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A REVIEW OF NECROTISING ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT BABIES IN A TERTIARY HOSPITAL IN JOHANNESBURG

A RETROSPECTIVE STUDY

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine Johannesburg, 2020

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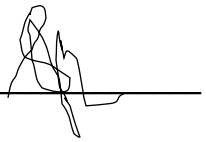
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DECLARATION

I, Sandra Lucky Motsisi, declare that this dissertation report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of Witwatersrand Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed: _____



On this: _20___ day of: _NOVEMBER_____2020

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Daynia Ballot, for all her patience and support at every point of development of this research project. Her door was always open for any query I had, and she resolved all challenges I was faced with. Her help has made this research a success.

DEDICATION

I would like to thank God; My partner and my family, for all the emotional support and sacrifices made to help me through this journey; your help kept me going and saw this project through.

PUBLICATION AND PRESENTATION ARISING FROM THESIS

None yet

ABSTRACT

Background: Necrotising enterocolitis (NEC) is the most common gastrointestinal complication in premature infants. There are risk factors and modifying factors that have been identified and studied over the years, but not many studies have been done in middle-income countries.

Objectives: The objectives of this study were to describe the maternal, obstetric and neonatal characteristics in very low birth weight (VLBW) babies with NEC at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa. The survival to hospital discharge in VLBW babies with NEC was determined.

Methods: A retrospective cross-sectional observational study of VLBW babies admitted to a tertiary neonatal unit between January 2013 and December 2017. The population comprised babies <1 500g and <37 weeks gestation. Maternal and neonatal risk factors of NEC were compared in infants with and without NEC.

Results: In this study, 173 out of 2111 (8%) babies were diagnosed with NEC**.** Maternal age and HIV increase the risk of NEC. Neonatal factors, including late-onset sepsis, respiratory support after initial resuscitation, administration of surfactant and blood transfusion were associated with an increased risk of NEC. Babies diagnosed with NEC had an increased risk of mortality.

Conclusion

Risk factors for NEC in our population are similar to other countries, with some variations such as HIV. Even though some prevention measures have been implemented, the mortality rate remains high.

ABBREVIATIONS

BMV: Bag mask ventilation

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

ET: Endothelin

IgA: Immunoglobulin A

IL: Interleukin

LPS: Lipopolysaccharide

NEC: Necrotising enterocolitis

NO: Nitric oxide

PAF: Platelet-activating factor

PDA: Patent ductus arteriosus

REDCap: Research electronic data capture

VLBW: Very low birth weight.

NCPAP: Nasal continuous positive airway pressure

HFOV: High frequency oscillatory ventilation

CMV: Continuous mechanical ventilation

NVD: Normal vertex delivery

REPORT IN PUBLICATION SUBMISSABLE FORMAT

1. BACKGROUND

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in very low birth weight babies (VLBW) (1). NEC is described as inflammation and necrosis of the gastrointestinal system and commonly occurs in preterm babies (2). The clinical presentation of NEC is broad and nonspecific, and it is classified into three stages according to the modified Bells classification (3). NEC is one of the leading causes of neonatal deaths in intensive care units (1). In the current study unit, the rate of NEC was 5. 5% in 2010 and accounted for 10% of the total neonatal deaths (4).

Over the years, there has been a marked improvement in health care, better access to antenatal services for pregnant mothers and improved obstetric and neonatal care. There are also measures such as antenatal steroid administration which improve the outcome of preterm labour (5). These improvements have resulted in more premature babies surviving the neonatal period; however, these babies are then at risk of developing complications such as NEC which are associated with prematurity (6). The pathophysiology of NEC is unclear but has been shown to be multifactorial. NEC is an inflammatory disorder of the gastrointestinal system which occurs as a result of intrinsic and extrinsic factors (7). Several risk factors for NEC have been identified; these include prematurity, VLBW, asphyxia, anaemia, blood transfusion, sepsis and *patent ductus arteriosus* (PDA) (7). Babies who are asphyxiated or require resuscitation, are also at risk of developing NEC (8).

There is an association with anaemia and NEC, but it is not clear whether anaemia or blood transfusion causes NEC; usually, the babies who require transfusion are very ill.

In a retrospective study, it was shown that 27% of patients were transfused within 48 hours of being diagnosed with NEC (9). There are other factors such as a family history of allergic disease, postnatal asphyxia secondary to meconium aspiration and intrahepatic cholestasis in pregnancy leading to prematurity which has been linked to NEC, but they still require further study (10).

Human breast milk, as opposed to infant formula, has been shown to have a protective effect on the newborn gut (11). There are variations in the introduction and daily increments of feeds in different centres. What is important is early initiation of feeds to optimise nutrition and improve the babies' outcome (12). The gut microbiome is emerging as an important factor in human disease, and alteration of the gut microbiome has been shown to be beneficial in some intestinal diseases. Concerning NEC, research has shown an association between gut dysbiosis and NEC would, therefore, be worth researching whether alteration of the gut microbiome would have an impact on NEC (13). There are also factors, such as probiotics, that have been shown to be beneficial in preventing NEC; however, further investigation is still required (14).

Despite the fact that a lot of research has been done on NEC and potentially modifiable factors have been identified, there has not been a significant decrease in morbidity and mortality. Even with early aggressive treatment, NEC still progresses and has significant morbidity with chronic gastrointestinal complications and poor neurodevelopment.

South Africa is a middle-income country with limited resources, and this affects the outcome of VLBW babies; efforts should, therefore, be made to identify conditions which add to the burden on the health system. In previous studies on causes of neonatal death, NEC is listed as one of the contributors and a modifiable cause of neonatal death (15).

There is a paucity of studies in sub-Saharan Africa to review the risk factors for NEC in VLBW. The current study aims to show the risk factors for NEC in a tertiary hospital in Johannesburg, South Africa. The results of the study may contribute to preventing or improving the outcome of NEC in South Africa.

2. METHODOLOGY

The study was a retrospective, observational study. The population was VLBW babies (<1 500gm birth weight) admitted to the CMJAH neonatal unit from 1st January 2013 to 31st December 2017. VLBW babies who were admitted within 48 hours of birth were included in the study. Those VLBW babies who were less than 500gms birth weight, those with missing data and those who died within 72 hours of life were excluded.

Study Setting

CMJAH is a tertiary hospital in Johannesburg; the neonatal unit consists of four areas, admission, PICU (shared with Paediatrics), high- and low-care ward. House staff (intern and registrar) and neonatal consultants managed the patients. Paediatric surgery was available at CMJAH during the study period.

