



## Original Article

### Relationship Between Sonographic Foetal Thymus Transverse Diameter and Histological Chorioamnionitis in Patients with Preterm Rupture of Membranes in Ibadan, Nigeria.

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## Abstract

**Introduction:** One of the major challenges faced by the clinicians in the management of preterm rupture of the membranes (PROM) is to correctly identify when a significant chorioamnionitis is evolving to decide the appropriate time for delivery of the foetus. A promising diagnostic tool to serve as a surrogate marker for predicting the occurrence of subclinical chorioamnionitis is the use of sonographic foetal transverse thymus diameter (FTTD). The objective of this study was to determine the relationship between sonographic FTTD and histological chorioamnionitis in patients with PROM. **Methodology:** This hospital based prospective cohort study was conducted among consenting pregnant women who presented with PROM between gestational ages of 28 to 34 weeks at the University College Hospital, Ibadan, Nigeria over an 8-month period. Sonographic measurement of foetal thymus transverse diameter (FTTD) was performed on all foetuses at admission. After delivery, the placenta was histologically examined to diagnose chorioamnionitis. Ethical approval was obtained, and Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23 with level of statistical significance set at  $P < 0.05$  and CI at 95%. **Results:** One hundred and twenty-two women were recruited for this study The mean age was  $30.2 \pm 5.4$  years with 82 (77.2%) in the 25-35 years' age group. Ninety-one (74.6%) of the women presented with PROM at gestational age of 32 to 34 weeks. Seventy-three (59.3%) of the respondents had no constitutional symptoms. Majority (85, 69.7%) had spontaneous vaginal delivery. Forty-eight (39%) of the foetuses had TTD less than 5<sup>th</sup> Centile for their GA on ultrasound scan. Fifty-seven (46.7%) of the women had placenta histological features of chorioamnionitis and there was a significant association between small thymus and histological chorioamnionitis ( $P < 0.001$ ) compared with apparently normal thymus. The Sensitivity was increased with the number of thymic ultrasounds done before delivery. **Conclusion:** Foetal thymus ultrasound scanning seemed to be a promising sensitive predictor for the occurrence of chorioamnionitis in women with preterm rupture of membranes.

**Keywords:** Ultrasound, Fetal Thymus, PROM and Chorioamnionitis

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## Introduction

Prematurity has risen steadily in the past decades accounting for approximately 10% of all deliveries worldwide and it is considered important because of its

association with increased incidence of maternal morbidity and consequently increased perinatal and maternal mortality.<sup>1-3</sup> One of the factors associated with preterm deliveries is preterm rupture of membranes.

Preterm rupture of membranes (PROM) is defined as the spontaneous rupture of foetal membranes after the age of viability but before 37 completed weeks of gestation.<sup>1</sup> It complicates about 2% of all pregnancies and accounts for up to one-third of preterm deliveries.<sup>1,2</sup> When preterm rupture of foetal membranes occurs, the barrier surrounding the foetus is broken and there is increased risk of ascending infection from the lower genital tract to the upper genital tract with subsequent infection of the chorioamniotic membrane which is technically called chorioamnionitis.<sup>1,3,4</sup>

Possible maternal morbidities that may ensue if treatment is delayed in cases of chorioamnionitis include endometritis, septicaemia, secondary postpartum haemorrhage and long term sequelae such as secondary infertility while foetal complications may include: neonatal sepsis, bronchopulmonary dysplasia, periventricular leucomalacia, foetal cardiac dysfunction etc.<sup>2,4</sup> Chorioamnionitis is a feared complication of preterm rupture of membranes and it is better prevented. However, in cases when it occurs it is better detected early before the feared foetomaternal complications begin to appear.<sup>4,5</sup> The present tests and predictors used in clinical practice in sub-Saharan Africa to diagnose subclinical chorioamnionitis are non-specific; these include fever, abnormal vaginal discharge, maternal tachycardia, abdominal tenderness, maternal leucocytosis or neutrophilia and elevated maternal C reactive protein.<sup>2-5</sup>

