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Antenatal corticosteroid use in preterm birth at Kenyatta National Hospital

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Abstract

Background: Preterm birth causes about 75% of neonatal deaths that are not attributable to congenital malformations. Antenatal corticosteroids (ACS) given to mothers at risk of preterm birth reduce the incidence/severity of RDS, intraventricular haemmorhage, necrotizing enterocolitis and neonatal deaths. The WHO recommends use of antenatal steroids for all pregnant women 26-34 weeks gestation at risk of preterm delivery and after 34 weeks gestation only if there is evidence of fetal pulmonary immaturity. Despite this, ACS are widely used locally across all gestational periods.

Objective: To determine the frequency of administration and impact of ACS in reducing the morbidity and mortality in preterm neonates born 28- 37 weeks gestation at Kenyatta National Hospital.

Design: This was a hospital-based retrospective cohort study.

Setting: Kenyattah National Hospital labour ward, antenatal wards, NBU, NICU.

Methods: The study compared the neonatal outcomes of mothers with preterm birth who received antenatal steroids and those who did not receive. The study populations were mothers with preterm birth due to preterm labor, PPROM and severe pre eclampsia and their neonates. Mothers who met the inclusion criteria were recruited immediately after delivery, interviewed, medical records scrutinized and information obtained entered into a questionnaire. Neonates were followed until discharge/death/ 7th day whichever came earlier. The outcome measures considered were the occurrence and severity of RDS, NBU admissions and neonatal deaths.

Results: Two hundred and six mother/neonate pairs were recruited**.** Overall 35% of mothers/neonates were exposed to ACS. Forty six percent of those who delivered <34 weeks received ACS compared to 26% of those who delivered >34 weeks. Only 3% of mothers received a complete course of ACS. ACS significantly reduced the occurrence and severity of RDS in preterm neonates up to 34 weeks gestation. Sixty eight percent of neonates delivered before 34 weeks and not exposed to ACS developed RDS compared to 38% of those exposed (RR 0.6, 95% CI 0.4-0.9, P= 0.005). Exposure to ACS >34 weeks gestation did not reduce occurrence and severity of RDS. Forty percent of those exposed to ACS developed RDS compared to 37% of those not exposed (RR 1.2 95% CI 0.7-1.8, P =0.755). ACS reduced neonatal mortality across all gestational ages. The neonatal mortality within 7 days of life was 26% among those exposed to ACS <34 weeks compared to 38% among those not exposed (RR1.2, 95% CI 0.9-1.6, p=0.224). for those delivered after 34 weeks mortality was 3.3% in the exposed group compared to 9.2% in the non exposed group (RR 1.1 95%CI 1.0-1.2 p=0.443). ACS did not reduce NBU/ NICU admissions across all gestational ages. Eighty five percent of neonates exposed to ACS before 34 weeks were admitted to NBU compared to 71% of those not exposed (RR1.2, 95% CI 1-2.1, p=0.113). Fifty percent of neonates exposed to ACS after 34 weeks were admitted to NBU compared to 32.2% of those not exposed (RR 1.3 95% CI 0.9-2.1, p=0.225).

Conclusions: ACS are underutilized**.** ACS significantly reduce the incidence/severity of neonatal RDS and mortality <34 weeks gestation.

Recommendations: There is need to upscale the utilization of ACS. The study provides local evidence to discourage routine use of ACS >34 weeks.

Introduction

A normal pregnancy lasts between 38 and 42 weeks. Pregnancies that end before 37 completed weeks are termed as preterm (1-4). Corticosteroids given to women at risk of preterm birth before 34 weeks reduce neonatal deaths, RDS, intraventricular haemorrhage and necrotizing enterocolitis (5, 6). The use of antenatal steroids after 34 weeks gestation is controversial. After this gestation corticosteroids are still thought to be effective but the number of women who will need to be treated to prevent an adverse outcome would be much higher. The WHO recommends the use of one course of antenatal steroids for all pregnant women between 26 and 35 weeks of gestation who are at risk of preterm delivery while both ACOG and RCOG recommend their use >34 weeks' gestation if there is evidence of pulmonary immaturity (5-10). Despite the well documented evidence on their lack of efficacy beyond 34 weeks gestation, these drugs are widely used locally across all gestations. This is partly because there are no local studies to support or refute their use. Clinicians feel that most studies on ACS are done in high income countries. The main objective of the study was to find out how frequently ACS are

administered and their impact in preventing neonatal morbidity and mortality in neonates with preterm birth at Kenyatta National Hospital(KNH). The specific objectives were:

(i) To determine the frequency of ACS administration at KNH in mothers with PPROM, PTL, and severe preeclampsia at 28-37 weeks.
(ii) To determine the incidence of RDS at KNH among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
(iii) To determine the severity of RDS at KNH among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
(iv) To determine the prevalence of neonatal admissions (NBU) among the ACS and the non ACS group.
(v) To compare the neonatal mortality among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS with those whose mothers did not receive ACS.

