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Infectious causes of stillbirths among women at Rahima Moosa Mother and Child Hospital

Thendo P. Tshivhase

thendo.tshivhase@gmail.com

Department of Obstetrics and Gynaecology

Clare L. Cutland

African Leadership in Vaccinology Expertise

Reubina Wadee

Department of Anatomical Pathology

Amy J. Wise

Department of Obstetrics and Gynaecology

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Abstract

Background

Stillbirths are associated with socio-economic consequences including physical- and mental impairment to the bereaved family as well as financial implications to the family and the health-care system. There is a close association between stillbirths and infections, particularly in developing countries, however, causative microorganisms are often not identified.

Objectives

To determine the prevalence and causes of intrauterine infections by describing the microbiology, culture and sensitivity (MCS) as well as histopathological findings identified in placental samples of stillbirths.

Methods

In this retrospective descriptive study, medical records of women who delivered stillborn infants at ≥ 22 weeks' gestation or with a birth weight ≥ 500g between 1st January 2020 and 31st December 2020 at a tertiary care hospital in Johannesburg, South Africa were reviewed. Demographic, clinical, microbiological, and placental histopathology data were analyzed to identify chorioamnionitis, causative pathogens, and their antibiotic sensitivity patterns. Data analysis was performed using STATA version 17.

Results

Out of 103 records reviewed, 79/103 (76.7%) had placental reports, 33/79 (41.7%) of which confirmed evidence of chorioamnionitis. Microbiological analysis was performed on 50/79 (63.3%) placental membranes, yielding 35 organisms from 25 specimens. Identified organisms included: *Staphylococcus epidermidis* 9/35 (25.7%), *Escherichia coli* 7/35 (20.0%), *Enterococcus faecalis* 5/35 (14.3%), *Staphylococcus haemolyticus* 4/35 (11.4%), *Staphylococcus aureus* 3/35 (8.6%), and Group B *Streptococcus* 3/35 (8.6%). Most of the Gram-negative organisms were 100% sensitive to amoxicillin - clavulanic acid, cephalosporins and carbapenems. One case (2.9%) had *Candida albicans* cultured which was sensitive to fluconazole.

Conclusion

Chorioamnionitis was present in 41.7% of stillbirths. *S. epidermidis*, *E. coli*, and *E. faecalis* were the most common isolates, mostly sensitive to amoxicillin-clavulanic acid, cephalosporins, ciprofloxacin, and

ertapenem. The findings support routine placental histopathology and microbiological testing in stillbirths, with prompt review and follow-up to improve outcomes.

Introduction

Stillbirths are associated with socio-economic consequences including physical and mental impairment to the bereaved family as well as financial implications to the family and the health-care system.[1] A high burden of stillbirths remains in low-to-middle income countries (LMICs) including Sub-Saharan Africa and South Asia.[1]

Maternal, foetal and placental factors all contribute to foetal demise.[2] The stillbirth rate in Gauteng Province increased from 18.7 per 1 000 total births in 2019 to 19.9 per 1 000 total births in 2022.[3, 4] Infections are one of the main contributors to foetal death.[5] About 16% of the stillbirths in LMICs have been associated with infections although this has been mainly based on hospital audits and verbal autopsies without specific microorganisms identified.[1]

The definition of chorioamnionitis is foetal membrane inflammation, which includes both the chorion and the amnion.[6] Most cases of chorioamnionitis are subclinical, with insufficient clinical evidence at birth and needs evaluation of the placenta to be confirmed.[7] Histopathology and microbiological analysis of the placenta can be used to diagnose chorioamnionitis, with histopathology considered the gold standard.[5] The Global Alignment of Immunization safety assessment in pregnancy (GAIA) case definition for chorioamnionitis includes clinical diagnosis such as maternal fever, uterine tenderness, and foetal tachycardia along with confirmation by histopathology or positive culture at 22 – 0/7 weeks or greater gestational age.[8] More than 130 bacteria are associated with intra-uterine infections, many of these being associated with stillbirths.[9] The most frequently isolated bacterial microorganisms in intrauterine infections are *Escherichia (E) coli*, *Ureaplasma urealyticum* and Group B Streptococcus (GBS).[10, 11] Similar studies found *GBS*, *Escherichia coli* and *Enterococcus faecalis* to be main causative pathogens of congenital infections resulting in stillbirths.[12]

Intrauterine microbial infection especially in placental tissue has been associated with adverse outcomes including preterm birth, foetal distress, stillbirth and adverse neurological outcomes later in life.[13] Knowledge of the burden of disease and the responsible pathogens can assist in directing management strategies.

