RESEARCH ARTICLE

REVISED Antenatal corticosteroids reduce neonatal mortality in settings without assisted ventilatory support: a retrospective cohort study of early preterm births on the Thailand-Myanmar border [version 2; peer review: 3 approved, 1 approved with reservations]

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Abstract

Background

Prematurity is the highest risk for under-five mortality globally. The aim of the study was to assess the effect of antenatal dexamethasone on neonatal mortality in early preterm in a resource-constrained setting without assisted ventilation.

Methods

This retrospective (2008-2013) cohort study in clinics for refugees/migrants on the Thai-Myanmar border included infants born

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<34 weeks gestation at home, in, or on the way to the clinic. Dexamethasone, 24 mg (three 8 mg intramuscular doses, every 8 hours), was prescribed to women at risk of preterm birth (28 to <34 weeks). Appropriate newborn care was available: including oxygen but not assisted ventilation. Mortality and maternal fever were compared by the number of doses (complete: three, incomplete (one or two), or no dose). A sub-cohort participated in neurodevelopmental testing at one year.

Results

Of 15,285 singleton births, 240 were included: 96 did not receive dexamethasone and 144 received one, two or three doses (56, 13 and 75, respectively). Of live-born infants followed to day 28, (n=168), early neonatal and neonatal mortality/1,000 livebirths (95%CI) with complete dosing was 217 (121–358) and 304 (190–449); compared to 394 (289–511) and 521 (407–633) with no dose. Compared to complete dosing, both incomplete and no dexamethasone were associated with elevated adjusted ORs 4.09 (1.39 to 12.00) and 3.13 (1.14 to 8.63), for early neonatal death. By contrast, for neonatal death, while there was clear evidence that no dosing was associated with higher mortality, adjusted OR 3.82 (1.42 to 10.27), the benefit of incomplete dosing was uncertain adjusted OR 1.75 (0.63 to 4.81). No adverse impact of dexamethasone on infant neurodevelopmental scores (12 months) or maternal fever was observed.

Conclusions

Neonatal mortality reduction is possible with complete dexamethasone dosing in pregnancies at risk of preterm birth in settings without capacity to provide assisted ventilation.

Keywords
Preterm birth, Early preterm birth, Antenatal corticosteroids (ACS), Dexamethasone, Low resource settings, neonatal mortality, assisted ventilation, CPAP

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REVISED **Amendments from Version 1**

In this version, we have improved the description of the study setting so that it is better compared to the two main trials on ACS (ACT and ACTION). We have also compared early neonatal mortality and neonatal mortality in the same cohort of neonates i.e. only those followed to 28 days. To improve the readability of the manuscript, we have made this version more focused by making the tables clearer and reduced the number of tables and figures. We have also incorporated changes suggested by the reviewers and corrected some grammar and punctuation issues that were missed in the first version.

Any further responses from the reviewers can be found at the end of the article

Lay summary

Prematurity is still the leading cause of under-five mortality and neonatal deaths globally. Maternal antenatal corticosteroids (ACS), such as dexamethasone, have been used widely to decrease preterm mortality and morbidity. However, evidence of their impact without assisted ventilation in low-resource settings remains limited. We studied the effect of different doses of dexamethasone prescribed to women at risk of preterm birth between 28 to less than 34 weeks gestation on early neonatal and neonatal mortality in clinics at the Thai-Myanmar border. Results from our study suggest that complete dosing of dexamethasone could significantly reduce neonatal mortality in settings without basic assisted ventilation, such as continuous positive airway pressure (CPAP). We found no adverse effect of dexamethasone on maternal fever or infant neurodevelopmental scores.

Introduction

Globally, preterm birth (PTB), birth before 37 weeks gestational age, is the leading cause of under-five mortality[1]. The burden of mortality and morbidity before five years of age due to PTB is profound; affecting one million of 15 million preterm newborns annually[2]. Deaths are largely attributable to the lower end of survivable estimated gestational age from respiratory distress syndrome however in low-income settings other basic aspects of prematurity such as hypothermia, feeding problems, hypoglycaemia and infection, also contribute[3]. The risk of lifelong adverse outcomes is increased, for example, due to bronchopulmonary dysplasia, cerebral palsy, hearing impairments, intellectual or motor disability and retinopathy of prematurity[4].

Maternal antenatal corticosteroids (ACS) at less than 34 weeks of gestation are recommended to reduce preterm mortality and morbidity[5–7] and not indicated from 34 to less than 37 weeks[8]. ACS reduce neonatal respiratory distress syndrome by enhancing the production of surfactant binding proteins, foetal lung antioxidant enzymes and morphological development of type I and II pneumocytes, through which premature foetal lung function is improved[9]. For low- and middle-income countries dexamethasone is common, inexpensive and easy to store.

The generalizability of studies conducted in high-resource hospitals with neonatal intensive care facilities (surfactant, continuous positive airway pressure (CPAP) and assisted ventilation) to low-resource settings, where 81.8% of the global burden of PTBs occur, has been tested *via* a series of trials[10]. The cluster randomized Antenatal Corticosteroid Trial (ACT)[11] in six countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) contrary to the hypothesis, found an excess of 3.5 neonatal deaths for every 1,000 women exposed and maternal infections also increased. The ACT trial was conducted mostly in health centres, with unclear gestational age, limited laboratory confirmation of infection, and hypoglycaemia and hypothermia not measured, prevented or treated. Despite these constraints, the World Health Organization (WHO) modified its guidelines for ACS for low-resource settings[12]. The Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns (ACTION) trial[13] followed and was intentionally placebo-controlled to assess the safety and efficacy of ACS in at-risk women at 26 to <34 weeks of gestation in Bangladesh, India, Kenya, Nigeria, and Pakistan. Dexamethasone was associated with a significantly lower risk of neonatal death alone than the use of placebo, without an increase in the incidence of possible maternal bacterial infection. However, the hospitals were much better equipped and not representative of the majority of low-resource setting hospitals. Furthermore, in a cost-effectiveness analysis of the trial, dexamethasone was cost-saving when compared with no intervention[14]. In Tanzania, Massawe *et al.* combined ACS with antibiotics, in a low-cost care bundle or approximately $6 per patient, which was associated with a significant reduction in neonatal mortality and fresh stillbirth rates in a well-equipped tertiary centre[15]