These symptoms, signs and tests have been shown to have a relatively low sensitivity rate ranging between 67-81%.<sup>3,4</sup> More sensitive and specific investigations used in early prediction of subclinical chorioamnionitis are usually invasive, requiring the performance of amniocentesis. These include amniotic fluid leucocyte count, amniotic fluid glucose measurement, amniotic fluid culture and gram staining, interleukin-6 measurement in amniotic fluid etc.<sup>4</sup> These tests are also associated with the risk of trauma to the foetus, preterm labour and dissemination of infection, and are not practical to repeat in long term follow up. There is need for a test that has a high diagnostic accuracy, non-invasive and has a better sensitivity in predicting the occurrence of subclinical chorioamnionitis in women with preterm rupture of membranes. A promising diagnostic tool that is being put forward as a predictor of the occurrence of subclinical chorioamnionitis in women with preterm rupture of membranes based on the ease of performance, sensitivity and non-invasive nature is foetal thymus ultrasound scanning.<sup>6-10</sup>

Researches have shown that foetal thymus transverse diameter (FTTD) increases as gestational age increases in the absence of infections or inflammation, and the growth is maximal close to term. However, when there is microbial invasion of the chorioamniotic membrane, the thymus responds by undergoing involution.<sup>7</sup>

Many studies<sup>7-10</sup> have been done in the high-income countries but there is paucity of data in the low- and medium-income countries (LMIC) especially in the

Sub-Saharan Africa. This study aims to determine the relationship between small foetal thymus transverse diameter (FTTD) and histological chorioamnionitis in pregnancies complicated by preterm rupture of membranes in a black African population.

## Materials And Methods

This study was a prospective cohort study conducted between December 2019 and August 2020. The study was carried out among women presenting with preterm prelabour rupture of membranes between gestational age of 28 weeks to 34 weeks at the obstetric department of the University College Hospital, Ibadan. Informed consent was obtained from all patients.

A diagnosis of preterm prelabour rupture of membranes (PPROM) was made by complains of fluid drainage per vaginam followed by the sterile speculum examination and confirmation with the red litmus paper of the fluid collected from the posterior fornix of the vagina.

Gestational age was determined according to the last menstrual period and/or measurement of crown rump length in the first trimester for those who had first trimester ultrasound reports. All patients were admitted and managed conservatively on parenteral antibiotics and antenatal corticosteroid. Routine ultrasound examination was performed to assess foetal weight using the Hadlock formula, placenta site and amount of amniotic fluid. Indications for delivery included: foetal distress, clinical evidence of chorioamnionitis, labour or attainment of 34 weeks gestational age.

Sonographic measurement of foetal transverse thymus diameter was performed on a Voluson P6® ultrasound machine (General Electric Healthcare, Korea, 2016) with a multifrequency curvilinear transducer (2-5MHz). The foetal thymus gland was visualized within the thorax as a well delineated homogenous hypochoic structure posterior to the sternum and anterior to 3 great vessels- the pulmonary artery, ascending aorta and the Superior vena cava. The lateral margins are delineated from the lungs on either side by linear interphases. The transverse diameter of the thymus was taken at the widest points of the thymus (figure 1). Decreased foetal thymus transverse diameter (FTTD) on ultrasound was defined as any measurement below the 5% centile for GA according to the nomogram by Cho et al.<sup>7</sup>

The first FTTD was performed on all foetuses at the time of admission before the administration of antenatal corticosteroids for lung maturity, while weekly assessment was done at the bedside till delivery. All ultrasound measurements of the foetal thymus were performed by a radiologist with expertise in foetal sonography.

Expectant management was stopped, when labour progressed spontaneously, in the presence of foetal distress or in the presence of chorioamnionitis (maternal fever >38°C, uterine tenderness, foul smelling vaginal

discharge, maternal tachycardia >100beats/min, foetal tachycardia >160beats/min or white blood cell count >15,000 leucocytes/cubic millimetres. The route of delivery was chosen according to obstetric indication. Placenta samples were taken from the chorionic plate of the placenta disc and free foetal membrane stored in 10% formalin solution until samples were ready for analysis.

Data was collected using a data collection proforma which was adapted from the Cochrane data base and was administered to respondents who met the inclusion criteria

The proforma has 5-sections designed to take relevant information from the respondents who met the inclusion criteria. The data were coded and analysed using Statistical Package for the Social Sciences (SPSS) for windows version 23 (SPSS Inc, Chicago, IL, USA). Categorical variables were analysed with Chi square test; reported as Risk Ratios (RR) and 95% Confidence Intervals (95% CI) as appropriate for categorical data. A P-value <0.05 was considered statistically significant.