Definitions

NEC was defined as NEC 2 and 3, using modified Bell's criteria (3). Clinical features included increased gastric aspirates, vomiting, abdominal distension, bloody stools, metabolic acidosis, full blood count changes and x-rays showing pneumatosis or perforation. The attending physician assigned the stage of NEC. Babies were managed according to Bell's criteria by the attending physician. Management included a sepsis screen, empiric antibiotic therapy, gastric drainage and parenteral nutrition. Abdominal radiographs confirmed Pneumatosis *intestinalis* and were used to monitor disease progression. Abdominal sonography was not used during the study period. All cases of NEC were reviewed by the surgeons. Operative management of the NEC was at the discretion of the attending surgeon and included pencil drain insertion or laparotomy with or without bowel resection and intestinal diversion.

Data

The database from CMJAH was used; this is an ongoing data collection system in the neonatal unit. Data is captured onto a data collection sheet on the discharge of the patient. Details captured are maternal, obstetric and neonatal data which is then entered into the data collection programme. There are various points of verifying the data once it has been entered. The data is managed using Research Electronic Data Capture (REDCap^{TM}), hosted by the University of the Witwatersrand (16).

Data Analysis

Data was collected on an Excel spreadsheet for data cleaning; the sample size was 2 579. Categorical variables were described using frequencies and percentages. The study sample was divided into two groups, babies with NEC and those without and the two groups were compared. Categorical variables were compared using Chi-Square analysis, and continuous variables were compared using unpaired t-tests or non-parametric methods, as appropriate. A p-value of 0.05 was considered statistically significant. Those variables with a p-value of 0.1 were entered into a binary logistic regression model with NEC as the outcome variable, to determine adjusted odds ratios for the variables associated with NEC.

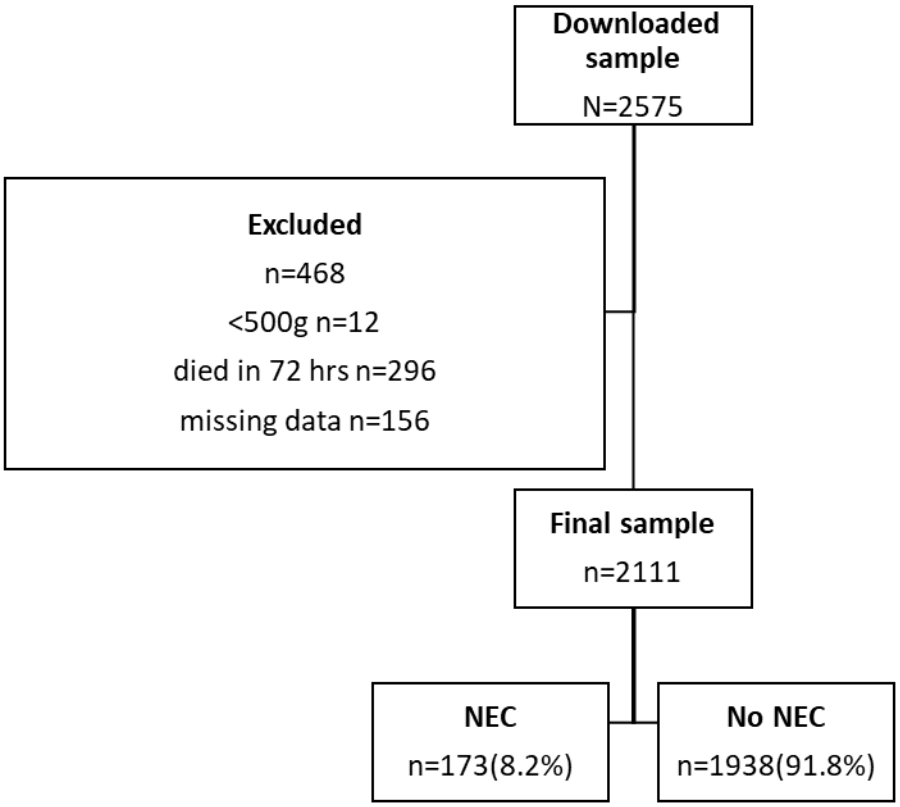
3. ETHICS

Permission to conduct the study was obtained from the CEO of CMJAH, and a clearance certificate (M180704) was received from the Human Research Ethics Committee (Medical) (HREC) of the University of Witwatersrand. The protocol was registered on the National Health Research Database.

4. POPULATION

There were 2 575 babies eligible for the study of whom 468 were excluded according to the exclusion criteria. The final sample consisted of 2 111 babies, 173 (8.2%) of whom were diagnosed with NEC (Figure 1).

FIGURE 1: Population selection



In this study, 916 (47, 8%) mothers were between 20 and 29 years of age, and the majority of them were black Africans. Other maternal characteristics are listed in Table 1. Concerning gestational age, the majority of the babies were less than 30 weeks old, and the majority weighed more than 1 kg at birth. Of the 2111 babies, 1133(53.8%) were female, one baby who was intersex, and the remainder were male; 1 769 (83.8 %) were born at CMJAH.

5. RESULTS

Table 1: Summary of statistics for maternal, obstetric and neonatal characteristics by NEC, N=2 111.

