The OFANNM Study: Obstetric factors associated with neonatal near miss, at a public mother and child hospital in Johannesburg, South Africa

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RESEARCH ARTICLE (PLOS ONE JOURNAL)

Full title

The OFANNM Study: Obstetric factors associated with neonatal near miss, at a public mother and child hospital in Johannesburg, South Africa

Short title

Obstetric factors associated with neonatal near miss

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Abstract

Background

Obstetric factors can impact pregnancy outcomes such as neonatal morbidity, mortality and near miss. Neonatal near miss has not been well documented in our environment.

Objective

We investigated the association between maternal socio-biological and obstetric characteristics and neonatal near miss at a teaching hospital in Johannesburg, South Africa.

Methods

A case-control study of 744 mother-infant pairs was conducted at a public mother and child hospital in Johannesburg, South Africa, from 1 January 2016 to 31 December 2016. Maternal Socio-demographic and obstetric factors of 372 cases of neonatal near miss and 372 cases of normal babies were obtained from clinical records. The annual neonatal near miss rate was calculated by dividing the number of near miss cases by total deliveries, for 2016. Descriptive statistics was conducted. We respectively used Pearson's Chi-Square, Mann Whitney U and Student's t-test, to compare categorical and continuous variables among the neonatal outcomes. Univariable and multivariable logistic regression was conducted to assess for factors associated with neonatal near miss.

Results

The neonatal near miss rate was 110 per 1000 deliveries for 2016. The mean maternal age and median parity for our study population were 28.07 (±5.97) years

and 2(IQR: 1-2) respectively. After multivariable logistic regression, advanced maternal age (OR=2.65, 95%CI:1.10-6.41, P-value=0.029), substance abuse (OR=4.48, 95%CI:1.54-13.05, P-value=0.006), underweight (OR=4.40, 95%CI:1.22-15.80, P-value=0.023), preterm delivery ≤33+6 weeks (OR=4.56, 95%CI:1.92-10.83, P-value=0.001), pregnancy specific antenatal disorders (OR=5.19, 95%CI:2.61-10.30, P-value<0.001), delivery by interns (OR=44.7 95%CI:2.27-880.06) and registrar doctors (OR=5.91 95%CI:1.61-21.74, P-value=0.008), had statistically significant association with neonatal near miss. Elective (Adjusted OR=0.22, 95%CI:0.06-0.88, P-value=0.032) and emergency (Adjusted OR=0.19, 95%CI:0.050.69, P-value=0.012) caesarean section deliveries, were respectively associated with reduced neonatal near miss risk.

Conclusion

This study identified risk factors of neonatal near miss in our environment, to improve policy and care. Elective and emergency caesarean delivery appear to be protective against neonatal near miss. Health policy interventions should be initiated to reduce and mitigate the impact of neonatal near miss in our environment.

1 INTRODUCTION

In 2015, more than 2.7 million deaths occurred in the neonatal period [1,2]. Neonatal mortality accounts for about 70% of the global burden of infant mortality [2]. At the conclusion of the millennium development goals in 2015, South Africa and most of the low and middle-income countries did not achieve a reduction in neonatal mortality to the expected target [3]. However, the Sustainable Development Goal 3.2 targets a reduction in the neonatal mortality rate (NMR) to 12 per 1000 births by 2030 [1]. Therefore, efforts geared towards preventing neonatal morbidity and mortality are of immense public health significance. In order to further reduce global and regional neonatal mortality, the concept of identifying and preventing neonatal near miss was initiated [1,4,5].

A neonatal near miss (NNM) can be defined as a neonate, within the first 28 days of life, who has significant morbidity and would otherwise die but survives either by chance or due to medical intervention [2,6]. The concept of NNM is analogous to that of maternal near miss, that is utilized to audit and monitor contemporary maternity practice. Likewise, NNM can be used to assess prenatal and intrapartum care in cases with severe neonatal morbidity [7]. Previously, some research focused on assessing neonatal mortality, which is an epidemiological tip of the iceberg of poor neonatal outcomes [1,5,8]. Moreover, Surve *et al*, in Mumbai, India reported that the ratio of NNM to neonatal mortality is approximately 9.4:1 [1]. Therefore, a more sensitive marker of the quality of perinatal and neonatal care would be the prevalence and pattern of NNM cases at a health facility [4].

Neonatal near miss may result in permanent or chronic debilitating conditions in adulthood. In addition to patients demanding explanations for poor outcomes, there has been a drastic upsurge in litigations related to intrapartum and perinatal care in South Africa [9]. Hence, a NNM surveillance system can highlight deficiencies in antenatal and intrapartum care, to improve neonatal practice in South Africa.

The range of global NNM rates was wide (21-72%) on account of varying diagnostic criteria [1]. In 2014, Pileggi-Castro *et al* developed a nearly universal NNM criteria after secondary data analysis of two World Health Organization (WHO) databases: WHO Global Survey on Maternal and Perinatal Health (WHOGS), and WHO Multi-country survey on Maternal and Newborn Health (WHOMCS) [6]. Subsequently, Pileggi-Castro *et al* classified the criteria for diagnosing NNM into pragmatic or management criteria.

Pragmatic criteria such as low Apgar score at 5 minutes of life (<7); low birthweight (<1750 g); and low gestational age (<33 weeks) are associated with prematurity and birth asphyxia, Fig. 1. Management criteria of NNM include the use of intravenous antibiotics; nasal continuous positive airway pressure; intubation within the first week of life; phototherapy administration within the first day of life; need for cardiopulmonary resuscitation; vasopressor, anticonvulsants, or steroids for hypoglycaemia use; surfactant administration; blood product transfusion; and the performance of any neonatal surgery [1,4].

Maternal socio-biological and obstetrics characteristics can impact on NNM and neonatal mortality. Extremes of maternal age, syphilis infection, severe pre-eclampsia, abruptio placenta, preterm delivery, low birth weight (LBW), poor

intrapartum care, intrapartum birth asphyxia, birth trauma, antepartum haemorrhage (APH), and caesarean section (C/S) delivery have been associated with either perinatal mortality or NNM [6,10–15]. However, a proportion of women have no recognizable obstetric or medical conditions at the time of a perinatal death [11]. Moreover, local obstetrics and neonatal practices, health systems and other environmental factors may modify and contribute to variation in the regional and sub-national prevalence of NNM [16].

South Africa is an upper middle-income country that abolished apartheid and commenced multi-racial democracy in 1994. Since then, the government of South Africa has made concerted efforts to expand access of qualitative reproductive health services to a larger percentage of the population [17]. A novel assessment of the outcome of current obstetrics and neonatal care is a review of NNM using a standardized tool [1].

We therefore conducted a case control study to evaluate the association of maternal socio-biological and obstetric factors and occurrence of NNM at a high-volume, public, mother and child hospital, in Johannesburg, South Africa. The OFANNM study aimed to assess factors in our setting which may be associated with the occurrence of neonatal near miss.

2 MATERIALS AND METHODS

2.1 Site and Study

A case-control study of 744 mother and new-born pairs was conducted at a mother and child hospital, from 1 January 2016 to 31 December 2016. Our study was conducted at Rahima Moosa Mother and Child Hospital, a public tertiary hospital in

Johannesburg, South Africa. A total of 13151 deliveries were conducted at this hospital, during the study period. Maternal sociodemographic and obstetric characteristics of babies diagnosed with NNM (n=372) based on the hospital's neonatal database were extracted from the database, using a Research Electronic Data Capture (REDCap) online data collection tool [18].

The database stored case information for babies admitted to the paediatric intensive care unit (PICU) and ward 16b (neonatal admission ward). These case files were the pool from which neonatal near miss cases were selected. Babies which had normal outcomes were selected from the admissions list of the postnatal ward, as this was the destination for all normal outcome babies, prior to discharge, Fig1.

The diagnosis of NNM was made in cases which satisfied either pragmatic or management criteria for NNM, as used by Santos *et al* [14]. The rationale for using these criteria for the identification of neonatal near miss, Fig.1, was that recent studies show a growing acceptance of these criteria as the standard for defining NNM. They were originally described by Pileggi-Castro *et al* in their 2013 publication [4] and have subsequently been used in multiple studies, exploring neonatal near miss [16,23,30].

The control group (n=372) comprised of mothers of normal babies born during the study period. Mothers who had early neonatal deaths were excluded from the study, because they no longer fit the definition of a neonatal near miss [2,6]. Poorly documented files were also excluded.

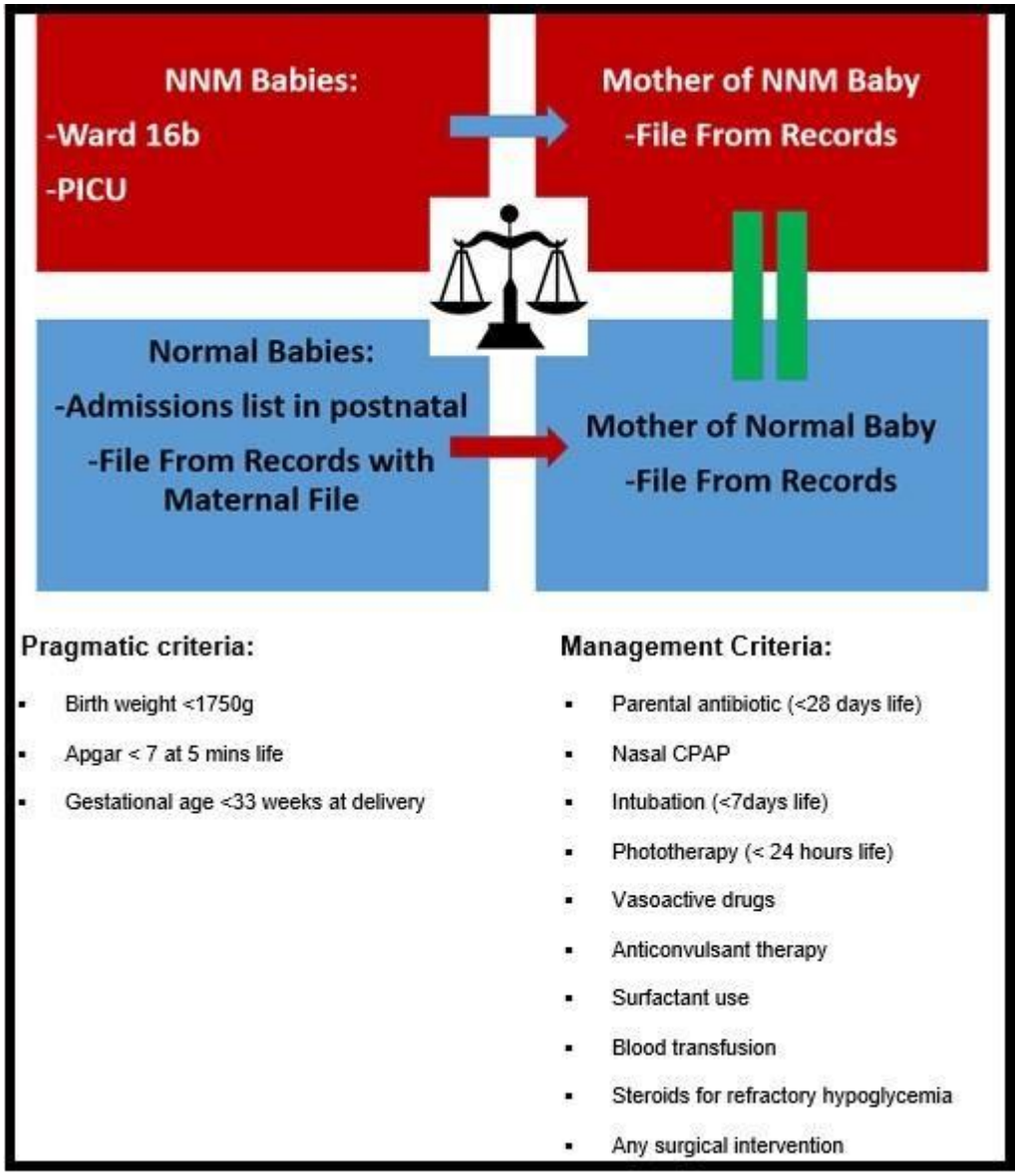

Figure 1. Selection Matrix and Neonatal Near Miss criteria: Neonatal near miss cases were obtained from the database of babies admitted to either ward 16b or Paediatric Intensive Care Unit (PICU). Normal cases were recruited from the postnatal wards admissions lists. Maternal files for both groups were then retrieved from records department for analysis. Pragmatic and Management inclusion criteria are as listed in the figure.

