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Presentation and outcomes of listeria-affected pregnancies in Johannesburg Tertiary Hospitals: a 2 year review

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2022

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Presentation and Outcomes of Listeria-affected pregnancies in Johannesburg Tertiary Hospitals: A 2-Year Review

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine (Obstetrics and Gynaecology).

June 2022

DECLARATION

I, Olivia-Joan Ndahambelela Iiyambo (student number 1815720), submit this research report as my own, unaided work. It is being submitted for the degree of Master of Medicine in Obstetrics and Gynaecology at the University of the Witwatersrand. It has not been submitted before for any degree or examination at any other university.



Signed on 3 March 2022 in Johannesburg, South Africa.

DEDICATION

This report is dedicated to my mother, Olivia Iiyambo, and my late father, Jesaya Iiyambo. Thank you for the guidance and love that drives me daily.

ACKNOWLEDGMENTS

I would like to thank Dr Poovangela Naidoo for her guidance and assistance with my raw data. I will forever be appreciative of her persistent encouragement throughout the formulation of this report.

To the Department of Obstetrics and Gynaecology at the University of Witwatersrand; thank you for making the journey bearable and making me realise the work ethic and passion that drives us to provide quality healthcare to our communities even when outbreaks and pandemics plague us.

Thank you to my family and friends for availing their time, skills and resources to aid in the compilation of this report.

ABSTRACT

Objective

This study aimed to describe maternal risk factors, presentations, peripartum findings and pregnancy outcomes in listeria infected pregnant women.

Methods

A cross-sectional retrospective descriptive study was performed and the records of 51 pregnant women infected with listeriosis that had delivered between 01/02/2016 and 28/02/2018 at three tertiary care hospitals in Johannesburg, South Africa were assessed. The diagnosis of listeriosis was made on maternal/neonatal sampled blood or tissue cultures.

Results

Forty-eight (82.3%) listeria infections of maternal and neonatal listeriosis were diagnosed on blood culture. The median gestational age at diagnosis was at a preterm gestation of 33 (20 -43) weeks. Twenty-eight women (54.9%) had normal vaginal deliveries. Precipitous labour was described in 18 (39%) of these women. Fetal distress was the indication for caesarean section in 22 (41.2%) women. Meconium-stained liquor was found in 21 (61.7%) women at the time of delivery. The category of very low birth weight had 14 (27.4%) neonates with an Apgar score of <7 at 5 minutes. Maternal morbidities included chorioamnionitis (5.8%) and puerperal infections (13.7%).

Conclusion

Symptoms for listeriosis were non-specific and diagnosis was detected on blood culture sampling. Risk factors for listeriosis included HIV seropositivity and were found to be associated with puerperal infections.

TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
ACKNOWLEDGMENTS iv
ABSTRACT v
TABLE OF CONTENTS vii
LIST OF ABBREVIATIONS viii
INTRODUCTION 1
MATERIALS AND METHODS 2
RESULTS 5
DISCUSSION 8
AUTHOR CONTRIBUTIONS 13
ACKNOWLEDGEMENTS 13
CONFLICTS OF INTEREST 13
REFERENCES 14
FIGURES 19
TABLES 20
APPENDIX 1: Approved research protocol 23
APPENDIX 2: Data collection sheet 30
APPENDIX 3: Ethics Clearance Certificate 35
APPENDIX 4: Author guidelines from International Journal of Gynaecology and Obstetrics 36
APPENDIX 5: Turnitin plagiarism report 39

LIST OF ABBREVIATIONS

APL	Active phase of labour
ART	Antiretroviral therapy
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
FHR	Fetal heart rate
FSB	Fresh still birth
HIV	Human Immunodeficiency Virus
LPL	Latent phase of labour
MSB	Macerated still birth
MSL	Meconium-stained liquor
NICD	National Institute for Communicable Diseases
NICE	National Institute for Health and Care Excellence
PCR	Polymerase Chain Reaction
PPROM	Preterm prelabour rupture of membranes
PROM	Prolonged rupture of membranes
RMMCH	Rahima Moosa Mother and Child Hospital

INTRODUCTION

Listeriosis is a condition resulting from *Listeria monocytogenes* infection. This food-borne pathogen has created a health care burden both locally and internationally and has negatively influenced the morbidity and mortality of neonates and pregnant women.[1]

In December 2017, the National Institute for Communicable Diseases (NICD) South Africa announced an outbreak of listeriosis following an increasing trend of listeria-related infections. The World Health Organisation labelled this the largest globally recorded listeriosis outbreak.[2,3] A report , from January 2017 to March 2018, showed that in South Africa, 56% of infected cases were adult females and 41% were neonates.[2] HIV infection decreases the efficacy of cell-mediated immunity and has been previously reported to contribute to the severity of listerial disease.[4,5] In South Africa, 27% of reproductive age women are HIV seropositive.[6]

In of the absence of an outbreak, the low prevalence of listeriosis has resulted in the paucity of literature on this condition, with minimal to no literature pertaining to the pattern of presentation in pregnancy, pregnancy outcomes and cardiotocography findings, especially in a South African population.[2]

The specific objectives of the study were: to describe maternal risk factors and presentations where listeria infection was proven in pregnancy; to describe the peripartum findings of women who had listeria-infected pregnancies as well as maternal and fetal outcomes.

MATERIALS AND METHODS

This was a cross-sectional descriptive retrospective review of pregnant women who from 1 February 2016 to 28 February 2018 had been diagnosed with *L. monocytogenes* or had a neonate diagnosed with *L. monocytogenes* during the early neonatal period.

Johannesburg is the most densely populated city in the province of Gauteng that has a population of 14.3 million in South Africa .[7] It is serviced by three tertiary level facilities (Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Rahima Moosa Mother and Child Hospital (RMMCH)). Together, these facilities serve as referral centres from maternity obstetric units and local clinics within Johannesburg and annually provide obstetric care for over 42000 women. During the listeria outbreak of 2017, all women presenting with gastrointestinal symptoms, with or without flu-like symptoms or fever, were investigated with blood cultures including Listeria sub-cultures. All blood cultures that flagged positive for *Listeria monocytogenes* were sent to the National institute for communicable diseases (NICD) for sub-typing. Women that tested positive received treatment as in-patients or out-patients depending on the severity and progression of the disease for a duration of 3 to 7 days.[3] This treatment included penicillin-based regimens and gentamicin for severe cases. Trimethoprim-sulfamethoxazole was used where penicillin was contraindicated. Placentae were sent for histological analysis if the Apgar score at 5 minutes was less than 7. Neonates were managed in conjunction with the neonatology unit and those admitted to the neonatal intensive care unit received a sterile blood culture upon admission.