Objectives

We aimed to describe the prevalence of chorioamnionitis in stillbirths delivered at a tertiary hospital in Johannesburg, South Africa, and to identify the common infectious causes and describe their characteristics.

Methodology

This was a retrospective, descriptive study in which medical records, including placental microbiological and placental histopathological reports, from women who delivered stillborn infants between 1st January 2020, and 31st December 2020 were reviewed. The microbiology and histopathology results were obtained from the NationalHealth Laboratory Services (NHLS) and analysed with corresponding maternal case files.

3.1 Study setting: The study was conducted at Rahima Moosa Mother and Child Hospital (RMMCH), a publicly-funded teaching hospital located in Coronationville, Johannesburg, Gauteng province, South Africa.

3.2 Study population: The study was limited to women who delivered at least one stillborn infant from 22 weeks' gestational age or a birthweight of ≥500 grams. There were no exclusion criteria in this study.

3.3 Sampling and sample size:A list of women who delivered stillbirths was obtained from birth records in the labour ward, antenatal wards, Obstetrics and Gynaecology wards and operating theatres.

3.4 Measurements: Maternal and foetal clinical data were obtained from maternity records. Results of the histopathological examination and MCS were obtained from NHLS' Corporate Data Warehouse (CDW).

3.5 Data analysis: REDCap (Research Electronic Data Capture) electronic data capture tools, supported by the University of the Witwatersrand (Wits), was used to capture and manage data. REDCap is a safe, secure and reliable, web-based software platform made to facilitate the capturing of data for the purpose of research.[14] Analysis of data was done with assistance of a biostatistician at Wits utilising Statistical software (STATA) version 17. Descriptive data were expressed using means and medians with standard deviations.

3.6 Ethical considerations: The study was approved by the the University of the Witwatersrand's Human Research Ethics Committee (Medical), (Clearance certificate number M211102). Permission to conduct the study was granted by RMMCH and was registered on the NHLS' Academic Affairs and Research Management System (AARMS).

Results

Of the 227 women who delivered a stillborn baby during the study period, the files of 103 (45.4%) patients who delivered 105 babies (including 2 sets of twins with one alive in each pregnancy) were available for review. Records of 103 women and 103 stillborn babies were reviewed. A total of 76.7% (79/103) women had histopathology reports available for review of which, 63.3% (50/79) also had microbiology results available for assessment.

The mean age of patients was 29.1 years at the time of delivery with 28/103 (27.2%) patients being primigravidas and 76 (73.8%) having a parity of one or more. Eighty-four (81.6%) women were booked and attended at least one antenatal care visit before delivery. The overall median gestational age at delivery was 35 weeks and 0 days (35 – 0/7) with an interquartile range (IQR) of 31 – 0/7 to 38 – 0/7 weeks. The demographic and clinical characteristics of the study population are summarized in Table 1.

Ninety-nine (96.1%) women were syphilis negative and one (1.0%) woman was syphilis positive and completed Penicillin G Benzathine treatment 15 weeks prior to the delivery. Three (2.9%) patients did not have a syphilis test done. Twenty 20/103 (19.4%) women were Human immunodeficiency virus (HIV) positive and 19/20 (95.5%) of them were on antiretroviral treatment. Seventeen of 19 (89.5%) were on Tenofovir/Lamivudine/Dolutegravir fixed dose combination and 2/19 (10.5%) on Tenofovir/Emtricitabine/Efavirenz fixed dose combination. A CD4 + count was done on 14/20 (70.0%) of the HIV positive women. The latest (test done within 6 months of delivery) median CD4 + count was 281 (221–480) cells per microlitre. Eleven (55.0%) out of the 20 HIV positive women had their viral load done during pregnancy with 6 /11 (30.0%) women having had a viral load that was lower than detectable recorded, less than 20 copies per millilitre.

Almost 3% (3/103; 2.9%) women were Coronavirus disease of 2019 Polymerase Chain Reaction (COVID-19 PCR) positive at delivery.

Comorbidities including hypertension, gestational diabetes and asthma were diagnosed in 26/103 (25%) of women, and 5/103 (4.9%) women were diagnosed clinically with an infection at the time of the stillbirth. Three of the five cases had clinical chorioamnionitis and two had a urinary tract infection. Clinical chorioamnionitis incidence reported was markedly lower compared to the findings of chorioamnionitis from histopathology and microbiology results. Ninety-eight (95.1%) of the women were clinically well post-partum. Two (1.9%) patients had puerperal sepsis, one diagnosed with endometritis and the other with pyelonephritis, but both recovered and were discharged. No maternal deaths were recorded from the 103 maternal files reviewed.