A sample size of 744 mother-infant pairs was determined using the ClinCalc.com online sample size calculator, (assuming 80% power, 95% confidence interval and 5% margin of error with a 1:1 sample of cases and control) [19]. The prevalence of NNM was taken as 7.25%, as it was reported in the WHO Multicountry Survey on Maternal and Newborn Health (2010-2011) [4]. The neonatal database identified 1517 NNM cases between 1 January to 31 December 2016. In-hospital deliveries

were 13151, while babies born before arrival (BBA) were 618, making total deliveries of 13769. A random number table was used to select 372 cases from the NNM cases. Similarly, 372 controls were selected from a total of 12252 non-NNM babies during the same period. [20]. Ethical clearance was obtained for the study from the Human Ethics Research Committee (Medical) of the University of the Witwatersrand (Clearance certificate no. M180108).

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2.2 Statistical analysis

The overall NNM and perinatal mortality rate (PMR) were calculated by dividing the annual and perinatal mortality for 2016 by the total deliveries in 2016 and then expressed per 1000 birth. Subsequently, NNM:PMR ratio was calculated. Data was exported from REDCap to Stata® version 13.0 (STATACorp, Texas, U.S.A.) statistical software for analysis [21]. Continuous variables such as maternal age or gestational age at delivery were described as mean (±standard deviation) or median (interquartile range), if not normally distributed. Categorical variables, such as mode of delivery, were described using frequencies and percentages.

Some continuous variables such as age were categorized into clinically relevant categories. Age was categorized into teenager (age <20 years), normal age (20-34 years) and advanced maternal age (≥ 35 years). Continuous variables were compared between the cases and controls using Student's t-test or Mann-Whitney U test (if not normally distributed). Association between categorical variables and outcome (near miss vs normal) was assessed using the Pearson's Chi square test (or Fischer's exact test for small numbers). Univariable logistic regression was conducted, using NNM as the outcome. Maternal factors were the explanatory

variables. The multivariable modelling was conducted using the backward elimination technique. Variables with P-value<0.2 were included in the multivariable model.

Some variables were included due to their presumed clinical relevance or suggested relevance, from the literature review. Eleven variables were included in our final model: age; race; non-sober social habits such as smoking, alcohol and illicit drug use; parity; BMI; RVD status; gestational age at delivery; chronic medical disorder; antenatal pregnancy specific disorder; delivering healthcare worker; and delivery type. Crude and adjusted odds ratios (with 95% confidence interval) were reported. The statistical significance level was set at a confidence interval of 95% (P-value of 0.05). Two-tailed test of significance was assumed. Collinearity of the variables were assessed with Variance inflation factor.

3 RESULTS

Of the 13769 births that occurred at our study site, from 1 January to 31 December 2016 , the perinatal deaths for 2016 was 400, giving a perinatal mortality rate of 30.4 per 1000 births [22]. The neonatal database identified a total of 1517 NNM cases, based on the pragmatic and management criteria. Therefore, the NNM rate was 110 per 1000 births, for 2016. Furthermore, NNM:PMR ratio was 3.6:1.

3.1 Sociodemographic Characteristics

The maternal mean age of the study population were 28.1(±5.97) years. About 6.5% (n=48) of the study population were teenage pregnancy while about 15.19% (n=113) were advanced maternal age (AMA). However, Teenage pregnancy and AMA were more prevalent in the NNM group compared to the controls (7.5% vs 5.4% and 19.4% vs 11 respectively, P-value=0.002), as seen in Table 1. There was no

statistically significant difference between the two groups with respect to the other sociodemographic factors.

Table 1. Comparison of the sociodemographic characteristics of NNM patients and controls.

Characteristics	NNM (%)	Controls (%)	Total (%)	P-value
Age (years) (n=744)				
Mean (±SD)	28.50 (±6.4)	27.66 (±5.8)	28.07 (±5.97)	0.066[a]
≤19	28 (7.53)	20 (5.38)	48 (6.45)	**0.002*[b]**
20-34	272 (73.12)	311 (83.6)	583 (78.36)	
≥35	72 (19.35)	41 (11.02)	113 (15.19)	
Race (n=735)				
Black	317 (86.14)	317 (86.38)	634 (86.26)	0.435[c]
White	9 (2.45)	9 (2.45)	18 (2.45)	
Coloured	36 (9.78)	30 (7.18)	66 (8.98)	
Indian/Asian	6 (1.63)	11 (3.00)	17 (2.32)	
Employment (n=713)				
Employed	112 (31.37)	136 (38.20)	248 (34.78)	0.056 [b]
Unemployed	245 (68.63)	220 (61.80)	465 (65.22)	
Habits (n=744)				
No Habits	333 (89.52)	356 (95.70)	689 (92.61)	**0.031[c]**
Alcohol use	7 (1.88)	4 (1.08)	11 (1.48)	
Smoking	16 (4.30)	10 (2.69)	26 (3.49)	
Recreational drugs	16 (4.30)	2 (0.54)	18 (2.42)	

NNM: Neonatal Near Miss, SD: standard deviation, [b]Pearson's chi-square test. [a]Student's t-test, [c]Fischer's Exact test, *P-value<0.05

3.2 Antenatal Care Characteristics

Antenatal characteristics, depicted in Table 2, had similar prevalence in the two study groups for: pregnancy risk classification, rapid plasma reagin (RPR), rhesus (Rh), retro viral disease (RVD) and RVD treatment statuses. Multiple pregnancies were more frequent in the near miss group as compared to the controls (8.6% vs 5%, P-value<0.001). The median gestational age at delivery was lower among the

NNM group as compared to the controls (36 (31-39) vs 38 (37 – 40), P-value<0.001). Early preterm deliveries (≤33^{+6} weeks) were about five-fold as common among the NNM group as compared to the controls (41.52% vs 7.71%, P-value<0.001).

Table 2. Comparison of the antenatal care characteristics of patients who sustained neonatal near miss and controls.

	NNM (%)	Controls (%)	Total (%)	[a]P-value
Characteristics				
Gestation (n=744)				
Singleton	340 (91.4)	367 (98.66)	707 (95.03)	**<0.001***
Multiple	32 (8.60)	5 (1.34)	37 (4.97)	
Gravidity (n=744)				
Median (IQR)	2(1-3)	2(2-3)	2(1-3)	0.8264
Primigravida	101 (27.15)	85 (22.85)	186 (25.00)	0.176
≥2 Pregnancies	271 (72.85)	287 (77.15)	558 (75.00)	
Parity (n=740)				
Median (IQR)	2(1-2)	2(1-2)	2(1-2)	0.4661
Nulliparous	113 (30.38)	102 (27.72)	215 (29.05)	0.649
Multiparous (P1-P4)	256 (68.82)	264 (71.74)	520 (70.27)	
Grand Multiparous (≥5)	3 (0.81)	2 (0.54)	740 (100.00)	
History of TOP (n=744)				
No Previous TOP	328 (88.17)	347 (93.28)	675 (90.73)	
Previous TOP	44 (11.83)	25 (6.72)	69 (9.27)	**0.016***
History of Ectopic (n=744)				
No Previous Ectopic	340 (91.40)	346 (93.01)	686 (92.20)	0.412
Previous Ectopic	32 (8.60)	26 (6.99)	58 (7.80)	
Delivery Gestational Age (n=680)				
Median (IQR)	36 (31-39)	38 (37-40)	38 (35-39)	**<0.001***
≤33^{+6}	137 (41.52)	27 (7.71)	164 (24.12)	**<0.001***
34-37^{+6}	70 (21.21)	77 (22.00)	147 (21.62)	
38-40^{+6}	115 (34.85)	236 (67.43)	351 (51.62)	
≥41	8 (2.42)	10 (2.86)	18 (2.65)	
Booking Status (n=744)				
Booked	347 (93.28)	359 (96.51)	706 (94.89)	**0.046***
Unbooked	25 (6.72)	13 (3.49)	38 (5.11)	
Time of Booking (n=744)				
Booked ≤13^{+6}/40	34 (9.14)	41 (11.02)	75 (10.08)	0.05
Booked ≥14/40	309 (83.06)	317 (85.22)	626 (84.14)	
Unspecified	29 (7.8)	14 (3.76)	43 (5.73)	
Antenatal Visits (n=676)				

≤2 visits	87 (26.77)	59 (16.81)	146 (21.60)	**0.002***
≥3 visits	238 (73.23)	292 (83.19)	530 (78.40)	
Antenatal Risk Class (n=744)				
Low	179 (57.53)	214 (48.12)	393 (52.82)	0.055
Medium	62 (16.67)	56 (15.05)	118 (15.86)	
High	54 (14.52)	37 (9.95)	91 (12.23)	
Unclassified	77 (20.70)	65 (17.47)	142 (19.05)	
BMI (n=382)				
≤19.8 (underweight)	16 (8.89)	8 (3.96)	24 (6.28)	0.267
19.9-24.9 (normal)	45 (25.00)	62 (30.69)	107 (28.01)	
25-29.9 (overweight)	57 (31.67)	70 (34.65)	127 (33.25)	
30-34.9 (obese class1)	33 (18.33)	35 (17.33)	68 (17.80)	
35-39.9 (obese class2)	17 (9.44)	19 (9.41)	36 (9.42)	
≥40 (obese class3)	12 (6.67)	8 (3.96)	20 (5.24)	
Booking Hb (g/dL) (n=744)				
Mean (±SD)	11.96 (1.91)	11.93 (1.59)	11.95 (1.77)	0.8153[b]
Normal (≥11)	233 (62.63)	244 (65.59)	477 (64.11)	**<0.001***
Anaemic (≤10.9)	98 (26.34)	115 (30.91)	213 (28.63)	
Untested	41 (11.02)	13 (3.49)	54 (7.26)	
RPR test Status (n=744)				
Non-Reactive	339 (91.13)	351 (94.35)	690 (92.74)	0.200
Reactive	5 (1.34)	2 (0.54)	7 (0.94)	
Unknown	28 (7.53)	19 (5.11)	47 (6.32)	
Rh Group Status (n=744)				
Positive	351 (94.35)	357 (95.97)	708 (95.16)	0.559
Negative	10 (2.69)	8 (2.15)	18 (2.42)	
Unknown	11 (2.96)	7 (1.88)	18 (2.42)	
RVD Status (n=744)				
Positive	64 (17.20)	74 (19.89)	138 (18.55)	0.635
Negative	277 (74.46)	269 (72.31)	546 (7.39)	
Unknown	31 (8.33)	29 (7.80)	60 (8.06)	
RVD Rx Status (n=138)				
Non-applicable (HIV neg)	308 (82.80)	298 (80.11)	606 (81.45)	0.728
Positive on ART	59 (92.19)	70 (94.59)	129 (93.48)	
Positive ART naïve	3 (4.69)	2 (2.7)	5 (3.62)	
Positive and unknown treatment	2 (3.13)	2 (2.7)	4 (2.9)	

NNM: Neonatal Near Miss, BMI: Body Mass Index (weight/[height(M^2)]^2, TOP: Termination of Pregnancy, SD: standard deviation, RPR: Rapid Plasma Reagin, Rh: Rhesus, RVD: Retroviral disease, [a]Pearson's chi-square analysis, [b]Student's t-test, *P-value <0.05

A higher incidence of previous pregnancy termination (TOP) was observed in the NNM group (11.83% vs 6.72%, P-value 0.016). Unbooked status was almost twice as common in the near miss group versus the controls (6.72% vs 3.49%, P-value=0.046). Mothers of babies with NNM that attended less than 3 antenatal visits had a higher more prevalent in the near miss group (26.77% vs 16.81%, P-value=0.002).

Anaemia was more prevalent in the control group (30.91% vs 26.34%, P-value<0.001). However, there was a greater number of individuals with untested haemoglobin levels in the near miss group (11.02% vs 3.49%, P-value<0.001). Frequencies of pre-existing medical disorders were not significantly different across the study groups, as shown in Table 3. Pregnancy specific complications were generally more frequent in the near miss group as about 35.02% of the study population were complicated by hypertensive disorders in the index pregnancy. Hypertensive disorders were more common in the near miss group compared to the controls (38.39% vs 24.24%, P-value<0.001). Preterm labour (22.75% vs 13.64%, P-value<.001) and APH (8.06% vs 4.55%, P-value<0.001) were more frequent among the near miss group versus the controls. Interestingly, the diagnosis of foetal Distress occurred more frequently in the control group (18.18% vs 7.11%, P-value<0.001).