Ethical approval was obtained from the Joint Institution Review Committee (IRC) of the University College Hospital and the College of Medicine, University of Ibadan.

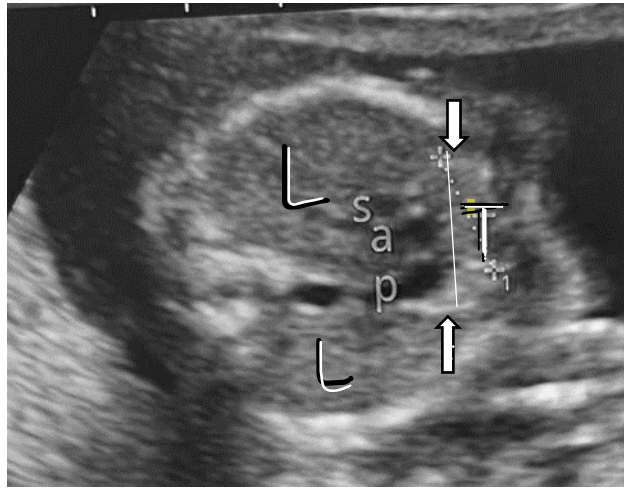


Figure 1: Transverse plane of the foetal thorax on ultrasound scan, showing the thymus(T) lying anterior to the 3 vessels - pulmonary artery (p) Aorta (a) and superior vena cava(s). A linear echogenic interphase (white arrows) demarcates its margins from the lungs (L) on either side. The transverse diameter was measured from one linear interphase to the other (white straight line)

**Results**

One hundred and twenty-five women were recruited for this study but three were not suitable for ultrasound foetal thymus size assessment on account of inappropriate positioning of the foetus and severe oligohydramnios, hence were excluded from the study, making 122 eligible pregnant women. The mean age of the women was 30.2

±5.4 years with 82 (77.2%) in the 25-34 years’ age group. Majority (82.0%) of the respondents were less than 34years while 28.0% were 34years and above.

Table 1: History of rupture of membrane and constitutional symptoms

Variables	Frequency	Percent
Duration from rupture of membranes before presentation in the hospital (hours)		
<1	01	0.8
1-5	42	34.4
6-10	07	5.7
11- 24	36	29.5
> 24	36	29.5
Total	112	100
Time of onset of Abdominal pains (hours)		
<1	27	22.1
1-5	00	0.0
6-10	09	7.4
11- 24	05	4.1
> 24	76	62.3
No abdominal pain	112	100.0
GA at rupture of membranes(weeks)		
28-29 <sup>+6</sup>	16	13.1
30-31 <sup>+6</sup>	15	12.3
32-34	91	74.6
Constitutional Symptoms of PROM		
Nil	73	59.3
Fever	3	2.5
Abdominal pains	46	37.7

GA: Gestational age; PROM-Preterm rupture of membranes.

Almost three quarter (91, 74.6%) of the women presented with PROM at gestational age of 32 to 34 weeks. Forty-two (34.4%) presented with history of rupture of membranes of 1 to 5-hour duration, 36 (29.5%) presented after 24 hours while only one woman (0.8%) presented to the hospital within one hour of rupture of membrane. (Table 1)

Majority (73, 59.3%) of the respondents had no constitutional symptom besides history of membrane rupture at presentation while those with symptoms presented mainly with abdominal pain (46, 37.7%) and fever (3, 2.5%). Twenty-seven (58.7%) of those who had abdominal pain developed it between 1 and 5 hours after the occurrence of ruptured membranes. (Table 1)

Table 2: Management of the pregnant women with PROM and mode of delivery

Variables	Frequency	Percent
Duration of conservative management before delivery (weeks)		
< 1	88	72.1
1	20	16.5
2	09	7.4
3	01	0.8
4	04	3.3
Stimulation of labour		
Yes	67	54.9
No	55	45.1
Mode of delivery		
SVD	85	69.7
EMLSCS	35	28.7
Urgent Caesarean section	02	1.6

SVD- Spontaneous vaginal delivery; EMLSCS- Emergency lower segment caesarean surgery

Majority (88, 72.1%) of the women were conservatively managed for less than a week before delivery, while only 4(3.3%) were managed conservatively for up to 4 weeks before delivery. Majority (85, 69.7%) of the respondents had spontaneous vagina delivery (SVD) while 37 (30.3%) delivered through emergency caesarean section (EMLSCS) (Table 2)

Seventy-four (61%) of the foetuses had normal transverse Thymic diameter (TTD) on ultrasound scan while 48 (39%) had TTD less than 5<sup>th</sup> Centile for their GA (Figure 1). Fifty-seven (46.7%) of the patients had placenta histological features of chorioamnionitis out of which 43(89.6%) had small FTTD (Table 3)

Majority (43, 89.6%) of the pregnancies complicated by chorioamnionitis had smaller TTD and this was statistically significant (P<0.001). Conversely, no significant difference was found in other parameters: gestational age at PPRM, duration of preterm PROM and parity (Table 3).

There was a significant relationship between the number of ultrasound scans (US) done and the presence of chorioamnionitis. At the first US done by all the foetuses, (43, 85.6%) of the foetuses with small TTD developed chorioamnionitis. This resulted in a sensitivity of 75.4%, specificity of 92.2%, positive predictive value of 89.6%, negative predictive value of 80.8% for predicting the occurrence of chorioamnionitis. Out of the fifteen foetuses that had a second US, five developed chorioamnionitis, of which 4(80%) had small TTD. Therefore, the presence of a small TTD at 2<sup>nd</sup> US, had sensitivity and specificity of 83.3% and 100.0% respectively for the identification of chorioamnionitis. (Table 4).

## THYMUS TRANSVERSE DIAMETER

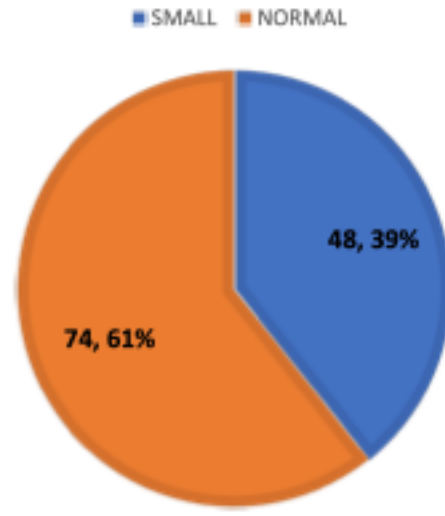


Figure 1: Frequency of the foetuses with normal and small thymus transverse diameters on ultrasound

Table 3: Relationship between sonographic fetal thymus size and maternal Characteristics

Variable	Thymus size		P value
	Small	Normal	
Parity			
None (%)	27(56.2)	34(45.9)	0.53
Primiparous (%)	10(20.8)	18(24.3)	
Multiparous (%)	11(22.9)	22(29.7)	
GA at PROM (weeks)			
≤ 31 <sup>+6</sup>	09 (18.8)	22(29.7)	0.17
32-34	39(81.2)	52(70.3)	
Duration of Preterm PROM			
≤ 24hours	33(68.8)	53(71.6)	0.73
>24hours	15(31.2)	21(28.4)	
Histological Chorioamnionitis			
Yes (%)	43(89.6)	14(19.2)	<0.001
No (%)	05(10.4)	59(80.8)	
Mode of delivery			
SVD (%)	30(63.8)	55(74.3)	0.18
CS (%)	18(36.2)	19(25.7)	

Only 4 of the foetuses had a third ultrasound, only one foetus had a small TTD and same was the only one with evidence of chorioamnionitis, giving a specificity and sensitivity of 100% respectively. (Table 4)

Table 4: Effect of sonographic fetal thymus size assessment in predicting occurrence of chorioamnionitis

Variable	Occurrence of Chorioamnionitis		$\chi^2$	RR (95%CI)	P-value
	Yes (%)	No (%)			
Thymus size (1 <sup>st</sup> USS)			57.61	7.8 (3.4-17.9)	<0.0001
Small	43(75.4)	5(7.7)			
Positive Predictive Value (%)	89.6	---			
Sensitivity (%)	75.4	---			
Normal	14(24.6)	60(92.3)			
Negative Predictive Value (%)	---	80.8			
Specificity (%)	---	92.2			
Thymus size (2 <sup>nd</sup> USS)			-	0.1 (0.01-0.64)	0.002*
Small	5 (83.3)	0(0.0)			
Positive Predictive Value (%)	100.0	---			
Sensitivity (%)	83.3	---			
Normal	1(16.7)	9(100.0)			
Negative Predictive Value%	---	90.0			
Specificity (%)	---	100.0			
Thymus size (3 <sup>rd</sup> USS)			-	-	0.25*
Small	1(100.0)	0(FP)			
Positive Predictive Value%	100.0	---			
Sensitivity (%)	100.0	---			
Normal	0(0.0)	3(100.0)			
Negative Predictive Value (%)	---	100.0			
Specificity (%)	---	100.0			

