also reported that clinical signs and symptoms of chorioamnionitis were not always associated with placental evidence of infection.[17,18]

Although not very sensitive and accurate in its prediction, the combination of three signs (maternal temperature >37.8^{0}C, fetal tachycardia, and maternal tachycardia) appears more accurate in diagnosing histologic chorioamnionitis in women with PROM compared to other combinations of signs. This finding is similar to a previous report by Curtin *et al.*[27] that clinical signs (fever, maternal tachycardia, and fetal tachycardia) were strongly associated with histologic chorioamnionitis but were diagnostically insensitive. A similar report by Newton revealed that apart from objective measurements of maternal fever, maternal and fetal tachycardia, other signs of chorioamnionitis are highly subjective, with uterine tenderness and malodourous vaginal discharge occurring in only 4–25% of cases of chorioamnionitis.[28]

Although this study suggests that clinical signs of chorioamnionitis are not very sensitive in diagnosing histological chorioamnionitis, they remain relevant in sub-Saharan African countries including Nigeria where histological diagnosis is not readily available in many centers. In centers, where the service is available, it can only be done after delivery. This suggests that clinical signs of chorioamnionitis may continue to play a role in diagnosing chorioamnionitis in patient with PROM in developing countries including Nigeria but should be used with caution.

The study showed a significant association between low birth weight, low Apgar score and NICU admission, and the presence of histological chorioamnionitis in women that had PROM. From the study, women that had low birth weight babies were four times more likely to have histological chorioamnionitis compared to women that had normal birth weight babies (RR =4.07, 95% CI 1.67–9.91, $P = 0.002$). Also women that delivered babies with Apgar score of ≤6 were almost six times more likely to have histological chorioamnionitis (RR =5.76, 95% CI 1.89–18.09. $P = 0.003$). Also, women that delivered babies that were admitted into NICU were almost eleven times more likely to have associated histological chorioamnionitis (RR =10.7, 95% CI 4.41–25.9, $P = 0.001$). This was not unexpected as PROM in the absence of intervention is often associated with chorioamnionitis and preterm delivery. These findings agreed with previous reports by Han *et al*. that histological chorioamnionitis was associated with early-onset sepsis and combined perinatal comorbidities.[29] Chorioamnionitis reportedly is a risk factor for long-term neurodevelopmental disability especially when it occurs before term.[29,30] In term and near-term infants, it is associated with a fourfold increase in the frequency of cerebral palsy.[31]

The strength of the study was the blinding of the histopathologists to avoid bias. The study appears to be one of the few studies if any, to the best of our knowledge from a low resource country that evaluated the sensitivity, specificity, and accuracy of clinical signs of infection in diagnosing chorioamnionitis in women with PROM. However, future study with larger sample size is recommended. Also due to laboratory logistics, maternal leukocytosis (>15,000 cells/mm^3) was not used as a clinical indicator of infection in this study.

In conclusion, clinical signs of chorioamnionitis alone and in combination are not very sensitive and are not accurate in predicting histologic chorioamnionitis in women with PROM.

Author contributions

AOA, ECE conceptualized the research idea and designed the study, AOA, ECE, OIC, FKA, GUE, EOC, HUE were actively involved drafting the article and revising it critically for important intellectual content. All the authors approved the final draft and its submission.

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Conflicts of interest

There are no conflicts of interest.

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