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A review of the benefits of antenatal steroids in premature neonates in a middle income country

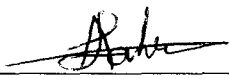
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Declaration

I declare that this research report is my own work and any publications consulted have been appropriately referenced. This research report is submitted for the Degree of Master of Medicine in Paediatrics at the University of Witwatersrand. It has not been submitted for any other degree and has not been submitted to any other university.

Signed: _____

Dr Anees Laher

Date: 27 September 2017

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List of abbreviations

ANS: antenatal corticosteroids

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CPAP: continuous positive airway pressure

HICS: high income countries

HIV: human immunodeficiency virus

IVH: intraventricular haemorrhage

LMICS: low-middle income countries

NEC: necrotising enterocolitis

PDA: patent ductus arteriosus

RDS: respiratory distress syndrome

WHO: World Health Organisation

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A review of the benefits of antenatal steroids in premature neonates in a middle income country

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Table of Contents Summary:

Little information is known about antenatal corticosteroid use in low-middle income countries. This study is a review of antenatal corticosteroids in a middle income country.

What is known? Antenatal steroids have become a standard of practice in preterm deliveries. Recently, there have been questions asked if the benefits of antenatal steroids apply to low-middle income countries.

What this study adds? This study reviews antenatal steroids in a hospital in South Africa, a middle income country.

Contributor's Statement

Dr Laher conceptualized and designed the study, collected data, carried out data analysis, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Professor Ballot conceptualized and designed the study, assisted with data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr Ramdin assisted with the design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Abstract

Background: Antenatal corticosteroids have become a standard of practice. However, there is low antenatal corticosteroid coverage in low-middle income countries. Recent studies have questioned the efficacy of antenatal corticosteroids in low-middle income countries.

Objectives: To review the use of ANS in preterm neonates at Charlotte Maxeke Johannesburg Academic Hospital.

Methods: This study was a retrospective observational study. The population included all neonates, with a birth weight of 500-1800 grams, born at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2013 and 30 June 2016. Neonatal and maternal characteristics of neonates exposed to antenatal corticosteroids were compared to those who were not exposed to antenatal steroids.

Results: The antenatal corticosteroid coverage of the final sample was 930/2109 (44.1%). The mean birth weight was 1292.4 grams (SD323.2) and the mean gestational age was 30.2 weeks (SD2.9). Antenatal care and maternal hypertension were associated with increased use of antenatal corticosteroids, whereas vaginal delivery was associated with decreased antenatal corticosteroid use. In neonates, the use of antenatal corticosteroids was associated with decreased mortality, decreased intraventricular haemorrhage and decreased patent ductus arteriosus in neonates <1500 grams. There was no association between antenatal corticosteroids and respiratory distress syndrome, necrotising enterocolitis, sepsis and need for respiratory support in all premature neonates and there was no association with improved outcomes in babies $\geq$ 1500 grams.

Conclusion: The benefits associated with neonatal morbidity in the current study were not as marked as those published in high income countries. Perhaps, a randomised control trial is indicated in low-middle income countries.

Abstract word count: 249

Background

Worldwide, neonatal mortality is a major problem with 38% of all deaths in children under five years attributed to neonatal mortality.(1) Every year, it is estimated that four million babies die in the neonatal period.(1) Preterm birth is the most common cause of neonatal mortality; accounting for 28% of neonatal deaths.(1) Of great concern, 99% of neonatal deaths occur in low income countries with poverty being strongly associated with an increased risk of neonatal mortality.(1)

Africa accounts for 28% of neonatal deaths worldwide.(1) South Africa has shown some improvement in recent years in reducing childhood mortality but has not met the fourth millennium development goal of reducing mortality by two-thirds in children under five years.(2) South Africa is one of the countries in which neonatal mortality has not decreased over the past 20 years.(3) **Preterm births and perinatal asphyxia still account for more than 50% of neonatal deaths.**(3)

Addressing neonatal mortality is imperative to reduce childhood mortality. More specifically, reducing mortality in preterm neonates can be the most beneficial as this is the most common cause of neonatal mortality.(1)

In 1972, Liggins and Howie conducted the first trial using antenatal corticosteroids (ANS) for the prevention of respiratory distress syndrome (RDS) in preterm neonates.(4) Liggins and Howie noted a reduction in the incidence of RDS in preterm neonates where maternal ANS were given, as compared to preterm neonates where maternal ANS were not given.(4) Since

the landmark trial by Liggins and Howie, ANS therapy has become a standard of care to prevent preterm neonatal complications.(5)

A Cochrane review of 21 articles evaluating the effect of ANS on preterm neonates showed that ANS reduced the risk of RDS, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), early onset sepsis, mortality, need for respiratory support, and a trend in the reduced need for surfactant therapy.(5) However, from these 21 articles, 17 studies were conducted in high income countries, and only four in middle income countries.(5) In addition to the benefits shown in the Cochrane review, there seems to be a beneficial effect of ANS on symptomatic patent ductus arteriosus (PDA).(6)

The use of ANS in low-middle income countries (LMICS) remains low.(7) The main reason is due to mothers being admitted in advanced labour.(8) Other reasons include inevitable abortion, obstetric emergencies necessitating immediate delivery, incorrect assessment of gestational age, refusal of hospital treatment and obstetricians missing an opportunity to provide mothers with ANS.(8) The latter should be reduced as the National Institute for Health and Care Excellence recommends routine administration of ANS to women who are in suspected or established preterm labour at a gestational age less than 34 weeks.(9)

A recent article by Azad and Costello suggests that caution is needed before increasing the use of ANS in LMICS.(10) Azad and Costello question the efficacy of ANS in LMICS to improve mortality in premature neonates less than 33 weeks and state that there is no benefit with the use of ANS after 33 weeks gestation.(10)

Althabe et al conducted a randomised trial in six LMICS (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) to implement strategies to reduce neonatal mortality.(11) Strategies included identifying women at risk for preterm birth and upscaling ANS in these women whereas standard practice was continued in the control group. These strategies resulted in an increase in ANS coverage from 10% in the control group to 45% in the intervention group.(11) Despite the increase in ANS coverage, the intervention group showed an increase in neonatal mortality with an excess of 3.5 neonatal deaths for every 1000 women exposed to this strategy.(11) The cause of this increased mortality was not clear.

There is limited information on ANS use in South Africa. The Dexiprom study is the only study that has looked at effects of ANS in South Africa but this study only involved mothers who had preterm premature rupture of membranes.(12) There is concern over the use of ANS in LMICS. The aim of this study is to review ANS use at a hospital in South Africa, a middle income country.

Method

Study Design

This study was a retrospective observational study. The study population included all neonates, with a birth weight between 500 and 1800 grams, born at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the period between 1 January 2013 and 30 June 2016. Exclusion criteria included babies with lethal birth defects and those with unobtainable records. The total sample was divided into 2 groups: babies weighing ≥ 1500 grams and babies weighing < 1500 grams. Each of the 2 groups was further divided into an ANS exposed group and an ANS unexposed group, and these groups were then compared. The ANS exposed group included neonates where maternal ANS were given and the ANS unexposed group were neonates where maternal ANS were not given. At CMJAH, two doses of 12mg betamethasone 12 hours apart are given intramuscularly to mothers < 34 weeks gestational age or if the estimated fetal weight is less than two kilograms.

Data

This was a secondary review of an existing database. Neonatal records are kept in a CMJAH neonatal database. Data is managed using Research Electronic Data Capture (REDCAP) which is hosted by the University of Witwatersrand.(13) Data is collected by clinicians using hospital records and is verified at several different points. Permission was obtained for using this neonatal database.

Data Analysis

Maternal and neonatal variables were evaluated. Valid cases were analysed and missing data excluded. Data was described using standard statistical methods. Categorical variables were described using frequencies and percentages, while continuous variables were described

using mean and standard deviation or median and interquartile range, depending on the distribution of the data. Chi Square tests were used to compare categorical variables. The student independent t-test was used to compare continuous variables with a normal distribution. Non-parametric tests were used for skewed data. A P-value of <0.05 was considered significant. Analysis was done using SPSS version 24. Associations with the use of ANS were determined using logistic regression. All variables which approached significance ($p<0.06$) on univariate analysis were explored **on multivariate analysis**.

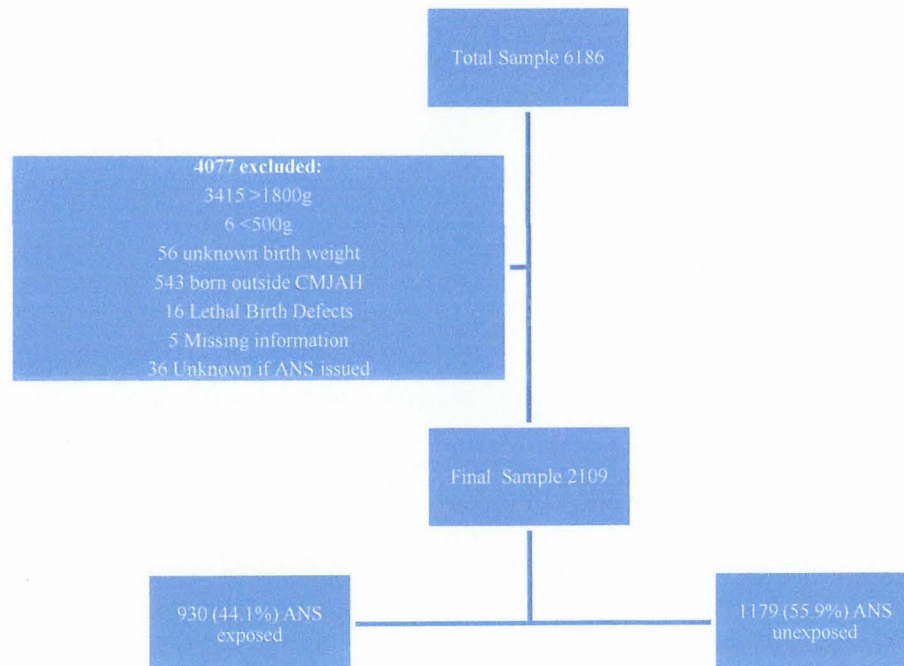
Ethics

This study was approved by the Human Research Ethics Committee of the University of Witwatersrand; clearance certificate number M160730.

Results

There were a total of 6186 neonates on the REDCap database (accessed on 27 September 2016) between 01 January 2013 and 30 June 2016. Of the 6186, there were 3415 neonates with a birth weight >1800 grams and six neonates with a birth weight <500 grams. A further 656 were excluded (see Figure 1) resulting in a final sample size of 2109 neonates. The mean birth weight of the final sample was **1292 grams (SD323)**. The mean gestational age was **30.2 weeks (SD2.9)**. The ANS coverage of the final sample was less than half with 930/2109 (44.1%) neonates exposed to ANS and 1179/2109 (55.9%) not exposed to ANS.