Materials and methods

Design: This was a hospital based retrospective cohort study. The researcher and the data clerks had no influence in patient care. The diagnosis of the study conditions and management of mothers/neonates was left to the primary doctors managing the patient(s). Randomization of patients was not done. Recruitment was done after delivery. Mothers/neonate pairs with the study conditions were identified from the admissions register in labour ward and then they were traced to the post natal wards and neonates to nursery. The mothers were counseled and requested to participate. Those who met the inclusion criteria and consented for the study were then recruited sequentially on a daily basis. They were interviewed and data from their medical records extracted and entered into a structured questionnaire. Neonates were followed up till discharge, death or 7 days after delivery, whichever came earlier.

Setting: KNH labour ward, antenatal wards, NBU, NICU.

Participants: Mothers with spontaneous preterm labour with intact membranes, PPROM and severe pre-eclampsia at 28-37 weeks gestation.

Sample size estimation: The sample size computed for this study using the Fischer's formula and an expected prevalence of RDS in preterm deliveries to be 15% was 196 mother/neonate pairs. Gestation was confirmed by LMP, early pregnancy ultra-sound scan, fundal height recording at admission, quickening, positive pregnancy test after first missed period and serial ANC attendance fundal height recordings. The inclusion/exclusion criteria were strictly adhered to. The research assistants were trained on interviewing and information retrieval. Recording of clinical findings in the files was only entered after thorough scrutiny. The filled questionnaires were scrutinized daily. When the questionnaires were found to be incomplete or in cases where there was a discrepancy between gestation and expected birth weight as it occurred on three occasions the questionnaires were withdrawn, serialization rectified before recruitment was continued.

Inclusion criteria**:**

(i) Mothers who gave informed consent.
(ii) Mothers with spontaneous preterm labour between 28-37 weeks' gestation.
(iii) Mothers with PPROM between 28-37 weeks' gestation
(iv) Mothers with severe pre –eclampsia between 28-37 weeks' gestation.

Exclusion criteria:

(i) Mothers with diabetes mellitus, thyrotoxicosis, cardiac disease, tuberculosis
(ii) Mothers with twins, IUFD, congenital fetal malformations and chorioamnionitis diagnosed on/ before admission.
(iii) A mother with a combination of the conditions under investigation.

Results

Neonates were grouped into those exposed to ACS and those not exposed. The neonatal outcomes were compared for gestational age i.e. overall (28-37 weeks); 28-33^{+6}weeks) and 34 -37^{+6} weeks.

Table1 shows that 35% of the mothers received ACS. Only 3% of patients received a complete course, majority (62.5%) received two doses. All the mothers received dexamethasone.

Table 1: Descriptive analysis of ACS use

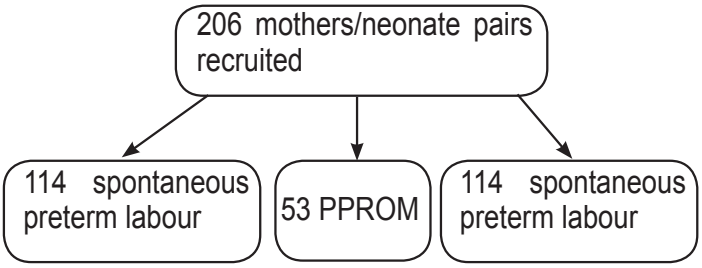


Figure 1: Received ACS (n=206)

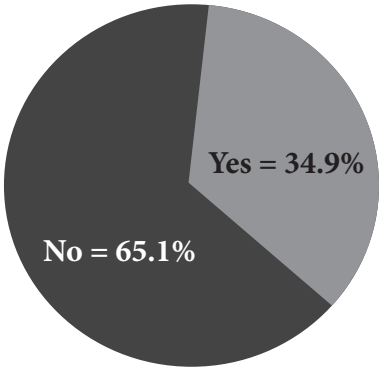


Figure 2: Duration between 1st dose and delivery (n=72)