The NICD was contacted for a list of all women presenting during the study period who were of reproductive age as well as neonates in the early neonatal period who had a positive polymerase chain reaction (PCR),or culture for *L. monocytogenes.* These women or neonates were only included if delivery or miscarriage had taken place at one of the three tertiary hospitals. The maternal records of women who either had a positive culture or an infected neonate (positive neonatal blood culture) were then traced. Data pertaining to antenatal care, monitoring, investigations and delivery were extracted. Exclusion criteria consisted of women who had not delivered at one of the tertiary hospitals or where maternal files were not located.

For the purpose of this study, the following definitions were used: anaemia was a haemoglobin concentration of less than 11 g/dL[8]; antenatally booked included women with a single antenatal visit where screening tests for Rhesus, HIV, haemoglobin and syphilis had been performed; the early neonatal period refers to the first 7 days of life, flu-like symptoms included the presence of either a cough, hoarseness, nasal drainage, nasal stuffiness or sore throat; reproductive ages included 18-45 years; chorioamnionitis was defined as “an acute inflammation of the membranes or chorion of the placenta whilst clinical chorioamnionitis included signs of fever, uterine fundal tenderness, maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), and purulent or foul amniotic fluid”[9]; and precipitous labour was defined as “the expulsion of the fetus within 3 hours of commencement of regular contractions”.[10] Antiretroviral therapy for patients in the cohort were in line with the national prevention of mother to child transmission programme which included tenefovir, emitricitabine and efavirenz as first line treatment. Women on second line antiretroviral therapy received lamivudine, zidovudine, lopinavir and ritonavir. Cardiotocography or non-stress tests were assessed by specialist

obstetricians and senior registrars using National Institute for Health and Care Excellence (NICE) guidelines.[11]

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC number M180505). Permission to collect and assess data from patient files was obtained from the clinical executive officers of CHBAH, CMJAH and RMMCH. Access to the NICD database was obtained from the Head of the Centre of Enteric Diseases. Case numbers were used to ensure anonymity. The data was analyzed using Epi info v3.5.1 software with the aid of a statistician. Descriptive statistics were employed by using medians with ranges. Categorical data are presented as frequencies expressed as numbers and percentages. The Chi-squared test was used to assess the relationship between categorical variables.

RESULTS

During the study period, there were a total of 84570 deliveries between the 3 academic hospitals. The incidence of listeria-affected pregnancies in this study was 1.2/1000 births.

The NICD recorded 115 cases of listeriosis in women of reproductive age or neonates in the early neonatal period that had a positive blood or tissue culture. Seven women that were not pregnant and 8 that had not delivered in any of the 3 tertiary hospitals were excluded. Forty-nine women, whose names and medical records could not be located in the admission registers of the three tertiary hospitals, were also excluded. Fifty-one women were found to have delivered at one of the three tertiary hospitals in Johannesburg and were included in the study (Figure 1). The maternal demographics and comorbidities of the 51 women are represented in Table 1. Eighty four percent were antenatally booked. The median gestational age at diagnosis was 33 (20 -43) weeks. Twenty seven percent of women were HIV sero-positive at the time of diagnosis and 13 of these women were on anti-retroviral therapy (ART). The median CD4 count in HIV positive women was 154 (0-628) cells/mm^3. There were no women with overt or gestational diabetes.

The most common symptom at diagnosis was lower abdominal pain (88.2%) (Table 2). Four women (7.8%) had preterm pre labour rupture of membranes and 23% had prolonged rupture of membranes. Seven (13.7%) women complained of decreased fetal movements.

Table 3 contains the specimens from which the primary diagnosis of *L.* monocytogenes was made. Confirmatory samples for *L. monocytogenes* were via blood culture in 82.3% of mother or baby isolates. Isolates were sent for 24 of the 51 cases (47%). All 24 isolates underwent Whole Genome Sequencing. Twenty one of

the 24 (88%) were *L. monocytogenes* ST6 (sequence type 6) while the other 3 isolates were other sequence types (i.e. non-ST6).

Table 4 represents cardiotocography and non- stress tests on the fetuses on arrival in hospital (Trace 1) and the latter being the last tracing before delivery (Trace 2). The p value is less than 5%, therefore there is sufficient statistical evidence to reject the null hypothesis at a 5% level (as well as 0.5% level) and conclude that there are significant differences in “Decelerations” in Trace 1 and Trace 2. There is sufficient statistical evidence to reject the null hypothesis at a 5% level and we can conclude that there are significant differences in the “Overall Assessment” of “Trace 1” and “Trace 2”.

In the group of women that had vaginal deliveries (Table 5), 1 woman had a second trimester miscarriage. The median duration of latent phase of labour was 5 (0-24 hours) versus 2 (0-12 hours) for the active phase of labour. Thirty nine percent of these women had precipitous labour. None of these women had received an intrapartum dose of antibiotics. Caesarean sections were performed in 45% of women, where all fetuses had a fetal distress including one woman that had an abruptio placenta. There were no planned elective caesarean sections. Observations for the quality of liquor were only done in 34 out of the 51 women. At the time of delivery, 38.2% of women had particulate meconium-stained liquor, while another 23.5% had aparticulate meconium-stained liquor which were subjective observations by a doctor or midwife present at the delivery.

Fetal outcomes are presented in Table 6. One woman, at 21 weeks’ gestation, had a second trimester miscarriage and retained products of conception that resulted in an evacuation in theatre.

Adverse maternal outcomes are described in Table 7. Three women had chorioamnionitis. There was an atypical presentation of mastoiditis with a facial abscess that recured in a woman after 2 completed courses of ampicillin regimen antibiotics. A woman with a history of previous deep vein thrombosis, presented with a pulmonary embolus. One woman required intensive care unit admission. This woman initially presented with pre-eclampsia and later developed peripartum cardiomyopathy that required intensive care. Her blood culture at admission revealed listeriosis.

DISCUSSION

The listeriosis incidence of 1.2/1000 births is higher than 3-4/100 000 as previously documented in a review by Craig A, et al during an epidemic in North America. [12] Food-borne infections affect certain socio-economic groups due to population, income status and ethnicity, which may affect dietary practices. [13, 14] The women in this study were predominantly black, of lower-middle income status (88.2%), which is representative of the Gauteng population. In 2017, this metropolitan area was worst affected during the South African outbreak. Most women (84%) were antenatally booked.