Table 3. Characteristics of antepartum conditions complicating the current pregnancy of NNM patients and controls.

Characteristics	NNM (%)	Controls (%)	Total (%)	[a]P-value
Pre-existing medical disorders (n=744)				
No medical disorder	345 (92.74)	359 (96.51)	704 (94.62)	
Chronic Hypertension	19 (70.37)	7 (53.85)	26 (65.00)	**0.043***
Diabetes Mellitus	3 (11.11)	1(7.69)	4 (10.00)	
Asthma/COAD	4 (14.81)	2 (15.38)	6 (15.00)	
Thyroid Disorder	0 (0.00)	3 (23.08)	3 (7.50)	

Cardiac Disorder	1 (3.70)	0 (0.00)	1 (2.50)	
Pregnancy specific complication (n=744)				
None	161 (43.28)	306 (82.26)	467(62.77)	
[b]Hypertensive Disorder	81 (38.39)	16 (24.24)	97 (35.02)	**<0.001***
Antepartum Haemorrhage	17 (8.06)	3 (4.55)	20 (7.22)	
Gestational Diabetes	8 (3.79)	4 (6.06)	12 (4.33)	
Preterm Labour	48 (22.75)	9 (13.64)	57 (20.58)	
PPROM	8 (3.79)	1 (1.52)	9 (3.25)	
PROM	6 (2.84)	8 (12.12)	14 (5.05)	
Chorioamnionitis	3 (1.42)	0 (0.00)	3 (1.08)	
Malpresentation	4 (1.90)	6 (9.09)	10 (3.61)	
IUGR	4 (1.90)	0 (0.00)	4 (1.44)	
Foetal Distress	15 (7.11)	12 (18.18)	27 (9.75)	
[c]Other Complication(s)	17 (8.06)	7 (10.61)	24 (8.66)	

COAD: Chronic Obstructive Airway Disease, NNM: Neonatal Near Miss, PROM: Pre-labour Rupture of Membranes, PPROM: Preterm Pre-labour Rupture of Membranes, IUGR: Intrauterine Growth restriction, [a]Pearson's chi-square test, [b]Hypertensive disorders include: Gestational Hypertension, Pre-Eclampsia, HELLP Syndrome, Imminent Eclampsia and Eclampsia, [c]Other Complications included: liver dysfunction, non-eclamptic seizures, respiratory tract infections, urinary tract infections, vaginal discharge syndrome, cephalopelvic disproportion, foetal macrosomia, fibroids in pregnancy, *P-value <0.05

3.3 Intrapartum and delivery factors

There was no statistically significant difference in terms of intrapartum factors such as mode of delivery, induction methods, augmentation of labour, partogram use, electronic foetal monitoring and delivery difficulties, among the two groups, shown in Table 4. However, emergency C/S was performed at a greater frequency in the near miss group (77.97% vs 60.19%, P-value<0.001). In contrast, elective C/S rate was higher in the control group (39.81% vs 22.03%, P-value<0.001). Spontaneous labour was more frequent in the control group (94.98% vs 89.38, P-value=0.024), whereas induction of labour (IOL) was twice as frequent in the near miss group as in the controls (10.62% vs 5.02%, P-value=0.024).

Table 4. Comparison of intrapartum events between cases and controls.

	NNM (%)	Controls (%)	Total (%)	[a]P-value
Characteristics				
Previous C/S (n=167)				
No previous C/S	303 (81.45)	274 (73.66)	577 (77.55)	**0.038***
1 Previous C/S	49 (71.01)	70 (71.43)	119 (71.26)	
2 Previous C/S	17 (24.64)	27 (27.55)	44 (26.35)	
≥3 Previous C/S	3 (4.35)	1 (1.02)	4 (2.40)	
Mode of Delivery (n=744)				
Vaginal Delivery	145 (39.98)	156 (41.96)	301 (40.46)	0.565
NVD (in hospital)	129 (34.68)	143 (38.44)	272 (36.56)	
BBA (out of hospital)	13 (3.49)	12 (3.23)	25 (3.36)	
Assisted Vaginal Delivery	3 (0.81)	1 (0.27)	4 (0.58)	
Caesarean Section Delivery	227 (61.02)	216 (58.06)	443 (59.54)	**<0.001***
Elective C/S	50 (22.03)	86 (39.81)	136 (30.70)	
Emergency C/S	177 (77.97)	130 (60.19)	307 (69.30)	
Labour Onset (n=465)				
Spontaneous Labour	202 (89.38)	227 (94.98)	429.7 (92.26)	**0.024***
Induction of Labour	24 (10.62)	12 (5.02)	36 (7.74)	
Induction Methods (n=27)				
Oral Misoprostol	11 (64.71)	8 (80.00)	19 (70.37)	0.233
Vaginal Prostaglandin	1 (5.88)	2 (20.00)	3 (1.11)	
Intravenous Oxytocin	4 (23.53)	0 (0.00)	4 (14.81)	
Foley's Catheter	1 (5.88)	0 (0.00)	1 (3.70)	
Augmentation of Labour (n=40)				
Oxytocin	18 (8.33)	19 (7.95)	3 (8.13)	0.881
Successful augmentation	9 (50.00)	7 (36.84)	16 (43.24)	0.419
Unsuccessful augmentation	9 (50.00)	12 (63.16)	21 (56.76)	
Partogram Use (n=326)				
Adequate 2 hourly plot	104 (80.62)	170 (86.73)	274 (84.31)	0.138
Inadequate 2 hourly plot	25 (19.38)	26 (13.27)	51 (15.69)	
Foetal Monitoring (n=744)				
EFM done	295 (79.30)	311 (83.60)	606 (81.45)	0.131
EFM not done	77 (20.70)	61 (16.40)	138 (18.55)	
[b]EFM Category (n=597)				
Unsigned Trace	53 (18.21)	63 (20.59)	116 (19.43)	**0.026***
Cat1/Reassuring/Reactive	126 (43.30)	160 (52.29)	286 (47.91)	
Category 2/Suspicious/Non-Reassuring	58 (19.93)	47 (15.36)	105 (17.59)	
Category 3/Abnormal/Pathological	54 (18.56)	36 (11.76)	90 (15.08)	
Delivering Healthcare Worker (n=744)				
Not applicable (BBA/Unknown)	29 (7.80)	18 (4.84)	47 (6.32)	
Midwife	99 (26.61)	134 (36.02)	233 (31.32)	**<0.001***
Intern Doctor	11 (2.96)	3 (0.81)	14 (1.88)	

Community Service Doctor	17 (4.57)	68 (18.28)	85 (11.42)	
Registrar Doctor	216 (58.06)	149 (40.05)	365 (49.06)	
Delivery Difficulty (n=744)				
No Delivery Difficulty	352 (94.62)	361 (97.04)	713 (95.83)	0.101
Documented Delivery Difficulty	20 (6.13)	11 (3.40)	31 (4.77)	

BBA: Born Before Arrival, C/S: Caesarean Section, EFM Electronic Foetal Monitoring, NVD: Normal Vaginal Delivery, NNM: Neonatal Near Miss, [a]Pearson's chi-square analysis, [b]EFM was documented in 9 cases to have been done however, CTGs were not in files for analysis. Thus n=597, *P-value <0.05

Electronic foetal monitoring (EFM) was performed in about four-fifth (81%, n=606) of the study population. There was no statistically significant difference between the two groups, regarding the frequency of performing EFM. Pathological (18.56% vs 11.76%, P-value=0.026) and suspicious traces (19.93% vs 15.36%, P-value=0.026) were more common among the near miss group as to the controls.

Most of the deliveries were conducted by registrar doctors or midwives (49.06% and 31.32% respectively). NNM was more prevalent in patients delivered by registrar doctors (58.06% vs 40.05% control, P-value<0.001).

3.4 Regression analyses

Univariable logistic regression analysis showed that; AMA, social habits, underweight, preterm delivery, previous TOP, unbooked status, untested Hb, chronic medical disorder, antenatal pregnancy complication, IOL, pathological trace, delivery by an intern or registrar, multiple pregnancy, 2 or less ANC visits, having a high-risk classification and emergency C/S delivery were all significantly associated with an increased prevalence of NNM. Deliveries by a community service doctor and elective caesarean section deliveries were associated with a decrease in NNM (P-value <0.05) (Table 5).

Table 5: Univariable and multivariable logistic regression of maternal factors of neonatal near miss.

Factors	Univariable logistic regression			Multivariable logistic regression		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age (Years)						
20-34	1.00	Ref	Ref	1.00	Ref	Ref
Teenage Pregnancy (≤19)	1.60	0.88-2.90	0.122	0.61	0.12-3.13	0.555
Advanced Maternal Age (≥35)	2.01	1.32-3.05	**0.001***	2.65	1.10-6.41	**0.029***
Race						
White	1.00	Ref	Ref	1.00	Ref	Ref
Black	0.48	0.39-2.55	1.000	1.01	0.18-5.52	0.991
Coloured	0.64	0.42-3.41	0.732	1.21	0.16-8.95	0.850
Indian/Asian	0.38	0.14-2.12	0.382	0.67	0.06-7.20	0.741
Social Habits						
No Habits	1.00	Ref	Ref	1.00	Ref	Ref
Habits	2.61	1.43-4.75	**0.002***	4.48	1.54-13.05	**0.006***
Parity						
Nulliparous	1.00	Ref	Ref	1.00	Ref	Ref
Multiparous	0.87	0.64-1.20	0.453	0.62	0.33-1.12	0.145
BMI						
19.9-24.9 (normal)	1.00	Ref	Ref	1.00	Ref	Ref
≤19.8 (underweight)	2.76	1.09-6.99	**0.033***	4.40	1.22-15.80	**0.023***
≥25 (Increased BMI)	1.24	0.79-2.00	0.352	1.13	0.58-2.19	0.724
RVD Status						
Negative	1.00	Ref	Ref	1.00	Ref	Ref
Positive	0.84	0.58-1.22	0.361	0.56	0.26-1.18	0.128
Unknown	1.04	0.61-1.77	0.891	1.79	0.50-6.48	0.373
Delivery Gestational Age						
38-40+6 weeks	1.00	Ref	Ref	1.00	Ref	Ref
≤33+6	10.41	6.51-16.64	**<0.001***	4.56	1.92-10.83	**0.001***
34-37+6	1.87	1.26-2.76	**0.002***	1.35	0.68-2.67	0.394
≥41	1.64	0.63-4.27	0.309	0.72	0.16-3.23	0.663
Chronic Medical Disorder						
No disorders	1.00	Ref	Ref	1.00	Ref	Ref
Chronic d/o present	2.16	1.09-4.26	**0.026***	0.52	0.11-2.46	0.406
Antenatal Pregnancy Specific Disorder						
No Antenatal disorder	1.00	Ref	Ref	1.00	Ref	Ref
Antenatal disorder developed	6.08	4.34-8.50	**<0.001***	5.19	2.61-10.30	**<0.001***
Delivering Healthcare Worker						
Midwife	1.00	Ref	Ref	1.00	Ref	Ref
Intern	4.96	1.35-18.26	**0.016***	44.7	2.27-880.06	**0.012***
Community Service	0.34	0.19-0.61	**<0.001***	0.44	0.81-2.39	0.341