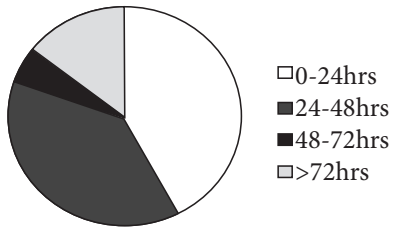
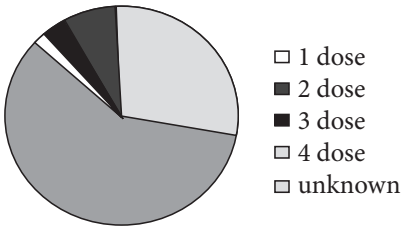


Figure 3: Number of ACS doses received (n=72)



Eighty one percent of mothers delivered within 48 hours of administration of the first dose.

Table 2 above shows that overall, 35% of neonates were exposed to ACS. Forty seven percent of neonates delivered <34 weeks were exposed to ACS compared to 26% of those delivered >34 weeks.

Table 2: Frequency of ACS use by gestational age (n=206)

Gestational-age (weeks)	Steroid use Yes (%)	No (%)	Total(%)
28-33	42(47.2)	47(52.8)	89(43.2)
34-37	30(25.6)	87(74.4)	117(56.8)
Overall(28-37)	72(34.9)	134(65.1)	206(100)

Table 3: Impact of ACS use on occurrence of RDS

Gestational age (Weeks)	Exposure to ACS	RDS Yes (%)	RDS No (%)	Relative risk (95 % CI)	P-value
Any number of ACS doses, any interval between first dose and delivery:					
28- 33 (n=89)	Yes	16(38.1)	26(61.9)	0.6 (0.4-0.9)	0.005
	No	32(68.1)	15(31.9)		
34- 37 (n=117)	Yes	12(40)	18(60)	1.1 (0.7 – 1.8)	0.755
	No	32(36.8)	55(63.2)		
Overall/ 28- 37 (n=206)	Yes	28(38.8)	44(61.2)	0.7 (0.6 – 1.1)	0.223
	No	64(47.8)	70(52.2)		
2 doses of ACS versus no ACS					
28-33 weeks (n=73)	2 doses	13(33.3)	23(66.7)	0.5 (0.3 – 0.8)	0.004
	No ACS	32(68.1)	15(31.9)		
34-37 weeks (n=97)	2doses	3(30)	7(70)	0.8 (0.3 – 2.2)	1.000
	No ACS	32(36.8)	55(63.2)		
Overall (n=180)	2doses	16(34.8)	30(65.2)	0.7 (0.5 – 1.1)	0.127
	No ACS	64(47.8)	70(52.2)		
48 hours of ACS exposure versus no ACS					
28-34 weeks	>48hours	3(30)	7(70)	0.4 (0.2–1.2)	0.0035
	No ACS	32(68.1)	15(31.9)		
34-37 weeks	>48hrs	0(0)	3(100)	--	0.550
	No ACs	32(36.8)	55(63.2)		
Overall (28-37)	>48hours	3(23.1)	10(76.9)	0.5 (0.2 -1.3)	0.157
	No ACS	64(47.8)	70(52.2)		

Any exposure to ACS <34 weeks gestation significantly reduced the incidence of RDS. Exposure to ACS >34 weeks did not result in a statistical difference between the two groups. Exposure to 2 doses of ACS <34 weeks gestation significantly reduced the incidence of RDS compared to no exposure while there was no significant reduction >34 weeks. Exposure to ACS for 48 hours before delivery significantly reduced the incidence of RDS among neonates delivered <34 weeks gestation compared to those delivered >34 weeks.

Impact of ACS use on severity of RDS

Table 4(a): Oxygen therapy

Gestational age (weeks)	Exposure to ACS	Oxygen use		Relative risk (95 % CI)	P-value
		Yes (%)	No (%)		
Need for oxygen therapy (n=201)					
28- 33	Yes	17(40.5)	25(59.5)	0.7 (0.4-1.0)	0.047
	No	29(61.7)	18(38.3)		
34- 37	Yes	11(36.7)	19(63.3)	1 (0.6 – 1.7)	0.994
	No	30(36.6)	52(63.4)		
Overall (28- 37)	Yes	28(38.9)	44(61.1)	0.9 (0.6–1.3)	0.429
	No	59(45.7)	70(54.3)		
Total		87(43.3)	114(56.7)		
Duration of oxygen Therapy (n= 74)					
		<24hours	>24hours		
28- 33 weeks	Yes	10(62.5)	6 (37.5)	0.5 (1.1 – 5.3)	0.025
	No	6 (25)	17(75.0)		
34- 37 weeks	Yes	9(100.0)	0 (0)	–	1.000
	No	23(95.8)	2(4.2)		
Overall (28-37 weeks)	Yes	19(76.0)	6 (24.0)	0.6 (0.9 -1.6)	0.284
	No	29(59.2)	20(40.8)		
Total		48(65)	26(35)		