HIV seropositivity presents an immunocompromised state, which theoretically increases the susceptibility to listeriosis. This is further amplified by the weakened cell-mediated immunity state in pregnancy.[15] Background data reports 78% of recorded listeriosis cases in South Africa were HIV positive during this outbreak.[3] Our study found a 27.5% incidence of HIV seropositive pregnant women, which is in keeping with the 2017 national data that reflect a 27% background incidence of HIV seropositivity among women of the reproductive age.[6] This is important as it reflects that whilst we believe HIV seropositivity presents a susceptible population of immunocompromised women, the incidence of listeriosis was not significantly higher in comparison to the population incidence of HIV seropositivity.

Women presented with various symptoms as reflected in Table 2. The three most frequent presenting complaints were abdominal pain (88.2%), pre-labour rupture of membranes (23%) and decreased fetal movements (13.7%). In 2017, Fouks Y, et al. described the clinical presentations of 7 pregnant women.[16] In their report, women with listeriosis most frequently presented with lower abdominal pain , which was thought to be associated with either gastrointestinal symptoms (42.8%), premature

contractions (57.1%) or preterm labour (100%).[16] In the index study, pyrexia was present in only one woman, a feature that was also more frequently observed by Fouks Y, et al. [16] The finding of decreased fetal movements has previously been described in a cohort of eight women, where the reduced fetal movements may have been attributed to amnionitis or placental insufficiency caused by the listeriosis.[17] In our cohort, only 7 (13.7%) women complained of decreased fetal movements. All these women had pathological cardiotocographs. Cardiotocography or non-stress tracing assessments revealed worsening of decelerations and overall assessment between arrival to the hospital and prior tp delivery if the neonate. This finding has not previously been described and may be related to placental insufficiency in the presence of listeriosis. [18]

In 2015, Tunkyi K and Moodley J reported a 42.7% prevalence of anaemia during pregnancy in low-middle- income countries like South Africa.[19] Of the 26 women that had haematological investigations, 6 (23%) had a mild anaemia with a mean haemoglobin of 9.4 g/dL with a range of 8.2-9.8 g/dL. This is also a new finding and its association with listeriosis is uncertain and may be reflective of the background incidence of anaemia during pregnancy in South African women.

Blood culture samples (82.3%), from the women or their neonates, were the most frequent positive laboratory investigation in this study. Standardized blood culture sampling on all admitted neonates may have contributed to the higher positive yield in this group. This practice may improve the detection rate of listeria especially during future outbreaks. Seven placentae were submitted for histology and showed micro- and macro-abscesses as described in previous studies and may have contributed to intrauterine growth restriction and fetal distress.[18] Isolates of 47% of the samples were sent for PCR and in 88% of these, *L. monocytogenes* ST6

sequences were isolated. Whole genome sequencing allows for focused attention for source identification and epidemiology, as it did in this outbreak. [14,20]

The most significant peripartum finding was precipitate labour in 39% of the women that had normal vaginal deliveries (Table 3). In these women, the median duration of latent phase and active phase were 5 hours (range 0-24) and 2 hours (range 0-12), respectively. This is a unique observation that has not been reported before. Previous reports pertaining to precipitous labour have documented infection as a possible cause. [10, 21]

Lennon D, et al. described the findings of epidemic perinatal listeriosis where 73.7% of cases had meconium-stained liquor at the time of delivery. [22] In the index study, 61.9% of women that had intrapartum meconium (particulate) staining of the amniotic fluid. The differences between the neonatal outcomes in neonates with meconium-stained liquor versus clear liquor could be explored in future studies.

Twenty-three (45%) women required an emergency caesarean section, of which 21(41%) were emergency primary caesarean sections for fetal distress.[23] All of these women recovered well and did not have a prolonged hospital stay. In 2002, Benshurshan A, reported a similar (39%) caesarean section rate for fetal distress in listeria infected women.[24] This percentage is compared to the background incidence of fetal distress contributing 49.66% to the indications for emergency caesarean sections at CHBAH in 2015 in a study by Adam Y, et al.[25] There is currently no literature to inform whether early diagnosis and treatment would reduce the incidence of caesarean delivery for fetal distress or a slower progression of labour.

Most neonates in this study were born alive. Very low birth weight (<1500g) was the most frequent birth weight category, constituting 27.4% of births, with a median 1 minute and 5-minute Apgar score of <7. The low Apgar score may be attributed to prematurity as the mean gestational age was 33 weeks' gestation. Fouks Y, et al, reported on Apgar scores in 7 listeria infected pregnancies where the mean gestation was 29 weeks with a persistently low Apgar of <7 at 5 minutes.[16] There is a 4-week difference between their mean gestational age at delivery and our cohort. This may be reflective of the difference in sample size or the natural history of infection in a South African population.

Maternal adversities included puerperal infections in 13.7% women and clinical chorioamnionitis was diagnosed in 5.8%. One woman required re-admission for intravenous antibiotic therapy a few days later as a fever commenced in the puerperium. An initial course of penicillin-based therapy (in conjunction with gentamycin in invasive infections) should suffice and do not usually require re-admission. Trimethoprim-sulfamethoxazole may be used for patients with penicillin-intolerance.[16]

One woman with pre-eclampsia complicated by peripartum cardiomyopathy was found to have listeria on a blood culture. The finding of peripartum cardiomyopathy was attributed to the presence of pre-eclampsia. Maternal mortality resulting from listeria infection is a rare, especially when the pregnant woman does not present with other co-morbidities. [16,26]

The rarity of the condition, even in an epidemic, presents a relatively small sample size. It is important, however, to note that other mothers and their neonates were delivered at midwife obstetric units outside of the three tertiary hospitals and fell out

of the sample group. The statistics for these infections were only collected by the researcher if the clinician recorded them in the maternal file.

In conclusion, listeriosis in a South African population resulted in a high frequency of preterm delivery, fetal distress, caesarean section, and low Apgar scores at birth. Maternal morbidities included antepartum and puerperal infections. This study highlights the need for a higher index of suspicion of listeriosis, especially during an epidemic, as this may provide invaluable opportunity to perform a blood culture, which appears to be the most frequent positive laboratory investigation.

AUTHOR CONTRIBUTIONS

All authors contributed to information and editing of this document equally.

ACKNOWLEDGEMENTS

The managerial and administrative staff of the Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Rahima Moosa Mother and Child Hospital.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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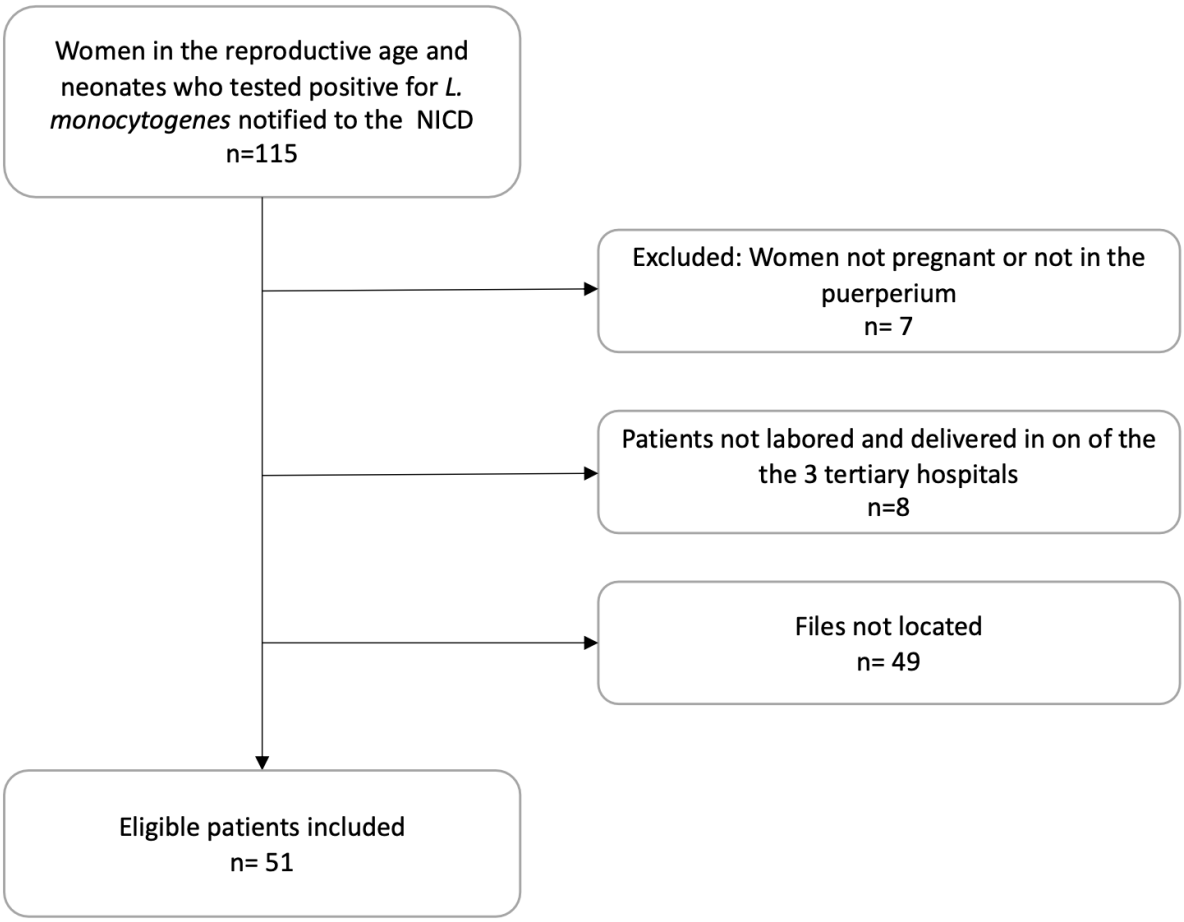
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FIGURES

Figure 1: Study flow diagram of L. *monocytogenes* infected women obtained from the NICD



TABLES

Table 1: Maternal demographics and comorbidities

Maternal demographics and comorbidities		No (%) Median (range) n=51
Antenatally booked n=50		43 (84)
Race	Black	45 (88.2)
	Caucasian	1 (1.92)
	Mixed	5 (9.8)
Previous Caesarean Section		11 (22)
Previous Miscarriage		4 (7.8)
Gestational age at diagnosis n=49		33.1 (20.1-42.9)
HIV[a]	Seropositive	14 (27.45)
	On ART[b] n=14	13 (92.85)
	CD4 Count (cells/mm^3) n=12	154 (0-628)
	Viral Load n=12 (copies/mL)	170 (0-270000)
Chronic hypertension		2 (3.9)
Gestational hypertension		1 (1.9)
Pre-eclampsia		1 (1.9)
Hepatitis B		1 (1.9)

[a]HIV=Human immunodeficiency virus,
[b]ART=Antiretroviral therapy

Table 2: Maternal presentation

Maternal presentation	No (%) n=51
Vomiting	4 (7.8)
Diarrhoea	2 (3.9)
Flu-like symptoms	1 (1.9)
Per vaginal bleeding	5 (9.8)
PROM[a]	12 (23)
PPROM[b]	4 (7.8)
Lower abdominal pain	45 (88.2)
Cough	2 (3.9)
Myalgia	4 (7.8)
Headache	5 (9.8)
Dizziness	2 (3.9)
No foetal movements	7 (13.7)
Dysuria	1 (1.9)
Frequency	1 (1.9)
Anaemia n=26	6 (23)

[a]PROM= Prolonged rupture of membranes
[b]PPROM= Preterm prelabour rupture of membranes

Table 3: Diagnosis of Listeria monocytogenes

Specimen	**No (%) n=51**
Blood only	42 (82.3)
Blood and Tissue	5 (9.8)
Tissue only	3 (5.8)
Blood and Cerebrospinal Fluid	1 (1.9)

Table 4: Characteristics of cardiotocographs and non-stress tests

NST /CTG Parameters	**Trace 1 No (%) N=40**			**Trace 2 No (%) n=41**			**p value (χ^2)**
	Reassuring/ Normal	Non-reassuring/ Suspicious	Pathological/ Abnormal	Reassuring/ Normal	Non-reassuring/ Suspicious	Pathological/ Abnormal	
Baseline FHR[a]	22 (55.0)	17 (42.5)	1 (2.5)	15 (36.6)	25 (61.0)	1 (2.4)	0.247
Accelerations	23 (57.5)	17 (42.5)		21 (51.2)	20 (48.8)		0.574
Decelerations	14 (35.0)	18 (45.0)	8 (20.0)	5 (12.2)	8 (19.5)	28 (68.3)	0.0005
FHR[a] Variability	25 (62.5)	15 (37.5)		17 (41.5)	24 (58.5)		0.061
Overall Assessment	11 (27.5)	11 (27.5)	18 (45.0)	3 (7.3)	10 (24.4)	28 (68.3)	0.036

[a]FHR= Fetal heart rate

Table 5: Delivery characteristics

Delivery characteristics				**n**	**No (%) Median(range) n=51**
Mode of delivery	Vaginal delivery	Total		51	28 (54.9)
		Duration of LPL[a] in hours		46	5 (0-24)
		Duration of APL[b] in hours		46	2 (0-12)
		Precipitous labour		46	18 (39)
		Intrapartum antibiotics		51	21 (41.1)
	Caesarean section	Total		51	23 (45)
		Primary	Total	51	13 (25)
		Repeat[c]	Total	51	10 (19.6)
			Abruptio placenta	51	1 (1.9)
		Fetal distress		51	22 (41.2)
Liquor quality at the time of delivery		Clear		34	13(38.2)
		Particulate MSL[d]		34	13(38.2)
		Aparticulate MSL[d]		34	8(23.5)
Miscarriage				51	1 (1.9)

[a]LPL= Latent phase of labour
[b]APL= Active phase of labour
[c]= All these caesarean sections were performed for an indication of fetal distress or abruptio placenta
[d]MSL= Meconium-stained liquor

Table 6: Fetal outcomes

Birth weight (grams)	Fetal Outcome at Birth	No (%) n=49	Apgar score 1 minute Median(range) n= 46	Apgar score 5 minute Median(range) n= 46
501-999	Alive	2 (4.1)	2 (2-5)	6 (6-7)
	FSB[a]	1 (2.0)		
	MSB[b]	1 (2.0)		
	Miscarriage	1 (2.0)		
1000-1499	Alive	14 (28.6)	5 (1-9)	6 (3-9)
1500-1999	Alive	9 (18.4)	6 (2-7)	8 (4-9)
2000-2499	Alive	9 (18.4)	6 (2-8)	8 (4-9)
>2500	Alive	12 (24.5)	6 (3-7)	9 (6-10)

[a]FSB= Fresh still birth
[b]MSB= Macerated still birth

Table 7: Adverse maternal outcomes

Adverse maternal outcomes		n	No (%) Median(range)
Haemoglobin <11g/dL	Anaemia	26	6 (23.0)
	Haemoglobin in g/dL	26	9.4 (8.2-9.8)
Chorioamnionitis		51	3 (5.8)
Intensive care unit admission		51	1 (1.9)
Readmission		51	1 (1.9)
Venous thromboembolism		51	1 (1.9)
Abruptio placenta		51	1 (1.9)
Acute kidney injury		51	3 (5.8)
Puerperal infection		51	7 (13.7)
Other infections		51	2 (3.9)

APPENDIX 1: Approved research protocol

Presentation and Outcomes of Listeria-affected pregnancies in Johannesburg Tertiary Hospitals: A 2 Year Review

Faculty of Health Sciences University of Witwatersrand

Researcher: Olivia-Joan Iiyambo

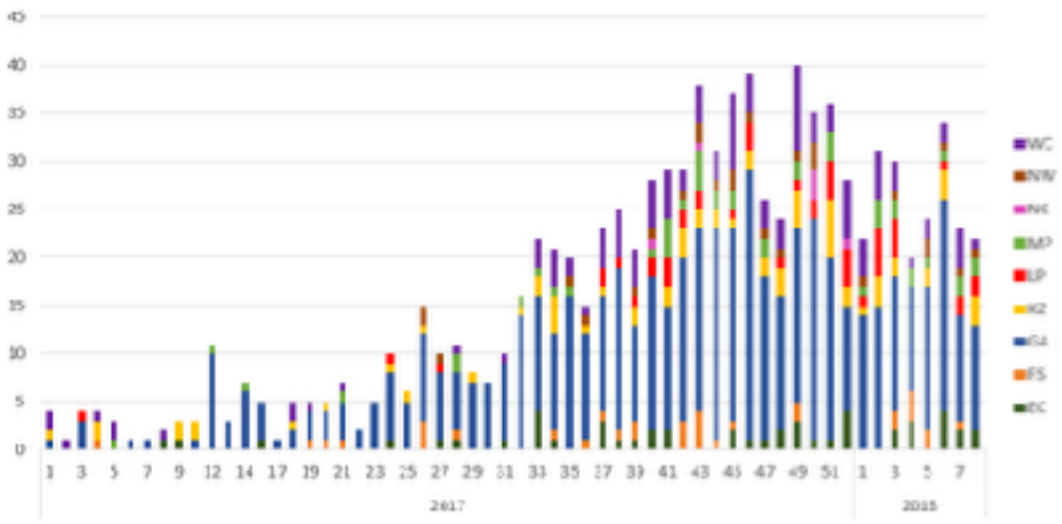
Supervisors: Dr Poovangela Naidoo, Dr Vuyelwa Baba

1. INTRODUCTION

The National Institute for Communicable Diseases (NICD) South Africa announced an outbreak of listeriosis following an increasing trend of listeria-related infections in December 2017, also marking it to be the largest listeriosis outbreak recorded globally by the World Health Organisation. The incidence of listeriosis in South Africa has increased from from January 2017 to the mid-2017 as illustrated in *Figure1* with a bulk of the cases being Gauteng based.[1,2] Fourteen cases were reported in January 2017 and 129 Cases reported in October 2017 during each month respectively, thus raising concern.[2]

Figure 1: Epidermic curve of listeriosis as confirmed, weekly, by the NHLS as per province in the Republic of South Africa between January 2017 to February 2018.[1]

Listeriosis is a condition resulting from *Listeria monocytogenes* infection and has become a burden both locally and internationally with particular influence on neonates, infants, pregnant women, the elderly and immunocompromised individuals resulting in severe outcomes.[3,4,5] In the positive cases reported in South Africa between January 2017 to 2 March 2018, where gender was recorded, 56% of infected cases were female and 41% were neonates.[1] HIV infection decreases efficacy of cell-mediated immunity and thus adds the impact of disease severity.[3,6] 78% of cases where HIV status is known were positive.[2] In South Africa, 20% of women in the reproductive ages are HIV positive.[7]



The low background incidence of listeriosis contributes to the sparse documentation and studies of the condition in of the absence of outbreak. [1,8]

2. LITERATURE REVIEW

A. Incidence

One to ten individuals per million per annum are infected with listeriosis globally.[5] Fourteen percent of cases of listeriosis are in pregnant women who are “10 times more likely” to be infected with the disease as compared to the general populace.[3]

B. Risk Factors

Individuals are more like to have listeria infections in the following subgroups: pregnant women, geriatric individuals, patients on immunosuppressive treatment, neonates, individuals with malignant disease and those that are HIV positive.[2,3,5] In pregnancy, cell-mediated immunity (via T Helper Cells) is moderately down-regulated to aid treating the foetus as an allograft. This process potentiates immunosuppression in pregnant women and further makes the pregnant woman susceptible to listeriosis.[3]

C. Pathogenesis and Resistance Strains

Listeria monocytogenes is a gram positive food-borne pathogen and the listeriosis disease process usually starts after the ingestion of contaminated foods. The Listeria genus has a total of 17 species and are all rod-shaped anaerobes with the 4b subtype being the most prevalent pathogen in human listeriosis.[3,9,10] The *Listeria* spp. are versatile and generally withstand changes to low temperatures, decreased pH and high salt concentrations.[9,11] These properties allow the pathogen to withstand various processes in food production.[11] Although there are various precautions taken by processing plants to prevent proliferation of pathogens in ready to eat foods, it needs to be taken into account that there is a possibility of cross-contamination of products from machinery or down to the level of retail shelves.[11, 12] It is thus vital to continue educating women on food- consumption awareness especially whilst pregnant.[12]
Once ingested, *L. monocytogenes* crosses the mucosal barrier of the small bowel, for transportation via the blood stream to intestinal lymph nodes for further dissemination to major organs such as the liver, spleen and uterus.[3,9,13] In immunocompromised states, there may be crossing of *L. monocytogenes* through the blood-brain barrier or the fetal-placental membrane.[9,13] Retro-infection from the placental blood reservoir aids maintenance and amplification of listeriosis in pregnancy as the placenta has immunological properties aided, partially by immunosuppressive human leukocyte antigen G.[3,4,13]

D. Symptomatology in Pregnant Women

Most cases of listeriosis present in the third trimester. The incubation period is said to be 27.5 days.[2]
The following are syndromes noted post infection with Listeria monocytogenes:

1. Asymptomatic: 1-5% individuals are affected with transient disease, lasting four to 5 days.[2]
2. Gastroenteritis: nonspecific symptoms starting with gastrointestinal symptoms (nausea, vomiting and diarrhoea) followed by fever, headache, backache, myalgia and lasting 1-7 days.[2,3] This disease progress may progress to a listerial bacteraemia.[2]
3. Bloody per vaginal discharge.[3]
4. Spontaneous miscarriage.[3,10]

5. Pre-labour rupture of membranes with or without meconium stained liquor.[3] 6. Preterm labour.[3, 4]

E. PharmacologicalManagement

1. Gastroenteritis is usually self-limiting but should be treated with oral ampicillin or trimethoprim-sulphonmethoxazole for 3 to 7 days in patients who are high risk for example pregnant women or in individuals who present with febrile disease. Gentamycin is used in addition to these in intravenous therapy.[2]
2. Listeria meningitis is treated with intravenous ceftriaxone, cefotaxime or ampicillin.[2]

F. Maternal Outcomes

Poor maternal outcomes occur predominantly in immunocompromised individuals. “Nuchal rigidity, hemiparesis, cranial nerve deficits, cerebellar signs, unconsciousness and sensory loss” are described in addition to listeria meningitis with or without concurrent brain abscesses, conjunctivitis, pericarditis, endocarditis, pleuritis, cholecystitis and hepatitis.[3] Maternal death secondary to listeriosis is a rare occurrence, barring the existence of co-morbid diseases.[3, 4]

G. Fetal Outcomes

1. *Complications before 20 weeks gestation*

   Spontaneous abortion and intrauterine fetal demise occur.[3]

2. *Complications after 20 weeks gestation*

   Listeriosis triggers prelabour rupture of membranes secondary to uterine infection, placental invasion and also chorioamnionitis.[3,4]

A fetus may become infected via ingestion of amniotic fluid, via vertical transmission of maternal bacteraemia through the placenta and also via

horizontal transmission in the vaginal canal during the delivery process. [3, 4,13]

Fetal distress may occur 1-14 days after presentation of a symptomatic mother. Septicaemia or bacteraemia may lead to preterm labour or intrauterine fetal demise.[3,4,13]

H. Neonatal Outcomes

It is important to note the congenital listeriosis is a disease process that responds well to antibiotics.[4]
Early onset cases are described as neonates from day 1 to 6 of life with neonatal listeriosis which includes “septicaemia, respiratory distress, pneumonia, meningitis” and more adversely granulamatosis infantiseptica which involves spread of abscesses and granulomas to multiple organs. This condition has links to intrauterine infection, chorioamnionitis and preterm labour. [3,4] There is a mortality rate of 20% described in this group with 40% of surviving individuals having to live with neurological and mental disabilities.[4]

Late onset neonatal cases are described from day 7 to 28 of life that presents with

nonspecific septicaemia and meningitis. This group has a mortality rate of 10%.[4] This group shows more link to horizontal transmission and from nosocomial contamination. [3,4]

3. PROBLEM STATEMENT

There is limited incidence data regarding listeriosis for the AFRO E WHO subregions under which South Africa falls.[8] Minimal documentation exists regarding the pattern of presentation of listeriosis in pregnancy and pregnancy outcomes in South Africa. This study presents an opportunity to describe pregnancy characteristics and outcomes where listeriosis has been described.

4. STUDY OBJECTIVES

1. To describe maternal risk factors and presentations where listeria infection was proven in pregnancy.
2. To describe the peripartum findings of women who had listeria-affected pregnancies.
3. To describe the listeria-affected pregnancies relating to obtstetric, maternal and fetal outcomes.

5. METHODS

A. Setting

Gauteng is the most densely populated province in the Republic of South Africa with a population of approximately 14.3 million.[7] Central Johannesburg is the most densely populated district and it serviced by three tertiary level facilities which are: Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Rahima Moosa Mother and Child Hospital. These facilities host over 42000 deliveries per annum in their Obstetrics and Gynaecology departments collectively. The tertiary hospitals see mainly high risk maternity referrals from the surrounding local clinics, primary and secondary hospitals. The women are assessed in the antenatal clinic or emergency admission area and then either admitted to the antenatal wards, labour wards, emergency theatres, high care areas or, in the presence of adversity, to the intensive care units in the circuit.

Unwell neonates are managed in conjunction with the neonatology units which also have admission criteria for high care and intensive care unit admissions.

B. Study Design

A retrospective cross-sectional descriptive study.

C. Study Population

Previously, listeriosis was not a notifiable disease but in the presence of outbreak, the NICD has made it legally mandatory for healthcare workers and laboratories to report cases directly to the Department of Health in South Africa. The information to be supplied makes case-tracing possible and thus adequate follow up and further treatment and testing of affected cases, where necessary, possible.