Registrar	1.96	1.40-2.74	**<0.001***	5.91	1.61-21.74	**0.008***
Delivery Type						
Vaginal/BBA	1.00	Ref	Ref	1.00	Ref	Ref
Emergency C/S	1.46	1.06-2.02	**0.019***	0.19	0.05-0.69	**0.012***
Elective C/S	0.63	0.41-0.95	**0.027***	0.22	0.06-0.88	**0.032***
Employment						
Unemployed	1.00	Ref	Ref			
Employed	0.74	0.54-1.01	0.056			
Booking Status						
Booked ≤13+6/40	1.00	Ref	Ref			
Booked ≥14/40	1.18	0.73-1.90	0.510			
Unspecified/Unbooked	2.50	1.14-5.47	**0.022***			
Booking Hb						
Normal (≥11)	1.00	Ref	Ref			
Anaemic (≤10.9)	0.89	0.65-1.23	0.491			
Untested	3.30	1.73-6.32	**<0.001***			
Labour Onset						
Spontaneous Labour	1.00	Ref	Ref			
Induction of Labour	2.25	1.10-4.61	**0.027***			
EFM Category						
Category1/Reassuring/Reactive	1.00	Ref	Ref			
Category2/Suspicious/Non-Reas	1.57	1.00-2.46	0.050			
Category3/Abnormal/Pathological	1.93	1.18-3.13	**0.008***			
Unsigned Trace	1.03	0.66-1.59	0.896			
History of TOP						
No TOP	1.00	Ref	Ref			
Previous TOP	1.86	1.11-3.11	**0.018***			
Previous Caesarean Section						
1 Previous C/S	1.00	Ref	Ref			
2 Previous C/S	0.90	0.44-1.83	0.769			
≥3 Previous C/S	4.29	0.43-42.42	0.213			
Gestation Type						
Singleton	1.00	Ref	Ref			
Multiple	6.91	2.66-17.93	**<0.001***			
Antenatal visits						
≥3 visits	1.00	Ref	Ref			
≤2 visits	1.81	1.25-2.63	**0.019***			
Antenatal Risk Classification						
Low	1.00	Ref	Ref			
Medium	1.32	0.88-2.00	0.183			
High	1.74	1.10-2.77	**0.018***			
Unclassified	1.42	0.96-2.08	**0.077***			
RPR Status						

Non-Reactive	1.00	Ref	Ref
Reactive	2.59	0.50-13.43	0.258
Unknown	1.53	0.84-2.78	0.168
Rh group			
Positive	1.00	Ref	Ref
Negative	1.27	0.50-3.26	0.617
Unknown	1.60	0.61-4.17	0.338
Partogram Use Adequacy			
Adequate 2 hourly plot	1.00	Ref	Ref
Inadequate 2 hourly plot	1.57	0.86-2.87	0.140
Electronic Foetal Monitoring			
EFM done	1.00	Ref	Ref
EFM not done	1.36	0.94-1.98	0.107
Reported Difficulties with Delivery			
No difficulty reported	1.00	Ref	Ref
Difficulty reported	1.86	0.88-3.95	0.106

BBA: Born Before Arrival, BMI: Body Mass Index (weight/[height(M^2)]^2, C/S: Caesarean Section, EFM: Electronic Foetal Monitoring, Habit: includes alcohol ingestion, smoking and illicit drug use. Hb: haemoglobin, Non-Reas: Non-reassuring, NVD: Normal Vaginal Delivery, Rh: Rhesus, RPR: Rapid Plasma Reagin, RVD: Retroviral disease, TOP: Termination of Pregnancy, *P-value <0.05

After adjusting for potential confounders, in a multivariable regression model, the study found that patients with advanced maternal age had about 2.7-fold odds of NNM (OR=2.65 95% CI: 1.10-6.41, P=0.029) as compared to women aged 20-34 years. Women who had non-sober social habits were about 4.5 -fold more likely to experience NNM as compared to women with no habits (OR=4.48, 95% CI: 1.54-13.05, P=0.006).

Those who were underweight (BMI ≤19.8) were 4-fold more likely to have a NNM as compared to normal weight patients (OR=4.40, 95% CI: 1.22-15.80, P=0.023). Gestational age <33^{+6} weeks was associated with a four and half-fold increased odds of NNM as compared to term babies (OR=4.56, 95% CI: 1.92-10.83, P=0.001). Women whose pregnancies were complicated with an antenatal pregnancy disorder

had about 5-fold increased odds of having NNM as compared to women who had no complication (OR=5.19, 95% CI: 2.61-10.30, P<0.001).

Intern doctor delivery was associated with 44-fold increase in NNM compared to midwife deliveries (OR=44.7, 95% CI: 2.27-880.06, P=0.012), whilst registrar doctor delivery was associated with a near 6-fold increase in NNM (OR=5.91, 95% CI: 1.61-21.74, P=0.008). At multivariable logistical regression level, both elective and emergency C/S delivery were found to be protective. Elective C/S was associated with a 78% reduction in odds of having a NNM (OR=0.22, 95% CI: 0.05-0.87, P=0.031). Emergency C/S was associated with an 81% decrease in NNM (OR=0.19, 95% CI: 0.05-0.69, P<0.012).

4 Discussion

Neonatal near miss is a useful contemporary means of evaluating the quality of obstetric and neonatal services [5–7]. This study was therefore conducted to assess the obstetric factors associated with NNM at a large public mother and child hospital in Johannesburg to guide practice. Multiple obstetric factors were identified to be associated with NNM.

We found that mothers of babies with NNM were older than mothers of babies in the control group. Advanced maternal age (≥ 35 years) was significantly more prevalent in the NNM group. Furthermore, we found that there was an over two-fold increase in NNM among women with advanced age at multivariable regression. This report was in line with the report of Mersha *et al*, who also found an association between AMA and NNM [16]. Our results however contrast with those of de Lima *et al*, that found AMA to be protective against NNM [23].

Advanced maternal age has been associated with pregnancy complications, such as hypertensive disorders, diabetes mellitus, large for gestational age, foetal growth restriction, preterm birth, dysfunctional labour, leiomyomata in pregnancy, multiple gestation, congenital anomalies, placenta previa and abruptio, and caesarean section delivery [24]. Thus, women with AMA should be considered high-risk and monitored to prevent NNM.

Our study showed that mothers who had non-sober social habits such as smoking, alcohol use or illicit drug use, had an approximately 4-fold likelihood of having a baby with NNM as compared to women with none of those habits. Our findings agreed with those of Kale *et al*, that was conducted among a Brazilian population [13]. Smokers are predisposed to develop foetal growth restriction, placenta previa and abruptio placenta [25]. Likewise, alcohol has been associated with reduced weight and length of the foetus/babies while cocaine use has been associated with preterm delivery and reduced foetal head circumference [25]. These associations may be extrapolated to contribute towards severe neonatal morbidity, manifesting as NNM.

There was no statistically significant difference in the risk of having NNM between primigravid and multiparous patients in our study. This finding differs from those of Mersha *et al*, who found multiparous patients to be at increased risk of NNM [16]. The large prospective cohort study of De Lima *et al* also found primigravid patients to be at lower risk of NNM [23]. Primigravid patients have an increased incidence of unbooked status, hypertensive disorders of pregnancy, IUGR, preterm labour and LBW, oligohydramnios, and emergency C/S delivery. These factors contribute to adverse neonatal outcomes; therefore, one would expect a higher rate of NNM

among primigravid women [26]. A further study, looking into the relationship between parity and NNM may be needed to clarify this finding.

In this study, mothers who were underweight showed increased risk of NNM. NNM was about 4-fold more prevalent amongst underweight women as compared to normal weight women. Whilst most literature reports that maternal obesity contributes to poor neonatal outcomes, our study rather suggests that underweight presents a more ominous sign for developing NNM [27]. Although emphasis should be placed on counselling women about the deleterious impact of obesity and the need to lose weight, intervention should also be undertaken for underweight women to achieve normal weight for height. Further studies are needed to evaluate underweight and perinatal outcomes.

Medical conditions, such as hypertension and diabetes mellitus are well associated with NNM [2,10,11,14]. Our study suggests that the development of any medical or pregnancy specific disorder during the pregnancy carries a higher risk for neonatal near miss than that of a chronic disorder. We could postulate that levels of control of chronic disorders are high in our population whilst new disorders arising during pregnancy may be allowed to have a greater impact due to delays between diagnosis and management.

Induction of labour doubled the risk, when compared to spontaneous onset labour. This is in keeping with the findings of a large Austrian cohort study, which concluded that IOL increases risk of poor foetal outcome, however due to confounding factors recommendations on its use are still to be determined [28]. Indications for IOL should

be further assessed, as well as the appropriateness of intrapartum care in these groups.

Partogram use was adequate in most cases, with an insignificant difference in outcomes, in cases where it was not used adequately. Whilst poor progress of labour and the lack of partogram use may be clinically relevant and expected to influence neonatal outcome, no significant difference was found between the two groups. Also, our study did not assess the partogram diagnosis of poor progress of labour, so a further study might be required to further explore the role of poor labour progress and NNM.

Caesarean section delivery was significantly associated with NNM. Elective C/S reduced the risk of NNM. Whilst Emergency C/S was associated with a 46% increase in NNM in the univariable logistic regression, multivariable regression found it to reduce the risk of NNM. This would suggest that emergency caesarean section be considered only when multiple risk factors for NNM exits. These findings also suggest that elective C/S delivery be the preferred mode of delivery when wanting to decrease NNM in high-risk patients. It was also found that more emergency C/S deliveries were performed in the NNM group as compared to elective C/S deliveries, which would suggest that the delivery of high-risk cases be done on an elective basis. Benzounia *et al* had a similar finding in their study, that emergency C/S has a higher rate of poor foetal outcomes when compared to elective C/S [29].

A delivery conducted by a registrar had an almost six-fold increased odds in NNM rates. This was an expected result since difficult and high-risk deliveries are likely to be referred to and managed by the registrar. On the other hand, deliveries by interns

are expected to be among low-risk pregnancies. However, inexperience might have led to a very high odds of NMM (up to 44 folds) among the few deliveries (n=14) conducted by Interns, possibly during a very busy shift and an acute emergency situation, when the more experienced registrars were busy in theatre or attending to other cases. There was no statistically significant difference in the odds of NNM among community service doctors and midwives.

An unforeseen finding was the association of previous pregnancy TOP with subsequent pregnancy NNM. Our study found that one had an almost 2-fold odds increase of having a NNM if they had a previous TOP. A recent study in South Ethiopia showed that 9.4% of women with NNM had experienced one or more previous TOP [30]. Therefore, patients who have undergone a previous TOP should be considered at risk of a poor neonatal outcome. Further research into the association of TOP and subsequent pregnancy NNM is needed.

The association between HIV and NNM is not well documented. However, HIV infection and ART use has been associated with adverse pregnancy outcome such as preterm delivery, LBW and pre-labour rupture of membranes, among others [31]. One would expect such adverse outcomes to increase the risk of NNM. Surprisingly, HIV infection was not found to be associated with increased prevalence of NNM among our cohort of participants. This contrasts with another study that found significant risk for cerebral palsy.

Maternal Health in South Africa is significantly affected by the HIV/AIDS epidemic [32]. Our result may suggest that the concerted public health and obstetric interventions such as widescale HIV testing, expansion of ART access and obstetric

prevention of mother to child transmission strategies, might have reduced the incidence of HIV associated adverse pregnancy outcomes. Furthermore, it is likely that most HIV positive patients presented with suppressed and undetectable viral loads before pregnancy. A further study is required to validate this finding.

We found that there was no statistically significant association between ethnicity or employment status and NNM. This is contrary to what is suggested by most literature, which finds these factors to have an impact on adverse pregnancy outcome [33]. This is because ethnicity and employment status may be a surrogate for socio-economic status. Education level which is commonly assessed in literature is not regularly documented in our antenatal files and thus was not assessed in our study. More research is needed to further investigate the importance of this factor.

Women with higher socio-economic status tend to have lower incidence of adverse pregnancy outcome [33]. American studies report that disparities in outcome exist not only in differing income and education groups, but also in racial groups of similar higher education [33]. A Brazilian cross-sectional study found the impact of race and ethnicity as individual factors statistically insignificant. They concluded that rather poorer socioeconomic status, access to healthcare services, and lower education levels should be the focus of research, evaluating risks for poor outcome [34].

Our findings may be because our study site is a public hospital that mainly serves low and middle-class women. Furthermore, most of the patients that access care at the hospital, are blacks. Hence, race and ethnicity may not impact on outcome at the hospital, due to homogeneity of the population. In South Africa, patients from a higher socio-economic class are likely to seek care at private hospitals [35]. In

addition to this, white patients are reported to have the lowest propensity to use public healthcare of all the races [35].

