BMJ Open

Association between antenatal corticosteroids use and perinatal mortality among preterm singletons and twins in Mwanza, Tanzania: an observational study

Stanley Mwita ,[1] Benjamin Anathory Kamala,[2,3] Eveline Konje,[4] Emmanuela Eusebio Ambrose,[5] Angelina Izina,[6] Elieza Chibwe,[7] Gilbert Kongola,[8] Deborah Dewey[9]

To cite: Mwita S, Kamala BA, Konje E, *et al*. Association between antenatal corticosteroids use and perinatal mortality among preterm singletons and twins in Mwanza, Tanzania: an observational study. *BMJ Open* 2022;**12**:e059030. doi:10.1136/bmjopen-2021-059030

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059030).

Received 08 November 2021
Accepted 18 March 2022

For numbered affiliations see end of article.

Correspondence to
Stanley Mwita;
stanleymwita@gmail.com

ABSTRACT

Objectives To examine the association between antenatal corticosteroids (ACS) use and perinatal mortality in singletons and twins delivered before 35 weeks of gestation.

Design Secondary analysis of data from an observational prospective chart review study that investigated if exposure to ACS was associated with lower rates of perinatal mortality in preterm infants.

Setting This study was conducted in four hospitals located in Mwanza region, Tanzania.

Participants The study population included all preterm singletons and twins delivered at these hospitals between 24 weeks 0 days and 34 weeks 6 days of gestation from July 2019 to February 2020.

Outcome measures The primary outcome was perinatal mortality; the secondary outcome was respiratory distress syndrome (RDS).

Results The study included 844 singletons and 210 twin infants. Three hundred and fourteen singletons (37.2%) and 52 twins (24.8%) were exposed to at least one dose of ACS. Adjusted multivariate analyses revealed that among singletons' exposure to ACS was significantly associated with a lower likelihood of perinatal mortality, adjusted relative risk (aRR) 0.30 (95% CI 0.22 to 0.40) and RDS, aRR 0.92 (95% CI 0.87 to 0.97). In twin infants, exposure to ACS was associated with a reduced risk of RDS only, aRR 0.87 (95% CI 0.78 to 0.98).

Conclusion The use of ACS between 24 weeks 0 days and 34 weeks 6 days of gestation in both singletons and twins in low-resource settings is associated with positive infant outcomes. No adverse effects were noted. Further research that examines the benefits of ACS for twin infants is needed.

Strengths and limitations of this study

- ► This is the first study in Tanzania to evaluate the benefits of ACS use in both singleton and twin infants.
- ► Relevant covariates were controlled for in the multivariable analyses, which provided an unbiased estimate of the true association between ACS exposure and perinatal outcomes.
- ► As the study design was observational, causality cannot be inferred.
- ► Data on the potential confounding factor of chorionicity in twins were not available.
- ► The number of twins in our sample was small, which may have limited our ability to detect statistically significant associations between ACS exposure and perinatal mortality.

INTRODUCTION

Globally, preterm birth is one of the leading causes of perinatal mortality and morbidity.[1] Women with a twin pregnancy are at higher risk of preterm birth[2] with approximately 60% of twins are delivered prematurely.[3] Perinatal mortality includes stillbirth and neonatal death during the first week of life, and the overall rate of perinatal mortality is higher in twins than singletons.[4] Respiratory distress syndrome (RDS), a serious complication of preterm birth, is a significant contributor to perinatal mortality among both singletons and twins.[5] Antenatal corticosteroids (ACS) are considered a key intervention for moderating the adverse effects of a preterm birth.[6] A single course of ACS is recommended between 24 weeks and 34 weeks of gestation in women who are at risk of preterm delivery within 7 days[7] and may be considered at 22 0/7 weeks to 23 6/7 weeks of gestation if neonatal resuscitation is planned and after appropriate counselling.[8 9]

Some studies have reported that the positive effects of ACS exposure in twins are similar to that observed in singletons[10 11]; however, others have not reported beneficial effects in twins.[12 13] A recent Cochrane Review

suggested that further research is needed to support the use of ACS in twin pregnancies, particularly in low-resource countries.[14] To address this issue, we examined the association between ACS exposure in singletons and twins delivered before 35 weeks of gestation and the risk of perinatal mortality and RDS in Tanzania, a low-resource country.