Figure 1. Patient selection



Maternal Characteristics

Maternal characteristics are shown in Table 1. Mothers who attended antenatal care were significantly more likely to receive ANS ($p<0.001$). It was observed that mothers with hypertension were more likely to receive ANS ($p<0.001$) whereas mothers with HIV were less likely to receive ANS ($p=0.001$). There were 718/2101 (34.2%) vaginal deliveries and 1383/2101 (65.8%) caesarean section deliveries. Vaginal deliveries were associated with decreased ANS coverage ($p<0.001$). Multiple gestation was associated with less antenatal steroid use in babies weighing <1500 g. There was no significant difference with ANS coverage and maternal age, parity, chorioamnionitis and diabetes.

Variable	Total sample	≥ 1500 g				<1500 g			
		Total	ANS	No ANS	P value	Total	ANS	No ANS	P value
Antenatal Care n/N (%)	1773/2085 (85.0)	587/676 (86.8)	178/193 (92.2)	409/483 (84.7)	0.009	1186/1409 (84.2)	668/729 (91.6)	518/680 (76.2)	<0.001
Maternal Hypertension n/N (%)	552/2100 (26.3)	126/685 (18.4)	54/197 (27.4)	72/488 (14.8)	<0.001	426/1415 (30.1)	260/732 (35.5)	166/683 (24.3)	<0.001
Maternal HIV n/N (%)	648/2101 (30.8)	227/688 (33.0)	53/197 (26.9)	174/491 (35.4)	0.031	421/1413 (29.8)	197/731 (26.9)	224/682 (32.8)	0.015
Vaginal Delivery n/N (%)	718/2101 (34.2)	237/688 (34.4)	52/196 (26.5)	185/492 (37.6)	0.006	481/1413 (34.0)	204/730 (27.9)	277/683 (40.6)	<0.001
Multiple Gestation n/N (%)	433/2100 (20.6)	172/689 (25.0)	51/197 (25.9)	121/492 (24.6)	0.723	261/1411 (18.5)	114/729 (15.6)	147/682 (21.6)	0.004

Table 1. Maternal characteristics associated with receiving ANS

ANS: Antenatal corticosteroids

Neonatal Characteristics

Neonatal characteristics of the total sample are shown in Table 2 and continuous variables are shown in Table 3. Valid data are shown in the table and percentages are expressed in columns.

Table 2. Neonatal characteristics associated with ANS exposure

Variable	Total sample	≥1500g				<1500g			
		Total	*ANS	No ANS	P value	Total	ANS	No ANS	P value
Resuscitation at birth n/N (%)	766/2089 (36.67)	158/691 (22.9)	50/197 (25.4)	108/494 (21.9)	0.320	608/1398 (43.5)	274/725 (37.8)	334/673 (49.6)	<0.001
Early onset sepsis n/N (%)	73/2103 (3.47)	13/691 (1.9)	3/197 (1.5)	10/494 (2.0)	0.661	60/1412 (4.2)	31/728 (4.3)	29/684 (4.2)	0.986
Late onset sepsis n/N (%)	451/2102 (21.46)	56/690 (8.1)	16/197 (8.1)	40/493 (8.1)	0.997	395/1412 (28.0)	205/729 (28.1)	190/683 (27.8)	0.899
*IVH n/N (%)	209/852 (24.53)	14/81 (17.3)	2/27 (7.4)	12/54 (22.2)	0.096	195/771 (25.3)	88/395 (22.3)	107/376 (28.5)	0.049
*RDS n/N (%)	1628/2109 (77.19)	352/691 (50.9)	106/197 (53.8)	246/494 (49.8)	0.341	1276/1418 (90.0)	654/733 (89.2)	622/685 (90.8)	0.322
*CPAP n/N (%)	1200/2103 (57.06)	229/691 (33.1)	64/197 (32.5)	165/494 (33.4)	0.818	971/1412 (68.8)	498/728 (68.4)	473/684 (69.2)	0.763
Ventilation n/N (%)	274/2101 (13.04)	40/691 (5.8)	8/197 (4.1)	32/494 (6.5)	0.219	234/1410 (16.6)	107/727 (14.7)	127/683 (18.6)	0.051
Surfactant n/N (%)	1203/2100 (57.29)	225/686 (32.8)	62/196 (31.6)	163/490 (33.3)	0.681	978/1414 (69.2)	495/729 (67.9)	483/685 (70.5)	0.288
*PDA n/N (%)	138/2099 (6.57)	16/691 (2.3)	3/197 (1.5)	13/494 (2.6)	0.576	122/1408 (8.7)	50/725 (6.9)	72/683 (10.5)	0.015
*NEC n/N (%)	124/2095 (5.92)	23/684 (3.4)	6/195 (3.1)	17/489 (3.5)	0.794	101/1411 (7.2)	50/729 (6.9)	51/682 (7.5)	0.652
Outcome-Survived N (%)	1749/2108 (82.97)	674/690 (97.7)	193/197 (98.0)	481/493 (97.6)	0.750	1075/1418 (75.8)	584/733 (79.7)	491/685 (71.7)	<0.001

*ANS: antenatal corticosteroids; IVH: intraventricular haemorrhage; RDS: respiratory distress syndrome; CPAP: continuous positive airway pressure; PDA: patent ductus arteriosus; NEC: necrotising enterocolitis.

Gender, spontaneous gastrointestinal perforation, oxygen required on day 28 of life, and home oxygen required were not included in the above table as all these variables were not significantly different. Reported associations with ANS were included in the table even though these variables were not significant in the current study.

Table 3. Continuous variables associated with ANS exposure

Variable	≥1500g			<1500g		
	ANS	No ANS	P value	ANS	No ANS	P value
Birth Weight in grams Mean (Standard Deviation)	1633.78 (84.682)	1656.75 (88.235)	0.002	1129.67 (234.225)	1105.70 (250.635)	0.063
Gestational age in weeks Mean (Standard Deviation)	31.97 (1.640)	32.67 (2.332)	<0.001	29.12 (2.325)	29.04 (2.766)	0.531
Duration of CPAP Median (Interquartile Range)	1 (0)	1 (1)	0.164	2 (3)	2 (2)	0.440
Duration of Ventilation Median (Interquartile Range)	8 (13)	4 (3)	0.069	5 (9)	5 (6)	0.608
Duration of Stay Median (Interquartile Range)	10 (9)	9 (9)	0.002	30 (28)	26 (31)	0.001

ANS: Antenatal corticosteroids; CPAP: continuous positive airway pressure

Neonates ≥1500g (See Table 2 and Table 3)

In the subgroup of neonates ≥1500 grams, there were 197/691 (28.5%) neonates exposed to ANS and a survival rate of 674/690 (97.7). There was a significantly lower mean birth weight ($p=0.002$) and mean gestational age ($p<0.001$) in neonates exposed to ANS as compared to neonates not exposed to ANS. It was observed that neonates exposed to ANS had a longer duration of stay than neonates not exposed to ANS ($p=0.002$). There was no significant difference between exposure to ANS and RDS, IVH, NEC, PDA, early and late onset sepsis and other neonatal characteristics. The variables most significantly associated with ANS using logistic regression (see Table 4) were antenatal care ($p=0.015$), vaginal delivery ($p=0.043$), maternal hypertension ($p=0.002$), birth weight ($p=0.034$) and gestational age ($p<0.001$). Maternal HIV and duration of stay were not significant after logistic regression.

Table 4. Logistic regression for significant variables in neonates ≥ 1500 grams exposed to antenatal corticosteroids

Variable	Odds Ratio	95% Confidence Interval	P value
Antenatal Care	2.132	1.157 – 3.921	0.015
Vaginal Delivery	0.656	0.436 – 0.987	0.043
Maternal Hypertension	2.008	1.305 – 3.096	0.002
Birth Weight	0.998	0.996 – 1.000	0.034
Gestational age	0.826	0.754 – 0.906	<0.001

Neonates <1500 grams (See Table 2 and Table 3)

In the subgroup of neonates <1500 grams, there were 733/1418 (53.1%) neonates exposed to ANS and a survival rate of 1075/1418 (75.8%). Neonates exposed to ANS were significantly less likely to have a PDA ($p=0.015$), less likely to have an IVH ($p=0.049$), and less likely to require resuscitation at birth ($p<0.001$). There was a significant association with exposure to ANS and increased survival ($p<0.001$). It was also observed that neonates exposed to ANS had a longer duration of stay in hospital than neonates not exposed to ANS ($p=0.001$). There was no significant association between ANS and RDS, NEC, early and late onset sepsis and other neonatal characteristics. The variables most significantly associated with ANS using logistic regression (see Table 5) were antenatal care ($p<0.001$), vaginal delivery ($p=0.038$), multiple gestation ($p<0.001$), resuscitation at birth ($p=0.001$), PDA ($p=0.001$), and duration of stay ($p=0.012$). Variables that were not significant after logistic regression were conventional ventilation, IVH, outcome, maternal hypertension and HIV.

Table 5. Logistic regression for significant variables in neonates <1500 grams exposed to antenatal corticosteroids

Variable	Odds Ratio	95% Confidence Interval	P value
Antenatal Care	3.086	1.953 - 4.878	<0.001
Vaginal Delivery	0.705	0.508 - 0.980	0.038
Multiple Gestation	0.493	0.334 – 0.728	<0.001
Resuscitation at birth	0.581	0.427 – 0.791	0.001
Patent ductus arteriosus	0.462	0.290 – 0.736	0.001
Duration of Stay	1.009	1.002 – 1.016	0.012

Discussion

The current study showed ANS coverage of 44.1% at CMJAH. This coverage has increased since 1993 where the coverage was only 20%.(8) However, this ANS coverage is less than other LMICS which had coverage of 52% according to WHO Multicountry Survey on Maternal and Newborn Health.(14) The ANS coverage at CMJAH is substantially lower than the 80% coverage in high income countries (HICS).(11) An increase in gestational age was associated with decreased exposure to ANS. This trend is also noted in HICS where ANS coverage reduces by more than half at 34 weeks; as compared to coverage at 24-30 weeks.(15) Reasons for this are not clear. It may represent inaccurate gestational age estimation or reduced attention to 'moderately preterm' babies.(15)

In the current study, vaginal delivery was associated with decreased ANS use. This is true in other LMICS and HICS.(14, 15) Mothers presenting in advanced labour is the main reason for this decrease ANS use, resulting in no opportunity for ANS to be provided.(8) In the present study, unbooked mothers were significantly less likely to receive ANS. Lack of antenatal care is consistently associated with reduced ANS coverage in LMICS and HICS.(14, 15) This is a difficult problem to address as it is likely associated with low socio-economic status and poor maternal education and is a point for improvement.

In the present study, maternal hypertension had an association with increased ANS use. This is likely due to mothers with hypertension are followed up regularly during the antenatal period and are usually admitted if preterm delivery is necessary. The decreased ANS exposure associated with maternal HIV infection was an interesting observation but cannot be explained by our study. It was, however, not significant on logistic regression. **Multiple gestation was associated with less ANS use in babies weighing <1500 g. A possible reason for this could be due to incorrectly estimating gestational age with multiple gestation.**

Our study showed no association between ANS exposure and RDS, NEC, early onset sepsis, and need for respiratory support. This contradicts the Cochrane review on the effect of ANS on preterm neonates but Pattinson et al also showed no statistical significance in RDS, NEC, early onset sepsis, and need for ventilation in their study in South Africa.(5, 12) Our study showed that neonates exposed to ANS were less likely to have a PDA. This supports Salhab et al which showed a benefit of ANS on PDA.(6) Possible mechanisms for this are a steroid effect on prostaglandin synthesis, reduced sensitivity of the ductal muscle to prostaglandin E2, and increased activity of prostaglandin E2 inactivation enzyme.(6)

Our study found a significant association between ANS exposure and survival in neonates <1500 grams. This finding is in agreement with Pattinson et al and the Cochrane review on the effect of ANS on preterm neonates.(5, 12) Our study did not find the same association as Althabe et al which showed an increase in neonatal mortality in LMICS with the upscaling of ANS and disagrees with Azad and Costello who questioned if ANS improves neonatal mortality.(10, 11) Our study also showed an association between ANS exposure and reduced IVH. This association was only significant in neonates <1500 grams and agrees with the Cochrane review that ANS exposure reduces the risk of IVH.(5) **However, it must be mentioned that increased survival and decreased IVH were both no longer significant after multivariate analysis.**

The current study demonstrated a longer duration of stay in both groups, <1500 and $\geq$ 1500 grams, for neonates exposed to ANS, compared to no exposure to ANS. This was an interesting observation and could be explained by a significantly higher survival rate and a lower mean birth weight (1236 grams) in the ANS exposed group compared to the birth

weight (1336 grams) in the ANS unexposed group, resulting in a longer duration for neonates to gain weight to 1600 grams, the discharge weight at CMJAH. Most deaths at CMJAH occur within the first seven days of life.

There were no associations with ANS exposure and improved neonatal outcomes in neonates ≥ 1500 grams in our study. This supports Azad and Costello's observation that there is no benefit with the use of ANS after 33 weeks gestation in LMICS.

Limitations and Conclusion

Limitations

This study was a retrospective study and there was a low ANS coverage. The number and timing of ANS doses were not known. This study can only comment on associations and cannot address effects of ANS in LMICS. **This study was not randomised and it could not determine the reasons why some neonates were exposed to antenatal steroids and others were not.**

Conclusion

Preterm birth is associated with multiple complications. There have recently been questions on the efficacy of ANS in LMICS. This study has shown an association between ANS and increased survival, decreased PDA and decreased IVH in neonates <1500 grams. However, there was no association between ANS and RDS, NEC, and sepsis; and there were no associations of improved neonatal outcome in neonates ≥ 1500 grams. This suggests a review of the birth weight cut off for issuing ANS in our setting and perhaps indicates a need for a randomised control trial on the effects of ANS in LMICS.

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Appendix A: Pediatrics Author guidelines

Pediatrics Author Guidelines

Pediatrics is the official peer-reviewed journal of the [American Academy of Pediatrics](#). *Pediatrics* publishes original research, clinical observations, and special feature articles in the field of pediatrics, as broadly defined. Contributions pertinent to pediatrics also include related fields such as nutrition, surgery, dentistry, public health, child health services, human genetics, basic sciences, psychology, psychiatry, education, sociology, and nursing. *Pediatrics* considers unsolicited manuscripts in the following categories: reports of original research, particularly clinical research; review articles; special articles; and case reports. When preparing a manuscript for *Pediatrics*, authors must first determine the manuscript type and then prepare the manuscript according to the specific instructions below. The electronic edition of *Pediatrics* is the journal of record. Some accepted articles may also be presented in full in the print version. The editors reserve the right to determine whether an accepted manuscript will be published in the print edition in addition to the electronic edition of *Pediatrics*.

Introduction	Manuscript Preparation	Manuscript Submission	Article Types	Additional Guidelines
	Formatting Requirements		Regular Article	
Acceptance Criteria	Title Page		Case Report	Reader Comments
Publication Ethics	Contributors' Statement Page	Cover Letter	Commentary	Letters to the Editor
Journal Style	Word Count	Getting Started	Diagnostic Dilemmas and Clinical Reasoning	Errata
Clinical Trials	Figures, Tables &	Submitting Your Manuscript	Ethics Rounds	Supplements to Pediatrics
Reuse of Data Sets	Supplementary Material			Pediatrics Editorial Offices

[Family
Partnerships](#)

[Monthly Feature](#)

[Pediatrics
Perspectives](#)

[Quality Report](#)

[Review Article,
Systematic
Review & Meta-
Analyses](#)

[Special Article](#)

[State-of-the-Art
Review Article](#)

["From the
American
Academy of
Pediatrics"](#)

Acceptance Criteria

Relevance to readers is of primary importance in manuscript selection. The readership includes general and specialist pediatricians, pediatric researchers and educators, and child health policy-makers. *Pediatrics* receives many more high quality manuscripts than can be accommodated based on our available space. The current acceptance rate is approximately 10%. An article that is thought by the editors to be not relevant to readers, outside of scope or

very unlikely to be accepted may be rejected without review. All manuscripts considered for publication are peer reviewed. Peer reviewers are selected by the editors based on their expertise in the topic of the manuscript; generally at least 2 reviews are required before a decision is rendered. Authors may suggest appropriate reviewers and may also suggest reviewers who should not review the manuscript.

Authors should carefully follow instructions for manuscript preparation, and ensure that the manuscript is proofread before submission. Manuscripts that do not adhere to the author instructions will not be considered for review. Careless preparation of a manuscript suggests careless execution of the research and therefore makes acceptance unlikely. Manuscripts are scanned for plagiarism using the latest software; if potential plagiarism is detected, the editors will contact the authors for clarification, and may also contact the authors' institution.

Submissions of original research are judged on the importance and originality of the research, scientific strength, clinical relevance, the clarity of the manuscript, and the number of submissions on the same topic. *Pediatrics* does not publish manuscripts that involve animal research.

Pediatrics accepts review articles, with preference given to systematic reviews, which may include meta-analyses. State-of-the-Art Review Articles and Perspectives are generally solicited by the editors or the associate editors for their respective sections. Special Articles reflect topics or issues of relevance to pediatric health care that do not conform to a traditional study format. Case Reports must challenge an existing clinical or pathophysiologic paradigm; provide a starting point for novel hypothesis-testing clinical research; and/or focus on topics pertinent to the pediatric generalist. Quality Reports provide a venue for manuscripts that describe the implementation and outcome of quality-improvement projects. Authors should review and follow the comprehensive reporting guidelines for a wide variety of study designs that are available at <http://www.equator-network.org/home/>. Authors submitting manuscripts involving adverse drug or medical device events or product problems should also report these to the appropriate governmental agency.

Unsolicited commentaries will be considered for publication; however, most commentaries are solicited by the editors. Responses to a published article should be submitted as online comments; selected comments may be considered for publication in the journal as Letters to the Editor.

Incorrect grammar, language use, or syntax may distract readers from the science being communicated and may lead to less favorable reviews. To help reduce this possibility, we strongly encourage authors to have their manuscripts reviewed for clarity by colleagues. If the authors' native language is not English, we strongly encourage review and editing by a colleague whose native language is English or the use of an English language editing service.

Peer reviewers are asked to assess each manuscript for originality; for interest to scientists, practitioners and policy makers; for quality of the analysis; and for quality of the presentation, and are asked to assess the priority of the paper for publication. After the reviews are received, the editors may take one of the following actions: *Accept*; *Accept with Revisions*; *Reject with option to Resubmit*; or *Reject*. A rejected manuscript may not be resubmitted. A manuscript may be rejected with an option to resubmit when additional data or analyses are requested by reviewers, or when extensive revision of the text is needed. The resubmitted manuscript receives an additional round of peer review (which may include new reviewers), and the manuscript may or may not be accepted. A decision of *Accept with Revision* indicates that the editors intend to accept the manuscript contingent on adequate response to reviewers. A decision of *Accept* (which is exceedingly rare on first submission)

indicates that the manuscript is ready to place into production without further modification. Decisions by the editors are final.

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Publication Ethics

Authorship. An “author” is someone who has made substantive intellectual contributions to a published study. Each author is required to meet ALL FOUR of the following criteria:

1. Substantial contribution(s) to conception and design, acquisition of data, or analysis and interpretation of data; **and**
2. Drafting the article or revising it critically for important intellectual content; **and**
3. Final approval of the version to be published, **and**
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NOTE: Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute a sufficient basis for authorship.

All persons listed as authors must meet these criteria, and all persons who meet these criteria must be listed as authors. Although *Pediatrics* does not specifically limit the number of authors (except for Case Reports), articles submitted with an unusual number of authors invite scrutiny by editors and reviewers for clear justification for the presence of each person on the authorship list. *Pediatrics* does not permit more than one author to claim any particular position in the author list (e.g., two first authors, or two senior authors).

Decide authorship issues, including the order, before submission. Except in instances where the editorial office has determined that a person does not qualify for authorship, *Pediatrics* does not allow changes to the author order, including adding or removing authors from a paper or any subsequent revisions.

Conflict of Interest and Disclosure. After a paper is accepted by *Pediatrics* for publication, all authors must submit conflict of interest and disclosure forms. *Pediatrics* adheres to the policy and uses the standardized disclosure form of the International Committee of Medical Journal Editors (ICMJE). The collection of the forms is automated within the online system.

IRB Approval. All studies that involve human subjects must be approved or deemed exempt by an official institutional review board; this should be noted in the Methods section of the manuscript.

Industry Sponsorship. *Pediatrics* generally does not accept reports of studies in which all authors are employed by a commercial entity with a financial interest in the results of the study.

Registration of Clinical Trials. All clinical trials must be registered in a World Health organization-approved Clinical Trial registry prior to enrollment of the first subject. The registry name and registration number should be included on the title page. Reports of unregistered trials will be returned to authors without review. Publication of the results of a trial that was initiated prior to the ICMJE requirement for trial registration will be considered by the editors on a case-by-case basis.

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Journal Style

All aspects of the manuscript, including the formatting of tables, illustrations, and references and grammar, punctuation, usage, and scientific writing style, should be prepared according to the most current *AMA Manual of Style* (<http://www.amamanualofstyle.com>).¹

Author Listing. All authors' names should be listed in their entirety, and should include institutional/professional affiliations and degrees held.

Authoring Groups. If you choose to include an organization, committee, team, or any other group as part of your author list, you must include the names of the individuals as part of the Acknowledgments section of your manuscript. This section should appear after the main text prior to your References section. The terms "for" or "on behalf of" must also be used when referencing the authoring group in the by-line.

Titles. *Pediatrics* generally follows the guidelines of the *AMA Manual of Style* for titles. Titles should be concise and informative, containing the key topics of the work. Declarative sentences are discouraged as they tend to overemphasize a conclusion, as are questions, which are more appropriate for editorials and commentaries. Subtitles, if used, should expand on the title; however, the title should be able to stand on its own. It is appropriate to include the study design ("Randomized Controlled Trial"; "Prospective Cohort Study", etc.) in subtitles. The location of a study should be included only when the results are unique to that location and not generalizable. Abbreviations and acronyms should be avoided. The full title will appear on the article, the inside table of contents, and in MEDLINE. Full titles are limited to 97 characters, including spaces. Short titles must be provided as well and are limited to 55 characters, including spaces. Short titles may appear on the cover of the journal as space permits in any given issue.

Abbreviations. List and define abbreviations on the Title Page. Unusual abbreviations should be avoided. All terms to be abbreviated in the text should also be spelled out at first mention, followed by the abbreviation in parentheses. The abbreviation may appear in the text thereafter. Abbreviations may be used in the abstract if they occur 3 or more times in the abstract. Abbreviations should be avoided in tables and figures; if used they should be redefined in footnotes.

Units of Measure. Like many US-based journals, *Pediatrics* uses a combination of Système International (SI)^{2,3} and conventional units. Please see the *AMA Manual of Style* for details.

Proprietary Products. Authors should use nonproprietary names of drugs or devices unless mention of a trade name is pertinent to the discussion. If a proprietary product is cited, the name and location of the manufacturer must also be included.

References. Authors are responsible for the accuracy of references. Citations should be numbered in the order in which they appear in the text. Reference style should follow that of the *AMA Manual of Style*, current edition. Abbreviated journal names should reflect the style of Index Medicus. Visit: <http://www.nlm.nih.gov/tsd/serials/lji.html>

References

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Clinical Trials

A study is considered a clinical trial if it prospectively assigns human subjects (whether randomized or not) to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

If authors report the results of a clinical trial, they must affirm that the study has been registered at www.clinicaltrials.gov or another WHO-approved national or international registry prior to the enrollment of the first subject. Information on requirements and appropriate registries is available at www.icmje.org. The trial registration number must be listed on the title page, and at the end of the abstract.

Authors are required to complete both pages of a CONSORT Form (flowchart and checklist) and submit these with their manuscript. In our submission system, these files appear under “Instructions and Forms”. For observational epidemiological studies, follow the appropriate [STROBE checklist](#).

- [Download a CONSORT form checklist \(PDF\) here.](#)
- [Download a CONSORT form flowchart \(PDF\) here.](#)

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Reuse of Data Sets

If a manuscript uses the same or similar data contained in previously published articles, the authors must state this in the initial letter of submission and provide citations to the related or possibly duplicative materials.

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Formatting Requirements

All submissions must adhere to the following format:

- Times New Roman font, size 12, black
- Title Page, Contributors' Statement Page, Abstract, Acknowledgments, and References should be **single-spaced**
- Only the Main Body Text should be **double-spaced**
- Main Submission Document as Microsoft Word or RTF file (no PDFs)
- Do **not** include page headers, footers, or line numbers in new submissions.
- Do **not** include footnotes within the manuscript body. Footnotes are allowed only in tables/figures.

Refer to the “Article Types” section for specific guidelines on preparing a manuscript in each category. Note in particular the requirements regarding abstracts for different categories of article.

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Title Page

The “title page” should appear first in your manuscript document, and depending on the individual needs of a paper may encompass more than one page.

Title pages for all submissions **must** include the following items (as shown in the [sample Title Page](#)):

1. **Title** (97 characters [including spaces] or fewer)
2. **Author listing.** Full names for all authors, including degrees, and institutional/professional affiliations.
3. **Corresponding Author.** Contact information for the Corresponding Author (including: name, address, telephone, and e-mail).
4. **Short title** (55 characters [including spaces] or fewer). Please note: the short title may be used on the cover of the print edition.
5. **Financial Disclosure Statement** for all authors. Disclose any financial relationships that could be broadly relevant to the work. If none, say “Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.”
6. **Funding source.** Research or project support, including internal funding, should be listed here; if the project was done with no specific support, please note that here. Technical and other assistance should be identified in Acknowledgments. If your funding body has open access requirements, please contact the Editorial Office prior to submission. Pediatrics has a 12 month embargo on articles (followed by a 4 year open access period) and does not allow articles to be opened for Creative Commons or similar licenses.
7. **Conflict of Interest Statement** for all authors. If none, say “Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.”
8. **If applicable, Clinical Trial registry name and registration number.** We adhere to ICMJE guidelines, which require that all trials must be registered with ClinicalTrials.gov or any other WHO Primary registry.
9. **Abbreviations.** List and define abbreviations used in the text. If none, say "Abbreviations: none".
10. **Table of Contents Summary.** This is required for all articles with abstracts. This brief summary is limited to 25 words. For accepted manuscripts, this will appear under the author names in the table of contents to give the reader a brief insight into what the article is about. It should entice the reader to read the full article. For example: *"Through linkage of state*

Medicaid and Child Protective Services databases, this study captures similarities and differences in health care expenditures based on a history of child maltreatment."

11. For Regular Article submissions, include the **"What's Known on This Subject; What This Study Adds"** (see below under article type for description). This is not needed for any other article type.

If a title page does not include all of the above items, the submission may be returned to the authors for completion.

- **Download and view a sample Title Page (PDF)** [here](#).
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Contributors' Statement Page

All submissions must contain a Contributors' Statement Page, directly following the Title Page. Manuscripts lacking this page will be returned to the authors for correction.

All persons designated as authors should qualify for authorship ([see "Publication Ethics" above](#)), and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. The Contributors' Statement Page should list the authors and specify the contribution(s) made by each individual. If multiple individuals have identical contributions they may be listed together; do not list an author more than once.

You must follow the required format shown in this example when creating your Contributors' Statement Page or your manuscript will be returned for correction. Each author should only appear once. Use names, not initials. If multiple authors have identical contributions, you can list them on the same line; otherwise, list each author separately.

Contributors' Statement:

Dr Smith conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Drs Jones, Lee, and Weber carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Ms Green designed the data collection instruments, and coordinated and supervised data collection at two of the four sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

Note: Contributors who do not meet the criteria for authorship (such as persons who helped recruit patients for the study, or professional editors) should be listed in an Acknowledgments section placed after the manuscript's conclusion and before the References section. Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged. These permissions do not need to be submitted with the manuscript unless requested by the editors.

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Word Count

To determine article length, count the body of the manuscript (from the start of the Introduction to the end of the Conclusion). The title page, contributors' statement page, abstract, acknowledgments, references, figures, tables, and multimedia are not included.

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Figures, Tables, and Supplementary Material

Figures

Authors should number figures in the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure must include a legend (placed on the figure itself or as a list appearing after the References) that does not exceed 50 words. Abbreviations previously expanded in the text are acceptable. If a figure is reproduced from another source, authors are required to obtain permission from the copyright holder, and proof of permission must be uploaded at the time of submission.

Figure arrays should be clearly labeled, preassembled, and submitted to scale. Figure parts of an array (A, B, C, etc.) should be clearly marked in capital letters in the upper left-hand corner of each figure part.

Technical requirements for figures: The following file types are acceptable: TIFF, PDF, EPS, and PNG. Color files must be in CMYK (cyan, magenta, yellow, black) mode.

Style for figures: Readers should be able to understand figures without referring to the text. Avoid pie charts, 3-dimensional graphs, and excess ink in general. Make sure that the axes on graphs are labeled, including units of measurement, and that the font is large enough to read. Generally delete legends or other material from the graph if it makes the picture smaller. Color graphs should be interpretable if photocopied in black and white.

Pediatrics cannot accept Excel or PowerPoint files for any part of your submission.

Tables

Tables should be numbered in the order in which they are cited in the text and include appropriate headers. Tables should not reiterate information presented in the Results section, but rather should provide clear and concise data that further illustrate the main point. Tabular data should directly relate to the hypothesis. Table formatting should follow the current edition of the *AMA Manual of Style*.

Style for tables: Tables should be self-explanatory. Avoid abbreviations; define any abbreviations in footnotes to the table. Avoid excess digits and excess ink in general. Where possible, rows should be in a meaningful order (e.g., descending order of frequency). Provide units of measurement for all numbers. In general, only one type of data should be in each column of the table.

Presentation of Numbers and Statistics

- Results in the abstract and the paper generally should include estimates of effect size and 95% confidence intervals, not just P- values or statements that a difference was statistically significant.
- Statistical methods for obtaining all P-values should be provided
- Units of independent variables must be provided in tables and results sections if regression coefficients are provided
- Authors should avoid expressing effect sizes in the form of highly derived statistics.

Equations should be typed exactly as they are to appear in the final manuscript. The following table, adapted from the guidelines for authors for the *Annals of Internal Medicine* by editors of *Medical Decision Making*, shows how to present certain percentages and some statistical measures:

Reporting:	Details:
	Report percentages to one decimal place (i.e., xx.x%) when sample size is greater than or equal to 200.
Percentages	To avoid the appearance of a level of precision that is not present with small samples, do not use decimal places (i.e., xx%, not xx.x%) when sample size is less than 200.
Error Measures	Report confidence intervals, rather than standard errors, when possible. Use "mean (error measures)" rather than "mean $\pm$ error measure" notation.
P values	Except when one-sided tests are required by study design, such as in noninferiority trials, all reported P values should be two-sided. In general, P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P [is less than sign]0.001. Notable exceptions to this policy include P values arising in the application of stopping rules to the analysis of clinical trials and genetic-screening studies.
"Trend"	Use the word trend when describing a test for trend or dose-response. Avoid the term "trend" when referring to p-values near but not below 0.05. In such instances, simply report a difference and the confidence interval of the

difference (if appropriate) with or without the p-value.

Supplemental Information

Authors may wish to include additional information as part of their article for inclusion in the online edition of *Pediatrics*. References to any online supplemental information must appear in the main article. Such supplemental information can include but are not limited to additional tables, figures, videos, audio files, slide shows, data sets (including qualitative data), and online appendices. If your study is based on a survey, consider submitting your survey instrument or the key questions as a data supplement. Authors are responsible for clearly labeling supplemental information and are accountable for its accuracy. Supplemental information will be peer reviewed, but not professionally copyedited.

Videos

Pediatrics encourages the submission of videos to accompany articles where relevant. Links can be placed in the article for use when it is accessed electronically. All videos must adhere to the same general permission rules that apply to figures (i.e.: parental consent when a patient is identifiable).

All videos should be submitted at the desired reproduction size and length. To avoid excessive delays in downloading the files, videos should be no more than 6MB in size, and run between 30 and 60 seconds in length. In addition, cropping frames and image sizes can significantly reduce file sizes. Files submitted can be looped to play more than once, provided file size does not become excessive. Video format must be either .mov or .mp4.

Authors will be notified if problems exist with videos as submitted, and will be asked to modify them if needed. No editing will be done to the videos at the editorial office—all changes are the responsibility of the author.

Video files should be named clearly to correspond with the figure they represent (i.e., figure1.mov, figure2.mp4, etc.). Be sure all video files have filenames that are no more than 8 characters long and include the suffix “.mov” or “.mp4.” A caption for each video should be provided (preferably in a similarly named Word file submitted with the videos), stating clearly the content of the video presentation and its relevance to the materials submitted.

IMPORTANT: One to four traditional still images from the video **must** be provided. These still images may be published with the article and will act as thumbnail images in the electronic edition that will link to the full video file. Please indicate clearly in your text whether a figure has a video associated with it, and be sure to indicate the name of the corresponding video file. A brief figure legend should also be provided.

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Regular Article

Abstract length: 250 words or fewer (structured, as noted below)

Article length: 3,000 words or fewer

Regular Articles are original research contributions that aim to inform clinical practice or the understanding of a disease process. Regular Articles include but are not limited to clinical trials, interventional studies, cohort studies, case-control studies, epidemiologic assessments, and surveys. Components of a Regular Article include:

- **What's Known on This Subject; What This Study Adds**
These brief summaries are each limited to 40 words. Please use precise and accurate language in paragraph form (i.e., not bullet points). For manuscripts accepted as Regular Articles, these summaries will become a highly visible part of your published paper, with prominence on the first page. Moreover, these summaries may be highlighted and presented in other areas of the journal. It is therefore paramount that you use language of the same caliber as the rest of your paper.
- **Structured Abstract (four paragraphs with headings in boldface type; single-spaced)**
The abstract should consist of: Background (or Objectives, or Background and Objectives), Methods, Results, and Conclusions. The Objective should clearly state the hypothesis; Methods, inclusion criteria and study design; Results, the outcome of the study; and Conclusions, the outcome in relation to the hypothesis and possible directions of future study.
- **Body of Article**
For the body of your article, follow this general outline:
- **Introduction**
A 1- to 2-paragraph introduction outlining the wider context that generated the study and the hypothesis.
- **Patients and Methods**
This section should detail inclusion criteria and study design to ensure reproducibility of the research. All studies that involve human subjects must be approved or deemed exempt by an official institutional review board; this should be noted here.
- **Results**
This section should give specific answers to the aims or questions stated in the introduction. The order of presentation of results should parallel the order of the methods section.
- **Discussion**
The section should highlight antecedent literature on the topic and how the current study changes the understanding of a disease process or clinical situation, and should include a section on the limitations of the present study.
- **Conclusion**

A brief concluding paragraph presenting the implications of the study results and possible new research directions on the subject.

General submission instructions (including cover letter, title page requirements, contributors' statement page, journal style guidance, and conflict of interest statements) apply to Regular Articles.

- **Download and view a sample Regular Article manuscript (PDF) [here](#).**
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Appendix B- Research Protocol

MMED PROTOCOL

**A review of the benefits of antenatal steroids in
premature neonates in a middle income country**

**University of Witwatersrand
Department of Paediatrics and Child Health**

**Student: Anees Laher
Student number: 0601767X**

**Supervisors: Prof D Ballot
Dr T Ramdin**

Title

A review of the benefits of antenatal steroids in premature neonates in a middle income country.

Introduction/Background

Neonatal mortality is a major problem worldwide with 38% of all deaths in children under 5 years attributed to neonatal mortality.(1) Every year, it is estimated that 4 million babies die in the neonatal period.(1) Preterm birth is the most common direct cause of neonatal mortality; accounting for 28% of neonatal deaths.(1) This is followed by severe infections and asphyxia accounting for 26% and 23% respectively.(1) Of great concern, 99% of neonatal deaths occur in low income countries with poverty being strongly associated with an increased risk of neonatal mortality.(1)

Closer to home, Africa accounts for 28% of neonatal deaths worldwide.(1) Even closer to home, South Africa has shown some improvement in recent years but has not met the fourth millennium goal, of reducing mortality by two-thirds in children under 5 years.(2) South Africa is one of the countries in which neonatal mortality has not decreased over the past 20 years.(3)

From the above, it is clear that addressing neonatal mortality is imperative to reduce childhood mortality. More specifically, reducing mortality in preterm neonates can be the most beneficial as this is the most common neonatal cause of mortality.

In 1972, Liggins (an obstetrician) and Howie (a neonatologist) conducted the first trial using antenatal corticosteroids for the prevention of respiratory distress syndrome in preterm babies.(4) Liggins and Howie noted that there was a reduction in the incidence of respiratory distress syndrome in preterm babies where maternal antenatal steroids were given, as compared to preterm babies where maternal antenatal steroids were not given.(4) Since the landmark trial by Liggins and Howie, antenatal corticosteroid therapy has become a standard of care to prevent preterm neonatal complications.(5)

A Cochrane review reviewing 21 articles evaluating the effect of antenatal steroids on preterm neonates showed that antenatal steroids reduced the risk of Respiratory Distress Syndrome, Intraventricular Haemorrhage, necrotising enterocolitis, and neonatal death.(5) Antenatal steroid use was also associated with a reduced risk for respiratory support and the need for mechanical ventilation and a trend in the reduced need for surfactant therapy.(5) However, from these 21 articles, 17 studies were conducted in high income countries, and only 4 in middle income countries.(5) In addition to the benefits shown in the Cochrane review, there seems to be a beneficial effect of antenatal steroids on symptomatic patent ductus arteriosus (PDA).(6)

The Cochrane review shows the clinical benefit in using antenatal steroids. Besides the above clinical benefits, there is also a cost benefit in using antenatal steroids. A study in a Brazilian tertiary hospital showed a reduction in cost of hospitalisation of preterm babies.(7) This cost was mainly due to a decreased duration of hospital stay and a decrease in ICU admissions. The benefit was more significant in babies born at a gestational age of less than 30 weeks and

a birth weight of less than 1500g.(7) Another study showed that antenatal steroids reduce cost and result in a better outcome in preterm babies less than 2kg.(8)

Even though antenatal steroids have been shown to be effective in neonatal outcome, antenatal steroid coverage in low-middle income countries (LMICS) remains low.(9) There are many reasons why antenatal steroid coverage is reduced. The main reason is due to mothers being admitted in advanced labour.(10) Other reasons include inevitable abortion, obstetric emergencies necessitating immediate delivery, incorrect assessment of gestational age, refusal of hospital treatment and obstetricians missing an opportunity to provide mothers with antenatal steroids.(10) The latter should be reduced as the Royal College of Obstetricians and Gynaecologists recommend routine administration of antenatal steroids to woman at risk for preterm delivery at a gestational age less than 35 weeks.(11)

A recent article by Azad and Costello suggests that caution is needed before increasing the use of antenatal steroids in LMICS.(12) Azad and Costello question the efficacy of antenatal steroids in LMICS to improve mortality in premature neonates less than 33 weeks and state that there is no benefit with the use of antenatal steroids after 33 weeks gestation.(12)

Another variable in the need for caution is the potential increase in sepsis in mothers who have received antenatal steroids.(12)

Althabe et al conducted a randomised trial in six low-income and middle-income countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) to implement strategies to reduce neonatal mortality.(13) There were 47 394 live births in the intervention group and 50 743 live births in the control group.(13) Strategies for the intervention group included

identifying women at risk for preterm birth and upscaling antenatal steroids in these women whereas standard practice was continued in the control group. These strategies resulted in an increase in antenatal steroid coverage from 10% in the control group to 45% in the intervention group.(13) Despite the increase of antenatal steroid coverage in the intervention group, neonatal mortality did not decrease in this group.(13) This study showed an increase in neonatal mortality in the intervention group with results showing an excess of 3.5 neonatal deaths for every 1000 women exposed to this strategy.(13)

Malloy looked at neonatal outcome with antenatal steroid use and stated that antenatal steroid use showed statistical significant reductions in neonatal mortality in all gestational ages except between 34 and 36+6 weeks.(14) However Gazquez Serrano et al looked at antenatal steroid use and late preterm infant morbidity and mortality (i.e. 34 to 36+6 weeks gestational age). Gazquez Serrano et al suggest that antenatal steroid use for preterm births between 34 and 36+6 weeks can significantly reduce morbidity from preterm birth.(15) When broken down into gestational age, neonates with a gestational age of 34-34+6 weeks, as compared to neonates with a gestational age of 35-36+6 weeks, were at a greater risk of having Hyaline Membrane Disease, needing Continuous Positive Airway Pressure (CPAP), Surfactant therapy and conventional mechanical ventilation ($p < 0.0001$).(15) The Cochrane review supports antenatal steroid use up to 34+6 weeks gestational age(5).

There is limited information on antenatal steroid use in South Africa. The Dexiprom study is only study that has looked at antenatal steroids in South Africa but this study only involved mothers who had preterm premature rupture of membranes.(16) In addition, lack of providing antenatal steroids has been identified as a probably avoidable factor in neonatal

deaths in South Africa.(17) There is concern over the use of antenatal steroids in LMICS.

This study will therefore review antenatal steroid use at a hospital in South Africa, a middle income country.

Aim and Objectives

Aim

To review the use of maternal antenatal steroids in premature neonates at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Objectives

1. To determine if maternal antenatal steroids have an effect on morbidity and mortality in preterm babies less than 1800g, at CMJAH.
2. To measure the maternal antenatal steroid coverage for premature births at CMJAH, and to determine the maternal characteristics of those who did not receive antenatal steroids.

Methods

Study Design

This will be a retrospective observational study. Two groups will be compared. The steroid exposed group will include neonates where maternal antenatal steroids were given and the steroid unexposed group will include neonates where maternal antenatal steroids were not given. Results will be used to perform stratification analysis by birth weight.

A secondary analysis of an existing database will be done.

Site of Study

This study will be conducted in the neonatal unit at CMJAH in Johannesburg, Gauteng.

Study Population

All neonates born at CMJAH, and admitted to the neonatal unit, in the period between 1 January 2013 and 31 December 2015.

Inclusion Criteria

Steroid exposed group: All premature neonates with a birth weight of >500g and <1800g, born at CMJAH, where maternal antenatal steroids were given.

Steroid unexposed group: Premature neonates with a birth weight of >500g and <1800g, born at CMJAH, where maternal antenatal steroids were not given.

Exclusion Criteria

1. Babies with major congenital malformations.
2. Any patient with unobtainable records.

Variables

Maternal information, delivery, gestational age, birth weight, clinical characteristics, ventilatory support and outcome will be obtained from the neonatal database. The variables that will be looked at are listed below:

- Maternal

- Age
- Parity
- Comorbidities
 - Hypertension
 - Diabetes
 - Chorioamnionitis
- Steroids received
- Mode of Delivery
- Multiple gestation
- Neonate
 - Gestational age
 - Birth weight
 - Gender
 - Resuscitation at birth
 - Hyaline membrane disease
 - Surfactant therapy
 - CPAP required and duration
 - IPPV required and duration
 - Necrotising enterocolitis (NEC Grade 2 or 3)
 - Intraventricular haemorrhage
 - Patent Ductus arteriosus
 - Sepsis (Defined as culture proven sepsis)
 - Early onset (before 3 days)
 - Late onset (after 3 days)
 - Duration of hospital stay

- Outcome

Data Collection

This is a secondary review of an existing database. Neonatal records are kept in a CMJAH neonatal database. Data is managed using Research Electronic Data Capture (REDCAP) which is hosted by the University of Witwatersrand. Data is collected by clinicians using hospital records. Data is verified at several different points. Permission will be obtained for using this neonatal database.

Sample size estimation

There are approximately 700 preterm babies (500 to 1800 g) admitted to CMJAH neonatal unit each year. An estimated 2100 preterm babies will be born during the study period. The steroid coverage is estimated to be 50% so there is an estimated 1050 babies in each group (steroid exposed and unexposed).

Data Analysis

Data will be described using standard statistical methods. Categorical variables will be described using frequency and percentages, while continuous variables will be described using mean and standard deviation or median and range, depending on the distribution of the data. Chi Square tests will be used to compare categorical variables using frequencies/percentages between the cases and control groups to assess if there is a statistically significant difference between the cases and control groups. The Student independent t-test will be used to compare continuous variables with a normal distribution. Non-parametric tests will be used for skewed data. A P-value of <0.05 will be considered significant. SPSS or Stata will be used for analysis. Associations with the use of antenatal

steroids will be determined using multivariate logistic regression. All variables which approached significance ($p < 0.1$) on univariate analysis will be explored.

Ethics

The protocol for this study will be submitted to the Postgraduate Committee of the University of the Witwatersrand and will be submitted to the Human Research Ethical Committee of the University of the Witwatersrand for approval.

Informed consent will not be needed as this is a retrospective study.

Confidentiality will be guaranteed by removing any patient-identifying markers from the data. Patient names, birth dates and file numbers will not be used and each patient will be assigned a study number.

Timing

	Mar 2016	Apr 2016	May 2016	Jun 2016	Jul 2016	Aug 2016	Sep 2016	Oct 2016	Nov 2016	Dec 2016	Jan 2017	Feb 2017	Mar 2017	Apr 2017
Literature review														
Preparing protocol														
Protocol assessment														
Ethics application														
Data collection														
Data analysis														
Writing up														

Funding

The cost for this study will be for printing and stationery. Costs are estimated to be five hundred rand. These costs will be dealt with by the investigator.

Limitations

As this is a retrospective study using already collected data, there is the possibility of incomplete data which can weaken the study. Another limitation is that the database does not include number of antenatal steroid doses or timing of doses, therefore it will not be possible to assess if adequate dosing was achieved for mothers who have received antenatal steroids. This study does not evaluate the reasons for mothers not receiving steroids.

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Data Sheet

Study number:

Maternal age:

Primiparous: Yes ☐ No ☐

Maternal diabetes: Yes ☐ No ☐

Maternal Hypertension: Yes ☐ No ☐

Chorioamnionitis: Yes ☐ No ☐

Maternal antenatal steroids received: Yes ☐ No ☐

Gestational age:

Birth weight:

Gender: M ☐ F ☐

Mode of delivery: Vaginal delivery ☐ Caesarean section ☐

Multiple gestation: Yes ☐ No ☐

Resuscitation at birth (Bag-mask ventilation): Yes ☐ No ☐

Hyaline membrane disease: Yes ☐ No ☐

Surfactant therapy: Yes ☐ No ☐ Number of doses:

CPAP required: Yes ☐ No ☐ Duration:

IPPV required: Yes ☐ No ☐ Duration:

NEC: Yes ☐ No ☐ Grade:

Treatment: Medical ☐ Surgical ☐

Intraventricular haemorrhage: Yes ☐ No ☐ Grade:

PDA: Yes ☐ No ☐

Sepsis: Yes ☐ No ☐

Early ☐

Late ☐

Duration of hospital stay:

Outcome: Discharged ☐ Demised ☐

Appendix C: Ethics Clearance



R1449 Dr. Anees Laher

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160730

NAME: Dr Anees Laher
(Principal Investigator)
DEPARTMENT: Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: A review of the Benefits of Antenatal Steroids in
Premature Neonates in a Middle Income Country

DATE CONSIDERED: 29/07/2016

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Dayna Bailot

APPROVED BY: 
Professor P. Cleaton-Jones Chairperson HREC (Medical)

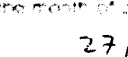
DATE OF APPROVAL: 01/08/2016

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, in Room 10004, 10th floor, Senate House, 2nd Floor, Philip Tobias Building, Parktown, University of the Witwatersrand. We fully understand the conditions under which I am/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 re-submit 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.


Principal Investigator Signature


Date

27/09/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: Turnitin

 Turnitin Originality Report
Submittableformat.docx by Null Null
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[Ballot, Daynia E, Tobias Chirwa, Tanusha Ramdin, Lea Chirwa, Irma Mare, Victor A Davies, and Peter A Cooper. "Comparison of morbidity and mortality of very low birth weight infants in a Central Hospital in Johannesburg between 2006/2007 and 2013", BMC Pediatrics, 2015.](#)

paper text:

A review of the benefits of antenatal steroids in premature neonates in a middle income country University of Witwatersrand Department of Paediatrics and Child Health Student: Anees Laher Student number: 0601767X Master of Medicine (Paediatrics) Supervisors: Prof D Ballot Dr T Ramdin Declaration I declare that this research report is my own work and any publications consulted have been appropriately referenced. This research report is submitted for the Degree of Master of Medicine in Paediatrics at the University of Witwatersrand. It has not been submitted for any other degree and has not been submitted to any other university. Signed:

_____ Dr Anees Laher Date: i Acknowledgements I would like to thank my supervisors, Professor D.E Ballot and Dr T Ramdin, for all their help, guidance and support

throughout this research project. I would also like to thank the Department

1 of

Paediatrics and Child Health at the **University of Witwatersrand**

to allow me to

pursue my dream of becoming a paediatrician. ii Table of Contents Declaration i Acknowledgements ii Table of Contents iii List of abbreviations iv

Your Submission

Inbox x

SAMJ <em@editorialmanager.com>

May 2, 2017 at
1:31pm

to me

CC: daynia.ballot@wits.ac.za, tanusharamdin@yahoo.com, tobias.chirwa@wits.ac.za

Ref.: SAMJ12246

A review of antenatal steroids in premature neonates in a middle income country
South African Medical Journal

Dear Dr Laher,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal.

Before we proceed to sending to the production team, please could you provide and/or correct the following:

1. Supply the figure in a pdf or jpeg format
2. Ref 15 is cited after reference 16?
3. Include a paragraph on author contributions.

Please send your amended version to claudian@hmpg.co.za.

Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD
Deputy Editor
South African Medical Journal



A review of antenatal corticosteroid use in premature neonates in a middle-income country

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Background. Antenatal corticosteroid (ANS) use in premature neonates has become a standard of practice. However, there is low ANS coverage in low- to middle-income countries (LMICs). Recent studies have questioned the efficacy of ANSs in such countries.

Objective. To review the use of ANSs in preterm neonates at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa.

Methods. This was a retrospective observational study of all neonates with a birth weight of 500 - 1 800 g born at CMJAH between 1 January 2013 and 30 June 2016. Neonatal and maternal characteristics of neonates exposed to ANSs were compared with those of neonates who were not exposed.

Results. The ANS coverage of the final sample was 930/2 109 (44.1%). The mean (standard deviation (SD)) birth weight was 1 292.4 (323.2) g and the mean gestational age 30.2 (2.9) weeks. Attending antenatal care and maternal hypertension were associated with increased use of ANSs, whereas vaginal delivery was associated with decreased use. In neonates weighing <1 500 g, the use of ANSs was associated with decreased mortality, decreased intraventricular haemorrhage and decreased patent ductus arteriosus. There was no association between ANSs and respiratory distress syndrome, necrotising enterocolitis, sepsis or need for respiratory support in all premature neonates, and no association with improved outcomes in those weighing ≥1 500 g.

Conclusion. The benefits of ANSs in terms of neonatal morbidity in this study were not as marked as those published in high-income countries. A randomised controlled trial may be indicated in LMICs.

S Afr Med J 2017;107(9):768-772. DOI:10.7196/SAMJ.2017.v107i9.12246

Neonatal mortality is a major problem worldwide, accounting for 38% of all deaths in children aged <5 years.^[1] Every year, it is estimated that four million babies die in the neonatal period.^[1] Preterm birth is the most common cause of neonatal mortality, accounting for 28% of neonatal deaths.^[1] Of great concern, 99% of neonatal deaths occur in low-income countries, with poverty being strongly associated with an increased risk of neonatal mortality.^[1]

Africa accounts for 28% of neonatal deaths worldwide.^[1] South Africa (SA) has had some success in reducing childhood mortality in recent years, but has not met the fourth Millennium Development Goal of reducing mortality by two-thirds in children aged <5 years.^[2] SA is one of the countries in which neonatal mortality has not decreased over the past 20 years.^[3]

Addressing neonatal mortality is of vital importance in reducing childhood mortality. Specifically, reducing mortality in preterm neonates can be the most beneficial, as prematurity is the most common cause of neonatal mortality.^[1]

In 1972, Liggins and Howie^[4] conducted the first trial using antenatal corticosteroids (ANSs) for the prevention of respiratory distress syndrome (RDS) in preterm neonates. They noted a reduction in the incidence of RDS in preterm neonates whose mothers were given ANSs compared with preterm neonates whose mothers were not.^[4] Since this landmark trial,^[4] ANS therapy has become a standard of care to prevent preterm neonatal complications.^[5]

A Cochrane review of 21 articles evaluating the effect of ANSs on preterm neonates^[5] showed that ANSs reduced the risk of RDS, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and early-onset sepsis, reduced mortality and the need for respiratory support, and resulted in a trend towards reduced need for surfactant

therapy. However, of these 21 studies, 17 were conducted in high-income countries and only 4 in middle-income countries.^[5] In addition to the benefits shown in the Cochrane review, there seems to be a beneficial effect of ANSs on symptomatic patent ductus arteriosus (PDA).^[6]

The use of ANSs in low- and middle-income countries (LMICs) remains low.^[7] The main reason is mothers being admitted in advanced labour.^[8] Other reasons include inevitable abortion, obstetric emergencies necessitating immediate delivery, incorrect assessment of gestational age, refusal of hospital treatment, and obstetricians missing an opportunity to provide mothers with ANSs.^[8] The latter should decrease, as the National Institute for Health and Care Excellence recommends routine administration of ANSs to women who are in suspected or established preterm labour at a gestational age <34 weeks.^[9]

A recent article by Azad and Costello^[10] suggests that caution is needed before increasing the use of ANSs in LMICs. They question the efficacy of ANSs in LMICs to improve mortality in premature neonates at a gestational age of <33 weeks, and state that ANSs are of no benefit after 33 weeks' gestation.^[10]

Althabe *et al.*^[11] conducted a randomised trial in six LMICs (Argentina, Guatemala, India, Kenya, Pakistan and Zambia) to implement strategies to reduce neonatal mortality. Strategies included identifying women at risk for preterm birth and upscaling ANSs in these women, whereas standard practice was continued in the control group. These strategies resulted in an increase in ANS coverage from 10% in the control group to 45% in the intervention group.^[11] Despite the increase in ANS coverage, the intervention group showed an increase in neonatal mortality, with an excess of 3.5 neonatal deaths

for every 1 000 women exposed to this strategy.^[11] It was not possible to assess the weight or gestational age of the babies in the study, and the cause of this increased mortality was not clear.

There is limited information on ANS use in SA. The Dexiprom study is the only study that has looked at effects of ANSs in SA, but it only involved mothers who had preterm premature rupture of membranes.^[12] There is concern over the use of ANSs in LMICs.

Objective

To review ANS use in a hospital in SA, a middle-income country.

Methods

Study design

This was a retrospective observational study. The study population included all neonates with a birth weight between 500 g and 1 800 g born at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 2013 and 30 June 2016. Exclusion criteria included babies with lethal birth defects and those with unobtainable records. The total sample was analysed and then divided into two groups: babies weighing ≥ 1 500 g and those weighing < 1 500 g. Each of the two groups was further divided into an ANS-exposed group and an unexposed group, and these groups were then compared. The ANS-exposed group were neonates whose mothers were given ANS, and the ANS-unexposed group were those whose mothers were not. At CMJAH, two doses of 12 mg betamethasone 12 hours apart are given intramuscularly to mothers if the gestational age is < 34 weeks or if the estimated fetal weight is < 2 000 g. In this study, birth weight was used instead of gestational age because gestational age is not accurate in our setting, where antenatal ultrasound is not routinely done and patients' recollection of the date of their last menstrual period is often inaccurate.

RDS is diagnosed using chest radiographs and clinically (tachypnoea, subcostal recessions, intercostal recessions) in premature neonates requiring oxygen at CMJAH. The use of surfactant and continuous positive airway pressure (CPAP) is limited to neonates with a birth weight of > 750 g, and is at the discretion of the attending doctor. Early rescue surfactant is used at CMJAH. The combination of early rescue surfactant and CPAP has been shown to reduce morbidity and mortality associated with intensive care unit admissions at CMJAH.^[13]

Data

This was a secondary review of an existing database. Neonatal records are kept in a neonatal database at CMJAH. Data are managed using Research Electronic Data Capture (REDCap)^[14] which is hosted by the University of the Witwatersrand. Data are collected by clinicians using hospital records and verified at several different points. Permission was obtained to use this neonatal database.

Statistical analysis

Maternal and neonatal variables were evaluated. Valid cases were analysed and missing data excluded. Data were described using standard statistical methods. Categorical variables were described using frequencies and percentages, while continuous variables were described using means and standard deviations (SDs) or medians and interquartile ranges, depending on the distribution of the data. Chi-square tests were used to compare categorical variables. Student's independent *t*-test was used to compare continuous variables with a normal distribution. Non-parametric tests were used for skewed data. The level of significance was set at $p < 0.05$. Analysis was done using SPSS, version 24 (IBM, USA). Associations with the use of ANSs were

determined using logistic regression. All variables that approached significance ($p < 0.06$) on univariate analysis were explored.

Ethical approval

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M160730).

Results

There was a total of 6 186 neonates on the REDCap database (accessed on 27 September 2016) between 1 January 2013 and 30 June 2016. Of the 6 186 neonates, 3 415 had a birth weight > 1 800 g and six a birth weight of < 500 g. A further 656 were excluded (Fig. 1), resulting in a final sample size of 2 109. The mean (SD) birth weight of the final sample was 1 292.4 (323.2) g, and the mean gestational age was 30.2 (2.9) weeks. ANS coverage of the final sample was less than half, with 930/2 109 neonates (44.1%) exposed to ANSs and 1 179/2 109 (55.9%) not exposed.

Maternal characteristics

Maternal characteristics are shown in Table 1. Mothers who did not attend antenatal care were significantly less likely to receive ANSs ($p < 0.001$). It was also observed that mothers with hypertension were more likely to receive ANSs ($p < 0.001$), whereas HIV-positive mothers were less likely ($p = 0.001$). There were 718/2 101 vaginal deliveries (34.2%) and 1 383/2 101 caesarean sections (65.8%). Vaginal deliveries were associated with decreased ANS coverage ($p < 0.001$). There was no significant association between ANS coverage and maternal age, parity, chorioamnionitis or diabetes.

Neonatal characteristics

Neonatal characteristics of the total sample are shown in Table 2 and continuous variables in Table 3. Valid data are shown in the table and percentages are expressed in columns.

Gender, spontaneous gastrointestinal perforation, oxygen required by day 28 of life and home oxygen required were not included in Table 2, as none of these variables was significantly different. Reported associations with ANSs were included in the table, even though these variables were not significant in the current study.

Total sample (Table 2)

In the total sample, the variables late-onset sepsis ($p = 0.017$), RDS ($p < 0.001$), CPAP ($p = 0.002$) and surfactant therapy ($p = 0.016$) were

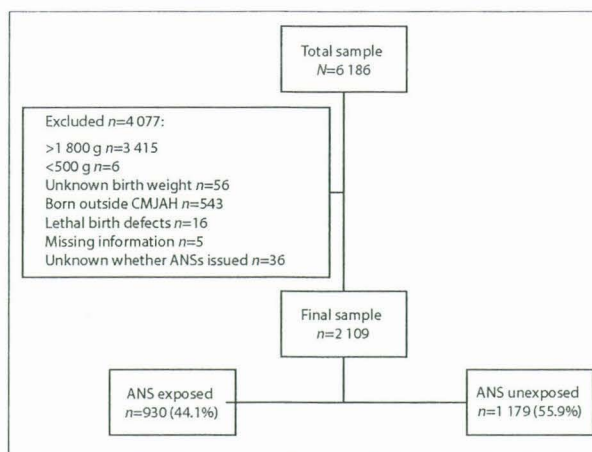


Fig. 1. Patient selection. (CMJAH = Charlotte Maxeke Johannesburg Academic Hospital; ANSs = antenatal steroids.)

Table 1. Maternal characteristics associated with receiving ANSs

Variable*	Total sample	≥1 500 g				<1 500 g			
		Total	ANSs	No ANSs	p-value	Total	ANSs	No ANSs	p-value
Antenatal care, n/N (%)	1 773/2 085 (85.0)	587/676 (86.8)	178/193 (92.2)	409/483 (84.7)	0.009	1 186/1 409 (84.2)	668/729 (91.6)	518/680 (76.2)	<0.001
Maternal hypertension, n/N (%)	552/2 100 (26.3)	126/685 (18.4)	54/197 (27.4)	72/488 (14.8)	<0.001	426/1 415 (30.1)	260/732 (35.5)	166/683 (24.3)	<0.001
Maternal HIV, n/N (%)	648/2 101 (30.8)	227/688 (33.0)	53/197 (26.9)	174/491 (35.4)	0.031	421/1 413 (29.8)	197/731 (26.9)	224/682 (32.8)	0.015
Vaginal delivery, n/N (%)	718/2 101 (34.2)	237/688 (34.4)	52/196 (26.5)	185/492 (37.6)	0.006	481/1 413 (34.0)	204/730 (27.9)	277/683 (40.6)	<0.001
Multiple gestation, n/N (%)	433/2 100 (20.6)	172/689 (25.0)	51/197 (25.9)	121/492 (24.6)	0.723	261/1 411 (18.5)	114/729 (15.6)	147/682 (21.6)	0.004

ANSs = antenatal corticosteroids.
*N differs owing to missing data.

significantly associated with ANS exposure. However, when the total group was divided according to birth weight <1 500 g and ≥1 500 g, late-onset sepsis, RDS, CPAP and surfactant therapy were no longer significant. This indicates that birth weight was a major confounding factor.

Neonates ≥1 500 g (Tables 2 and 3)

In the subgroup weighing ≥1 500 g, there were 197/691 neonates (28.5%) exposed to ANSs and a survival rate of 674/690 (97.7%). There was a significantly lower mean birth weight ($p=0.002$) and mean gestational age ($p<0.001$) in neonates exposed to ANSs compared with those who were not exposed. It was observed that neonates exposed to ANSs had a longer duration of stay than those who were not exposed ($p=0.002$). There was no significant difference between exposure to ANSs and RDS, IVH, NEC, PDA, early- and late-onset sepsis, and other neonatal characteristics. The variables most significantly associated with ANSs using logistic regression (Table 4) were antenatal care ($p=0.015$), vaginal delivery ($p=0.043$), maternal hypertension ($p=0.002$), birth weight ($p=0.034$) and gestational age ($p<0.001$). Maternal HIV and duration of stay were not significant after logistic regression.

Neonates <1 500 g (Tables 2 and 3)

In the subgroup weighing <1 500 g, there were 733/1 418 neonates exposed to ANS (51.7%) and a survival rate of 1 075/1 418 (75.8%). Neonates exposed to ANSs were significantly less likely to have a PDA ($p=0.015$), to have an IVH ($p=0.049$), and to require resuscitation at birth ($p<0.001$). There was a significant association between exposure to ANSs and increased survival ($p<0.001$). It was also observed that neonates exposed to ANSs had a longer duration of stay in hospital than those who were not exposed ($p=0.001$). There was no significant association between ANS and RDS, NEC, early- and late-onset sepsis and other neonatal characteristics. The variables most significantly associated with ANSs using logistic regression (Table 5) were antenatal care ($p<0.001$), vaginal delivery ($p=0.038$), multiple gestation ($p<0.001$), resuscitation at birth ($p=0.001$), PDA ($p=0.001$) and duration of stay ($p=0.012$). Variables that were not significant after logistic regression were conventional ventilation, IVH, outcome, maternal hypertension and HIV.

