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Antenatal Corticosteroid Use and Perinatal Mortality According to Gestational Age among Preterm Singletons Born at 27 to 34 Weeks of Gestation in Hospitals in Tanzania

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Abstract

Background: Antenatal corticosteroid (ACS) treatment has been proven to decrease rates of adverse perinatal outcomes when administered to pregnant women at risk for preterm delivery. Given the uncertainty about the benefit of ACS according to gestational age, we aimed to examine whether there was any benefit of ACS on perinatal mortality and respiratory distress syndrome (RDS) according to different gestational ages at birth. **Methods:** Secondary analysis of data from an observational prospective chart review study was conducted in four hospitals located in the Mwanza region, Tanzania. The study population consisted of singleton infants delivered between 27 and 34 weeks of gestation between July 2019 and February 2020. Sociodemographic and medical data were recorded from participants' medical records. **Results:** Over an eight-month period, 838 preterm singletons were delivered between 27 and 34 weeks of gestation. Three hundred and twelve (37.2%) pregnant women received at least one dose of ACS. Among infants exposed to ACS, perinatal mortality rates were significantly lower than those without exposure at the 27th week (27.8% vs 94.4%, $P < 0.001$), the 29th week (13.3% vs 51.4%, $P = 0.012$) and the 34th week (3.0% vs 18.2%, $P < 0.001$). Among infants exposed to ACS, the RDS rate was significantly lower than those without exposure only at the 32nd week (9.5% vs 25.0%, $P = 0.039$). **Conclusion:** Our findings add to the literature about the benefits of ACS for preterm infants of various gestational ages in low-resource settings. Compared to unexposed infants, those exposed to ACS and born at 27th and 34th weeks of gestation experienced lower rates of perinatal mortality. Future research, especially among infants born before the 27th week of pregnancy, is a priority.

Keywords

Antenatal Corticosteroid, Perinatal Mortality, Gestational Age, Preterm Singletons, Tanzania

1. Introduction

Preterm newborns frequently have breathing problems because their lungs are not fully grown. About half of those born before 28 weeks and a third of those born before 32 weeks have breathing abnormalities, and the majority do not survive [1]. Antenatal corticosteroid (ACS) treatment has been proven to decrease rates of adverse perinatal and neonatal outcomes (e.g., perinatal mortality, neonatal deaths, and respiratory distress syndrome (RDS)) when administered to pregnant women at risk for preterm delivery [2]. Evidence from a Cochrane systematic review supports the use of ACS to enhance fetal lung maturation [3]. A single course of ACS (*i.e.*, betamethasone injection 12 mg or dexamethasone injection 6mg) is recommended between 24 weeks and 34 weeks of gestation in women that are at risk of preterm delivery within 7 days [4].

Preterm delivery problems and perinatal outcomes are mostly determined by gestational age at birth [5]. The earlier an infant is born, the higher the chances of experiencing an adverse outcome [6] [7]. A previous study reported increased rates of neonatal morbidity rates with decreasing gestational age [8]. Though it is known that ACS reduces rates of adverse perinatal outcomes, it is unclear at what gestational age this effect starts to occur and whether the benefits of ACS differ by gestational age [9]. In part because of the small sample size, meta-analyses of trials including participants with a lower gestational age (*i.e.*, 26 weeks) revealed no significant reduction in neonatal mortality and morbidity in the corticosteroid group as compared with non-intervention [10].

Given the uncertainty about the benefit of ACS according to gestational age, we analysed the data available from an observational prospective chart review study that investigated whether exposure to ACS was associated with lower rates of perinatal mortality among preterm births in hospitals in Tanzania [11] to see if there was any difference in the effect of ACS on perinatal outcomes according to different gestational ages at birth.

2. Methods

This is a secondary analysis of data from an observational prospective chart review study [11]. It took place in four hospitals in the districts of Nyamagana and Sengerema, which are two of the seven districts in the Mwanza area of northwest Tanzania. The facilities that took part were: Bugando Medical Centre (a tertiary consultant zonal referral hospital), Sekou Toure Regional Referral Hospital, Nyamagana District Hospital, and Sengerema District Designated Hospital. These hospitals serve a substantial percentage of the population in Tanzania's

lake zone, providing obstetric and neonatal care.

All singletons born between July 2019 and February 2020 who met the following inclusion criteria were included in the study: 1) Infants born to mothers with preterm birth indicators like antepartum hemorrhage, pre-eclampsia or eclampsia, premature preterm rupture of membranes, or preterm labor; 2) infants born in-hospital between 27 and 34 weeks of gestation; and 3) infants born within 7 days of the mother receiving ACS. Infants with a congenital abnormality as documented in the medical record were excluded.