Table 1

Characteristics of women who delivered stillborn infants at RMMCH in 2020

Variable	**Category**	**N = 103, n (%)**
Age in years	Mean (SD)	29.1 (6.6)
Race	Black	95 (92.2)
	Caucasian	1 (1.0)
	Coloured	6 (5.8)
	Indian	1 (1.0)
Gravidity	One	27 (26.2)
	Two	20 (19.4)
	Three	33 (32.0)
	Four	15 (14.6)
	Five or more	8 (7.8)
Parity	Zero	28 (27.2)
	One	23 (22.3)
	Two	34 (33.0)
	Three	14 (13.6)
	Four or more	4 (3.9)
Ascertainment of GA		
First Ultrasound (before 24 weeks)		25 (24.3)
Last Normal Menstrual Period (LNMP)		69 (67.0)
First palpation		8 (7.7)
SFH at delivery		1 (1.0)
Gestational age at delivery (weeks)		

ART- Antiretroviral, SD- Standard deviation, IQR-Interquartile range, GA- gestational age, LNMP- last normal menstrual period, SFH- symphysis fundal height, g/dl- grams per decilitre, RPR- rapid plasma reagin, HIV- human immunodeficiency virus, CD4- clusters of differentiation 4, mm^3 – cubic millimetre, HbsAg- hepatitis B surface antigen, PIH- pregnancy-induced hypertension, PET- preeclampsia, HELLP- haemolysis, elevated liver enzymes and low platelet count, TEE- tenofovir/emtricitabine/efavirenz, TLD- tenofovir/lamivudine/dolutegravir

Variable	Category	N = 103, n (%)
LNMP	Median (IQR)	36.3 (32.0–38.4)
First Ultrasound	Median (IQR)	33.3 (29.0–35.6)
First palpation	Median (IQR)	35.0 (29.1–38.0)
SFH	Median (IQR)	34.0 (34.0–34.6)
Overall gestational age	Median (IQR)	35.0 (31.0–38.0)
Antenatal care	Booked	84 (81.6)
	Un-booked	19 (18.4)
Haemoglobin (g/dl) at booking	Median (IQR)	12.1 (10.8–13.0)
Haemoglobin (g/dl) before/at delivery	Median (IQR)	11.2 (10.2–12.6)
Syphilis	Positive	1 (1.00)
	Negative	99 (96.1)
	Not done	3 (2.9)
Titre RPR (positive) (n = 1)	1:8	1
Syphilis treatment (n = 1)	Penicillin G Benzathine	1
Rhesus status	Positive	94 (91.3)
	Negative	2 (1.9)
	Unknown	7 (6.8)
Antibodies if Rhesus negative (n = 2)	Absent	1
	Unknown	1
COVID-19 Rapid/PCR	Positive	3 (2.9)

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Variable	Category	N = 103, n (%)
	Negative	32 (31.1)
	Unknown	50 (48.5)
	Not done	18 (17.5)
HIV status	Positive	20 (19.4)
	Negative	81 (78.6)
	Unknown	2 (1.9)
CD4 + test (HIV positive, n = 20)	Done	14 (70.0)
	Not done	6 (30.0)
CD4 + count (mm^3)	Median (IQR)	281 (221–480)
Last viral load (copies/mm^3) recorded (HIV positive, n = 20)	Lower than detectable	6 (30.0)
	Unknown	9 (45.0)
	> 20	5 (25.0)
Viral load (if > 20 copies/mm^3) N = 5	Median (IQR)	16810 (901–20800)
HepBsAg (HIV positive, n = 20)	Positive	0 (0.0)
	Negative	17 (85)
	Unknown	3 (15)
On ART (HIV positive, n = 20)	Yes	19 (95.0)
	No	1 (5.0)
ART (n = 19)	Tenofovir/Emtricitabine/ Efavirenz (TEE)	2 (10.5)
	Tenofovir/ Lamivudine/Dolutegravir (TLD)	17 (89.5)
Comorbidities		

ART- Antiretroviral, SD- Standard deviation, IQR-Interquartile range, GA- gestational age, LNMP- last normal menstrual period, SFH- symphysis fundal height, g/dl- grams per decilitre, RPR- rapid plasma reagin, HIV- human immunodeficiency virus, CD4- clusters of differentiation 4, mm^3 – cubic millimetre, HbsAg- hepatitis B surface antigen, PIH- pregnancy-induced hypertension, PET- preeclampsia, HELLP- haemolysis, elevated liver enzymes and low platelet count, TEE- tenofovir/emtricitabine/efavirenz, TLD- tenofovir/lamivudine/dolutegravir