Discussion

The current study showed ANS coverage of 44.1% at CMJAH. This figure has increased since 1993, when coverage was only 20%,^[8]

but it is lower than in other LMICs, which according to the WHO Multicountry Survey on Maternal and Newborn Health had an average coverage of 52%.^[15] ANS coverage at CMJAH is substantially lower than the average of 80% in high-income countries (HICs).^[11] An increase in gestational age was associated with decreased exposure to ANS. This trend is also noted in HICs, where ANS coverage decreases by more than half at 34 weeks compared with coverage at 24 - 30 weeks.^[16] The reasons for this are not clear. It may represent inaccurate gestational age estimation or reduced attention to 'moderately preterm' babies.^[16]

Our study showed surprising results when the total sample was analysed, as certain results were significant in the total sample and not significant in either group when stratified by birth weight. This is because more small babies (51.7%), than larger babies (28.5%), were exposed to ANSs, showing that birth weight is a confounding factor.

In our study, vaginal delivery was associated with decreased ANS use. This is true in other LMICs and HICs.^[15,16] The main reason for this decrease in ANS use is mothers presenting in advanced labour, giving no opportunity for ANSs to be provided.^[8] We also found that unbooked mothers were significantly less likely to receive ANSs. Lack of antenatal care is consistently associated with reduced ANS coverage in LMICs and HICs.^[15,16] This is a difficult problem to address, as it is probably associated with low socioeconomic status and poor maternal education and is a point for improvement.

In our study, maternal hypertension had an association with increased ANS use. This is probably because mothers with hypertension are followed up regularly during the antenatal period and are usually admitted if preterm delivery is necessary. The decreased ANS exposure associated with maternal HIV infection was an interesting observation, but cannot be explained by our study. It was, however, not significant on logistic regression.

We found no association between ANS exposure and RDS, NEC, early-onset sepsis or need for respiratory support. This contradicts the Cochrane review^[5] on the effect of ANSs on preterm neonates, but Pattinson *et al.*^[12] also showed no statistical significance in RDS, NEC, early-onset sepsis and need for ventilation in their study in SA. It must be pointed out, however, that the neonates in Pattinson *et al.*'s study had a higher mean birth weight than those in our study.

We found that neonates exposed to ANSs were less likely to have a PDA than those who were not exposed. This supports Salhab *et al.*'s^[6] finding of a beneficial effect of ANSs on PDA. Possible mechanisms for this are a steroid effect on prostaglandin synthesis, reduced sensitivity of the ductal muscle to prostaglandin E_2 , and increased activity of the prostaglandin E_2 inactivation enzyme.^[6]

Table 2. Neonatal characteristics associated with ANS exposure

Variable*	Total sample				≥1 500 g				<1 500 g			
	Total	ANSs	No ANSs	p-value	Total	ANSs	No ANSs	p-value	Total	ANSs	No ANSs	p-value
Resuscitation at birth, n/N (%)	766/2 089 (36.7)	324/922 (35.1)	442/1 167 (37.9)	0.198	158/691 (22.9)	50/197 (25.4)	108/494 (21.9)	0.320	608/1 398 (43.5)	274/725 (37.8)	334/673 (49.6)	<0.001
Early-onset sepsis, n/N (%)	73/2 103 (3.5)	34/925 (3.7)	39/1 178 (3.3)	0.650	13/691 (1.9)	3/197 (1.5)	10/494 (2.0)	0.661	60/1 412 (4.2)	31/728 (4.3)	29/684 (4.2)	0.986
Late-onset sepsis, n/N (%)	451/2 102 (21.5)	221/926 (23.9)	230/1 176 (19.6)	0.017	56/690 (8.1)	16/197 (8.1)	40/493 (8.1)	0.997	395/1 412 (28.0)	205/729 (28.1)	190/683 (27.8)	0.899
IVH, n/N (%)	209/852 (24.5)	90/422 (21.3)	119/430 (27.7)	0.031	14/81 (17.3)	2/27 (7.4)	12/54 (22.2)	0.096	195/771 (25.3)	88/395 (22.3)	107/376 (28.5)	0.049
RDS, n/N (%)	1 628/2 109 (77.2)	760/930 (81.7)	868/1 179 (73.6)	<0.001	352/691 (50.9)	106/197 (53.8)	246/494 (49.8)	0.341	1 276/1 418 (90.0)	654/733 (89.2)	622/685 (90.8)	0.322
CPAP, n/N (%)	1 200/2 103 (57.1)	562/925 (60.8)	638/1 178 (54.2)	0.002	229/691 (33.1)	64/197 (32.5)	165/494 (33.4)	0.818	971/1 412 (68.8)	498/728 (68.4)	473/684 (69.2)	0.763
Ventilation, n/N (%)	274/2 101 (13.0)	115/924 (12.4)	159/1 177 (13.5)	0.473	40/691 (5.8)	8/197 (4.1)	32/494 (6.5)	0.219	234/1 410 (16.6)	107/727 (14.7)	127/683 (18.6)	0.051
Surfactant, n/N (%)	1203/2 100 (57.3)	557/925 (60.2)	646/1 175 (55.0)	0.016	225/686 (32.8)	62/196 (31.6)	163/490 (33.3)	0.681	978/1 414 (69.2)	495/729 (67.9)	483/685 (70.5)	0.288
PDA, n/N (%)	138/2 099 (6.6)	53/922 (5.7)	85/1 177 (7.2)	0.176	16/691 (2.3)	3/197 (1.5)	13/494 (2.6)	0.576	122/1 408 (8.7)	50/725 (6.9)	72/683 (10.5)	0.015
NEC, n/N (%)	124/2 095 (5.9)	56/924 (6.1)	68/1 171 (5.8)	0.807	23/684 (3.4)	6/195 (3.1)	17/489 (3.5)	0.794	101/1 411 (7.2)	50/729 (6.9)	51/682 (7.5)	0.652
Outcome – survived, n/N (%)	1 749/2 108 (83.0)	777/930 (83.5)	972/1 178 (82.5)	0.530	674/690 (97.7)	193/197 (98.0)	481/493 (97.6)	0.750	1 075/1 418 (75.8)	584/733 (79.7)	491/685 (71.7)	<0.001

ANSs = antenatal corticosteroids; IVH = intraventricular haemorrhage; RDS = respiratory distress syndrome; CPAP = continuous positive airway pressure; PDA = patent ductus arteriosus; NEC = necrotising enterocolitis.

*N differs owing to missing data.

Our study demonstrated a significant association between ANS exposure and survival in neonates weighing <1 500 g. This finding is in agreement with Pattinson *et al.*^[12] and the Cochrane review on the effect of ANSs on preterm neonates,^[9] but contrasts with Althabe *et al.*^[11] observation of an increase in neonatal mortality in LMICs with the upscaling of ANSs and differs from the conclusions of Azad and Costello,^[10] who questioned whether ANSs improve neonatal mortality. Our study also showed an association between ANS exposure and reduced IVH. This association was only significant in neonates weighing <1 500 g and supports the findings of the Cochrane review^[9] that ANS exposure reduces the risk of IVH.

Our study demonstrated a longer duration of stay in both weight groups, <1 500 and ≥1 500 g, for neonates exposed to ANSs compared with those who were not exposed. This interesting observation could be explained by a significantly higher survival rate in the ANS-exposed group, and the fact that the lower mean birth weight (1 236 g) in this group than in the unexposed group (1 336 g) meant that it took longer for the babies who had been exposed to reach 1 600 g, the discharge weight at CMJAH. Most deaths at CMJAH occur within the first 7 days of life.

There were no associations between ANS exposure and improved neonatal outcomes in neonates weighing ≥1 500 g in our study. This supports Azad and Costello's^[10] observation that the use of ANSs is of no benefit after 33 weeks' gestation in LMICs.

Study limitations

This was a retrospective study, and there was low ANS coverage. The number and timing of ANS doses were not known. We can only comment on associations and cannot address effects of ANSs in LMICs. Since birth weight instead of gestational age was used, babies with intrauterine growth restriction may have been included in our sample.

Conclusions

Preterm birth is associated with multiple complications. There have recently been questions on the efficacy of ANSs in LMICs. The present study showed an association between ANSs and increased survival, decreased PDA and decreased IVH in neonates weighing <1 500 g. However, there was no association between ANSs and RDS, NEC or sepsis, and there were no associations with improved neonatal outcome in neonates weighing ≥1 500 g. This suggests a review of the birth weight cut-off point for

Table 3. Continuous variables associated with ANS exposure

Variable	≥1 500 g			<1 500 g		
	ANSs	No ANSs	p-value	ANSs	No ANSs	p-value
Birth weight (g), mean (SD)	1 633.8 (84.7)	1 656.8 (88.2)	0.002	1 129.7 (234.2)	1 105.7 (250.6)	0.063
Gestational age (wk), mean (SD)	32.0 (1.6)	32.7 (2.3)	<0.001	29.1 (2.3)	29.0 (2.8)	0.531
Duration of CPAP (d), median (IQR)	1 (0)	1 (1)	0.164	2 (3)	2 (2)	0.440
Duration of ventilation (d), median (IQR)	8 (13)	4 (3)	0.069	5 (9)	5 (6)	0.608
Duration of stay (d), median (IQR)	10 (9)	9 (9)	0.002	30 (28)	26 (31)	0.001

ANSs = antenatal corticosteroids; CPAP = continuous positive airway pressure; SD = standard deviation; IQR = interquartile range.

Table 4. Logistic regression for significant variables in neonates weighing ≥1 500 g exposed to ANSs

Variable	OR	95% CI	p-value
Antenatal care	2.132	1.157 - 3.921	0.015
Vaginal delivery	0.656	0.436 - 0.987	0.043
Maternal hypertension	2.008	1.305 - 3.096	0.002
Birth weight	0.998	0.996 - 1.000	0.034
Gestational age	0.826	0.754 - 0.906	<0.001

ANSs = antenatal corticosteroids; OR = odds ratio; CI = confidence interval.

Table 5. Logistic regression for significant variables in neonates weighing <1 500 g exposed to ANSs

Variable	OR	95% CI	p-value
Antenatal care	3.086	1.953 - 4.878	<0.001
Vaginal delivery	0.705	0.508 - 0.980	0.038
Multiple gestation	0.493	0.334 - 0.728	<0.001
Resuscitation at birth	0.581	0.427 - 0.791	0.001
PDA	0.462	0.290 - 0.736	0.001
Duration of stay	1.009	1.002 - 1.016	0.012

ANSs = antenatal corticosteroids; PDA = patent ductus arteriosus; OR = odds ratio; CI = confidence interval.

issuing ANSs in our setting, and perhaps indicates a need for a randomised controlled trial on the effects of ANSs in LMICs.

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