This study highlights that significant patient demographic, sociobiological, antenatal, and intrapartum factors exist, that are associated with NNM. If we are to target specific areas of perinatal management, it can be assumed that the factors identified in this study should be chief targets for intervention. From the OFANNM study outcome, it can be deduced that within the group of high-risk obstetric patients, there exist a subgroup of patients that can be deemed at risk of NNM (the NNMr patient). The NNM risk patient factors, as suggested from our OFANNM study, can be seen in infographic figure 2, below. Factors significant at multi-logistic regression level are summarized in table 6.

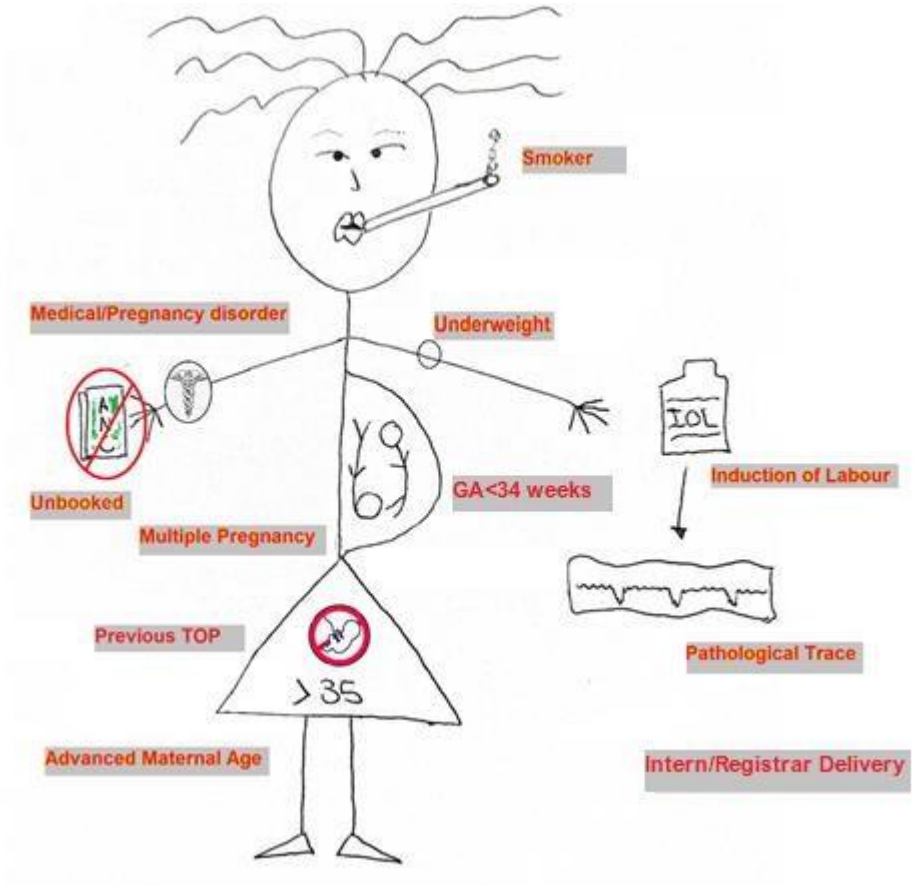

Figure 2 Patient NNMr sketch. A practical diagrammatic representation of the patient at risk of neonatal near miss

Table 6: Major neonatal near miss risk patient factors

Sociodemographic Factors	Antenatal Factors	Delivery Factors
Advanced maternal age Smoking/alcohol/drugs Previous TOP	Underweight BMI Pathological trace Gestational age ≤33+6 Pregnancy specific disorder Unbooked Medical/Pregnancy disorder Multiple pregnancy	Induction of labour Intern delivery Registrar delivery Community Service doctor delivery* Elective C/S* Emergency C/S*

Key: BMI: body mass index, C/S: caesarean section, TOP: termination of pregnancy, *indicates a protective factor

The outcome of this study should be interpreted within its limitations. Although replicable, the study used a definition of NNM that in many cases may be subjective and may vary, based on the criteria used by different institutions. Another issue relating to the NNM definition, used in our study is that of selection bias, which may have arisen from the inclusion of preterm gestation <33+6 and birth weight <1750g.

These pragmatic criteria were used by Pileggi-Castro *et al* [4], and thus adopted into our study. Delivery gestation of <33+6 and birth weight <1750g do not necessarily translate into morbidity or a poor outcome, although they were used in the defining criteria for NNM. It is likely that this is contributory to the significant association with gestational age in the multivariable logistic regression analysis (Table 5).

Some variables such as duration of labour were not explicitly stated in the records. Furthermore, some data such as CD4 counts and viral loads, in the case of HIV positive patients, would have been collected from the mothers if the study were to be prospective. Due to the study being retrospective, diligent filing and documentation was not guaranteed. Bias might have been introduced due to the exclusion of poorly documented files from the study.

A strength of this study is the relatively large sample size which powered the study adequately to minimize type II error. The population chosen was a random selection of patients that are serviced by our study hospital and so findings are truly representative of the catchment population. Furthermore, several possible maternal explanatory variables were evaluated in this study.

Now that obstetric factors have been identified as markers for NNM, further study is needed to assess if there is a cumulative effect of having one or more of the factors on the risk for NNM. Strategies targeted at augmenting the modifiable OFANNMs should be explored, and reduction rates assessed. The near miss concept should be incorporated into broader practice and patients that have any of the identified

markers that would describe patient NNMr should be managed at higher centres with C/S and paediatric services with a near miss outcome being anticipated.

5 Conclusion

Some obstetric factors, associated with NNM, are similar to those that contribute to adverse outcomes and perinatal mortality. Significant demographic, antenatal, and intrapartum/delivery factors have been identified which should be focus points of intervention strategies to reduce NNM. Advanced maternal age, social habits, underweight BMI, delivery gestations ≤33+6 weeks, pregnancy specific disorders and delivery by intern or registrar are associated with NNM. Caesarean section delivery is protective.

Some key obstetric factors such as maternal HIV infection, ethnicity, employment status and anaemia status did not have a statistically significant association with NNM. More research is encouraged to further explore these factors and assess the efficacy of interventions. This report will guide counselling and development of protocols to prevent NNM in Johannesburg South Africa.

6 Acknowledgements

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Supporting Information

Figure 1. Selection Matrix and Neonatal Near Miss criteria

(.png)

Table 1. Comparison of the sociodemographic characteristics of NNM patients and controls.

(docx)

Table 2. Comparison of the antenatal care characteristics of patients who sustained neonatal near miss and controls.

(docx)

Table 3. Characteristics of antepartum conditions complicating the current pregnancy of NNM patients and controls.

(docx)

Table 4. Comparison of intrapartum events between cases and controls.

(docx)

Table 5. Univariable logistic regression of maternal factors of neonatal near miss. (docx)

Table 6. NNMr patient factors

(docx)

Data file.

(DTA)

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Conflicts of Interest

The authors declare that no conflict of interest exist.

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Appendix

1. Turnitin Report
2. PLOS one Journal Author Guide
3. OFANNM Research Protocol
4. HREC Ethical Clearance

Appendix1:

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Accepted, unpublished articles	Same as published articles, but substitute “Forthcoming” for page numbers or DOI.
Online articles	Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14

Source	Format
Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
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Deposited articles (preprints, e- prints, or arXiv)	Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity. arXiv:1403.3301v1 [Preprint]. 2014 [cited 2014 March 17]. Available from: https://128.84.21.199/abs/1403.3301v1 Kording KP, Mensh B. Ten simple rules for structuring papers. BioRxiv [Preprint]. 2016 bioRxiv 088278 [posted 2016 Nov 28; revised 2016 Dec 14; revised 2016 Dec 15; cited 2017 Feb 9]: [12 p.]. Available from: https://www.biorxiv.org/content/10.1101/088278v5 doi: 10.1101/088278
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Multimedia (videos, movies, or TV shows)	Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

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List of Abbreviations

Caesarean Section (C/S)

Continuous Positive Airway Pressure (CPAP)

Hypoxic Ischaemic Encephalopathy (HIE)

Midwife obstetric units (MOUs)

Neonatal near miss (NNM)

Normal vaginal deliveries (NVDs)

Paediatric Intensive Care Unit (PICU)

Perinatal mortality rate (PNMR)

Research electronic data capture (REDCap)

Rahima Moosa Mother and Child hospital (RMMCH)

World Health Organization (WHO)

WHO Global Survey on Maternal and Perinatal Health (WHOGS)

WHO Multicountry survey on Maternal and Newborn Health (WHOMCS)
University of the Witwatersrand (Wits)

1. Introduction

Neonatal Health: An Unaccomplished Goal

The reduction of neonatal mortality is a yet to be achieved target of the millennium development goals, set by the World Health Organization (WHO), for women and children's health. As of 2015, 2.7 million deaths or up to 45% of all under five deaths occur in the neonatal period. The Sustainable Development Goal target 3.2 aims at reducing the neonatal mortality rate to 12 per 1000 births by 2030. Currently the inability to reduce the burden of neonatal death is likely to hinder the achievement of this goal (1).

In Latin America a reduction of 77% in infant mortality from 1990-2012 was maligned by a minimal decrease in mortality of the neonatal age group. Recent literature reports that neonatal mortality accounts for up to 70% of the infant mortality rate (2). It is therefore vital that efforts are undertaken to address this problem.

The neonatal near miss (A concept analogous to the maternal near miss)

The concept of the maternal near miss, as a tool for assessing and improving the quality of maternal healthcare, is growing and it has been used in clinical audits and epidemiological surveillance(3). One benefit of this concept is that it analyses cases of morbidity and poor outcome as opposed to analyzing cases of death (4). This allows it to be used even in settings in which the incidence of maternal death is relatively low.

The newer concept of the neonatal near miss (NNM) can be paralleled to this and similarly used to assess and improve neonatal outcomes. A neonatal near miss can be defined as a neonate who had a severe morbidity, and otherwise would've died, but survived either by chance or due to medical intervention (5). The period for neonatal near miss is generally accepted as the above stated occurring before the first 28 days of life (2). The WHO millennium development goals include the reduction of the mortality rate in the under-five age groups as one of the goals. Literature reports that a significant amount of infant deaths within this group occur during the neonatal period and this highlights the importance and need for a tool that may serve to identify deficiencies in care (1)(6).

Mortality vs Morbidity: A False Sense of Wellbeing

The frequency of NNM is more common than that of neonatal mortality. Whilst most studies focus on mortality, a false sense of wellbeing can be gained from not including the significant number of neonatal near miss cases that go unstudied(4). It therefore makes sense that a trend towards exploring cases of neonatal morbidity has developed. In a study done in Mumbai of NNM cases from September 2012 till August 2013 the Near miss rate was 4.6% with a NNM to mortality rate of 9.4:1 respectively (1).

Benefits of evaluating neonatal near miss cases

NNM can be used to evaluate cases in which the outcome was morbidity as opposed to fatality. The incidence of perinatal morbidity is up to four fold higher than that of perinatal mortality (6)(7). This means there are more available cases and hence data that can be analyzed. From this data we can then target and recommend solutions to problem areas identified. It can be assumed that prior to a neonatal death, the neonate will go through phases that would classify them with markers for NNM and thus lessons learnt from cases of neonatal death can be reinforced by assessing NNM (6). Comparative statistical data can also be calculated, such as a "neonatal mortality index"(3). Similarly to the "maternal mortality index" which is calculated from assessing maternal near miss in relation to maternal deaths, similar extrapolations can be made with neonatal cases (7). Auditing NNM is an important tool in developing strategies for improving perinatal care (4).

Can obstetric factors contributing to perinatal mortality be used for neonatal near miss?

Biological factors such as maternal age extremities have been associated with higher neonatal mortality rates. Teenagers less than 18 years old and women older than 34 where each found to have increasing rates of pregnancy complication leading to mortality (8). The Saving Babies report of 2006-2007 highlighted the top three causes of a high perinatal mortality rate. It was found that intrapartum birth asphyxia, birth trauma and spontaneous preterm delivery were common causes for an increased perinatal mortality (8)(9).

Severe obstetric complications significantly contribute to both neonatal deaths and NNM cases. Conditions such as severe pre-eclampsia, abruptio placenta, caesarean section (C/S) delivery and prematurity have all been associated with foetal demise (7).

One study reviewed during a literature search reports that birth weight is significantly different between groups of normal outcome, morbidity and mortality (11). Whilst another

study states that a significant amount of women have no recognizable obstetric or medical conditions at the time of a perinatal death, Intrapartum care and hypertension were implicated as factors for morbidity (12)(9).