Exposure to ACS significantly reduced the need for oxygen therapy among neonates delivered <34 weeks while this exposure did not result in a reduction in oxygen therapy requirement in those neonates delivered >34weeks.

Exposure to ACS resulted in a reduction in need for oxygen therapy for more than 24 hours across all gestational ages. For neonates delivered <34weeks, there was a significant reduction in the need for oxygen therapy for more than 24 hours. For neonates born >34weeks, none of those exposed to ACS required oxygen for more than 24 hours.

Table 4(b) shows that exposure to ACS reduces the need for mechanical ventilation across all gestational ages. This reduction however did not reach statistical significance.

Table 4(b): Impact of ACS use on need for mechanical ventilation

Gestation (Weeks)	Exposure to ACS	Mechanical ventilation		Relative risk	P-value
		Yes (%)	No (%)		
28- 33	Yes	1 (2.4)	41 (97.6)	0.3 (0.0 -2.4)	0.210
	No	4 (8.5)	43 (91.5)		
34- 37	Yes	0 (.0)	30(100.0)	--	0.180
	No	5(5.7)	82 (94.3)		
Overall (28-37)	Yes	1 (1.4)	71(98.6)	0.4 (0.0 -1.6)	0.427
	No	9(6.7)	125(93.3)		

Table 5 shows that there was no significant statistical difference in frequency of NBU and NICU admissions between ACS exposed neonates compared to those who were not exposed. Contrary to expectation a greater proportion of those exposed to ACS were also admitted to either NBU or NICU.

Table 5: Impact of ACS use on NBU and NICU admissions

Gestation (Weeks)	Exposure to ACS	Admission		Relative risk (95% CI)	P-value
		Yes (%)	No (%)		
NBU admission (n=198)					
28- 33	Yes	35 (85.4)	6 (14.6)	1.2(1.0-1.9)	0.113
	No	35 (71.4)	14(28.6)		
34- 37	Yes	15 (50.0)	15(50.0)	1.3 (0.9-2.1)	0.225
	No	29 (37.2)	49(62.8)		
28-37(overall)	Yes	50(70.4)	21(29.6)	1.4 (1.1-1.8)	0.242
	No	64(50.4)	63(49.6)		
NICU admission (n= 206)					
Overall (28-37)	Yes	6(9.1)	66(90.9)	1.9 (0.6-5.6)	0.349
	No	6(4.5)	128(95.5)		
28- 33	Yes	4(9.5)	38 (90.5)	4.5 (0.5-38.6)	0.130
	No	1 (2.1)	46 (97.9)		
34- 37 weeks	Yes	2 (6.7)	28 (92.3)	1.1 (0.2-5.7)	0.855
	No	5 (5.7)	82 (94.3)		

Table 6 shows that exposure to ACS reduced neonatal mortality across all gestational ages

Table 6: The impact of ACS use on neonatal deaths (n=206)

Gestation (Weeks)	Exposure to ACS	Neonatal status		Relative risk (95% CI)	P-value
		Alive (%)	Dead (%)		
28- 33	Yes	31 (73.8)	11(26.2)	1.2 (0.9-1.6)	0.224
	No	29 (61.7)	18(38.3)		
34- 37	Yes	29(96.7)	1 (3.3)	1.1 (1.0-1.2)	0.443
	No	79 (90.8)	8 (9.2)		
28- 37	Yes	60(83.3)	12(16.7)	1 (0.9-1.8)	0.631
	No	108(80.6)	26(19.4)		

Discussion

The overall frequency of ACS use at KNH was 35% with 47% of those with a gestational age of <34weeks receiving ACS compared to 26% of those with a gestational age >34 weeks. This is low compared to the findings of a study in the USA in 2003 (11) where the frequency of ACS use stood at 75%. The low uptake of ACS could be due to several factors among them late presentation of patients, drug stock outs, infrequent use of tocolytics and some clinicians not appreciating the impact of even one dose of ACS. Additionally, a number of obstetricians rarely follow up neonates in NBU hence may not appreciate the impact the ACS have on both short and long term neonatal outcomes.