	NEC		Total	P-value
	No	Yes		
	(N = 1 938)	(N = 173)	(N = 2 111)	
Maternal age (years)				0.217
less than 20	171 (9.7)	12 (7.7)	183 (9.5)	
20 to 29	851 (48.3)	65 (41.9)	916 (47.8)	
30 to 39	669 (37.9)	72 (46.5)	741 (38.6)	
40 +	72 (4.1)	6 (3.9)	78 (4.1)	
Maternal race				0.826
Other	61 (3.2)	6 (3.5)	67 (3.2)	
Black	1 868 (96.8)	167 (96.5)	2 035 (96.8)	
Antenatal Steroids				0.837
No	890 (50.1)	78 (51.0)	968 (50.2)	
Yes	886 (49.9)	75 (49.0)	961 (49.8)	
Maternal HIV				0.011
Negative	1 308 (69.0)	98 (59.4)	1 406 (68.2)	
Positive	589 (31.0)	67 (40.6)	656 (31.8)	
Birth weight				0.388
Less than 1kg	491 (25.3)	49 (28.3)	540 (25.6)	
At least 1kg	1 447 (74.7)	124 (71.7)	1 571 (74.4)	
Gestational age (weeks)				0.021
Less than 30	1 366 (70.9)	137 (79.2)	1 503 (71.6)	
At least 30	560 (29.1)	36 (20.8)	596 (28.4)	
Gender				0.927
Male	892 (46.1)	80 (46.5)	972 (46.2)	
Female	1 041 (53.9)	92 (53.5)	1 133 (53.8)	
HIV Prophylaxis given				0.302
No	24 (4.1)	1 (1.5)	25 (3.9)	
Yes	555 (95.9)	64 (98.5)	619 (96.1)	
Mode of delivery				0.133
NVD	803 (42.0)	81 (47.9)	884 (42.5)	
Caesar	1 110 (58.0)	88 (52.1)	1 198 (57.5)	
Initial resuscitation on delivery				0.845
No	486 (26.5)	43 (27.2)	529 (26.6)	
Yes	1 348 (73.5)	115 (72.8)	1 463 (73.4)	
Face Mask Ventilation				0.186
No	1 078 (58.8)	86 (53.4)	1 164 (58.3)	
Yes	756 (41.2)	75 (46.6)	831 (41.7)	
Nasal CPAP				0.038
No	522 (28.2)	35 (20.7)	557 (27.5)	
Yes	1331 (71.8)	134 (79.3)	1465 (72.5)	
NEC surgery				<0.001
No	1762 (100.0)	117 (70.9)	1879 (97.5)	
Yes	0 (0.0)	48 (29.1)	48 (2.5)	
Gastrointestinal perforation				<0.001
No	1923 (99.7)	155 (92.3)	2078 (99.1)	
Yes	5 (0.3)	13 (7.7)	18 (0.9)	

TABLE 1 CONTINUED…

Conventional Ventilation				<0.001
No	1468 (80.3)	65 (38.2)	1533 (76.7)	
Yes	360 (19.7)	105 (61.8)	465 (23.3)	
High-Frequency Ventilation				0.007
No	1 782 (98.9)	160 (96.4)	1 942 (98.7)	
Yes	20 (1.1)	6 (3.6)	26 (1.3)	
Surfactant therapy at any time				0.027
No	572 (29.7)	36 (21.6)	608 (29.0)	
Yes	1 356 (70.3)	131 (78.4)	1 487 (71.0)	
Bacterial sepsis on/ before day 3				0.626
No	1 840 (95.6)	162 (96.4)	2 002 (95.7)	
Yes	84 (4.4)	6 (3.6)	90 (4.3)	
Sepsis after day 3				<0.001
No	1 348 (69.7)	65 (38.2)	1 413 (67.2)	
Yes	586 (30.3)	105 (61.8)	691 (32.8)	
Fungal sepsis				0.013
No	495 (86.5)	81 (77.1)	576 (85.1)	
Yes	77 (13.5)	24 (22.9)	101 (14.9)	
Indomethacin for any reason				0.453
No	1 919 (99.7)	172 (99.4)	2 091 (99.7)	
Yes	5 (0.3)	1 (0.6)	6 (0.3)	
Blood transfusion				<0.001
No	1 140 (59.7)	59 (34.5)	1 199 (57.6)	
Yes	771 (40.3)	112 (65.5)	883 (42.4)	
Exchange transfusion				0.319
No	1 273 (99.1)	115 (100.0)	1 388 (99.2)	
Yes	11 (0.9)	0 (0.0)	11 (0.8)	
Feeds on discharge				0.947
Formula milk	738 (48.6)	39 (48.1)	777 (48.5)	
Breast milk	695 (45.7)	38 (46.9)	733 (45.8)	
Mixed	87 (5.7)	4 (4.9)	91 (5.7)	
Birth PCR result				0.678
Negative	368 (95.3)	41 (93.2)	409 (95.1)	
Positive	9 (2.3)	1 (2.3)	10 (2.3)	
Outstanding	9 (2.3)	2 (4.5)	11 (2.6)	

Risk factors for NEC

Maternal race (p=0.826) and antenatal steroids were not statistically significant (p=0.837). Although the majority of the babies (73.1%) were resuscitated at birth, this was not shown to be significant (p=0.845); however, respiratory support after resuscitation with all forms of ventilator support NCPAP, conventional mechanical and high-frequency ventilation during hospital admission had a significant association with NEC.

Logistic regression was performed to assess the association between significant variables; conventional ventilation, late-onset sepsis and blood transfusions were significant, birth weight, maternal HIV and age, NCPAP, HFOV and surfactant were non-significant (Table 2).

Table 2: Results of fitting logistic regression models for factors associated with NEC

VARIABLE	Odds ratio (95% Confidence interval)	P-value
Maternal age		
less than 20	Reference	
20 to 29	1.09 (0.58; 2.06)	0.794
30 to 39	1.53 (0.81; 2.89)	0.186
40 +	1.19 (0.43; 3.29)	0.741
Maternal HIV positive		
No	Reference	
Yes	1.52 (1.10; 2.10)	0.012
Birth weight		
Less than 1 kg	Reference	
At least 1 kg	0.86 (0.61; 1.21)	0.388
Resuscitation		
No	Reference	
Yes	0.96 (0.67; 1.39)	0.845
Face Mask Ventilation		
No	Reference	
Yes	1.24 (0.90; 1.72)	0.186
CPAP		
No	Reference	
Yes	1.50 (1.02; 2.21)	0.039
Conventional Ventilation		
No	Reference	
Yes	6.59 (4.74; 9.16)	<0.001
High-Frequency Ventilation		
No	Reference	
Yes	3.34 (1.32; 8.44)	0.011
Surfactant therapy at anytime		
No	Reference	
Yes	1.53 (1.05; 2.25)	0.028
Bacterial sepsis		
No	Reference	
Yes	0.81 (0.35; 1.89)	0.627
Fungal sepsis		
No	Reference	
Yes	1.90 (1.14; 3.19)	0.014
Sepsis after day 3		
No	Reference	
Yes	3.72 (2.69; 5.14)	<0.001
Blood transfusion		
No	Reference	
Yes	2.81 (2.02; 3.90)	<0.001

Outcomes as defined by morbidity and mortality

Of the infants (173) who were diagnosed with NEC, the majority 125 (72.3%) did not need surgery, only 48 (27.7%) required surgery and, of those, more infants required laparotomy than those who received a pencil drain. The mortality rate of infants with NEC was 22.7%, and the mortality rate for babies without NEC was 77.3%.