A prospective cohort study done in Brazil 2011 investigated factors associated with neonatal deaths and near miss cases and found statistical significance in a number of factors. Maternal syphilis, lack of perinatal care, C/S and hospital delivery were all associated with NNM. Hemorrhage, lack of prenatal care and hospital access were associated with death. This study concluded that access to qualified care was necessary to reduce life-threatening situations (13).

Scoring for neonatal morbidity and poor outcomes

Various scoring systems already exist, for assessing neonatal morbidity. Currently there is no standardized and internationally accepted criteria for NNM. The NNM rate from studies to date ranges from 21-72%. The reason suggested for this discrepancy is the broad and nonstandardized criteria for identifying the NNM (1).

There are various proposed criteria from which to identify cases. Early and smaller studies suggested Hypoxic Ischaemic Encephalopathy (HIE) as a potential near miss marker for perinatal death from intrapartum asphyxia (14). Another study has linked intrapartum complications such as uterine rupture to adverse outcomes (3).Recommendations suggest that simpler scoring systems should be employed with more variables being looked at e.g. Congenital Malformations which weren't looked at in prior studies (1).

More recent studies have looked at a broader range of possible markers. Factors used to serve as markers for severe neonatal morbidity have a high accuracy for diagnosing neonatal death as found by two large WHO surveys. The WHO Global Survey on Maternal and Perinatal Health (WHOGS) and WHO Multicountry survey on Maternal and Newborn Health (WHOMCS) allowed for the evolution of specific criteria for identitfying NNM (5). A study of extreme importance is that done by Pileggi et al. which developed these criteria from a database analysis of these two studies (1). The criteria proposed by this landmark study were categorized as Pragmatic criteria and management criteria, as follows;

Pragmatic criteria:

- Birth weight <1750g
- Apgar < 7 at 5 mins life
- Gestational age <33 weeks at delivery Management Criteria:
- Parental antibiotic therapy (before 28 days of life)
- Nasal CPAP
- Any intubation within the first 7 days of life
- Phototherapy within the first 24 hours life
- Vasoactive drugs
- Anticonvulsant therapy
- Surfactant use
- Blood transfusion
- Steroid for refractory hypoglycaemia
- Any surgical intervention

Where the management criteria served as a proxy for organ system dysfunction sustained by the neonate during the case, signifying the poor outcome. This study paved the way for subsequent studies which assessed factors associated with morbid outcomes.

a. Problem statement

Neonatal mortality and morbidity is a significant challenge, especially in resource poor settings such as Rahima Moosa Mother and Child hospital (RMMCH). The quality of obstetric care that a patient receives affects the outcome of a case. In the University of the Witwatersrand (Wits) circuit the association between the obstetric care and the NNM has not yet been studied. A study exploring the association between obstetric factors and NNM, specifically in our setting, is needed to provide insight into the impacts of obstetric care on neonatal outcomes. I believe such a study will offer new knowledge on issues contributing to poor neonatal outcomes and thus lay a platform for us to improve our quality of care.

2. Study Aim

This study aims to investigate obstetric factors that are associated with neonatal near miss cases at RMMCH, during the year 2016. In doing so the study will hopefully contribute

towards service improvement and further studies that will explore strategies directed at improving these factors.

a. Objectives

1. To describe the sociobiological and clinical characteristics of cases with neonatal near miss and cases with normal baby outcomes.
2. To compare the sociobiological and clinical characteristics of cases with neonatal near miss and cases with normal baby outcomes.
3. To evaluate the relationships between obstetric factors and having a neonatal near miss.

3. Methods

a. Study Site

RMMCH is a regional hospital in Johannesburg, South Africa and forms a complex with the nearby Helen Joseph Hospital. It is part of the University of the Witwatersrand Academic Hospitals Circuit. It consists of an Obstertrics and Gynaecolocgy department and a Paediatrics department. Ancillary departments serving to assist in service provision are an, Anaesthesiology, Psychiatry, Occupational Health, Speech Therapy, Dietetics, Polyclinic, Social Work, Radiology, Emergency Department and Empilweni H.I.V department. RMMCH serves as the referral center for multiple clinics, midwife obstetric units (MOUs) and district hospitals in the Johannesburg Metro region.

Approximately 700 Normal vaginal deliveries (NVDs) and 300 C/S deliveries per month occur in this institution. Deliveries consist of both low risk and high risk pregnancies. In South Africa the perinatal mortality rate (PNMR) is 33.4/1000 total births and in regional hospitals it is 42.7/1000 (8). At RMMCH the rate was 30.5/1000 in 2016.

b. Study Design

This study is a retrospective case control study comparing cases of patients with neonatal near miss and normal pregnancy outcomes in the year 2016.

c. Study Groups

Babies that fit any of the neonatal near miss criteria (group 1) and normal outcome babies (group 2) will be selected from the neonatal database at RMMCH. A control group of babies with normal outcomes will then be selected for comparison. The mothers of these two groups of babies (respectively group 3 & group 4) will then be analyzed for obstetric factors which may be deemed of significance.

1. **Recruitment strategy**

Step 1 will be to scan the neonatal database for near miss cases during 2016. These babies would either have been admitted to ward 16b or the Paediatric Intensive Care Unit (PICU) (fig.1 Appendix A). Their data is already collected into the RMMCH database using data collection tools (see appendix B and C).

The next step will be to recruit a control group of normal babies. Group 2 comprises of babies that will not have been admitted for prolonged periods of time, given their normal outcome. Their files are usually kept with the corresponding maternal file and so they will be recruited from the postnatal ward admissions list over the same period of time, then sourced in the records department. A ratio of 1 NNM: 2 normal files will be recruited. This method will result in the maternal group of the normal babies being sourced simultaneously as the corresponding neonatal files.

The maternal files for the NNM cases are kept separately in the records department and will be sourced separately once the poor outcome list is complete. Each of the cases of neonatal near miss will then be pulled and analyzed for obstetric factors to be identified. Recruitment of cases will be at a rate of 1 NNM: 2 normal outcomes over the period 1st January 2016 to 31st December 2016.

2. **Inclusion Criteria**

Pragmatic Criteria: Any one or more of the following;

- Birthweight (≤1700g)
- APGAR (≤6 at 5mins)
- Gestational age (≤32/40)

Management criteria as a proxy for organ dysfunction: Any one or more of the following;

- Early parental antibiotics
- CPAP
- Intubation & Ventilation (Day1-Day27)
- Phototherapy (Day 0 to Day 1)
- Inotropic Support
- Anticonvulsant therapy
- Surfactant use
- Blood transfusion
- Steroids for refractory hypoglycaemia
- Any surgical intervention
- Therapeutic Cooling

3. **Exclusion Criteria**

- Inadequately kept records/documentation that doesn't allow for transcription onto data collections sheet
- Cases that became Early Neonatal Deaths/Late Neonatal Deaths

d. Data Collection

Data will be collected and managed using REDCap electronic data capture tools hosted at Wits (15). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

4. Data Analysis and Statistics

Data will be imported from Excel spreadsheet with Statistica® Version 13 Software. Descriptive statistics will be conducted for categorical and continuous data.

Objective 1: Categorical variables such as age, gender, mode of delivery and H.I.V status, will be described using frequencies, percentages and charts. Continuous variables such as

Gestational age, duration of labour and apgar score will be described as mean ±SD, if they are normally distributed and as median (IQR) if they are not normally distributed. *Objective 2*: The comparison of categorical variables amongst babies with NNM versus babies without NNM will be done using Pearson's Chi-Square test. Continuous variables will be compared using a Student's t-test, if they are normally distributed or a Mann-Whitney U test, if they are not normally distributed.

Objective 3: Categorical maternal factors such as mode of delivery, alcohol use and H.I.V will be compared using Pearson's Chi-Square test. Continuous variables will be compared using a Student's t-test, if they are normally distributed or a Mann-Whitney U test, if they are not normally distributed.

Univariable and multivariable logistic regression will be conducted with the NNM status of the baby (i.e. either near miss or normal) as the outcome, and the maternal factors will be the predictor and explanatory variables. The statistical significance level will be set at a confidence interval of 95% (P-value of 0.05).

5. Ethics

The study will be conducted with patient identification data being completely confidential, known only to the researcher. Patient identifiers such as names or hospital and file numbers will be kept separate from the data sheet (See Appendix). A study number will be allocated to patients used in the study. Ethics clearance for the study will be applied for with the University of the Witwatersrand Health Research Ethics Committee.

Given that this study will be analyzing poor outcomes, care must be taken when investigating and reporting on the factors of such sensitive cases. Furthermore there is the possibility of medicolegal progression, which further highlights the need for discretion when analyzing the cases. A confidential enquiries approach is of value such as that described by Buchmann et al, 2009 (12).

Intent to disseminate

Once complete the research will be available to the University of the Witwatersrand postgraduate committee as well as the College of Medicine South Africa as a required component of the registrar logbook. The research may be published or presented in the form of abstract, poster or PowerPoint at research days.

6. Timing

2017	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol development								X	X	X		
Submission											X	
Correction											X	
Ethics											X	
Data collection												X
2018	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
Analysis	X	X										
Write up			X	X								
Marking					X							
Corrections						X						

7. Funding

The study will be funded solely by the researcher to cover costs of printing materials, stationery and basic miscellaneous goods.

8. Potential Bias and Limitations

- The study is not blinded and is being performed by one person, while this should assist with consistency it does allow for bias.
- The definition of near miss in many cases may be subjective and may vary, based on the criteria used by the individual who entered the case as a near miss.
- As this is a retrospective approach, diligent file documented cannot guaranteed and this might lead to the exclusion of poorly documented files from the study.

9. Conclusion

My proposed study is one that has not been done before in the Wits circuit. I feel it carries relevance in that it will provide new insight into the obstetric factors that are associated with neonatal near miss cases, specifically in our setting. This new knowledge will contribute towards the improvement of quality of care and reduction of poor outcomes for our patients.

Partogram used during active phase
- ○ Yes
- ○ No

partogram filled 2 hourly till deliveryYes
- ○ No

Electronig Foetal Monitoring Done?Yes
- ○ No

Foetal monitoring typeSingle Strip
- ☐ Intermittent
- ☐ Continuous

Mode of DeliveryNormal Vaginal Delivery
- ○ Assisted Vaginal Delivery
- ○ Caesarean Section

Type of assisted vaginal deliveryForceps
- ○ Vacuum

Type of Caesarean SectionEmergency
- ○ Elective

Delivering Healthcare Worker(s)Midwife
- ☐ Intern Doctor
- ☐ Comm Serve Doctor
- ☐ Registrar Doctor
- ☐ Consultant Doctor

Delivery difficulties reported?Yes No

Delivery difficulty _____

11. Appendix A: Research Matrix

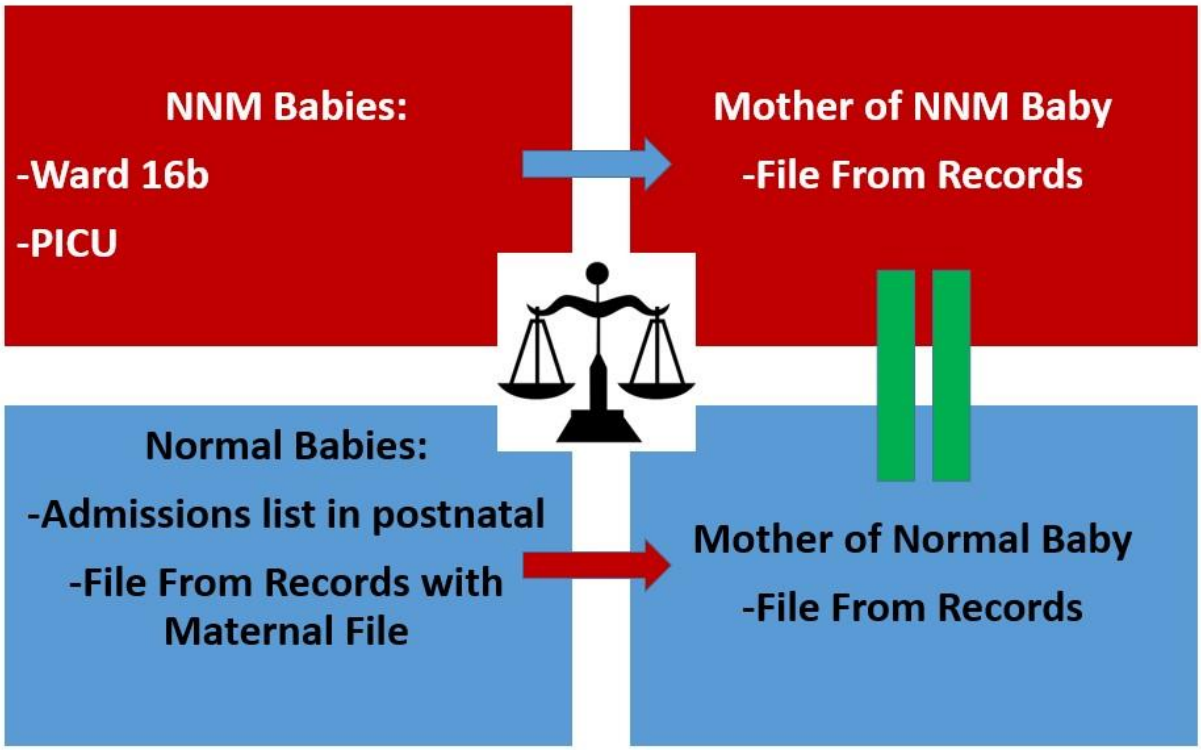

Figure 1Research Matrix: Recruitment strategy, leading to analysis and comparison.