MATERIALS AND METHODS

Study design

This is a secondary analysis of data from an observational prospective chart review study that investigated if exposure to ACS was associated with lower rates of perinatal mortality in preterm infants.[15] It was conducted in four selected hospitals located in Nyamagana and Sengerema districts, which are two of the seven districts of the Mwanza region, northwest Tanzania. The hospitals that participated 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 provide obstetric and neonatal care services to a large proportion of the population within the Lake zone in Tanzania.

The study population included all singletons and twins delivered between July 2019 and February 2020 who met the following inclusion criteria: (1) infants of a mother who displayed indicators of preterm birth, including antepartum haemorrhage, pre-eclampsia or eclampsia, premature preterm rupture of membranes or preterm labour, (2) infant delivered in-hospital between 24 weeks 0 days and 34 weeks 6 days of gestation and (3) infant delivered within 7 days of administration of ACS to the mother. Infants who were reported in the medical record to have a congenital malformation were excluded (figure 1).

The primary predictor variable was ACS (dexamethasone) exposure administered according to the recommended guideline for ACS, four doses of 6 mg of dexamethasone every 12 hours.[16] Study participants were classified into two groups, the No-ACS group and the ACS group (ie, women administered at least one does of ACS). The primary outcome was perinatal mortality, which was defined as stillbirth or early neonatal mortality (ie, death of a live born neonate between 0 and 7 days after birth). The secondary outcome was a diagnosis of RDS.

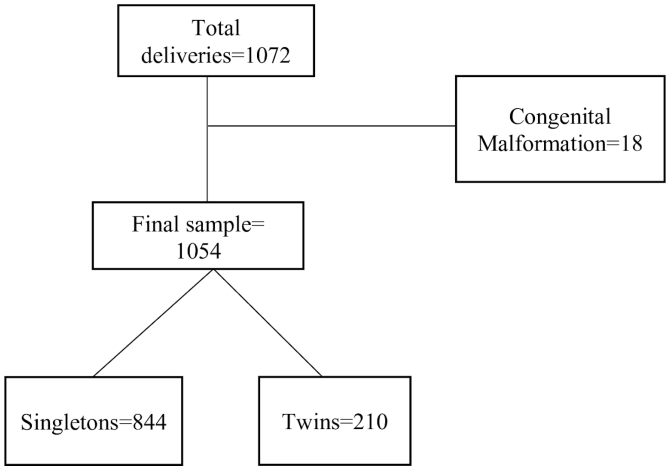

Figure 1 Flow diagram of study population inclusion and exclusion.

The medical records of women and their infants were reviewed by the principal investigator and trained research assistants who were enrolled/registered nurses working in the labour wards and neonatal units of the hospitals. To control for selection bias, we collected data on all pregnant women who were admitted to the hospital and were between 24 weeks 0 days and 34 weeks 6 days of gestation. For each participant, we recorded whether the mother was exposed or not exposed to ACS, the perinatal mortality and the RDS status of the infant. In addition, the following data were obtained from the women's and infant's medical records: parity, marital status, maternal age, maternal education, antenatal care visits (days), gestational age (weeks), mode of delivery, indication for delivery, level of health facility, birth weight (grams) and neonate sex. Gestational age was determined based on women's self-reports of their last normal menstrual period, fundal height and/or ultrasound.