Table 3: Summary statistics for maternal, obstetric and neonatal characteristics of infants with NEC, by mortality

	Infants with NEC			
	Survived	**Died**	**Total**	
	(N = 88)	(N = 85)	(N = 173)	p-value
Maternal age (Years)				0.141
less than 20	9 (11.1%)	3 (4.1%)	12 (7.7%)	
20 to 29	29 (35.8%)	36 (48.6%)	65 (41.9%)	
30 to 39	41 (50.6%)	31 (41.9%)	72 (46.5%)	
40 +	2 (2.5%)	4 (5.4%)	6 (3.9%)	
Maternal race				1.000
Other	3 (3.4%)	3 (3.5%)	6 (3.5%)	
Black	85 (96.6%)	82 (96.5%)	167 (96.5%)	
Antenatal Steroids				0.518
No	39 (48.1%)	39 (54.2%)	78 (51.0%)	
Yes	42 (51.9%)	33 (45.8%)	75 (49.0%)	
Maternal HIV				0.158
No	55 (64.7%)	43 (53.8%)	98 (59.4%)	
Yes	30 (35.3%)	37 (46.3%)	67 (40.6%)	
Birth weight (Grams)				0.399
Less than 1kg	22 (25.0%)	27 (31.8%)	49 (28.3%)	
At least 1kg	66 (75.0%)	58 (68.2%)	124 (71.7%)	
Gestational age (weeks)				0.455
Less than 30	72 (81.8%)	65 (76.5%)	137 (79.2%)	
At least 30	16 (18.2%)	20 (23.5%)	36 (20.8%)	
Gender				1.000
Male	40 (46.0%)	40 (47.1%)	80 (46.5%)	
Female	47 (54.0%)	45 (52.9%)	92 (53.5%)	
HIV Prophylaxis given				1.000
No	0 (0.0%)	1 (2.8%)	1 (1.5%)	
Yes	29 (100.0%)	35 (97.2%)	64 (98.5%)	
Mode of delivery				0.220
NVD	37 (43.0%)	44 (53.0%)	81 (47.9%)	
Caesar	49 (57.0%)	39 (47.0%)	88 (52.1%)	
Initial resuscitation in delivery				0.284
No	19 (23.2%)	24 (31.6%)	43 (27.2%)	
Yes	63 (76.8%)	52 (68.4%)	115 (72.8%)	
Face Mask Ventilation				0.637
No	45 (55.6%)	41 (51.2%)	86 (53.4%)	
Yes	36 (44.4%)	39 (48.8%)	75 (46.6%)	

TABLE 3 continued…..				
Nasal CPAP				0.850
No	19 (21.8%)	16 (19.5%)	35 (20.7%)	
Yes	68 (78.2%)	66 (80.5%)	134 (79.3%)	
NEC surgery				0.010
No	68 (80.0%)	49 (61.3%)	117 (70.9%)	
Yes	17 (20.0%)	31 (38.8%)	48 (29.1%)	
				1.000
Type of NEC surgery				
Laparotomy	14 (82.4%)	24 (77.4%)	38 (79.2%)	
Pencil drain	3 (17.6%)	7 (22.6%)	10 (20.8%)	
Gastrointestinal perforation				0.778
No	80 (93.0%)	75 (91.5%)	155 (92.3%)	
Yes	6 (7.0%)	7 (8.5%)	13 (7.7%)	
Conventional Ventilation				<0.001
No	46 (52.9%)	19 (22.9%)	65 (38.2%)	
Yes	41 (47.1%)	64 (77.1%)	105 (61.8%)	
High Frequency Ventilation				0.111
No	84 (98.8%)	76 (93.8%)	160 (96.4%)	
Yes	1 (1.2%)	5 (6.2%)	6 (3.6%)	
Surfactant therapy at any time				0.710
No	19 (22.9%)	17 (20.2%)	36 (21.6%)	
Yes	64 (77.1%)	67 (79.8%)	131 (78.4%)	
Bacterial sepsis on/ before day 3				0.682
No	82 (97.6%)	80 (95.2%)	162 (96.4%)	
Yes	2 (2.4%)	4 (4.8%)	6 (3.6%)	
Sepsis after day 3				0.018
No	41 (47.1%)	24 (28.9%)	65 (38.2%)	
Yes	46 (52.9%)	59 (71.1%)	105 (61.8%)	
Fungal sepsis				0.254
No	33 (71.7%)	48 (81.4%)	81 (77.1%)	
Yes	13 (28.3%)	11 (18.6%)	24 (22.9%)	
Indomethacin for any reason				0.491
No	88 (100.0%)	84 (98.8%)	172 (99.4%)	
Yes	0 (0.0%)	1 (1.2%)	1 (0.6%)	
Blood transfusion				0.203
No	26 (29.9%)	33 (39.3%)	59 (34.5%)	
Yes	61 (70.1%)	51 (60.7%)	112 (65.5%)	
Exchange transfusion				.
No	63 (100.0%)	52 (100.0%)	115 (100.0%)	
Feeds on discharge				.
Formula milk	39 (48.1%)	0 (. %)	39 (48.1%)	
Breast milk	38 (46.9%)	0 (. %)	38 (46.9%)	
Mixed feeding	4 (4.9%)	0 (. %)	4 (4.9%)	
Birth PCR result				0.476
Negative	22 (100.0%)	19 (95.0%)	41 (97.6%)	
Positive	0 (0.0%)	1 (5.0%)	1 (2.4%)	

6. DISCUSSION

The risks of NEC in CMJAH are similar to those in other studies. Babies who died within the first 72 hours of life were excluded as this time frame is earlier than the period when the disease would develop. According to a study done by Bisquera and colleagues (2002), infants who developed NEC stayed in the hospital longer than the infants who didn't (17). Maternal age and race were not significant; antenatal steroids were previously found to be protective in NEC (5) but, in this study, the contrary was found. Maternal HIV was found not to increase the risk of NEC in a study done previously at CMJAH (18). According to this study, the rate of NEC is higher in infants whose mothers were HIV positive (p=0.011); this is surprising as the PMTCT programmes have been improved over the past years and more mothers are receiving prophylaxis during the antenatal period. Concerning gender studies it has been shown previously that black males were at higher risk of NEC (19); however, in this study, females (53.8%) were at higher risk, but gender was not a significant risk for NEC (p=0.93).