When Haematinics started
- ◯ 1st Trimester
- ◯ 2nd Trimester
- ◯ 3rd Trimester

Antenatal TransfusionYes
- ◯ No

Syphilis (RPR positive)Reactive
- ◯ Non-Reactive

Gestational age at Diagnosis1st Trimester
- ◯ 2nd Trimester
- ◯ 3rd Trimester

Syphillis Treatment Received Yes
- ◯ No

(Only yes if completed treatment)

Syphillis Treatmet TypePenicillin
- ◯ Erythromycin
- ◯ Other

HIV Statuspositive negative unkown

cd4 count known?Yes
- ◯ No

cd count _____

Viral load known ◯ Yes No

viral load _____

(Latest VL before delivery)

HAART Started
- ◯ Yes
- ◯ No

When HAART started
- ◯ Pre pregnancy
- ◯ 1st Trimester
- ◯ 2nd Trimester
- ◯ 3rd Trimester

ARV regimen
- ◯ FDC
- ◯ Other

Rhesus Positive
- ◯ Positive
- ◯ Negative
- ◯ Unknown

Rhesus Maternal Antibodies
- ◯ Positive
- ◯ Negative
- ◯ Untested

Rhesus incompatibility Treatment
- ◯ Immunoglobulin Transfusion

Gestational Age _____

Gestational Age estimated by
- ◯ Dates
- ☐ Early Sonar
- ☐ Late Sonar
- ☐ Palpation

Comorbidities during index pregnancy
- ☐ Diabetes Mellitus
- ☐ Epilepsy
- ☐ Asthma/COPD
- ☐ Cardiac Disease
- ☐ Thyroid disorder
- ☐ Tuberculosis
- ☐ Hypertension
- ☐ Other

Other comorbidity (Specify) _____

Previous Pregnancy(ies) Complications
- ☐ Miscarriage
- ☐ Termination
- ☐ Ectopic
- ☐ Hypertension
- ☐ Antepartum Haemorrhage
- ☐ Postpartum Haemorrhage
- ☐ Diabetes in Pregnancy
- ☐ IUFD
- ☐ Preterm Labour

- ☐ Preterm prelabour rupture of membranes
- ☐ Prelabour rupture of membranes
- ◯ Chorioamnionitis
- ◯ Malpresentation
- ◯ Induced Labour
- ☐ Assisted Delivery
- ☐ Caesarean Section
- ☐ IUGR
- ☐ Postdates
- ☐ Foetal distress

No Previous C/Sone

- ☐ two three or more

Index Pregnancy Antepartum ComplicationHypertension

- ◯ Antepartum Haemorrhage
- ◯ Diabetes in Pregnancy
- ◯ Preterm Labour
- ☐ Preterm prelabour rupture of membranes
- ☐ Prelabour rupture of membranes
- ☐ Chorioamnionitis
- ☐ Malpresentation
- ☐ IUGR
- ☐ Congenital Abnormality
- ☐ Antepartum Foetal Distress

Class of HypertensionChronic Hypertension

- ☐ Gestational Hypertension
- ☐ Pre Eclampsia
- ☐ HELLP Syndrome
- ☐ Imminent Eclampsia
- ☐ Eclampsia

(HELLP syndrome and imminent eclampsia included)

HPT Treatment Started?Yes No

- ◯
- ◯

Hypertension control at last antenatal visit

- poor
- fair
- good

Gestation at diagnosis of hypertensive complication2nd trimester

- ◯
- ◯ 3rd trimester

(fisrt diagnosis in cases of multiple diagnosis)

APH Diagnosisuterine rupture

- ☐ abruptio placenta praevia
- ☐ vaginal/cervical lesion unknown

Gestational age at diagnosing diabetespre pregnancy (known)

- ☐ 1st trimester
- ☐ 2nd trimester
- ☐ 3rd trimester

Diabetes TreatmentYes

- ◯
- ◯ No

HBA1C _____

Prolonged Rupture of Membranes? ◯ Yes No

◯ ◯
◯ ◯
◯ ◯

☐ ☐ ☐ ☐ ☐ ☐ ☐

Duration of rupture of membranes _____
(Hours)

Antibiotics Given?Yes

No

Which antibiotics were givenCo-Amoxiclav

Amoxacillin
Ampicillin
Metronidazole
Azithromycin
Erythromycin Other

◯ ◯ ◯

specify (other) AB _____

malpresentation typeBreech

Transverse
Oblique

Congenital Abnormality _____

Labour onset ◯ Spontaneous Induced
◯

Induction indication _____

Induction MethodOral Misoprostol ☐ Vaginal Prostaglandin
☐ Vaginal Misoprostol
☐ Intravenous Oxytocin
☐ Catheter Induction

Augmentation of Labour?Yes No ○ ○

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Maternal Data

Study Number _____

Patient Age _____

Patient Height _____
(height in meters)

Patient BMI _____

Gravidity _____

Parity _____

Termination of Pregnancy _____

Ectopic Pregnancies _____

Multiple Pregnancies _____

EmployedYes
No

Race DescriptionWhite
Black
Coloured
Indian
Asian

HabitsAlcohol Use
Cigarette Smoking
other social/illicit Drugs

Singleton vs Multiple PregnancySingleton
Multiple

BookedYes
No

Time of booking< 14 weeks
>14 weeks

Antenatal visits< 3 visits
3 or more

Antenatal Classification of PregnaancyLow Risk
Medium Risk
High Risk
(As per ANC classifcation)

Anaemia in PregnanacyYes
No
(Hb< 11)

Booking Hb _____

Hb before Labour _____

Haematinics StartedYes No

13. Appendix C: Neonatal Collection Database Tools wd 16B (As per RMMCH)

RMMCH WARD 16 B ADMISSIONS

Record ID _____

DATA CAPTURED BY _____

EMAIL ADDRESS _____

DOCTOR'S NAME: _____

SPEED DIAL : _____

NEONATAL DETAILS

HOSPITAL NUMBER _____

PATIENT SURNAME _____

PATIENT NAME(IF APPLICABLE) _____

DATE AND TIME OF BIRTH _____

ADMISSION WARD

- ○ 16 B
- ○ ICU
- ○ H/C

REFERRAL CENTER

- ○ INBORN
- ○ DISCOVERER'S CLINIC
- ○ YUSUF DADOO HOSPITAL
- ○ LERATONG
- ○ CARLETONVILLE
- ○ CMJAH
- ○ CHB
- ○ TMH
- ○ EDENVALE
- ○ PRIVATE HOSPITAL
- ○ BBA
- ○ OTHER PLACES

GESTATIONAL AGE _____

GENDER

- ☐ MALE
- ☐ FEMALE
- ☐ DSD

BIRTH WEIGHT (IN GRAMS) _____

BIRTH LENGTH (IN CM) _____

BIRTH HEAD CIRCUMFERENCE (IN CM) _____

APGAR 1 MIN _____

APGAR 5 MIN _____

APGAR 10 MIN _____

APGAR 20 MIN _____

MATERNAL DETAILS

MOTHERS SURNAME & NAME _____

MOTHER'S HOSPITAL NUMBER _____

MOTHERS AGE _____

MOTHER'S PHONE NUMBER _____

RACE
- ○ BLACK
- ○ WHITE
- ○ COLOURED
- ○ INDIAN
- ○ OTHER

NATIONALITY
- ○ 1.RSA
- ○ 2.NOT RSA
- ○ 3.UNKNOWN

MODE OF DELIVERY
- ○ 1. NVD
- ○ 2. ELECTIVE C/S
- ○ 3.EMERGENCY C/S
- ○ 4. FORCEPS
- ○ 5. VACUUM
- ○ 6. BREECH
- ○ 7. OTHER

PARITY _____

GRAVIDITY _____

BOOKING STATUS
- ☐ BOOKED
- ☐ UNBOOKED
- ☐ UNKNOWN

MULTIPLE PREGNANCY
- ○ Yes
- ○ No

Rh
- ○ Negative
- ○ Positive
- ○ Unknown

RPR
- ○ Negative
- ○ Positive
- ○ Unknown

MOTHER'S WR TITRE _____

BABY'S WR TITER _____

MOTHER'S HIV RESULT
- ○ NEGATIVE
- ○ POSITIVE
- ○ UNKNOWN

MOTHER ON HAART
- ○ YES
- ○ NO
- ○ UNKNOWN

DURATION OF HAART
- ○ < 1 MONTH
- ○ > 3 MONTHS < 1 YEAR
- ○ > MORE THAN 1 YEAR

MOTHER VIRALLY SUPRESED
- ○ Yes
- ○ No

MOM'S FEEDING CHOICE
- ☐ BREAST
- ☐ FORMULA

PROBLEMS IN PREGNANCY
- ☐ PROM>24 hours
- ☐ Chorioamnionitis
- ☐ PIH
- ☐ Chronic hypertension
- ☐ Diabetes
- ☐ TB
- ☐ Teenage pregnancy
- ☐ Attempted TOP
- ☐ Alcohol use/abuse
- ☐ Illicit substance use/abuse
- ☐ Smoker
- ☐ Other antenatal problems
- ☐ Antenatal steroids 1 dose
- ☐ Antenatal steroids 2 doses/ more

PROBLEMS IN LABOUR
- ☐ MSL
- ☐ APH
- ☐ PPH
- ☐ Foetal distress
- ☐ Prolonged second stage
- ☐ Other problems in labour

NEONATAL INFORMATION

RESUSCITATION
- ☐ OXYGEN
- ☐ BLENDED OXYGEN
- ☐ SATURATION MONITORING
- ☐ ASSISTED BREATHS
- ☐ INTUBATION
- ☐ ADRENALIN
- ☐ NALOXONE
- ☐ CPR
- ☐ OTHER RESUSC PROCEDURES

CONGENITAL ABNORMALITY/SYNDROME
- ☐ TRISOMY 21
- ☐ TRISOMY 18
- ☐ TRISOMY 13
- ☐ VACTERL
- ☐ CATCH 22

OTHER CONGENITAL/SYNDROME _____

INITIAL BLOOD GAS _____

BIRTH HIV PCR
- ○ POSITIVE
- ○ NEGATIVE
- ○ INDETERMINATE
- ○ UNKNOWN

CONFIRMATORY HIV PCR
- ○ POSITIVE
- ○ NEGATIVE
- ○ INDETERMINATE
- ○ UNKNOWN

PULMONARY PATHOLOGY
- ☐ HMD
- ☐ CONGENITAL PNEUMONIA
- ☐ NOSOCOMIAL PNEUMONIA
- ☐ TTN
- ☐ MAS
- ☐ PULMONARY HAEMMORRHAGE
- ☐ BPD
- ☐ IC DRAIN
- ☐ OTHER PULMONARY PROBLEMS

VENTILATION
- ☐ NASAL PRONGS OXYGEN THERAPY
- ☐ BLENDED OXYGEN
- ☐ SURFACTANT
- ☐ NCPAP
- ☐ IPPV
- ☐ HFOV
- ☐ NITRIC OXIDE