Variable	Category	N = 103, n (%)
	Chronic hypertension	0
	PIH, PET/HELLP* syndrome	19 (18.4)
	Diabetes mellitus type 1	0
	Diabetes mellitus type 2	3 (2.9)
	Gestational diabetes mellitus	2 (1.9)
	Autoimmune disease	0
	Asthma	2 (1.9)
	None	77 (74.8)
Presence of infection (clinical assessment)	Yes	5 (4.9)
	No	98 (95.1)
Infections (n = 5)	Chorioamnionitis	3 (60.0)
	UTI	2 (40.0)
Other infections during pregnancy	Yes	1 (1.0)
	No	101 (98.0)
	Unknown	1 (1.0)
If yes, diagnosis	Syphilis	1
Diagnosis of stillborn	Antepartum (before onset of labour)	58 (56.3)
	Intrapartum (during labour)	34 (33.0)
	At delivery	11 (10.7)
Cause of intrapartum stillborn (n = 34)	Foetal distress	5 (14.7)
	Cord prolapse	1 (2.9)
	Placental abruption	10 (29.4)

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Variable	Category	N = 103, n (%)
	Uterine rupture	2 (5.9)
	Unknown	16 (47.1)

ART- Antiretroviral, SD- Standard deviation, IQR-Interquartile range, GA- gestational age, LNMP- last normal menstrual period, SFH- symphysis fundal height, g/dl- grams per decilitre, RPR- rapid plasma reagin, HIV- human immunodeficiency virus, CD4- clusters of differentiation 4, mm^3 – cubic millimetre, HbsAg- hepatitis B surface antigen, PIH- pregnancy-induced hypertension, PET- preeclampsia, HELLP- haemolysis, elevated liver enzymes and low platelet count, TEE- tenofovir/emtricitabine/efavirenz, TLD- tenofovir/lamivudine/dolutegravir

Of the 103 stillbirths, 28 (27.2%) were fresh stillbirths and 75 (72.8%) were macerated stillbirths. Among these, 58/103 (56.3%) were diagnosed antepartum, 34/103 (33.0%) intrapartum and 11/103 (10.7%) immediately following delivery. Intrapartum complications vincluded five (14.7%) cases of foetal distress, one (2.9%) case of cord prolapse, 10 (29.4%) placental abruption cases, two (5.9%) cases of uterine rupture and 16 (47.1%) cases that had unknown causes. Eighty-three (80.6%) patients were delivered vaginally and 20 (19.6%) delivered via caesarean section.

Among the stillborn babies, 62 (60.2%) were male, 40 (38.8%) were female and one (1.0%) was a 560 gram (g) macerated stillborn baby, with sex undocumented. The median birthweight was 2190g with an IQR of 1520- 2960g.

Seventy-nine out of the 103 women (76.7%) had their placentas submitted for histopathological assessment, and of those, 50/79 (63.3%) had placental membranes sent for MCS as well. Placental lesions were categorized according to the Amsterdam Placental Workshop Group's consensus definitions of placental lesions.[15] The mean placental weight was 384g (182g-589g). A total of thirty-three (41.8%) placentas showed evidence of chorioamnionitis with 32 (97.0%) of these categorized as acute chorioamnionitis. A representative histopathological photomicrograph demonstrating chorioamnionitis is shown in Fig. 1. A maternal response, which is characterized by infiltration of maternal neutrophils into placenta membranes [15] was present in all placentas that showed evidence of chorioamnionitis. Of the 33 histologically-confirmed chorioamnionitis cases, 19 (57.6%) were from preterm deliveries (< 37 completed weeks) and 14/33 (42.4%) were from term deliveries. A foetal response, defined as presence of foetal origin neutrophils within the umbilical cord and/or chorionic plate vessels [15], was present in 17 cases (51.5%) of chorioamnionitis and consisted mainly of stage 1 and grade 1 foetal response. Thirty-two (40.5%) specimens showed evidence of maternal vascular malperfusion with 8 (10.1%) cases showing both placental insufficiency and chorioamnionitis.

Figure 1: Photomicrographs of sections of placental membranes of women who delivered Courtesy of Prof. R Wadee.

Haematoxylin and eosin-stained section of placental membranes demonstrating chorioamnionitis (original magnification × 100).

Bacteria were observed in 25/50 (50.0%) cases of the placental membranes submitted for MC&S. Some specimens cultured more than one microorganism with a total of 35 microorganisms identified in this study. Twenty-two (44.0%) specimens had no bacteria observed, two (4.0%) specimens were contaminated, and one (2%) specimen was rejected due to incomplete seal and leakage. Of the 25 placental membrane specimens that cultured microorganisms, 13/25 (52.0%) had evidence of chorioamnionitis on histopathology and 12 (48.0%) had bacteria cultured without evidence of chorioamnionitis. The number of specimens submitted for histopathological and microbiological assessment analysis among stillborn infants is illustrated in Fig. 2.

Nine pathogenic microorganisms were observed with a total of 35 microorganisms from 25 specimens cultured. There were 9/35 (25.7%) cases of *Staphylococcus epidermidis*, 7/35 (20.0%) *Escherichia (E) coli*, 5/35 (14.3%) *Enterococcus faecalis*, 4/35 (11.4%) *Staphylococcus haemolyticus*, 3/35 (8.6%) *Staphylococcus aureus*, 3/35 (8.6%) *Streptococcus agalactiae*, 1/35 (2.9%) *Citrobacter koseri*, 1/35 (2.9%) *Staphylococcus lugdunensis*, 1/35 (1.0%) *Klebsiella oxytoca* and 1/35 (2.9%) *Candida albicans.* Most Gram-positive organisms including *Staphylococcus aureus, Staphylococcus epidermidis* and *Staphylo*coccus *haemolyticus* showed 100% sensitivity to ciprofloxacin, rifampicin and vancomycin. The majority of Gram-negative organisms, namely *E. coli* and *Klebsiella oxytoca* were 100% sensitive to amoxicillin -clavulanic acid, second, third and fourth generation cephalosporins (ceftriaxone, cefoxitin, cefuroxime and cefepime) and carbapenems (ertapenem, meropenem and imipenem). Both Gram-positive and Gram- negative organisms were resistant to ampicillin (44.4%) and trimethoprim-sulfamethoxazole (30.8%). One (2.9%) case had *Candida albicans* cultured, which was sensitive to fluconazole and amphotericin B.

Figure 2: Flowchart showing numbers of placenta specimens sent for analysis for stillborn infants.

Discussion

Chorioamnionitis as a cause of stillbirths is often underdiagnosed in LMICs as it may be sub-clinical, and placental histopathology may not be conducted due to limited resources.[16] Our study showed that 41.8% of stillbirths are associated with chorioamnionitis which was similar to findings from a Cape Town and a Zimbabwean study [17] which diagnosed chorioamnionitis on histopathology in 34% of women presenting with a stillbirth. These results show a higher prevalence compared to Soweto, which is a similar setting, which showed an association in 25% of cases. [1, 11] Many factors may contribute to the disparities of the prevalence such as resources, study population, criteria for placental evaluation, and antibiotic protocols of health care facilities. The socio- economic status, level of expertise, and availability of trained health care practitioners may also influence the prevalence of or identification of chorioamnionitis.[11] This study has shown poor correlation between clinically suspected chorioamnionitis and histopathologically confirmed chorioamnionitis as only 3/103 (2.9%) cases were

identified clinically compared to 33/79 cases (41.8%) diagnosed microscopically. This poor concordance is in line with the literature. [14, 18] This may be because some patients present with subclinical chorioamnionitis. Routine surveillance and antibiotics have been shown to be effective in decreasing chorioamnionitis incidence in women with preterm rupture of membranes but not in those in active preterm labour with intact membranes.[19] A total of 17/33 cases of chorioamnionitis (51.5%) showed a fetal response including funisitis, vasculitis and intervillositis, which suggests that the infection occurred prior to foetal demise. Chorioamnionitis may be present in almost all cases of funisitis while funisitis is present in up to 60% cases of chorioamnionitis.[19] Our results are similar to findings by Malusi et al, which showed a foetal response of 49.5%.[19] Villitis with an unspecified cause was documented in two (2.5%) of the 79 placentas examined and this has an increased risk of stillbirth recurrence in future pregnancies if the aetiology of the villitis is unknown.[20]

Bacterial infection and the subsequent inflammatory response have been shown to be responsible for most cases of chorioamnionitis.[21] The most common bacteria identified included *S. epidermidis, E. coli* and *Enterococcus faecalis.* These findings were similar to two studies. [10, 11] Madhi et al showed bacteria responsible for invasive foetal infection were GBS, *E coli, Enterococcus faecalis* and *S aureus*.[1] This similarity helps improve understanding of the microbiology related to stillbirths and enables us to address the issue more effectively. Some studies have identified GBS, *Listeria monocytogenes and P.aeruginosa* as common isolates in placentas. [1] A study at RMMCH by Orji et al reviewing urinary tract infections during pregnancy and associated microorganisms found that *E. coli* was the commonest bacterium cultured followed by *Klebsiella species, Enterococcus faecalis* and *coagulase negative Staphylococcus*, and that these microorganisms showed comparable antimicrobial sensitivity to our study, primarily cephalexin, cefuroxime and ceftriaxone.[22] It is important to note that finding an organism does not prove causality *per se* although some of these bacteria have been cultured in neonates with severe sepsis.[23] Many organisms associated with these infections colonize gastrointestinal tract of pregnant women which acts as a reservoir for such organisms.[24] Our research highlights the importance of further research on the relationship between maternal rectovaginal microbiome and the potential adverse outcome on fetuses including invasive bacterial disease.

There have been limited data on effective antimicrobial regimens to treat chorioamnionitis and prevent adverse outcomes. The majority of the identified microorganisms were sensitive to amoxicillin-clavulanic acid, cefepime, ceftriaxone, cefuroxime, ciprofloxacin and clindamycin. Most bacteria were resistant to ampicillin, cloxacillin and trimethoprim- sulfamethoxazole (cotrimoxazole). Several randomized control trial studies have evaluated the efficacy of antibiotics in women with clinical chorioamnionitis and interventions using ceftriaxone, clarithromycin, and metronidazole were shown to be effective against most microorganisms.[19] A few studies recommend use of aminopenicillin, gentamicin, clindamycin or metronidazole to treat chorioamnionitis and erythromycin, vancomycin or clindamycin in penicillin-allergic patients.[19] The American College of Obstetrics and Gynaecology [25] recommends use of ampicillin and gentamicin to treat intraamniotic infections. The current Wits guidelines recommend

ampicillin 1 gram 6 hourly with metronidazole 400 milligrams 8 hourly to be continued for 5 days post-delivery.[26] There have been concerns with regards to lack of data pertaining to antimicrobial use in South African public hospitals compounded by increasing antimicrobial resistance.[27] Similar to Orji et al, ampicillin, which is one of the commonest drugs used to treat infections in pregnancy, had the highest resistant pattern (45.8%) in our study.[22] Although viruses and parasites found in endemic parts of the country causing intra-uterine infections and associated with stillbirths including parvovirus B19 and malaria [5] were not found in this study, a study by Velaphi et al. reported that *cytomegalovirus (CMV)* disease accounted for 0.9% of stillbirths in LMICs participating in the Child Health and Mortality Prevention Surveillance (CHAAMPS) network.[26]

This study was limited to one hospital. Less than half of the stillbirth case records were available for review in the study period and therefore may not be representative of the population.

A need for prospective studies with a large population to better understand the effects of intra-uterine infections and pregnancy our setting. The use of minimally invasive tissue sampling (MITS) in stillbirths investigations to be considered.[28]

Conclusion

This study provides insight into the prevalence of infections associated with stillbirths in our setting. Chorioamnionitis was associated with 41.8% stillbirths and *S. epidermidis, E. coli* and *E. faecalis* were among the commonest microorganisms identified in this study with the majority of these being sensitive to amoxicillin-clavulanic acid, cephalosporins, ciprofloxacin and clindamycin. Histopathological examination of placentas provides valuable information in identifying infectious causes of stillbirth. The prevalence of stillbirth can be further reduced by additional research that compares the relationship between infections and stillbirths and further develops strategies to reduce adverse outcomes.

Abbreviations

AARMS - Academic Affairs and Research Management System

ART- antiretroviral therapy

CD4 - cluster of differentiation 4

CDW - Corporate Data Warehouse

CHAAMPS - Child Health and Mortality Prevention Surveillance

CMV - cytomegalovirus

COVID-19 coronavirus disease 2019

E. coli - Escherichia coli

GA - gestational age

GAIA - Global Alignment of Immunization Safety Assessment in Pregnancy

GBS - Group B Streptococcus

g - gram

g/dl - grams per decilitre

HBsAg - hepatitis B surface antigen

HELLP- haemolysis, elevated liver enzymes and low platelet count

HIV - human immunodeficiency virus

HREC - Human Research Ethics Committee

IQR - interquartile range LMICs- low- and middle-income countries

LNMP - last normal menstrual period

MCS - microbiology, culture and sensitivity

MC&S - microscopy, culture and sensitivity

MITS - minimally invasive tissue sampling

mm^3 - cubic millimetre

NHLS - National Health Laboratory Service

PCR - polymerase chain reaction

PET- pre-eclampsia

PIH - pregnancy-induced hypertension

REDCap - Research Electronic Data Capture

RMMCH - Rahima Moosa Mother and Child Hospital

RPR - rapid plasma reagin

SD- standard deviation

SFH - symphysis-fundal height

STATA - Stata statistical software

TEE - tenofovir/emtricitabine/efavirenz

TLD - tenofovir/lamivudine/dolutegravir

UTI - urinary tract infection

Wits - University of the Witwatersrand

Declarations

Ethical approval

Obtained Human Research Ethics Committee (HREC) Clearance certificate in accordance to the University of Witwatersrand, Johannesburg, South Africa (Clearance Certificate number: M 211102).

Consent to Participate

The requirement for informed consent was waived by the relevant Research Ethics Committee due to the retrospective nature of the study and the use of existing medical records.

There is no potentially identifiable participant data present in this study.

Consent for publication

All authors consent to publication. There is no participant identifying information, therefore participant consent is not applicable.

Availability of data and materials

The datasets used and analysed during this study may be available from the corresponding author upon request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Author TT conceptualised study, developed methodology, collected and curated data, performed analysis and drafted manuscripts.

Authors CC, RW and AW supervised the study, contributed to the interpretation of the findings and critical revision of the manuscript.

All authors read and agreed to the published version of the manuscript.

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Figures

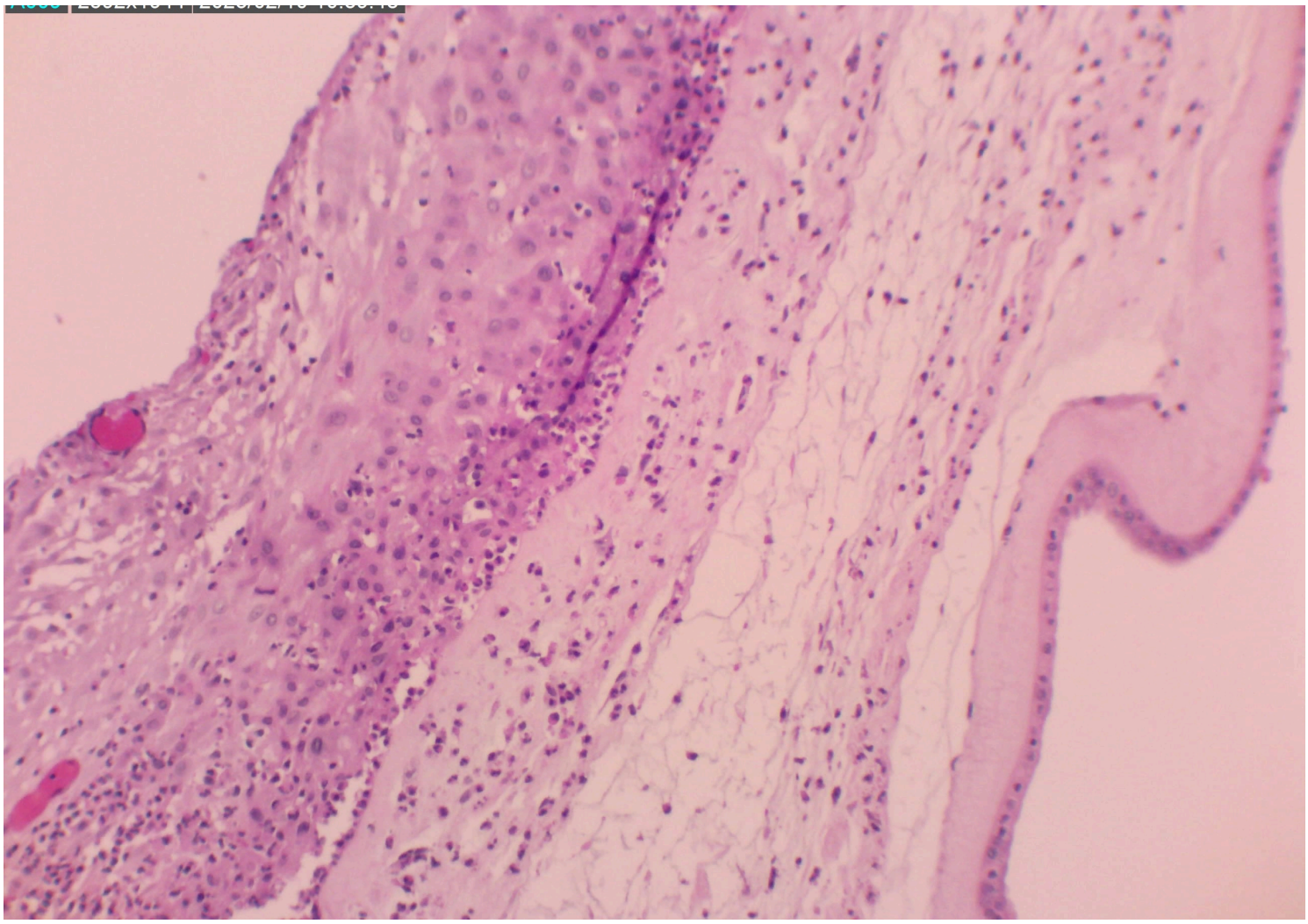


Figure 1

Photomicrographs of sections of placental membranes of women who delivered Courtesy of Prof. R Wadee.