Hypoxia and ischaemia have been implicated in the pathogenesis of NEC (8); in this study, resuscitation at birth was not shown to be significant (p=0.084), but respiratory support after resuscitation was significant (p=0.014). All forms of ventilator support NCPAP, conventional ventilation and high-frequency ventilation during hospital admission appeared to increase the risk of NEC in this study. In addition, the administration of surfactant has also been shown to increase the risk of NEC. The immaturity of the gut mucosa in VLBW babies predisposes them to bacterial infections and sepsis (8), in the current study, sepsis was shown to be significantly related to the development of NEC. However the day of life when the diagnosis of NEC was confirmed was not recorded, therefore it cannot be said whether sepsis was present before or at the time of NEC. The association between blood transfusions and NEC is unclear as the question is whether the blood

transfusion or the anaemia increases the risk of NEC (9). In the current study, blood transfusion was associated with NEC, but the time between transfusion and NEC was not recorded and, therefore, could not be analysed. Congenital cardiac lesions and the administration of Ibuprofen and PDA ligation were not significant.

Feeding practices differ in different hospitals. The initiation of feeds and the volume of increments differ between hospitals in South Africa. Previous studies have shown that breast milk is protective to NEC (11), but there are still questions about the comparison between fortified breast milk, formula and breast milk only (11). In the current study, there were babies with missing feeding data as a result of deaths and being transferred out of the unit. Of those who remained, more babies were formula-fed, followed by breastfed, fortified breast milk and then those who were mixed-fed. The number of infants with NEC who were breastfed and given fortified breast milk and formula-fed are similar, which raises the question of whether fortifying breast milk decreases its protective effect and increases the risk of NEC. With the implementation of PMTCT guidelines, it was expected that more mothers would be breastfeeding, but according to our results, that is not the case. Probiotics are not used in the unit; thus, their correlation with NEC could not be assessed.

In a study comparing morbidity and mortality in CMJAH in VLBW infants, the survival rate was 73.4%, and NEC was one of the modifiable factors concerning improved outcomes (15). In the current study, the survival rate was 82.3% overall. The survival rate of premature babies has improved over the years and this results in an increase in the complications of prematurity such as NEC. Hence the increase rate of NEC of 8.2% from 5% which was previously noted in a study in the unit. (4)

Similarly in an international article reviewing the incidence of NEC in high income countries, studies ranged from 1987-2014, it was also noted that there was an increase of NEC from 2% to 7% in babies <32 weeks gestation and an increase from 5% to 22% in babies <1000g. (20)

In the current study babies with NEC had a longer duration of hospital stay; some required surgery and had an increased risk of mortality.

Limitations

The study was retrospective; therefore, data were limited to information in the patient's records. Missing data could not be retrieved. Information such as feeds could not be analysed as data regarding the type of feeds was missing. We can only describe the association between the risk factors and NEC; further studies would be needed to address effects.

7. CONCLUSION AND RECOMMENDATIONS

According to this study, NEC remains a disease with multifactorial risk factors, as has been described in previous studies. In the VLBW infants in CMJAH, maternal age and HIV status, birth weight, respiratory support after initial resuscitation, ventilator support, blood transfusion, and late-onset sepsis are related to an increased risk of NEC. Concerning maternal characteristics, maternal HIV increases the risk of NEC, which is different from what has been described previously. Blood transfusions are also related, but it is still unclear as to whether this is because of the anaemia or the transfusion of packed cells itself. Among the types of feeds, breast milk remains protective, but further studies need to be done on fortification of breast milk and whether this increases the risk of NEC. Sepsis remains a significant risk for sepsis, more the late-onset sepsis with bacterial pathogens. Infants who require ventilator support are also at a higher risk of NEC, and this could be because hypoxic episodes cause insult to the gut mucosa.

RECOMMENDATIONS

Infection control measures such as hand washing and avoiding over handling of the babies need to continue to be improved. Avoiding excessive phlebotomy is also crucial as it increases the risk of infection and leads to anaemia. Mothers need more encouragement to breastfeed, more infants need to be breastfed, and this should be encouraged in the unit; facilities need to accommodate mothers to stay overnight. When feeds need to be fortified, sterility should be maintained to avoid contaminating the feed. A prospective study on probiotics and NEC is necessary

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APPENDIX A: PROTOCOL

REVIEW OF NECROTISING ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT BABIES IN A TERTIARY HOSPITAL IN JOHANNESBURG

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CONTENTS

1. **INTRODUCTION**
2. **PATHOPHYSIOLOGY**
3. **CLINICAL PRESENTATION**
4. **RESEARCH METHODS**
5. **DATA COLLECTION SHEET**
6. **REFERENCES**

GLOSSARY

NEC **Necrotizing enterocolitis**

VLBW **Very low birth weight**

CMJAH **Charlotte Maxeke Johannesburg Academic Hospital**

BMV **Bag mask ventilation**

PDA **Patent ductus arteriosus**

Redcap **Research electronic data capture**

DEFINITIONS

NEC is defined as Bell's stage 2 and 3: The NEC is diagnosed both clinically and radiographically by the attending physician. (16)

VLBW babies: will be babies who are less than 1500g at birth. (6)

Early onset sepsis: is defined as culture proven sepsis prior to 72 hours of age.

Late onset sepsis: is defined as culture confirmed sepsis after 72 hours of life. Fungal and bacterial organisms are analyzed separately.

Resuscitation: is defined as the need for bag mask ventilation at birth (this would include those few babies who required cardiac compressions and/or endotracheal intubation).

The diagnosis of **patent ductus arteriosus (PDA)**: is confirmed on echocardiograph

INTRODUCTION

Necrotising enterocolitis (NEC) is one of the leading causes of morbidity and mortality from a gastrointestinal cause in preterm babies. It is a disease which occurs mostly in preterm babies and still remains a leading cause of death in neonatal intensive care unit(1). NEC was first described in 1823 by Charles Billard as gangrenous enterocolitis; this was his description of the process of inflammation and necrosis in the neonates gut. The disease has been studied extensively but there has not been a significant decrease in morbidity or mortality of the disease over the years.(2) The rate of NEC in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) was 5, 5 percent in 2010 and it accounted for 10 percent of the total deaths. NEC is also a burden on the economy as it prolongs the patient's hospital stay and increases the cost to treat.(3) According to a study done by Bisquera and colleagues babies who developed NEC and were medically treated hospital stay exceeded the controls by twenty two days and for those who required surgery it was further extended by sixty days. This also resulted in higher hospital cost with surgical treatment costing more than medical treatment per patient per annum. These costs are excluding the cost to cover the morbidity with the babies who survive NEC. These babies will need parenteral nutrition as a result of short bowel syndrome. Further complications arise from the use of parenteral nutrition which cause liver dysfunction. (4)

Over the years there has been marked improvement in antenatal care for pregnant mothers. There is improved access to health care facilities and the initiation of strategies to improve outcome of preterm labour such as steroid administration before delivery. In addition over the past thirty years neonatal intensive care has improved, which has also improved preterm babies survival. More very low birth weight (VLBW) babies are surviving the neonatal period and this then puts them at a risk of developing NEC. Despite these improvements the rate of NEC has increased

and mortality remains unchanged. Even with early aggressive treatment the disease progresses, with bowel necrosis which leads to sepsis and death. For those who survive there is significant morbidity with chronic gastrointestinal complications and poor neurodevelopment outcomes.