CARDIOVASCULAR PATHOLOGY
- ☐ PDA
- ☐ CYANOTIC CONGEINTAL HEART DISEASE
- ☐ ACQUIRED HEART DISEASE
- ☐ CCF
- ☐ HYPOTENSION
- ☐ OTHER CVS DISEASE

GIT PATHOLOGY
- ☐ NEC I
- ☐ NEC II
- ☐ SURGERY
- ☐ OBSTRUCTION
- ☐ ITN
- ☐ DONOR BREAST MILK
- ☐ FM85
- ☐ OTHER GIT PATHOLOGY

HYPERBILIRUBINAEMIA
- ☐ Physiological jaundice
- ☐ Hepatitis
- ☐ Obstructive
- ☐ ABO incompatibility
- ☐ Rh incompatibility
- ☐ ITN related
- ☐ Other causes
- ☐ Phototherapy
- ☐ Exchange transfusion 1
- ☐ Exchange transfusion 2
- ☐ Immunoglobulin

CNS
- ☐ CONVULSIONS
- ☐ RECURRENT APNOEA
- ☐ MENINGITIS
- ☐ LEUKOMALACIA
- ☐ HYDROCEPHALUS
- ☐ OTHER CNS PATHOLOGY

NEONATAL ENCEPHALOPATHY
- ○ MILD
- ○ MODERATE
- ○ SEVERE

THERAPEUTIC HYPOTHERMIA
- ○ Yes
- ○ No

THERAPEUTIC HYPOTHERMIA INDICATED BUT NOT DONE,GIVE REASON FOR NOT COOLING _____

IVH

- ☐ I
- ☐ II
- ☐ III
- ☐ IV
- ☐ PHH
- ☐ BILATERAL

SEPSIS

- ☐ NO
- ☐ EARLY ONSET(< 72 HRS AFTER BIRTH)
- ☐ LATE ONSET

ORGANISM

- ☐ FUNGAL(CANDIDA SPECIES)
- ☐ KLEPSIELLA
- ☐ MRSA
- ☐ A.Baumanni
- ☐ CNS
- ☐ E.Coli
- ☐ GROUP B Strept
- ☐ OTHER ORGANISM

ETABOLIC

- ☐ HYPERGLYCAEMIA
- ☐ HYPOGLYCAEMIA
- ☐ HYPOCALCAEMIA
- ☐ HYPERCALCAEMIA
- ☐ HYPONATRAEMIA
- ☐ HYPERNATRAEMIA
- ☐ METABOLIC ACIDOSIS
- ☐ METABOLIC ALKALOSIS
- ☐ HYPOTHYROIDISM
- ☐ HYPERTHYROIDISM
- ☐ OTHER METABOLIC DISORDER

HAEMATOLOGY

- ☐ POLYCYTHAEMIA
- ☐ ANAEMIA OF PREMATURITY
- ☐ OTHER ANAEMIA
- ☐ THROMBOCYTOPAENIA
- ☐ NEUTROPAENIA
- ☐ PARTIAL EXCHANGE
- ☐ BLOOD TRANSFUSION
- ☐ PLATELET TRANSFUSION
- ☐ FFP
- ☐ CRYOPRECIPITATE

RUGS

- ☐ AMINOPHYLLINE
- ☐ CAFFEINE
- ☐ ADRENALINE
- ☐ HYDROCORTISONE
- ☐ IBRUPROFEN
- ☐ PARACETAMOL
- ☐ PHENOBARBITONE
- ☐ PHENYTOIN
- ☐ PEN G
- ☐ IMIPENEM
- ☐ VANCOMYCIN
- ☐ FLUCONAZOLE
- ☐ AMPHOTERICIN B
- ☐ GANCYCLOVIR
- ☐ DECADRON
- ☐ NVP
- ☐ AZT
- ☐ HAART
- ☐ IMMUNOGLOBULINS

OTHER DRUGS

_____

INVESTIGATIONS

- ☐ CXR
- ☐ AXR
- ☐ CRANIAL ECHO
- ☐ CT SCAN
- ☐ MRI
- ☐ aEEG
- ☐ ROP SCREEN

OTHER INVESTIGATIONS

AVOIDABLE RISK FACTORS

- ☐ LACK OF ADEQUATE MONITORING
- ☐ NOSOCOMIAL SEPSIS

OTHER AVOIDABLE RISK FACTORS

PROBLEMS FOR FOLLOW-UP

- ☐ ROP SCREENING
- ☐ AUDIOLOGY
- ☐ REPEAT CRANIAL US
- ☐ WEIGHT GAIN
- ☐ DEVELOPMENTAL
- ☐ HIV PCR TESTING(6-10 weeks)

OTHER PROBLEMS FOR FOLLOW-UP

OUTCOME IN 16 B

- ○ DISCHARGE HOME
- ○ DEMISED
- ○ PLACEMENT
- ○ ADOPTION
- ○ TRANSFERRED TO OTHER FACILITIES
- ○ KMC

DATE OF OUTCOME 16 B

OUTCOME IN KMC

- ○ DISCHARGE HOME
- ○ T/F 16 B
- ○ T/F ICU or H/C

DATE OF OUTCOME KMC

14. Appendix D: Neonatal Collection Database Tools PICU (As per RMMCH)

RMMCH PICU ADMISSIONS

Study ID _____

Patient Information

First Name _____

Last Name _____

Hospital Number _____

Date of birth _____

Age (years) _____

Race
- ○ Asian
- ○ Black
- ○ Coloured
- ○ Mixed Race
- ○ White
- ○ Other
- ○ Unknown
- ○ Not Reported

Gender
- ○ Female
- ○ Male
- ○ Intersex
- ○ Not Reported

Height (cm) _____

Weight (kilograms) _____

HIV STATUS
- ☐ HIV EXPOSED
- ☐ HIV NEGATIVE
- ☐ HIV POSITIVE
- ☐ HIV UNKNOWN

Date of Admission _____

Admission Ward
- ☐ ICU
- ☐ HC

Readmission
- ☐ Yes
- ☐ No

Referral Center
- ☐ Inborn
- ☐ Discoverers Clinic
- ☐ Yusuf Dadoo Hospital
- ☐ Leratong
- ☐ Carltonville
- ☐ CMJAH
- ☐ CHBAH
- ☐ TMH
- ☐ Edenvale
- ☐ Private Hospitals
- ☐ BBA
- ☐ Other

ential

Special Investigations

- ☐ CXR
- ☐ AXR
- ☐ CT scan
- ☐ MRI
- ☐ ECHO
- ☐ Sonar(cranial/abd)
- ☐ aEEG
- ☐ Other

Drugs

- ☐ Aminophyline
- ☐ Caffeine
- ☐ Dormicum
- ☐ Morphine
- ☐ Fentanyl
- ☐ Valium
- ☐ Methadone
- ☐ Phenobarbitone
- ☐ Valproate
- ☐ Lorazepam
- ☐ Ibuprofen
- ☐ Paracetamol
- ☐ Phenytoin

Antibiotics

- ☐ Penicillin G
- ☐ Gentamicin
- ☐ Ampicillin
- ☐ Imipenem
- ☐ Vancomycin
- ☐ Fluvonazole
- ☐ Amphotericin B
- ☐ Cotrimoxazole
- ☐ Gancyclovir
- ☐ Acyclovir
- ☐ NVP
- ☐ AZT
- ☐ ARV"s
- ☐ Anti TB
- ☐ Other drugs

Final diagnosis _____

Outcome

- ○ Transferred back to referral centre
- ○ ICU
- ○ H/C
- ○ 16 B
- ○ Paediatric Ward
- ○ Demised

Date of outcome _____

Cause of death _____

onfidential

Reason for Admission	_____
Ventilation	○ Yes ○ No
Mode of Ventilation	☐ CPAP ☐ SiPAP/DuoPAP ☐ CMV ☐ HFOV
Ventilation start date	_____
Ventilation end Date	_____
Inotropic Support	○ Yes ○ No
Inotropes	○ Adrenaline ○ Dopamine ○ Dobutamine ○ Hydrocortisone ○ Other
IV access	☐ CVP ☐ PICC ☐ Peripheral line
Nutrition	☐ Enteral ☐ Parenteral
Pulmonary conditions	○ Bronchilolitis ○ Choanal atresia ○ Subglottic stenosis ○ Foreign body ○ Pertussis ○ Bacterial pneumonia ○ TB ○ Viral pneumonia ○ Asthma/Status Asthmaticus ○ Pleural effusion/Pneumothorax ○ PJP ○ Other
Cardiovascular	○ Cyanotic congenital Heart disease ○ Acyanotic congenital heart disease, ○ Myocarditis ○ PDA ○ Shock ○ Other
CNS	○ Status epilepticus ○ Apnoea ○ Encephalopathy, ○ Cerebral Malaria ○ Coma ○ Meningitis ○ Neonatal encephalopathy ○ Apnoea of prematurity ○ Other
GIT	○ NEC I/II/III ○ Gastroenteritis ○ Hepatic failure ○ Congenital gastrointestinal anomalies

02/08/2016 12:25pm www.projectredcap.org REDCap

Electrolyte abnormalities

- ○ Hyponatraemia
- ○ Hypernatraemia.
- ○ Hypokalemia
- ○ Hyperkalemia
- ○ Hypoglycemia
- ○ Hyperglycemia
- ○ Metabolic acidosis
- ○ Metabolic alkalosis
- ○ Hypo/Hypercalcemia

Metabolic/Endocrine

- ○ DKA
- ○ Other

Haematology

- ○ Anemia of prematurity,
- ○ Anemia
- ○ Polycythemia
- ○ Throbocytopenia
- ○ DIC,
- ○ Neutropenia
- ○ Other

sis

- ○ Definite
- ○ Suspected

Bacterial sepsis

- ○ Yes
- ○ No

Bacterial organism

- ☐ Strep agalactiae
- ☐ Strep Pneumoniae
- ☐ Strep viridans
- ☐ Staph Aureas
- ☐ CONS
- ☐ MRSA
- ☐ H.Influenza
- ☐ E. coli
- ☐ Meningococcus
- ☐ Klebsiella
- ☐ Klebsiella ESBL
- ☐ Enterobacter sp
- ☐ Pseudomobnas
- ☐ Baumanii
- ☐ Enterococcus
- ☐ Other

Fungal infection

- ○ Yes
- ○ No

Fungal organism

- ☐ C. Albicans
- ☐ C. Parapsilosis
- ☐ C. Glabrata
- ☐ Other fungal

Viral infection

- ○ Yes
- ○ No

Viral organism

- ☐ Influenza
- ☐ RSV
- ☐ Adenovirus
- ☐ CMV
- ☐ Other

ential

Special Investigations

- ☐ CXR
- ☐ AXR
- ☐ CT scan
- ☐ MRI
- ☐ ECHO
- ☐ Sonar(cranial/abd)
- ☐ aEEG
- ☐ Other

Drugs

- ☐ Aminophyline
- ☐ Caffeine
- ☐ Dormicum
- ☐ Morphine
- ☐ Fentanyl
- ☐ Valium
- ☐ Methadone
- ☐ Phenobarbitone
- ☐ Valproate
- ☐ Lorazepam
- ☐ Ibuprofen
- ☐ Paracetamol
- ☐ Phenytoin

Antibiotics

- ☐ Penicillin G
- ☐ Gentamicin
- ☐ Ampicillin
- ☐ Imipenem
- ☐ Vancomycin
- ☐ Fluvonazole
- ☐ Amphotericin B
- ☐ Cotrimoxazole
- ☐ Gancyclovir
- ☐ Acyclovir
- ☐ NVP
- ☐ AZT
- ☐ ARV"s
- ☐ Anti TB
- ☐ Other drugs

Final diagnosis _____

Outcome

- ○ Transferred back to referral centre
- ○ ICU
- ○ H/C
- ○ 16 B
- ○ Paediatric Ward
- ○ Demised

Date of outcome _____

Cause of death _____

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Chileshe Mpehle

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180108

NAME: (Principal Investigator)	Dr Chileshe Mpehle
DEPARTMENT:	School of Clinical Medicine Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	Obstetric Factors Associated with Neonatal Nearmiss
DATE CONSIDERED:	26/01/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Lawrence Chauke and Dr Firdose Nakwa
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/04/2018

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 **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 26/04/2018.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES