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Pathological patterns of stillbirth placentas and related variables for both fresh and macerated stillbirth at Bugando Medical Center in Mwanza, Tanzania

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Pathological patterns of stillbirth placentas and related variables for both fresh and macerated stillbirth at Bugando Medical Center in Mwanza, Tanzania

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Abstract:

Background: Stillbirth is a very distressing experience for both families and doctors; therefore, identifying causative factors aids parents in the grieving process and informs future pregnancy therapies. Prior research indicates that pathological analysis of the placenta can elucidate the etiology of unexplained stillbirths in over 90% of instances. This study aimed to apply the Amsterdam criteria to describe pathological patterns of stillbirth placentas and related clinical variables for both fresh and macerated stillbirths at Bugando Medical Center in Mwanza, Tanzania.

Methods: The study was an analytical cross-sectional study involving 120 women who delivered stillbirths at BMC. The stillbirth's placenta and membranes were grossly examined for completeness, then fixed in 10% neutral buffered formalin for subsequent histopathology evaluation. The placental pathologies were defined according to the Amsterdam Placental Workshop Group Consensus. Data were analyzed using STATA version 15 computer software, and the p-value of <0.05 on the multivariate logistic regression model was considered significant.

Results: The incidence of stillbirth in this study was at 31.9/1,000 deliveries for 2022-2023 at BMC, and the majority, 61.2%(114), were macerated stillbirths. Maternal vascular malperfusion 71(59.2%) was the most common placental pathology in stillbirth. Comparing between the macerated and fresh stillbirth, the macerated stillbirths had higher rates of fetal

vascular malperfusion, chronic chorioamnionitis, and coagulation-related pathology with OR [95%CI] p-value of 0.6[0.04-8.2] p=0.689, 0.8[0.1-11.2] p=0.891, 0.8[0.1-10.2] p=0.829 respectively whereby the fresh stillbirths had higher rates of acute chorioamnionitis 14[1.14-19.2] p=0.039 on univariate analysis. On multivariate analysis, only acute chorioamnionitis had statistically significant association with fresh stillbirth, 6.6[1.3-33.1], p=0.022.

Conclusions: Integrating routine placental histopathology into stillbirth investigations at BMC is therefore essential for accurate prognostic stratification and the development of preventive strategies for future pregnancies

Keywords: Stillbirth, Placental, Pathology, and Clinical

Background: In 2015, there were 18.4 stillbirths per every 1000 live births worldwide, and 98% of all stillbirths worldwide occur in Lower and Middle-Income Countries (LMICs). Tanzania has the highest rate of stillbirths in East Africa, at 25.9 per 1,000 live births in 2015[1] which is unacceptably high considering the World Health Organization (WHO) target of equal to or less than 1.2% (12/1000 deliveries) in every country by 2030[2]Despite the availability of advanced diagnostic modalities such as biochemical evaluation, microbiology, and cytogenetics, the majority of stillbirth causes remain unidentified, which limits the effectiveness of prevention strategies[3], [4].

Maternal illnesses, such as syphilis, hypertensive disorders in pregnancy, diabetes mellitus, and Human immunodeficiency virus (HIV) infection, have been linked with an increased risk of stillbirth up to 50%[5]. Additionally, a study by Divya et al. discovered that severe anemia, severe oligohydramnios, pre-eclampsia, and eclampsia are all linked to stillbirths[6]. Combining clinical information and pathology evaluation of the placenta improves the identification of causes of stillbirths up to 85%[7].

There is evidence that placental abnormalities are implicated in up to 65% of stillbirths[8]–[11], but in the LMICs, the contribution of placental pathology in stillbirth is likely to rise if the placental examination adheres to the Amsterdam criteria[12][13]. The Amsterdam placental workshop group 2016 has standardized placental pathology examination to minimize reporting variations [14] and enhance the diagnostic accuracy of placental pathology[13]. According to the Amsterdam consensus, the placental pathologies are categorized as follows: Maternal vascular malperfusion, which includes retroplacental hemorrhage, infarction, and decidual arteriopathy; fetal vascular malperfusion, which includes umbilical cord anomalies, thrombosis, avascular villi, intramural fibrin deposition, hemorrhagic endo-vasculitis, stem vessels obliteration, and vascular ectasia; other categories are delayed villous maturation, villitis of unknown etiology, and inflammatory conditions[14]. Although each placental pathology in the current literature is analyzed independently, the systematic review and meta-analysis study by Brenda et al in 2024 indicates that maternal vascular malperfusion and fetal vascular malformation are the commonest placental pathology categories in stillbirth[15].