The National Institute for Communicable Diseases (NICD) will be contacted for all cases where there was listeria infection associated with pregnancy where delivery or management of miscarriage occurred at the three tertiary hospitals. This list will include women who delivered or miscarried in the three tertiary institutions and neonates in the early neonatal period born in the three tertiary institutions.

This list will be used as a guide to trace data regarding the admission, labour, delivery and fetal outcomes.

1. Inclusion criteria

1. Womenwhohadlisteria-affectedpregnanciesthatdeliveredorpresented with miscarriage to one of the three tertiary hospitals at any gestation and in the peuperium.
2. Positivemicroscopy,cultureandsensitivityfor*L.monocytogenes*onstool, stool, blood, swab, cerebrospinal fluid, placental or tissue cultures or

polymerase chain reaction(PCR) results from pregnant women or a neonate who had delivered in the three tertiary hospitals.

2. Exclusion Criteria

A. Listeria-affected pregnancies that had not delivered in the three tertiary hospitals.

D. Sample Size

This will relate to how many positive cases will be identified as described under “Study Population”. An expected thirty cases (or more) will be reported on.

E. Study Period

The study period will be from 1 February 2016 to 28 February 2018.

F. Data Collection and Tools

A list of women who had pregnancies related to listeriosis or their neonates that had positive cultures or PCR will be obtained from National Health Laboratory Services(NHLS) via the National Institute for Communicable Diseases (NICD) as stipulated under “Study Population”. Relevant maternal records will be retrieved to extrapolate data variables into a standardised data collection tool. *Appendix 1* will be the data collection sheet. Redcap will be used to tabulate the data.

6. DATA ANALYSIS

Collected data will be entered into Stata 15 for statistical analysis with the guidance from a statistician.

7. ETHICS

The application to do human research with the The University of Witwatersrand Human Research Ethics Committee to be sought and the study will only begin after approval. All information will be kept confidential and shared only among the researcher and supervisors.

Permission to conduct the study and access records of all three hospitals is will be sought via the National Health Research Database and Chief Executive Officers of the stipulated hospitals.

8. TIMELINES

2018/ 2019 Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Literature Review											
Preparing Protocol											
Protocol Assessment											
Ethics Application											
National Health Research Database Application											
Collecting Data											
Data Analysis											
Write Up											

9. FUNDING

Costs incurred during the study (including stationery, printing, internet and transport) will be sought by the researcher.

10. LIMITATIONS

Individuals who may have presented with a history of spontaneous miscarriage may not have presented with septicaemia. This may have lead to no cultures specimens being sent for testing; therefore decreasing the sample size.
This is a retrospective study and thus not all perimeters may be adequately documented in maternal records.

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APPENDIX 2: Data collection sheet

STUDY NUMBER:_____

Demographic and Booking				
Age				
Race	African	Caucasian	Asian	Coloured
Gestational age				
Booked	Y	N		
Rhesus Group	Positive	Negative		
RPR	Positive	Negative		
HIV	Negative	Positive	CD4 Count	Viral Load
ARVs	Y	N		

Obstetric History		
Gravidity		
Parity		
Miscarriage	1st Trimester Y/N	2nd Trimester Y/N
Ectopic Pregnancy	Y	N
Caeserian Section	Y	N
Normal Vaginal Delivery	Y	N

Co-morbidities		
Pre-Gestational Diabetes	Y	N
Gestational Diabetes	Y	N
Chronic Hypertensive	Y	N
Gestational Hypertension	Y	N
Pre-Eclampsia	Y	N
Eclampsia	Y	N
Epilepsy	Y	N
Tuberculosis	Y	N

Presenting Complaint					
Nausea	Y	N	**Muscle Pain**	Y	N
Vomiting	Y	N	**Fever**	Y	N
Diarrhoea	Y	N	**Headache**	Y	N
Flu-Like Symptoms	Y	N	**Visual Disturbances**	Y	N
Per Vaginal Bleeding	Y	N	**Necks Stifness**	Y	N
Pre-Labour Rupture of Memberanes	Y	N	**Dizziness**	Y	N
Lower Abdominal Pain	Y	N	**No Fetal Movements**	Y	N
Cough	Y	N			
Pleuritic Chest Pain	Y	N			

Vitals on presentation	
Blood Pressure	**Respiratory Rate**
Heart Rate	**Temperature**

Blood work on Admission	**Arterial or Venous Blood Gas**

Done	Y/ N	Done	Y/ N
White Cell Count		pH	
Haemoglobin		PCO2	
Hematocrit		PO2	
Platelets		HCO3-	
Sodium		sO2	
Potassium		BE	
Chloride		Lactate	
Bicarbonate		Na	
Urea		K	
Creatinine		Glu	
C- Reactive Protein		Ca2+	
		Cl	

Ultrasound			
Gestation			
Fetal Heart	Y	N	
Retained Products of Conception (in case of miscarriage)	Y	N	
Liquor Volume	Adequate	Increased	Decreased
Characteristics of Placenta	Placental Lakes	Placental Calcfications	Other
Fetal Presentation			
Additional commentary			

Miscarriage Y N		
Retained Products of Conception	Y	N
Manual Vacuum Aspiration	Y	N
Evacuation of the Uterus in Theatre	Y	N
Foul Smelling Products of Conception	Y	N

On Rupture of Membranes				
Clear Liquor	Y	N		
Meconium Stained Liquor	Y	N	MSL Particulate	MSL Aparticulate
Duration of Rupture of Membranes	Y	N		
Chorioamnionitis	Y	N		

NST or CTG on presentation			
Baseline FHR	<110	110-160	>160
Accelarations	Present	Absent	
Deceleartions	Early	Late	
Beat-to-Beat Variablity	Adequate	Absent	

NST or CTG on presentation

Assessment Reassuring Non-Reassuring Pathological

Antibiotics Administered Pre- delivery			
Initiation	Y	N	
Route	Oral	Intravenous	Both
Amoxycillin		Duration	
Ampicillin		Duration	
Bactrim		Duration	
Gentamycin			

Labour				
Gestational Age				
Misoprostol Induction	Y	N	Doses	Duration
Prandin Gel Induction	Y	N	Doses	Duration
Catheter Bulb Induction	Y	N		Duration
Spontaneous Labour	Y	N		
Duration of Latent Phase				
Duration of Active Phase				
Augmentation of Labour	Y	N		Duration

Vitals in Labour (Highest or Lowest Values)	
Blood Pressure	**Respiratory Rate**
Heart Rate	**Temperature**

Worst NST or CTG in Labour			
Baseline FHR	<110	110-160	>160
Accelarations	Present	Absent	
Deceleartions	Early	Late	
Beat-to-Beat Variablity	Adequate	Absent	
Assessment	Reassuring	Non-Reassuring	Pathological

Hospital at which delivered

Chris Hani Baragwanath Charlotte Maxeke Johannesburg Rahima Moosa Mother and Child Academic Hospital Academic Hospital Hospital

Vaginal Delivery Y		**N**	
	Spontaneous	Vacuum Assisted	Forceps Assisted
Placenta			

Caeserian Section Y		**N**	
Indication	Emergency	Elective	
	Reason:		
Placenta			
Liquor	Clear	Meconium Stained Particulate	Meconumium Stained Aparticulate

Neonatal Outcome and Birth Weight				
Apgar	1min	5min	Fresh Still Birth	Macerated Still Birth
Birth Weight				

Antibiotics Administered Post- delivery			
Initiation	Y	N	
Route	Oral	Intravenous	Both
Amoxycillin	Y	N	Duration
Ampicillin	Y	N	Duration

Antibiotics Administered Post- delivery			
Bactrim	Y	N	Duration
Metronidazole	Y	N	Duration
Gentamycin	Y	N	Duration

Culture or PCR Results Subtype or Strain		
Blood Culture	Y	N
Placenta	Y	N
Stool	Y	N
Vaginal Swab	Y	N
Pus Swab	Y	N
Uterus	Y	N
Other		

Maternal Outcome			
Admission to High Care	Y	N	
Admission to ICU	Y	N	
Maternal Death	Y	N	
Discharged	Y	N	
Readmission	Y	N	Reason:

Maternal Near Miss
Admission to ICU
Massive blood transfusion
Renal Dialysis
Prolonged Maternal Ventilation
Cardiac Arrest
Inotropic Support
Relook Laparotomy

Maternal Near Miss

Hysterectomy	
Vitals on Discharge	
Blood Pressure	Respiratory Rate
Heart Rate	Temperature

APPENDIX 3: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr O-J Iiyambo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180505

NAME: (Principal Investigator)	Dr O-J Iiyambo
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	Presentations and outcomes of Listeria-affected pregnancies in Johannesburg tertiary hospitals: A two year review
DATE CONSIDERED:	25/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs P Naidoo and V Baba
APPROVED BY:	CB Penny Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore reports and re-certification will be due early in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

5/09/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4: Author guidelines from International Journal of Gynaecology and Obstetrics

LAYOUT OF MANUSCRIPTS

Manuscript text should be in English (US spelling), double-spaced, font size 12, in Arial font.

5.1. First page

The first page of the manuscript should contain the following: (1) title; (2) full names of authors (6 maximum, although listing more authors may be considered on an individual basis if authorship requirements have been met and a request has been included in the cover letter); (3) affiliations of authors (i.e. department, section or unit of an institution, hospital or organization, city, and country where it is located; please note that street name/numbers are not required); (4) full contact details (postal address, email address) of the corresponding author; (5) a list of up to 8 keywords for indexing and retrieval; (6) synopsis (no longer than 25 words, stating the primary conclusion of the paper).

Footnotes linking author names to affiliations should be listed as 1,2,3 etc., rather than *,†,‡ or a,b,c etc.

The first page should also list the type of article: Clinical Article; Brief Communication; or Review Article.

5.2. Abstract

5.2.1. Clinical articles

A structured abstract not exceeding **200 words** is required for all full-length clinical articles. It should contain all and only the following headings: **Objective**; **Methods**; **Results**; and **Conclusion**.

The Objective reflects the purpose of the study: that is, the hypothesis that is being tested. The Methods should include the setting for the study, the participants (number and type), the treatment or intervention, and the type of statistical analysis. The Results include the outcome of the study and statistical significance, if appropriate. The Conclusion states the significance of the results.

5.3. Main text

In full-length articles, subject matter should be organized under the following headings, with no subheadings: **Introduction**; **Materials and methods**; **Results**; **Discussion**; **Author contributions**; **Acknowledgments**; **Conflicts of interest**; and **References**. Footnotes should be avoided and their contents incorporated into the text.

Brief communications should not have any headings separating the text.

5.3.1. Clinical articles

The main text of clinical articles should not exceed **2500 words**, excluding: the first-page information, abstract (**no more than 200 words**), author contributions, acknowledgments, Conflicts of interest,

references (**no more than 25**), figure legends, and tables and figures. Please include the word count in the cover letter and on the first page of the manuscript.

5.4. Power calculations, statistics, and reporting of numbers

5.4.1. Power calculations

Where appropriate (e.g. for clinical trials), power calculations should be performed as part of the study design, and a statement providing the power of the study should be included in the Materials and methods. Authors should state how the power calculation was determined, including what type of difference the calculation was powered to detect and on what studies the numbers are based.

5.4.2. Statistics

The statistical tests used and the significance level set should be listed in the methods for all studies that employed statistical analysis. Information regarding the statistical software programs used should be included in the methods: for example, “SPSS version 20 (IBM, Armonk, NY, USA).” This information should not be included in the reference list.

P values should be provided where calculated. The largest *P* value that should be expressed is $P>0.99$. The smallest *P* value that should be expressed is $P<0.001$.
For measures of effect (e.g. relative risks, risk ratios, odds ratios), authors should also report confidence intervals (e.g. 95%) so that the precision of the effect estimate can be assessed.

5.4.3. Reporting of numbers

Authors are urged to ensure that all reported numbers are accurate and listed consistently throughout the manuscript, tables, and figures.

All clinical trials should include the results of intention-to-treat analysis, and all surveys should include response rates.

5.5. Ethics approval and informed consent

Studies of patients, patient records, or volunteers require Ethics Committee approval and informed consent.

5.5.1. Ethics approval

Include a statement in the methods that the research protocol was approved by the relevant Institutional Review Board or Ethics Committee before the study began; if such approval was not needed/obtained, include an explanation. The name of the approving committee must be included in the manuscript. Authors must provide copies of the appropriate documentation if requested.

5.5.2. Informed consent

Include confirmation in the methods that all human participants gave written informed consent before the study began; if consent was not needed/obtained, include an explanation. Authors must provide copies of the appropriate documentation if requested.

5.6. Author contributions

Each author's individual contributions should be listed in support of their right to authorship. Their role in the design, planning, conduct, data analysis, and manuscript writing should be stated.

5.7. Acknowledgments

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