NEC is the most common gastrointestinal (GIT) emergency in premature infants especially the VLBW (<1500g). The incidence also shows an inverse relationship between birth weight and gestational age. NEC forms a large proportion of inpatient mortality in neonates but the mortality associated with NEC decreases as birth weight increases. In the birth weight (501-1500g) the NEC rate was 12% and this decreased to 3, 3 percent in birth weight (1251-1500g) range.(5) With regards to gender and race, black male infants are at a higher risk of developing NEC and they have a higher rate of mortality. Most patients may be treated medically but 20-40% will require surgical intervention and of those who require surgical intervention the mortality rate is about 50 %.(6)

PATHOPHYSIOLOGY

The pathophysiology of NEC is not well understood but it is has been shown to be multifactorial. NEC is an inflammatory disorder of the gastrointestinal system commonly affects the ileum and proximal colon but may affect any part. NEC can occur as a result of intrinsic or extrinsic factors. There is an initial insult which can be from different causes which is followed by disruption of the intestinal epithelium and an exaggerated response by the immature intestinal epithelial cells this then leads to inflammation, bacterial overgrowth and necrosis. NEC may occur in babies with a congenital cardiac lesion which results in an ischaemic insult. Other possible causes are bacterial infection with sepsis or formula feeding. (7)

The intestinal mucosa forms part of the immune system, the motility decreases the transit time of bacteria and prevents infections. The mucin layer forms a barrier layer which removes the

bacteria that have adhered to the wall and aids in their removal. It also traps enzymes near the surface to aid digestion. There are also normal flora which colonize the gut and play a vital role in modulating the immune system and maintaining the intestinal barrier. In a term baby an infection in the gut is confined to the gut by the local immune system. In premature babies the gut is not fully developed, the transit time in the gut is slower which increases bacterial load and can lead to septicaemia. The tight junctions are not fully developed which allows permeability of the gut wall. Secretory IgA in the gut is only developed a few weeks post natal. Most premature babies receive antibiotics after delivery which will also affect the normal gut flora and as a result the immune response is lost(8)

In addition to the above issues the preterm babies are prone to colonization with pathogenic bacteria such as Klebsiella, enterobacter and clostridium species. No specific bacterial species has been associated with NEC but the change in the gut flora leads to infiltration of the immature intestinal barrier which causes the inflammatory cascade which is implicated in the pathogenesis of NEC. (8)

Hypoxia and ischemia have also been implicated in the pathogenesis of NEC. In the mucosal blood vessel there is a balance between vasodilation and vasoconstriction. Nitric oxide (NO) causes vasodilation in the vessels which maintains a low systemic vascular resistance. When there is inflammation present it increases the production of NO which causes damage of the epithelial cells and apoptosis. In addition high concentrations of NO lead to delayed mucosal healing after the insult. As a result this causes a prolonged activation of the inflammatory cascade and a sustained defect in the barrier function. On the other hand endothelin (ET-1) leads to vasoconstriction in the intestinal circulation in newborns which can cause ischaemia for a few hours. The production of ET-1 can be stimulated by inflammation or hypoxia.

In pathologic states the balance between NO and ET-1 is disturbed and this causes vasoconstriction which leads to ischaemia in the intestinal tissue and tissue injury.(8)

There are several mediators which have been identified in NEC, three of which are lipopolysaccharides (LPS), tumour necrosis factor (TNF) alpha, and platelet activation factor (PAF). LPS is an inflammatory mediator which is found as an endotoxin in gram negative bacteria. It has been used in animal models to induce NEC as it impairs the function of the intestinal barrier and causes the release of other inflammatory mediators. Mediators such as nitric oxide and interferon gamma which are cytotoxic. TNF alpha has been found as a mediator in neonates who have NEC, it has been shown to promote production of PAF. PAF forms free radicals from oxygen which cause bowel injury and apoptosis. (9)

EXTRINSIC FACTORS

Feeding practices

The South African population represents a combination of developing and developed health systems, this poses a challenge regarding feeding practices for LBW babies. Human breast milk has been shown to have antimicrobial activity and anti-inflammatory which have a protective effect on the newborn baby's gut. Prospective studies have been done comparing feeding practices in SA to establish whether human breast milk vs. formula milk, fortification of the breast milk would increase the risk of NEC(10). The results showed that there is a decrease in NEC with breastfed babies. With regards to introduction of feeds and increment of daily there are variations amongst different centres. What is important is that initiation of feeds should not be delayed as optimizing nutrition will improve the baby's outcome.(11)

Gastric Ph

With babies who receive H2 receptor blockers, the gastric pH is altered and this causes an alteration in the normal gut flora and this has been seen as a cause of NEC.(12)

Anaemia

There is an association with anaemia and NEC but it is not clear whether anaemia or the blood transfusion is what causes NEC, usually the babies who do require transfusion are usually the very ill babies. In a retrospective study it was shown that 27% of patients had been transfused within 48 hours of being diagnosed with NEC.(13)

Risk factors for NEC

Advancements with treatment of NEC may not be able to improve NEC as the disease progression is fulminant so it is suggestive that improving identification of risk factors may be beneficial. There are maternal and neonatal risk factors associated with NEC. Neonatal factors include prematurity, low birth weight, enteral feeding, blood transfusions, congenital cardiac lesions and sepsis, there may be other factors which have not yet been linked to NEC. Other factors which still require more studies are family history of allergic disease, which is associated with sensitization of intestinal gut in the neonate. Cayabyab et al (14) reported post natal asphyxia or hypoxia secondary to meconium aspiration syndrome, causes foetal hypoxia and inflammatory response is triggered. Shemer et al showed that intrahepatic cholestasis in pregnancy increases premature delivery and leads to adverse foetal outcomes. In a study in China it was shown that the above risk factors increase the risk of NEC with a peak in the disease in January and a trough in August. In addition the use of breast milk and probiotics was shown to be beneficial for neonates in preventing NEC.