ACS (*i.e.*, dexamethasone 6 mg) exposure was the primary predictor variable. In this study, ACS treatment included a maximum of four doses of dexamethasone injections of 6 mg every 12 hours. The study participants were divided into two groups: those who did not receive ACS and those who received at least one dose of ACS. Perinatal mortality, which was defined as stillbirth or early neonatal mortality (*i.e.*, the death of a live-born neonate between zero and seven days after birth), was the primary outcome. A diagnosis of RDS was the secondary outcome.

The lead investigator and trained research assistants who were enrolled or registered nurses working in the hospitals' labor wards reviewed the medical records of women and their infants. We recorded whether the mother was exposed to ACS or not, perinatal death, and the infant's RDS status for each participant. From the women's and infant's medical records, information on parity, marital status, maternal age, antenatal care visits (days), gestational age (weeks), mode of delivery, indication for delivery, level of health facility, birthweight (grams), and neonate sex were also acquired. Women's gestational ages were determined using their last normal menstrual period, fundal height, and/or ultrasound results.

The software package STATA version 14 was used to perform the statistical analysis. Cross-tabulation and chi-square tests were conducted to determine differences in perinatal mortality and RDS by ACS exposure at each gestational age. P-values of less than 0.05 were considered statistically significant. Data are presented as frequencies (percentages) and median (interquartile range) as appropriate.

Patients' information was kept private, and because only secondary data was collected in this study, the ethics committee waived the requirement for participant informed consent. This study was approved by the Catholic University of Health and Allied Sciences and Bugando Medical Centre's Joint Ethics and Research Review Committee in May 2019 (IRB approval No. CREC/368/2019).

3. Results

Over an eight-month period, 838 preterm singletons were delivered between 27 and 34 weeks of gestation. Of those, the mothers of 272 (32.5%) were nullipara, while 715 (85.3%) were married. The median maternal age was 26 (21 - 31). Three hundred and four (38.2%) attended more than 3 antenatal care visits; the

median gestational age was 32 (29 - 34); 229 (27.3%) delivered through caesarean section; 312 (37.2%) received at least one dose of ACS; only 104 (12.4%) had a premature preterm rupture of membrane; and 337 (40.2%) delivered at a tertiary zonal hospital. Further, the median birth weight of infants was 2000 (1600 - 2450) and 444 (53.0%) were males (Table 1).

Table 2 shows the number of infants in each gestation group and the frequency (percentage) of ACS status. Compared to the overall proportion of ACS administration (*i.e.*, 37.2%), rates of exposure to ACS were higher among infants at the 27th, 31st, 33rd, and 34th weeks of gestation. The highest was in the 33rd week (*i.e.*, 60.9%), and the lowest was in the 28th gestation week (*i.e.*, 14.7%).

Among infants exposed to ACS, perinatal mortality rates were significantly lower than those without exposure at the 27th week (27.8% vs 94.4%, $P < 0.001$), the 29th week (13.3% vs 51.4%, $P = 0.012$) and the 34th week (3.0% vs 18.2%, $P < 0.001$) (Table 3).

Among infants exposed to ACS, the RDS rate was significantly lower than those without exposure only at the 32nd week (9.5% vs 25.0%, $P = 0.039$) (Table 4).

Table 1. Maternal and infants baseline characteristics (N = 838).

Maternal	Median/Frequency	*IQR/Percentage
Nulliparity	272	32.5
Married	715	85.3
Maternal age	26	21-31
More than 3 Antenatal care visits†	304	38.2
Gestational age	32	29-34
C- section delivery	229	27.3
ACS given	312	37.2
Indication for delivery		
Antepartum haemorrhage	108	12.9
Pre-eclampsia or Eclampsia	154	18.4
Premature preterm rupture of membrane	104	12.4
Preterm labor	472	56.3
Level of health facility		
Tertiary zonal hospital	337	40.2
Regional hospital	298	35.6
District hospital	203	24.2
Infants		
Birth weight	2000	1600 -2450
Males	444	53.0

†Denominator included only those who attended antenatal care (*i.e.*, 795). *IQR = Interquartile range.

Table 2. ACS administration status of infants by gestation age at birth.

Gestation weeks	ACS given (312)	No ACS (526)	Total
	N (%)	N (%)	
27	18 (50.0)	18 (50.0)	36
28	20 (14.7)	116 (85.3)	136
29	15 (30.0)	35 (70.0)	50
30	23 (33.8)	45 (66.2)	68
31	27 (49.1)	28 (50.9)	55
32	44 (31.6)	95 (68.4)	139
33	64 (60.9)	41 (39.1)	105
34	101 (40.6)	148 (59.4)	249

Table 3. Prevalence of perinatal mortality by ACS administration status and gestational age at birth.

Gestation weeks	ACS given	No ACS	P Value
	N (%)	N (%)	
27	5 (27.8)	17 (94.4)	<0.001
28	7 (35.0)	33 (28.4)	0.553
29	2 (13.3)	18 (51.4)	0.012
30	5 (21.7)	14 (31.1)	0.415
31	8 (29.6)	10 (35.7)	0.631
32	5 (11.4)	20 (21.1)	0.167
33	7 (10.9)	8 (19.5)	0.221
34	3 (3.0)	27 (18.2)	<0.001

Table 4. Prevalence of RDS by ACS administration status and gestational age at birth.

Gestation weeks	ACS given	No ACS	P Value
	N (%)	N (%)	
27	7 (38.9)	3 (75.0)	0.190
28	7 (35.0)	32 (36.0)	0.936
29	6 (40.0)	4 (22.2)	0.269
30	10 (43.5)	10 (29.4)	0.275
31	4 (16.7)	5 (23.8)	0.550
32	4 (9.5)	22 (25.0)	0.039
33	8 (12.7)	8 (22.9)	0.193
34	12 (11.9)	24 (18.5)	0.171

4. Discussion

According to this study, the prevalence of perinatal mortality among newborns exposed to ACS were considerably lower than those without exposure at the 27th, 29th, and 34th weeks, whereas the RDS rate was significantly lower only at the 32nd week. No adverse effects were observed among moderate preterm newborns (*i.e.*, 32 to 34 gestation weeks). Increased rates of death in very preterm neonates exposed to ACS during the 28th week were seen; however, they were not statistically significant. This finding contradicts a study undertaken in the United Kingdom (UK) by Manktelow *et al.*, which found a significant reduction in mortalities in the ACS treated group for the 27th, 28th, and 29th weeks of pregnancy [12]. The lack of evidence for better survival at higher gestations (30th to 33rd) could be explained by the fact that these newborns' baseline demographics and medical characteristics are outstanding, and any additional advantage gained through ACS is too modest to detect. However, more research is needed to look at the very strong relationship seen in reducing perinatal mortality rates for infants at the 34th gestation week.

We didn't include infants born at less than 27 weeks of gestation in this study since the number of babies born at those gestations was insufficient to detect a statistically significant effect. However, a large multicenter prospective cohort study conducted in the United States of America (USA) by Travers *et al.*, found that newborns at all low gestational ages (*i.e.*, less than 30 gestation weeks) who were exposed to ACS had lower rates of neonatal mortality and higher survival without serious hospital morbidities. As a result, the advantages of ACS appear to be greater in infants born at lower gestations [9]. The results of the academic center based National Institute of Child Health and Human Development (NICHD) Neonatal Research Network study of 10,541 infants delivered between 22- and 25-weeks' gestation found that infants exposed to ACS had a lower rate of death at each gestation from 23 to 25 weeks [12]. Results from an observational study of 11 607 infants from 22 to 33 weeks' gestation found a lower mortality rate among infants exposed to ACS only at 22-27 weeks' gestation [13]. It's worth noting that all the previous studies on the effects of ACS on infants born at less than 27 weeks were conducted in high-income countries. In low-resource settings, similar investigations should be conducted. The WHO recommends the use of ACS only when gestational age is known, preterm delivery is imminent, and the delivery will be in a facility that can provide care for the mother and the infant [14]. The benefits of ACS may depend on the patient population and health care environment in which the therapy is used [15].

To the best of our knowledge, no studies have been conducted in Sub-Saharan Africa, Tanzania in particular, that examined the use of ACS and perinatal mortality at different gestational ages among preterm births. Another strength of our study is the inclusion of infants who were delivered within the recommended time (*i.e.*, within seven days) after being administered ACS. However, our study has some limitations. First, it was an observational study. Thus, the inherent bi-

ases associated with observational studies (e.g., selection bias, information bias, confounding) could have influenced our outcomes. A second limitation is that we did not explicitly consider indications for preterm birth, which might differ at different gestational ages. Third, we did not control for potential confounders such as birth weight and mode of delivery, so we failed to report adjusted estimates due to small sample sizes and few adverse perinatal outcomes within gestational ages. Fourth, the gestational age of some of the newborns in this study was determined based on the women's self-reported last menstrual cycle rather than an ultrasonographic test. As a result, some of the study participants reported gestational ages may have been erroneous. However, in low-resource settings, using a woman's self-reported last menstrual period is a typical technique that has been proved to produce a reliable estimate of gestational age [16]. Finally, the current study was limited to four hospitals, which limits the findings' applicability to other healthcare settings.

5. Conclusion

Our findings add to the literature about the benefits of ACS for preterm infants of various gestational ages in low-resource settings. Compared to unexposed infants, those exposed to ACS and born at 27th and 34th weeks of gestation experienced lower rates of perinatal mortality. Future research, especially among infants born before the 27th week of pregnancy, is a priority.

Conflicts of Interest

The authors declare that there is no conflict of interests.

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