Studies using the Amsterdam criteria to assess placental pathology in stillbirths are scarce in the literature; however, a survey of maternal obesity showed that the most common stillbirth placental pathology was maternal vascular malperfusion, which accounted for 72.6%[16]. In two institutional studies, the frequency of maternal vascular malperfusion in stillbirth was 54% and 58.4%, respectively; fetal vascular malperfusion was 19%[17][18] and ascending infection accounted for 17%[17].

Comparing live births, stillbirths are more likely to have placental lesions such as thrombotic lesions, inflammation, and vascular degenerative alterations; their frequencies differ among fresh and macerated stillbirths. [12]. There is a lack of studies applying Amsterdam placental pathology criteria to compare placental pathology between fresh and macerated stillbirths. However, fresh and macerated stillbirths have different pathological abnormalities in their placentas; acute chorioamnionitis and placental abruption, such as retroplacental hematoma, are common placental diseases in fresh stillbirths[8], [19], [20] on the other hand, chronic illnesses such as maternal diabetes, fetal growth limitation, and anomalies of the umbilical cord are more commonly linked to macerated stillbirths[20].
Due to limited expertise in forensic pathology and related psychosocial concerns, the stillbirth autopsy to determine the cause of death is not performed in Tanzania. Thus, histopathology evaluation of placental tissues remains the most important tool to evaluate the causes of stillbirth. Therefore, this study aimed to apply the Amsterdam criteria to describe pathological patterns of stillbirth placentas and related variables for both fresh and macerated stillbirths at Bugando Medical Center in Mwanza, Tanzania.

Methods:

Study setting: The study was conducted at Bugando Medical Centre (BMC), Tanzania. BMC is a consultant, tertiary care, and teaching hospital serving around 20 million people in Northern Tanzania. The hospital provides routine obstetric services. In 2020, 135 stillbirths per 5,086 births were documented at BMC. Despite the availability of histopathology services, placental pathology examination is not routinely done at BMC.

Study design and duration: This study was a prospective hospital-based cross-sectional study from January 2022 to December 2022.

Study population: All women delivering stillbirths at BMC during the study period from January 2022 to December 2022.

Inclusion and exclusion criteria: The study included women who experienced stillbirth at a gestational age of 28 weeks or greater, or with a birth weight of at least 1000g, regardless of gestational age, provided that the placenta, membranes, and umbilical cord were intact for evaluation and maternal consent was obtained. Participants whose placentas were poorly fixed were excluded
Sampling: The study enrolled 120 women who met the inclusion criteria.

Data source:

Clinical Data: Demographic data**,** such as Age, Parity, Marital Status, Level of Education, Gestation Age, number of Antenatal Clinic (ANC) Visits, Occupation, and Residence, as well as Clinical data, such as history of HIV infection, Gestation Diabetes, Pre-eclampsia/Eclampsia, Antepartum Hemorrhage, Anemia, And Malaria, were obtained from the antenatal clinic cards and interviews using structured questionnaires.

Pathology examination: The placental pathology examination was performed in accordance with the Amsterdam consensus[21]. The placental area was macroscopically examined before fixation. After the examination, it was placed in 10% neutral buffered formalin (NBF) and fixed for 72 hours. The placenta was grossed, and tissues in cassettes were processed, paraffin-embedded, sectioned, and stained with hematoxylin and eosin. Two independent anatomical Pathologists evaluated histopathology, and placental pathologies were categorized according to the Amsterdam criteria.

Data analysis: Data were recorded in a Microsoft Office Excel 2010 sheet under the codes provided and then transferred to STATA version 15 software for analysis. Categorical variables were summarized in frequency distribution tables. Using a logistic regression model, the relationship between abnormal patterns in the placenta and stillbirth was studied. By estimating the highest likelihood, odds ratios (OR) and 95% Confidence intervals (CI) were calculated. The p-value was used to determine the degree of significance. Those who had a *p*-value <0.2 in the univariate logistic regression were then subjected to the multivariate logistic regression, where a *p*-value of less than or equal to 0.05 was deemed significant

Ethical review and approval: The study was submitted and reviewed by the joint Catholic University of Health and Allied Sciences/ Bugando Medical Centre (CUHAS/BMC) Ethics & Review Committee, and it issued the ethical clearance certificate with the number CREC/515/2022. Informed consent to participate in this study was obtained from each participant. The study adhered to the Declaration of Helsinki.

Results: In 2022, there were 5,825 deliveries at BMC, of which 186 were stillbirths (72 Fresh Stillbirths and 114 Macerated Stillbirths), making the stillbirth prevalence 31.9/1,000 (3.2%). 125 participants consented to the study, but 5 were excluded due to poor placental fixation.

"The median maternal age was 27 years, with the majority (91, 75.8%) being younger than 35 years. Most had attained only primary education (62, 51.7%), resided in urban areas (95, 79.2%), were unemployed (94, 78.3%), and were married (105, 87.5%). A significant proportion were multiparous (85, 70.83%) and had fewer than four antenatal care visits (81, 67.5%). The majority of stillbirths were preterm, occurring at less than 37 weeks of gestation (100, 83.3%). Clinically, most women with stillbirths presented with pre-eclampsia (58, 48.3%), antepartum hemorrhage (24, 20.0%), or anemia (26, 21.7%). (Table 1).

In determining the association between maternal comorbidities and stillbirth women with pre-eclampsia had higher odds of having a stillbirth (OR=2.32. 95% CI=1.08-4.93, p=0.031) in the univariate analysis; however this association was lost in the multivariable analysis. Women who were HIV positive had higher odds of a still birth in both the univariate and multivariate analyses however this association was not statistically significant. There was no statistically significant association between maternal anemia and stillbirth (Table 3). Generally, maternal

vascular malperfusion 71(59.2%) was the most prevalent placental pathology in stillbirth, followed by chronic inflammation 12(10.0%), while normal placentas were 7(5.8%) of all stillbirths (Table 2). Among placental histopathological findings, acute chorioamnionitis was significantly less likely to occur in macerated stillbirths compared with fresh stillbirths on univariate analysis (OR=0.1, 95% CI: 0.01–0.9, p=0.039). This association remained statistically significant after multivariate analysis (adjusted OR=0.1, 95% CI: 0.01–0.7, p=0.030). On the other hand, placentas with acute chorioamnionitis had higher odds of being associated with FSB compared with normal placentas (OR=14.0, 95% CI: 1.14–19.2, p=0.039). This association remained statistically significant after adjustment for potential confounders in multivariate analysis, with placentas showing acute chorioamnionitis having 6.6 times higher odds of FSB compared with normal placentas (AOR=6.6, 95% CI: 1.3–33.1, p=0.022).

Chronic inflammation, coagulation disorders, fetal vascular malperfusion, and maternal vascular malperfusion had no statistically significant associations with both fresh and macerated stillbirths (Table 4). Figure 1: H&E section showing placental pathologies including the retroplacental hematoma, intervillous hematoma, umbilical cord hematoma, and chronic chorioamnionitis.

Table 1: **Social demographic and clinical characteristics of study participants with their distribution in stillbirth type**

VARIABLE	STILLBIRTH		TOTAL
	FSB	MSB	
Social Demographic Characteristics			
AGE(Years)			
< 35	34(77.3 %)	57(75.0 %)	91(75.8 %)
≥ 35	10(22.7 %)	19(25.0 %)	29(24.2 %)
EDUCATION LEVEL			
Primary and below	20(45.5%)	42(55.3%)	62(51.7%)
Secondary and above	24(54.6 %)	34(44.7 %)	58(48.3 %)

RESIDENCE			
Rural	5(11.4%)	20(26.3%)	25(20.8%)
Urban	39(88.6%)	56(73.7%)	95(79.2%)
OCCUPATION			
Employed	9(20.5%)	17(22.4%)	26(21.7%)
Un employed	35(79.6%)	59(77.6%)	94(78.3%)
MARITALSTATUS			
Married	39(88.6%)	66(86.8%)	105(87.5%)
Single	5(11.4%)	10(13.2%)	15(12.5%)
Clinical Characteristics of Study Participants			
GESTATION_AGE			
<37	38(86.4 %)	62(81.6 %)	100(83.3 %)
≥ 37	6(13.6%)	14(18.4%)	20(16.7%)
PARITY			
Primipara	16(36.4%)	19(25.0%)	35(29.2%)
Multipara	28(63.6 %)	57(75.0%)	85(70.8 %)
ANC_VISITS			
< 4	35(79.6 %)	46(60.5 %)	81(67.5 %)
≥ 4	9(20.5%)	30(39.5%)	39(32.5%)
CLINICAL_DIAGNOSI			
Pre-eclampsia	27(61.4%)	31(40.8%)	58(48.3%)
APH	7(15.9%)	17(22.4%)	24(20.0%)
Anemia	6(13.6%)	20(26.3%)	26(21.7%)
HIV	4(9.1%)	0(0.0%)	4(3.3%)
Malaria	0(0.0%)	2(2.6%)	2(1.7%)
Diabetes mellitus	0(0.0%)	6(7.9%)	6(5.0%)

Table 2: **The association between stillbirth and placental pathologies on univariate analysis**

HISTOPATHOLOGY	STILL BIRTH		ASSOCIATION	
	MSB N (%)		UNIVARIATE	
	NO	YES	OR [95%CI]	p-value
Acute chorioamnionitis	7(70.0)	3(30.0)	0.07[0.01-0.88]	**0.039**
Chronic chorioamnionitis	2(16.7)	10(83.3)	0.83[0.06-11.2]	0.891
Coagulation disorders	2(18.2)	9(81.8)	0.75[0.05-10.23]	0.829
Fetal vascular malperfusion	2(22.2)	7(77.8)	0.58[0.04-8.14]	0.689
Maternal vascular malperfusion	30(42.3)	41(57.8)	0.23[0.03-1.99]	**0.181**
Normal	1(14.3)	6(85.7)	1	
	FSB N (%)			
Acute chorioamnionitis	3(30.0)	7(70.0)	14[1.14-19.2]	**0.039**
Chronic chorioamnionitis	10(83.3)	2(16.7)	1.20[0.09-16.24]	0.891
Coagulation disorders	9(81.8)	2(18.2)	1.33[0.09-18.2]	0.829
Fetal vascular malperfusion	7(77.8)	2(22.2)	1.71[0.12-23.93]	0.689
Matern vascular malperfusion	41(57.8)	30(42.3)	4.39[0.50-38.40]	**0.181**
Normal	6(85.7)	1(14.3)	1	

Table 3: The association between stillbirth and placental pathologies on multivariate analysis

VARIABLE	MSB		UNIVARIATE		MULTIVARIATE	
	NO	YES	OR [95%CI]	p-value	OR [95%CI]	p-value
HISTOPATHOLOGY						

Normal	1(14.3)	6(85.7)	1			
Acute chorioamnionitis	7(70.0)	3(30.0)	0.1[0.01-0.9]	**0.039**	**0.1[0.01-0.7]**	**0.030**
Chronic inflammation	2(16.7)	10(83.3)	0.8[0.1-11.2]	0.891		
Coagulation disorders	2(18.2)	9(81.8)	0.8[0.1-10.2]	0.829		
Fetal vascular malperfusio	2(22.2)	7(77.8)	0.6[0.04-8.2]	0.689		
Maternal vascular malperfusion	30(42.3)	41(57.8)	0.2[0.03-1.9]	**0.181**	0.3[0.03-2.4]	0.233
Age						
<34	34(37.4)	57(62.6)	1			
>/=35	10(34.5)	19(65.5)	1.2[0.5-2.7]	0.779		
Residence					1	
Urban	38(40.0)	57(60.0	1	**0.145**	1.8[0.6-5.3]	0.319
Rural	6(24.0)	19(76.0)	2.1[0.8-5.8]			
Number of ANC					1	
>/=4 visits	10(25.6)	29(74.4)	1	**0.085**	0.4[0.12-1.1]	0.082
< 4 visits	34(41.98)	47(58.0)	0.5[0.2-1.1]			
Pre-eclampsia					1	
No	17(27.4)	45(72.6)	1	**0.031**	0.7[0.2-2.2]	0.535
Yes	27(46.6)	31(53.5)	0.4[0.2-0.9]			
Anaemia					1	
No	38(40.4)	56(59.6)	1	**0.110**	1.9[0.5-7.6]	0.358
Yes	6(23.0)	20(77.0)	2.3[0.8-6.2]			
HIV					1	
No	41(35.3)	75(64.7)	1	**0.146**	0.2[0.1-2.9]	0.244
Yes	3(75.0)	1(25.0)	0.2[0.02-1.8]			
Education						
Formal	23(39.7)	35(60.3)	1			
Informal	21(33.9)	41(66.1)	0.8[0.3-1.6]	0.464		
Occupation						
Employed	9(34.6)	17(65.4)	1	0.806		
Unemployed	35(37.2)	59(62.8)	0.9[0.4-2.2]			

Table 4: **Association of FSB and other predictor variables in multivariate analysis**

VARIABLE	FSB		UNIVARIATE		MULTIVARIATE	
	NO	YES	OR [95%C	p-value	OR [95%CI]	p-valu
HISTOPATHOLOGY						
Normal	6(85.7)	1(14.3)	1			
Acute chorioamnionitis	3(30.0)	7(70.0)	14[1.14-19.	**0.039**	**6.6[1.3-33.1]**	**0.022**
Chronic inflammations	10(83.3)	2(16.7)	1.2[0.09-16.2	0.891		
Coagulation disorders	9(81.8)	2(18.2)	1.33[0.09-18	0.829		
Fetal vascular malperfusic	7(77.8)	2(22.2)	1.7[0.12-23.9	0.689		
Maternal vascular malperfusion	41(57.8)	30(42.3)	4.39[0.5-38.4	**0.181**		
Age						
<34	57(62.6)	34(37.4)	1			
>/=35	19(65.5)	10(34.5)	0.8[0.4-2.1	0.779		
Residence					1	
Urban	57(60.0)	38(40.0)	1	**0.145**	0.6[0.2-1.6]	0.285
Rural	19(76.0)	6(24.0)	2.1[0.8-5.8			
Number of ANC						
>/=4 visits	29(74.4)	10(25.6)	1	**0.085**	1	0.114
< 4 visits	47(58.1)	34(41.9)	2[0.9-4.9]		2.3[0.8-6.7]	
Pre-eclampsia						
No	45(72.6)	17(27.4)	1	**0.031**	1	0.292
Yes	31(53.4)	27(46.6)	2.3[1.1-4.9		1.8[0.6-5.1]	
Anaemia						
No	56(59.6)	38(40.4)	1	**0.110**	1	0.600
Yes	20(77.0)	6(23.0)	0.4[0.2-1.2		0.7[0.2-2.6]	
HIV						
No	75(64.7)	41(35.3)	1	**0.146**	1	0.165
Yes	1(25.0)	3(75.0)	5.5[0.6-54.		5.7[0.5-66.7]	
Education						
Formal	35(60.3)	23(39.7)	1	0.511		
Informal	41(66.1)	21(33.9)	0.8[0.4-1.6			
Occupation						
Employed	17(65.4)	9(34.6)	1			
Unemployed	59(62.8)	35(37.2)	1.1[0.5-2.8	0.803		

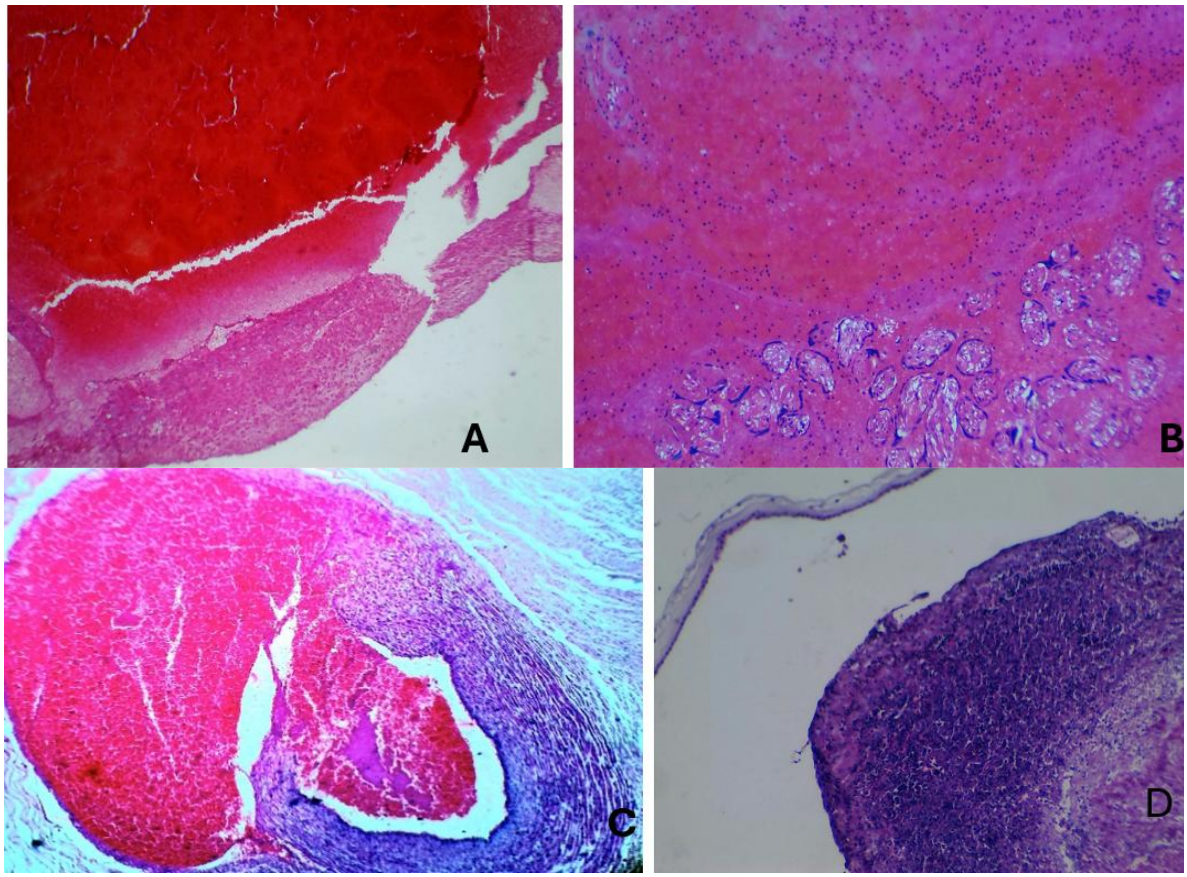


Figure 1: H&E section showing placental pathologies. A-Retroplacental hematoma at x40, B-Intervillous hematoma at x100, C-Umbilical cord hematoma at x 40 and D-Chronic chorioamnionitis at x40.

DISCUSSION:

The prevalence of stillbirth at Bugando Medical Center was found to be 31.9 per 1,000 deliveries, which is higher than the 25.9 per 1,000 estimated trend in Tanzania[1] and twice the WHO target in Sustainable Development Goals (SDG) number 3, targeting to reduce the neonatal mortality rate (NMR) to 12 or fewer deaths per 1,000 live births by 2030 for each country[2]. This prevalence was lower than the one reported at KCMC, which was 42 per 1,000 live births, reflecting the BMC and KCMC roles as the tertiary hospitals in the management of more complicated obstetric cases in Tanzania[8].

Using the Amsterdam reporting criteria of placental pathology, the maternal vascular malperfusion was the most frequent placental pathology, identified in more than half of the cases of stillbirths. These findings were similar to studies at Muhimbili National Hospital, Tanzania, Tel Aviv, Israel, and Milan, Italy, where the contribution of maternal vascular malperfusion was up to 72% [22][17][16] including in the systematic and meta-analysis review[15]. There is a well-established pathophysiology link of pre-eclampsia in maternal

vascular malperfusion, leading to placental infarction and decidual arteriopathy, resulting in the reduction of fetal supply with nutrients and oxygen[23], [24], thus not surprising that in this study, pre-eclampsia was the only maternal condition significantly associated with stillbirth, emphasizing the need for antenatal screening and treatment of hypertension.

The unique contribution of this study was to differentiate the placental pathology patterns in fresh and macerated stillbirths. Our results demonstrated that acute chorioamnionitis was significantly associated with both FSB and MSB. However, the strength of association was substantially greater for FSB, with placentas showing acute chorioamnionitis having 6.6-fold increased odds of FSB, whereas the odds of MSB were markedly reduced, thus suggesting that acute chorioamnionitis is more strongly linked to FSB than MSB. This observation is consistent with existing evidence indicating that ascending intrauterine infections are a major cause of sudden intrapartum or late-preterm fresh stillbirths, whereby the maternal and fetal inflammatory responses may precipitate preterm labor, acute fetal compromise, or fetal sepsis before maceration changes can develop [8][19][25]. While macerated stillbirths showed higher descriptive rates of fetal vascular malperfusion and chronic inflammation[20]. In the index study, these factors did not reach statistical significance in the multivariate model.

The results demonstrate that histopathological evaluation of the placenta can identify potential causes in the vast majority of stillbirths. The high detection rate of placental diseases in this study, utilizing the Amsterdam criteria, emphasizes the contribution of the criteria to giving a standard and objective classification of placental pathology[13][14]. In a setting like Tanzania, where fetal autopsies are infrequently performed due to cultural or resource constraints, the placenta pathology examination may provide a clue to the prenatal environmental conditions[7], [22].

Conclusion: Integrating routine placental histopathology into stillbirth investigations at Bugando Medical Centre is therefore essential for accurate prognostic stratification and the development of preventive strategies for future pregnancies.\

List of abbreviations

ANC-Antenatal care

APH-Antepartum hemorrhage

BMC-Bugando Medical Centre

CI-Confidence interval

CUHAS-Catholic University of Health and Allied Sciences

FBS-Fresh stillbirth

HIV-Human immunodeficiency virus

LMICs-Lower and middle-income countries

MSB-Macerated stillbirth

NBF-Neutral buffered formalin

NMR-Neonatal mortality rate

OR-Odds ratio

SDG-Sustainable Development Goals

STATA-statistical software for data science

WHO-World Health Organization

Declarations

Ethics approval and consent to participate

The study was submitted to and reviewed by the joint Catholic University of Health and Allied Sciences/Bugando Medical Centre (CUHAS/BMC) Ethics & Review Committee, which issued the ethical clearance certificate number CREC/515/2022. Informed consent to participate in this study was obtained from each participant. The study adhered to the Declaration of Helsinki.

Consent for publication

The study protocol was approved by the Joint CUHAS/BMC Research Ethics and Review Committee, and publication consent for research findings and related images was obtained from each participant.

Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

Competing interest

All authors have no conflict of interest

Funding

No funds were received.

Authors contributions

Concept and design: YYM, EE, and DM; acquisition of data: YYM and EE; analysis and interpretation: YYM, EE, BK, and DM; draft of the manuscript and review: YYM, EE, DM, MN, and BK. All authors reviewed and agreed on the manuscript.

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