Clinical presentation

NEC has a broad spectrum of presentations from nonspecific symptoms such as increased gastric aspirates, to slow indolent course to illness that progresses rapidly and results in death in a few hours. The clinical signs include apnoea, temperature instability, bradycardia, lethargy, need for ventilation, mottling. Gastrointestinal symptoms include increased aspirates, abdominal distension, increased abdominal girth, bloody stools, discoloration of abdominal wall or a mass is palpable.

Laboratory findings; raised white cell count, thrombocytopenia, anaemia, raised C-reactive protein (CRP) and a metabolic acidosis.(15)

Radiographic findings; nonspecific dilated bowel loops, air fluid levels, thickened bowel wall. Hallmark of NEC is pneumatosis intestinalis (linear or cystic). As a result of this broad and nonspecific presentation of NEC the Bells criteria was developed and is currently used to classify the groups of symptoms in these babies.

NEC in neonates has been classified into three stages in 1978 by Bell et al (16) using signs and symptoms and intestinal, systemic and radiological signs. This classification was then modified by Kliegman and Welsh who broke each into two categories which showed the differentiation in severity of the disease.

Modified Bell's staging for NEC

Stage 1(suspected) being nonspecific signs, apnoea, bradycardia, temperature instability, mild ileus and blood in the stools. Stage 2 (definite) pneumatosis noted on the abdominal x-ray. Stage 3(advanced disease) baby is critically ill, unstable in shock, DIC and perforation of bowel. This classification is important with staging of NEC and plays a vital role in choice of referral or management for these babies.(16)

The Millennium development goals (MDGS) set were to decrease under five mortality by two thirds before 2015. A few of the developing countries managed to achieve this goal but South Africa was not amongst those countries. In 2013 neonatal mortality was 45% of deaths in South Africa in children less than 5 years. South Africa's neonatal mortality is lower than the other African countries but it is still much higher than the European and Scandinavian counties. Efforts to improve neonatal care need to become a priority in the health system in South Africa. There have been strategies implemented in the health system such as the Sustainable development goals (SDG), which are strategies aiming to improve survival of low birth weight babies who then need improvement of facilities to survive the neonatal period to discharge with good outcomes.(17)

South Africa is a middle income country and with resource limitations and this may adversely affect the outcome of these babies. In a study in CMJAH comparing morbidity and mortality of very low birth weight babies the survival rate was 73, 4% and the most common cause of death was extreme multi organ prematurity. NEC was one of the few significant predictors of mortality. NEC also showed to be one of the modifiable factors with regards to improving outcome and survival rates.(18)

In developing countries there are challenges with regards to financial constraints, availability of equipment, poor staffing and increased volumes with overcrowding in the neonatal units. Babies who then develop NEC put a further strain on the system as their length of stay is prolonged and their cost to the health system is increased. NEC has poor neurological outcomes so the baby essentially will continue to impact on the health system financially.

Many studies have been done in other countries but a few have been done in South Africa to show the risk factors or NEC in VLBW babies in the developing countries. Studies have also shown that prevention of risk factors may prove to be more beneficial in decreasing NEC. This study aims to show the risk factors of NEC in a tertiary hospital in Johannesburg as these results can contribute to preventing NEC or improving early diagnosis of the condition. Improving survival of VLBW babies will improve their survival rate and outcome.

AIM

We aim to review the risk factors and outcomes for NEC in VLBW babies at CMJAH

STUDY OBJECTIVES

1. To describe the maternal, obstetric and neonatal characteristics in VLBW babies with NEC.
2. To determine the survival to hospital discharge in VLBW babies with NEC
3. To compare the maternal, obstetric and neonatal characteristics, as well as survival between VLBW babies with confirmed disease (NEC 2 and 3) and those without confirmed disease (NEC 1 and others).

METHODS

Study design

The study will be a retrospective case control observational study. This study will be a secondary analysis of existing data from CMJAH. The population will be made up of VLBW babies admitted to the neonatal unit over 5 year, between January 2013 and December 2017.

Inclusion and exclusion criteria

Inclusion criteria

VLBW babies admitted to the CMJAH neonatal unit within 48 hours of birth between January 1, 2013 and December 31, 2017. Cases will be babies diagnosed with NEC.

Exclusion criteria

Babies with a birth weight less <500g. Babies who died in first 72 hours of life.

DATA

The CMJAH neonatal unit is made up of four areas: admission area, neonatal ICU (which is shared with Paediatrics), high care and a low care ward. There is ongoing data collection for the purpose of quality improvement and clinical audits. Data is collected on discharge of each patient by attending house staff. The data includes maternal, labour room and neonatal characteristics. There are various points of verifying the data once it is entered into a computer database. Data is managed using research electronic data capture (REDCAP), hosted by University of the Witwatersrand(Harris).(19)

This study will be a secondary analysis of the existing database. Maternal, labour room, infant demographics and clinical characteristics will be analysed. (Please see data collection sheet)

Data collection sheet (appendix 1)

5. DATA ANALYSIS

Data will be collected on a spreadsheet in Excel for data cleaning. Sample size is estimated at 450 VLBW babies admitted per annum and the NEC rate in CMJAH is +/- 7% per annum which results in about 200 babies with NEC. Categorical variables will be described using frequencies and percentages, while continuous variables will be described using mean and standard deviation or median with interquartile range as appropriate. The study sample will then be divided into those infants with NEC and those without. These two groups will be compared. Categorical variables will be compared using Chi Square analysis and continuous variables will be compared using unpaired t tests or non- parametric methods as appropriate. A p-value of 0.05 will be considered statistically significant. Those variables with a p value of 0.1 will be entered into a

binary logistic regression model with NEC as the outcome variable, in order to determine adjusted odds ratios for the variables associated with NEC.

6. ETHICS

The study is a retrospective review of patient records, therefore no active participation of patients is required. No consent will be obtained from the parents. As a consideration of the patient's privacy the information will be de identified, no name, surname or date of birth will be used. The protocol will be submitted to the CEO of CMJAH to obtain permission to conduct the study in the hospital and to the Human Research Ethics committee (HREC) of the University of Witwatersrand for approval. The protocol will be registered on the National Health Research Database.