To address the primary research aim of the initial study, based on a power of 95%, an estimated minimum overall sample size of 1010 (both twins and singletons) was determined using Open-Source Epidemiologic Statistics for Public Health (Open Epi).[15 17]

Statistical analyses

The data were analysed using STATA V.13. χ^2 tests or Fisher exact tests as appropriate were conducted to determine whether singletons or twins differed by ACS exposure on the following variables: parity, marital status, education, antenatal care visits, mode of delivery, indication for preterm delivery and level of health facility. Mann-Whitney U tests were used to determine whether there were group differences in median maternal age, gestational age and birth weight. Differences between singletons and twins in the No-ACS and ACS groups in perinatal mortality and RDS were examined using cross-tabulation and χ^2 tests.

For singletons, modified Poisson regressions were used to investigate the associations between ACS exposure and perinatal outcomes. To account for the clustering effect and non-independence of twins, we used a mixed model approach. Specifically, the model was fitted with generalised estimating equations to account for the associations within a pair of twins from the same mother. Multivariate analyses were performed to examine the effects of ACS on perinatal mortality and RDS controlling for the following factors, gestational age, birth weight, level of health facility and mode of delivery.[15] P values of less than 0.05 were considered statistically significant. Data are presented as frequencies (percentages), median (IQR) and relative risks (RR) with 95% CIs as appropriate.

Table 1 Maternal and infant baseline characteristics of the ACS and No-ACS groups among singletons

	ACS (n=314)	No-ACS (n=530)	P value
Maternal			
Nulliparity, N (%)	119 (37.9)	155 (29.2)	**0.009**
Married, N (%)	272 (86.6)	447 (84.3)	0.366
Maternal age (years), M(IQR)	26 (22–31)	26 (21–31)	0.392
More than three antenatal care visits**, N (%)	152 (47.2)	198 (32.8)	**<0.001**
Gestational age (weeks), M (IQR)	33 (31–34)	32 (28–34)	**<0.001**
Mode of delivery, N (%)			
Assisted vaginal	9 (2.9)	10 (1.9)	**<0.001**
C-section	134 (42.7)	97 (18.3)	
Normal vaginal	171 (54.4)	423 (79.8)	
Indication for delivery, N (%)			
Antepartum haemorrhage	42 (13.4)	66 (12.4)	**0.017**
Pre-eclampsia or eclampsia	70 (22.3)	84 (15.8)	
Premature preterm rupture of membrane	45 (14.3)	59 (11.2)	
Preterm labour	157 (50.0)	321 (60.6)	
Level of health facility, N (%)			
Tertiary zonal hospital	228 (72.6)	110 (20.8)	**<0.001**
Regional hospital	75 (23.9)	226 (42.6)	
District hospital	11 (3.5)	194 (36.6)	
Infants			
Birth weight (g), M (IQR)	2000 (1600–2350)	2000 (1600–2500)	0.567
Sex (male), N (%)	170 (54.1)	277 (52.3)	0.598

*Denominator included only those who attended antenatal care (ACS 307 vs No-ACS 494).
†
‡Values in bold indicate statistically significant results
ACS, antenatal corticosteroids.

Patient and public involvement

No patient or member of the public were involved in the design of this study.

RESULTS

The study included 844 singletons and 210 twin infants (figure 1). Three hundred and fourteen singletons (37.2%) and 52 twins (24.8%) were exposed to at least one dose of ACS. In singletons, no significant differences in marital status or mean maternal age were found between women who received ACS and those who did not. However, the groups differ on the following variables: parity, antenatal care visits, gestational age, mode of delivery, indication for delivery and level of health facility where they delivered (table 1).

In twins, no significant differences in parity, mean maternal age, antenatal care visits, gestational age or indication for delivery were found between women who received ACS and those who did not. However, the groups differed on the following variables: marital status, mode of delivery, level of health facility where they delivered and infant birth weight (table 2).

Perinatal outcomes for the ACS and No-ACS groups among singletons and twins

Unadjusted estimates of perinatal outcomes are presented in table 3. Among singleton births, those who were exposed to ACS in utero had a lower rate of perinatal mortality (13.4% vs 28.5%) and RDS (18.8% vs 25.8%) compared with those not exposed to ACS. In twins, those who were exposed to ACS in utero had a significantly lower rate of RDS (12.0% vs 28.4%) compared with unexposed infants; a trend difference was observed for perinatal mortality (15.4% vs 27.2%).

Multivariate analyses of the association between ACS exposure and perinatal outcomes among singletons and twins

Adjusted multivariate analyses in singletons revealed that exposure to ACS was significantly associated with a lower likelihood of perinatal mortality, adjusted relative risk (aRR) 0.30 (95% CI 0.22 to 0.40), p<0.001 and RDS,

Table 2 Maternal and infant baseline characteristics of the ACS and No-ACS groups among twins

	ACS	No-ACS	P value
Maternal *	(n=52)	(n=158)	
Nulliparity, N (%)	6 (23.1)	25 (31.6)	0.240
Married, N (%)	24 (92.3)	78 (98.7)	**0.016**
Maternal age (years) M (IQR)	26 (24–30)	25 (23–32)	0.760
More than three antenatal care visits††, N (%)	16 (61.5)	39 (50.6)	0.174
Gestational age (weeks) M (IQR)	33 (32–34)	34 (30–34)	0.244
Mode of delivery, N (%)			
Assisted vaginal	3 (11.5)	6 (7.6)	**<0.001**
C- section	14 (53.9)	15 (19.0)	
Normal vaginal	9 (34.6)	58 (73.4)	
Indication for delivery, N (%)			
Antepartum haemorrhage	3 (11.5)	5 (6.3)	0.272
Pre-eclampsia or eclampsia	2 (7.7)	11 (13.9)	
Premature preterm rupture of membrane	2 (7.7)	7 (8.9)	
Preterm labour	19 (73.1)	56 (70.9)	
Level of health facility, N (%),			
Tertiary zonal hospital	15 (57.7)	17 (21.5)	**<0.001**
Regional hospital	9 (34.6)	15 (19.0)	
District hospital	2 (7.7)	47 (59.5)	
Infants			
Birth weight, (g), M (IQR)	1950 (1750–2100)	1500 (1150–1900)	**<0.001**
Sex (male), N (%)	21 (40.38)	77 (48.73)	0.295

*Number of women are half the number of twin infants (ACS 26 vs No-ACS 79).
†Denominator included only those who attended antenatal care (ACS 26 vs No-ACS 77).
‡Values in bold indicate statistically significant results
ACS, antenatal corticosteroids.

aRR 0.92 (95% CI 0.87 to 0.97), p=0.001. However, in twin infants, exposure to ACS was associated with a reduced risk of RDS only, aRR 0.87 (95% CI 0.78 to 0.98), p=0.026 (table 4).

DISCUSSION

ACS is an important component in the management of women at risk of preterm delivery as they stimulate fetal lung maturation and alveolar surfactant production.[18 19] Our study investigated the association between ACS use and perinatal outcomes in singleton and twin infants. We found a significantly lower risk of perinatal mortality and RDS for singleton infants exposed to at least one dose of ACS. In twins, exposure to ACS was associated with a lower risk of RDS. ACS administration was not associated with a reduced risk of perinatal mortality in twins.

Table 3 Perinatal outcomes for the ACS and No-ACS groups

	Singletons			Twins		
	ACS (n=314)	No-ACS (n=530)	P value	ACS (n=52)	No-ACS (n=158)	P value
Outcomes	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Perinatal mortality	42 (13.4)	151 (28.5)	**<0.001**	8 (15.4)	43 (27.2)	0.059
Respiratory distress syndrome *	58 (18.8)	109 (25.8)	**0.026**	6 (12.0)	40 (28.4)	**0.013**

*Denominator included live infants only, singletons (ACS 308 vs No-ACS 422) and twins (ACS 50 vs No-ACS 141).
†
‡Values in bold indicate statistically significant results
ACS, antenatal corticosteroids.

Table 4 Multivariate analysis of the associations between ACS exposure and perinatal outcomes among singletons and twins

Outcomes	Singletons		Twins	
	*Adjusted relative risk (95% CI)	P value	*Adjusted relative risk (95% CI)	P value
Perinatal mortality	0.30 (0.22 to 0.40)	<0.001	0.78 (0.39 to 1.56)	0.488
Respiratory distress syndrome	0.92 (0.87 to 0.97)	0.001	0.87 (0.78 to 0.98)	0.026

*Model adjusted for gestational age, birth weight, level of health facility and mode of delivery.
ACS, antenatal corticosteroids.

Consistent with current findings, a study of 1662 twins delivered between 25 weeks 0 days and 34 weeks 6 days of gestation in China from January 2013 to December 2014, reported that administration of at least one dose of ACS was associated with a reduced risk of RDS in twin preterm infants.[13] Previous research has reported limited benefits of ACS in reducing rates of mortality and morbidities in twins[12 20–22]; however, these studies are limited by their retrospective design,[12 20 22] which leaves them prone to information and selection bias. In addition, the sample sizes of some of these studies were small, which may have limited their ability to detect significant associations.[12 21] In contrast, two retrospective studies with large samples[11 23] and one with a small sample of twins[24] reported that the administration of ACS had a protective effect against adverse perinatal outcomes in both singletons and twins born preterm. Also, in a nationwide observational multicentre prospective cohort study of twins born between 22 and 34 completed weeks of gestation in 2011 in France, ACS administered ≤7 days prior to delivery were reported to be significantly associated with a reduced rate of in-hospital mortality.[25]

ACS are not frequently used in women at risk for preterm delivery in low-resource countries, although their use is recommended by the WHO as essential for reducing infant mortality and morbidities. Currently, the WHO recommends the use of ACS only when gestational age is known, there is no clinical evidence of maternal infection, preterm delivery is imminent and the delivery is in a facility that can provide adequate care for the mother and the infant.[26] Despite the benefits of ACS in reducing the risk of adverse perinatal outcomes, particularly in singletons, in the present study, less than 40% of the mothers of singletons were administered at least one dose of ACS. The main reason given by health professionals in these low-resource settings for not administrating ACS was that women arrived late at the hospital in well-established labour.[15] Another potential impediment to administering ACS in low-resource settings could be difficulty in obtaining an accurate estimate of gestational age. Before the positive effects of ACS can be realised in low-resource settings, women and healthcare professionals need to be educated on the clinical signs associated with preterm delivery, risk factors for preterm delivery and the importance of arriving at the hospital early if preterm delivery is anticipated. In addition, infrastructure in healthcare facilities that can accurately estimate gestational age and provide adequate care for mothers and their preterm infants is essential.[27]

There is a scarcity of randomised clinical trials that have enrolled women with multiples.[28 29] For example, the landmark study by Liggins and Howie showed that ACS significantly reduced rates of RDS and neonatal mortality, included only 11 pairs of twins.[30] In medical practice, a similar dose of ACS (ie, two doses of 12 mg of betamethasone every 24 hours or four doses of 6 mg of dexamethasone every 12 hours) is given regardless of pregnancy multiplicity.[31] It is possible that this dosing level used for singletons might not be adequate to produce a therapeutic level for lung maturation in twins.[12] Pharmacokinetic data suggest that higher doses of ACS are needed in twin gestations to decrease perinatal morbidities and mortality. Pharmacologically, ACS has been shown to have a higher volume of distribution, shorter half-life and greater clearance in twins compared with singleton pregnancies, which could result in a subtherapeutic dosage for lung maturation.[32–34] Randomised controlled trials need to be conducted to evaluate and develop recommendations regarding the dose levels of ACS that could be effective in improving perinatal outcomes in twin-level and higher level multiple pregnancies. Future studies in low-resource settings should also focus on examining associations between ACS therapy and other neonatal morbidities such as bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity, patent ductus arteriosus, need for mechanical ventilation and neonatal hypoglycaemia in both singleton and twins.