Haematoxylin and eosin-stained section of placental membranes demonstrating chorioamnionitis (original magnification × 100).

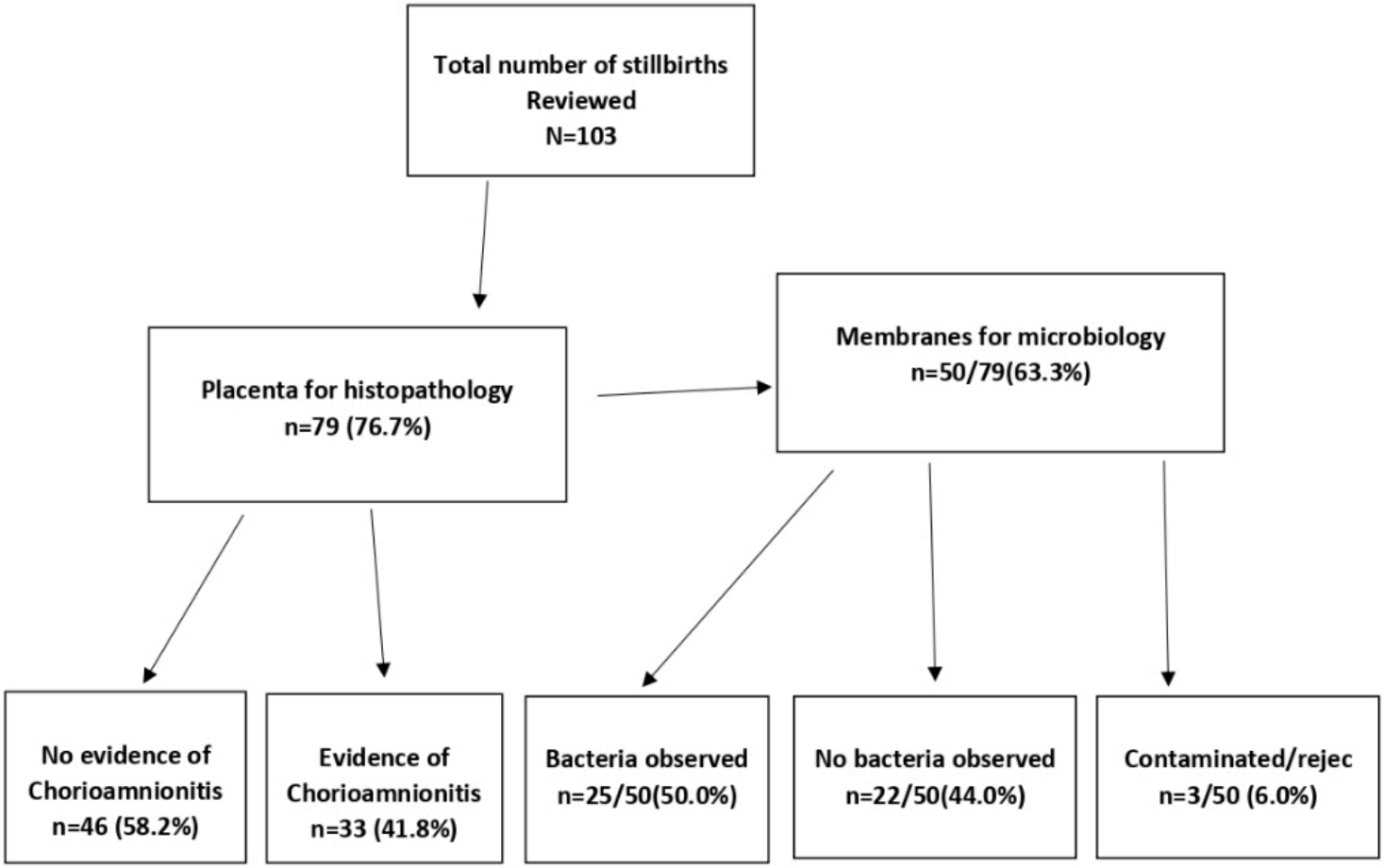


Figure 2

Flowchart showing numbers of placenta specimens sent for analysis for stillborn infants.