7. TIMING

	MAR	APRIL	MAY	JUN	JUL	AUG	SEP	OCT	NOV
Literature review									
Preparing protocol									
Protocol assessment									
Ethics application									

Collecting data									
Writing up-thesis									
Writing up-paper									

8. FUNDING

Projected expenses will include stationary, data and photocopying costs. The study will be funded by the researcher. The estimated cost of the study is R 500

9. LIMITATIONS

The study will be a retrospective study information will be obtained from database. We are limited to patient records as there are no active participants, the patient records may have incomplete details. The diagnosis of NEC is not standardized as the diagnosis is made by the attending physician. As this is an analysis of an existing database, additional details such as the rate of increase of feeds, time of introduction of breastfeeding, timing of transfusion and so on could not be analysed.

APPENDIX 1

DATA COLLECTION SHEET

STUDY NUMBER	
PLACE OF DELIVERY	
GESTATIONAL AGE	
AGE ON ADMISSION	
MATERNAL FACTORS:	
MATERNAL AGE	
ANTENATAL STEROIDS :Y/N	
MATERNAL HIV: Y/N	
BABY'S PCR AT BIRTH	
BABY: MODE OF DELIVERY	
RESUSCITATION AT DELIVERY- **BMV: Y/N**	
BIRTH WEIGHT:	
APGARS AT : ONE MINUTE **FIVE MINUTES**	
EARLY ONSET SEPSIS: Y/N	
ORGANISM IDENTIFIED	

LATE ONSET SEPSIS: Y/N **ORGANISM IDENTIFIED**	
RESPIRATORY DISTRESS **SYNDROME (RDS):Y/N**	
SURFACTANT GIVEN:Y/N	
VENTILATORY SUPPORT:Y/N **NCPAP: Y/N** **MECHANICAL VENTILATION: Y/N**	
NEC STAGE	
SURGERY FOR NEC **PENCIL DRAIN/LAPAROTOMY**	
BLOOD TRANSFUSION: Y/N	
PATENT DUCTUS ARTERIOSUS	
IBUPROFEN/PANADO Y/N	
FEEDS ON DISCHARGE: **BREASTMILK OR FORMULA**	
DIED (DURING HOSPITAL STAY)	
DURATION OF HOSPITAL STAY	

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APPENDIX B: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Sandra Motsitsi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180704

NAME: (Principal Investigator)	Dr Sandra Motsitsi
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Review of necrotising enterocolitis in very low birth weight babies in a tertiary hospital in Johannesburg
DATE CONSIDERED:	27/07/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/08/2018

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 the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

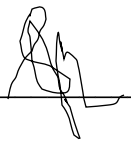
APPENDIX C: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS
SENATE PLAGIARISM POLICY:

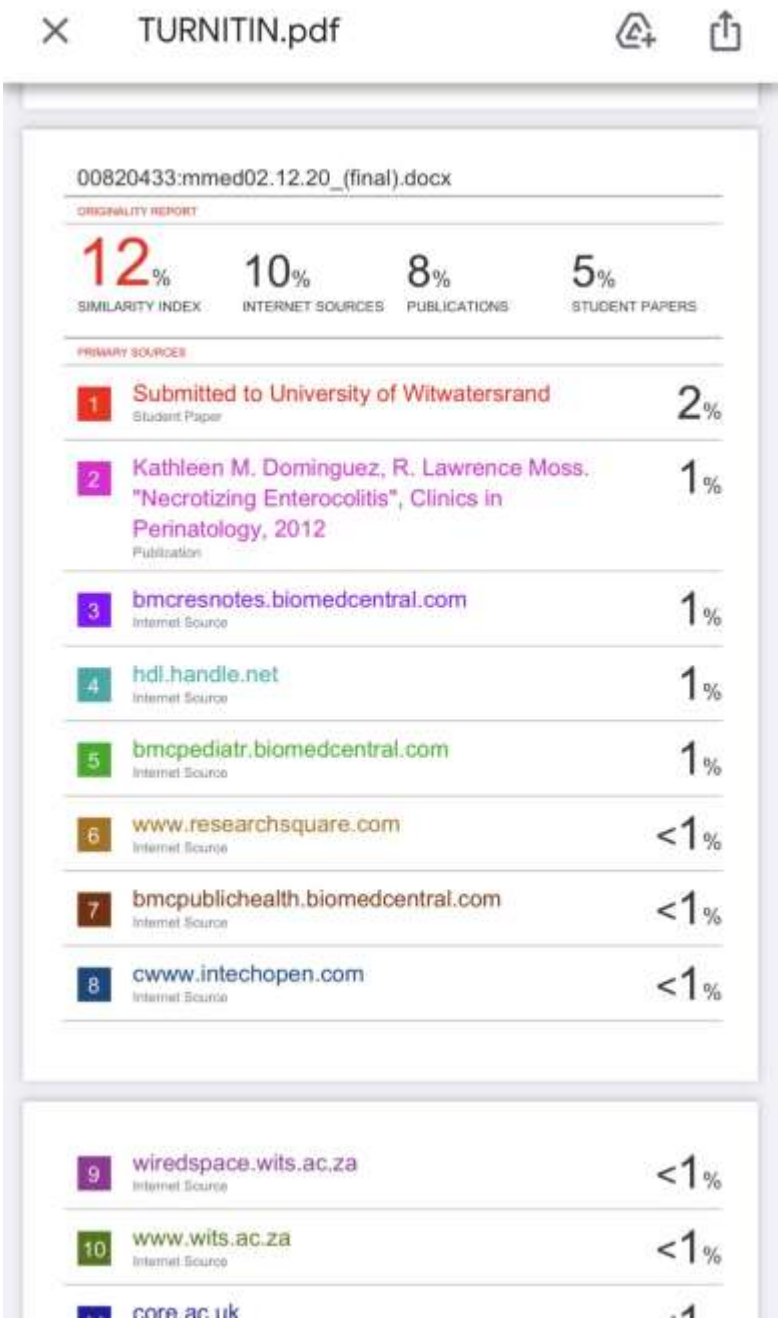
I _____Sandra Motsisi____ (Student number :_____) am a student registered for the degree of _____MMED_____ in the academic year _2020_____.

I hereby declare the following:

I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong. I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. I have followed the required conventions in referencing the thoughts and ideas of others. I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing. I have included as an appendix a report from "Turnitin"

Signature:  Date: ___20 NOVEMBER_2020__

APPENDIX D: TURNITIN REPORT



APPENDIX E: AUTHOR GUIDELINES FOR SUBMISSION

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