To the best of our knowledge, this is the first study in Tanzania to evaluate the benefit of ACS in singletons and twins in low-resource settings. A strength of our study was its ability to control for relevant covariates in the multivariable analyses. This resulted in unbiased estimates of the true association between ACS exposure and perinatal outcomes in singletons and twins. However, there are some limitations. First, it was an observational study. Thus, the inherent biases associated with observational studies (eg, selection bias, information bias, confounding bias) could have influenced our outcomes. A second limitation was that the small number of twins in our sample. This reduced the power of the study and may have limited our ability to detect statistically significant associations between ACS exposure and perinatal mortality. Future studies in low-resource settings with larger samples of

twins are needed to clarify the associations between ACS exposure and perinatal outcomes. A third limitation of this study is that data on the potential covariate of chorionicity in twins were not available in this low-resource setting. Fourth, the gestational age of some of the infants included in this study was based on the women's self-reported last menstrual period and was not verified by ultrasonographic examination. Thus, some reported gestational ages of study participants may have been incorrect. However, the use of women's self-reported last menstrual period is a common practice in low-resource settings and has been shown to provide a valid estimate of gestational age.[35] Finally, the current study was conducted in four hospitals only, which may limit the generalisability of the findings to other healthcare settings.

CONCLUSION

Our findings add new and important information to the literature on the benefits of ACS for singleton and twin infants in low-resource settings. They also support the use of ACS in both singleton and twin pregnancies at risk for delivery between 24 weeks 0 days and 34 weeks 6 days of gestation in low-resource settings as reduced risk of perinatal mortality and RDS was found and no adverse effects were noted. Further research is necessary to clarify the benefits of administration of ACS in twin pregnancies.

Author affiliations
[1]School of Pharmacy, Catholic University of Health and Allied Sciences, Mwanza, United Republic of Tanzania
[2]Department of Research, Haydom Lutheran Hospital, Mbulu, Manyara, United Republic of Tanzania
[3]Department of Epidemiology and Biostatistics, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania
[4]Department of Epidemiology and Biostatistics, Catholic University of Health and Allied, Mwanza, United Republic of Tanzania
[5]Department of Peadiatrics and Child Health, Bugando Medical Centre, Mwanza, United Republic of Tanzania
[6]Department of Radiology, Bugando Medical Centre, Mwanza, United Republic of Tanzania
[7]Department of Obstetrics and Gynaecology, Catholic University of Health and Allied Sciences, Mwanza, United Republic of Tanzania
[8]Department of Pharmacology, Catholic University of Health and Allied Sciences, Mwanza, United Republic of Tanzania
[9]Owerko Centre at the Alberta Children's Hospital Research Institute and Departments of Pediatrics and Community Health Sciences, The University of Calgary, Calgary, Alberta, Canada

Acknowledgments We thank Mpenihaka Kaitira, Angela Rwehumbiza, Dyness Tibakya, Elizabeth Masona and Beatrice Kalumuna for their invaluable support during data collection. We would also like to acknowledge Prof. Jim Todd for his help in data analysis.

Contributors SM is the guarantor. SM, BAK and DD contributed to the conception and design of the study. SM, EK, EEA, AI, EC and GK contributed to the acquisition of data, analysis and interpretation of data. All authors were responsible for drafting the manuscript and revising it critically.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by The Catholic University of Health and Allied Sciences and Bugando Medical Centre's Joint Ethics and Research Review Committee (IRB approval number: CREC/368/2019). Secondary data were collected from medical records. No patients were contacted for this study. To ensure confidentiality, all data were anonymised before being accessed by the study team. Medical records were accessed between July 2019 and February 2020. The ethics committee waived the need for participant informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD
Stanley Mwita http://orcid.org/0000-0003-0563-6705

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