**Discussion**

The thymus is one of the main organs involved in the development of the foetal immune system and it plays a major role in the immune response against infection and inflammation.<sup>10</sup> Prenatal measurement of the foetal thymic size has been realised to predict the presence of chorioamnionitis in patients with preterm rupture of membrane (PROM) much earlier than clinical and histological evidences. This is because foetuses are known to respond to infections with involution of the thymus.<sup>6-8</sup> Therefore, foetal thymus measurements can be used in early diagnosis of infections among high-risk patients. Many parameters can be used in the assessment of the

thymus, which include the thymic perimeter, surface, volume or diameter.<sup>10</sup> Using these parameters, thymus was assessed to grow with gestational age and the thymus was defined as small when any of these parameters was below the 5th centile for the gestational age. Some studies also used the thymic-thoracic ratio as a proxy to define a small thymus.<sup>11</sup> The foetal thymic transverse diameter (FTTD) was used in this study which is similar to the parameter used by Cetin et al,<sup>3</sup> Aksakai et al<sup>6</sup> and Musilova et al.<sup>2</sup>

In this study, we found that smaller FTTD were found more in women with histological diagnosis of chorioamnionitis than those without (89.6 % vs 19.2%) and this finding was statistically significant (P-value<0.001). This is comparable to the findings by Musilova et.al,<sup>2</sup> in Czech Republic where a small thymus was present in 80% (106/133) and 53% (44/83) of women with and without histological chorioamnionitis (HCA), respectively. Also, Yinon et al<sup>8</sup> observed small fetal thymus in 69% of the women with clinical or histological findings of chorioamnionitis while there was no evidence of clinical or histological chorioamnionitis in all the women with a normal-sized thymus. Di Naro et al<sup>9</sup> in their study also demonstrated small thymus in all cases with HCA and in 23.8% in cases without infection.

Serial sonographic measurement of FTTD on admission in women with PROM has been found to significantly predict the presence of HCA. In the present study, the presence of a small FTTD at first US, had a sensitivity of 75.4% and specificity of 92.2% for predicting the occurrence of HCA, while the sensitivity and specificity increased to 83.3% and 100.0% respectively at the 2<sup>nd</sup> US. However, out of the 4 women that had a 3<sup>rd</sup> US, only one foetus had small FTTD and it was the only one with HCA giving a specificity and sensitivity of 100% respectively. These findings are slightly different from the findings by Cetin et al where all the 40 women with PROM had fetuses with normal FTTD at the first US at presentation. Eight (33.3%) of the 24 women that had a second scan had small FTTD while 16 had 3<sup>rd</sup> measurement with 10 of them with FTTD. The reasons for the differences can be attributed to the duration of the PROM before presentation in the hospital. In the index study, only 1(0.8%) of the women presented within one hour of the PROM while 38(29.5%) presented after 24 hours.

Some studies<sup>12,13</sup> have shown that the administration of antenatal corticosteroid in patients with PROM leads to decrease in the fetal thymic size. To remove this bias, the first ultrasound scan to determine FTTD in patients with PROM is usually done before administration of the corticosteroid. In this study, the first scan was done at presentation and 43(75.4%) of the 57 women with HCA had small FTTD. This was similar to findings by Musilova et al.<sup>2</sup> who also evaluated the FTTD on the first day of admission in 216 foetuses with PPROM pregnancies and observed that a small FTTD was present in 80% (106/133) of women with HCA. A major limitation of this study is the small population size.

## Conclusion

Foetal thymus ultrasound scanning seems to be a promising sensitive predictor for the occurrence of chorioamnionitis in women with preterm rupture of membranes. However, to confirm the potential of this test in this environment, a larger study is recommended.

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