The steroid of choice at KNH is dexamethasone. Studies show that both betamethasone and dexamethasone are equally efficacious in reducing respiratory morbidity but the former is more expensive (12) hence dexamethasone is preferred in our setup.

A full course of ACS is either 12mg of betamethasone given 24 hours apart or 6mg of dexamethasone given 12 hourly to a total of 2 days. The optimal benefits of ACS are seen 24 hours after administration, peak at 48 hours, and continue for at least 7 days (5, 13,14). In our study, majority of the mothers received either one or two doses of dexamethasone and only 3% received a complete course. This could be due to the fact that some clinicians prescribe 2 doses of 12mg of dexamethasone or poor documentation. Most mothers delivered before 48 hours of the first dose of dexamethasone. Despite the fact that most mothers received an incomplete course of ACS and delivered before 48 hours after its administration, the study revealed a significant impact in reduction of morbidity and mortality as discussed subsequently.

The overall incidence of RDS among the study population was 44.7%; 53.9% among those delivered <34 weeks and 37.6% among those delivered >34 weeks. This is comparable to findings of other studies that found

RDS to affect 40–50% of babies born before 32 weeks and 20.6% of those born at 34-36 weeks (15, 16). In our study there was a significant reduction in both the incidence and severity of RDS in those neonates exposed to ACS and delivered <34 weeks compared to those neonates born >34weeks. This trend was seen even when controlling for dose and duration of therapy. These findings are similar to those found in similar studies. In an RCT to assess the effectiveness of ACS in mothers at risk of preterm birth, researchers found a significant reduction in occurrence of RDS in the treatment group (7/130) compared to the control group (16/132,) (17). Similar to our study the largest difference was noted in those <34 weeks gestation. This observation is due to the fact that ACS therapy is known to improve neonatal lung function by enhancing morphologic development in type 1 and type 2 pneumocytes, and by inducing lung enzymes in type 2 pneumocytes that stimulate phospholipid synthesis and subsequent release of surfactant. Both of these processes are thought to be in place by 34 weeks gestation (18).

Contrary to expectation ACS use did not result in a reduction in the need for NBU or NICU admissions; the trend in this study was that those exposed to ACS were also likely to be admitted to either NBU or NICU. This is probably due to the fact that some of the neonates were admitted to NBU/NICU for other reasons for example prematurity, low birth weight, birth asphyxia, neonatal sepsis or maternal condition all of which are not affected by ACS use. This assumption is supported by the fact that overall those who were exposed to ACS had a lower gestational age (32.65 versus 33.91weeks, P =0.003), lower birth weight (1844g versus 2134g, P =0.001), their mothers were likely to have preeclampsia and be delivered by caesarean section. These study findings are similar to those reported in a Cochrane review of 21 RCTs to assess the effectiveness of ACS in mothers at risk of preterm birth. In this review, ACS were found to reduce both the need for respiratory support and intensive care admissions in two studies only (19).

With regard to neonatal mortality, our study found that ACS use reduces neonatal mortalities within the first 7 days of life. This benefit occurs across all gestational ages but did not reach statistical significance. This could be because our study was not powered to detect a significant statistical difference in neonatal mortality. With regard to gestational age, the effect is greater in neonates delivered before 34 weeks compared to those delivered after. An RCT to assess the effectiveness of ACS found a significant reduction in neonatal deaths among the treatment group compared to the control group with the largest differences seen in those <34 weeks. A Cochrane review of 21randomized controlled studies of antenatal steroid administration found that treatment with antenatal corticosteroids was associated with an overall reduction in neonatal death in 18 studies(19, 20). This trend is due to the fact that a number of deaths in preterm neonates are due to respiratory morbidity, intraventricular haemmorhage and necrotizing enterocolitis all of which are reduced significantly by ACS exposure.

Conclusions

ACS are underutilized. Exposure to antenatal steroids reduces the incidence and severity of respiratory distress syndrome and neonatal mortality. This reduction is more significant in neonates delivered <34 weeks of gestation.

Recommendations

There is need to upscale the utilization of ACS. Measures should be put in place to ensure that patients receive complete courses. Based on the study findings there is need to discourage routine use of ACS >34 weeks.

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