In Southeast Asia a retrospective descriptive, hospital-based study in four countries, Indonesia, Malaysia, the Philippines and Thailand observed variable ACS administration rates, 9–73%, highest in Thailand, with ACS associated with a reduction in stillbirth and neonatal mortality[16].

The aforementioned trials included outcomes in neonates with access to: surfactant, CPAP and assisted ventilation[11,13,16]. We aimed to determine the impact of ACS on early neonatal and neonatal mortality in infants born 28 to <34 weeks gestation on the Thailand-Myanmar border, in clinics with a neonatal intensive care unit but without capacity for assisted ventilation.

Methods

Ethics

Ethical approval for retrospective analysis of hospital records at the Shoklo Malaria Research Unit was under the guidance of the Oxford University Ethics Committee (OXTREC: 28-09, 6th May 2009) and the local community advisory board in Mae-Sot, Thailand (TCAB-12/2/2015, 15th August 2015). The ethical committee approved the protocol for the retrospective analysis of hospital records in the absence of consent due to the complexity of finding patients and the fact that

all records were anonymised. Data collection from hospital records started in January 2021.

Study design
A retrospective cohort study in a setting where ACS (dexamethasone) use is prescribed for refugee and migrant women with a risk of PTB at 28 to <34 weeks gestational age.

Setting
The Shoklo Malaria Research Unit (SMRU) on the Thailand-Myanmar border is a field-based research organization, providing humanitarian care for refugees and migrants since 1986. Long-standing neglect of the health system in Myanmar leaves swathes of the population without health services. Maela Camp is the largest of a number of camps based along the Thailand-Myanmar border providing shelter for refugees (estimated at 140,000) from Myanmar since 1984 in one of the most protracted refugee situations globally. An estimated 200,000 migrants from Myanmar work in Tak Province, Thailand, and live in sub-optimal and semi-permanent accommodation.

Rates of homebirth in Myanmar particularly in rural areas are high[17,18] and SMRU has encouraged women to birth in unit facilities, resulting in a reversal from three-quarters born at home in 1986, to more than three-quarters being born in SMRU facilities by 2015[19].

SMRU provides integrated care services including antenatal, birth, postnatal, and infant care, in the local languages (Sgaw Karen, Poe Karen, Burmese). Neonatal intensive care has been available in the refugee camp from 2008[20] and in migrant camps from 2009 in Wang Pha and 2010 in Maw Ker Thai. Medics, midwives and nurses are assisted in the clinical work by expatriate doctors and quality of care has been assessed[21]. Malaria control relies on antenatal early diagnosis and treatment to prevent mortality and reduce the adverse perinatal effects of infection[22,23]. HIV and syphilis are low in this setting with screening offered at the first consultation[24].

Approximately 2,000 women birth at SMRU clinics annually in clinics that can provide the seven signal functions of Basic Emergency Maternal Obstetric and Newborn Care: parenteral administration of an oxytocic, antibiotics and anticonvulsants, removal of retained products of conception, assisted vaginal birth including breech birth, immediate resuscitation of the newborn using a bag and mask for infants ≥28 weeks' gestation, and screened blood transfusions. In these midwives-led units, staff are trained in emergencies with the Advanced Life Support in Obstetrics course[25]. Women who require caesarean section for obstetric indications such as placenta praevia are referred to the nearest Thai Hospital.

Overall the setting was less equipped than the ACTION trial settings and more in line with what would be found in the majority of low-income country health centres and clinics. The ACTION trial was conducted in either tertiary or secondary level hospitals[26], whereas our setting as described previously[20,21] is not and referral to a tertiary facility is prohibitive due to costs. Nevertheless, there can still be a lot of hospitals in low and middle-income countries that do not have the levels of resources described here, particularly ultrasound.

Ultrasound
Various scanners including Toshiba Powervision 7000, Dynamic Imaging (since 2001), Fukuda Denshi UF 4100, and General Electric Voluson-1 have been used locally to determine gestational age[27–29]. Women are routinely offered two scans: at booking to determine viability, the number of foetus and gestation, regardless of how far progressed the pregnancy is, but preferably between eight and 14 weeks; and at 22 (18–24) weeks to reassess viability, measure foetal biometry and major abnormalities and determine placental location. Repeat scans for clinical indications such as low fundal height are done as required. Late presenters to ANC get an ultrasound and the newborn also has a Dubowitz Assessment of gestational age, in use since 1993 with trained staff and annual quality control[30]. Staff are trained in gestational age assessment and fetal growth but not in congenital anomaly scanning although experienced sonographers will notice some anomalies and review these with the doctors.

Dexamethasone
The protocol for preterm labour recommends dexamethasone 24 mg (three doses of 8 mg intramuscular every eight hours) if gestation is 28 to <34 weeks, but in practice dexamethasone was occasionally given prior to 28 weeks. Repeat doses of dexamethasone were not given. All women with threatened preterm labour were screened for infection: malaria (Giemsa stained blood smear), urinary tract infection (urine stick and sediment), respiratory tract infection (lung auscultation and history of symptoms), with a sterile speculum examination to visually check for infection, rupture of membranes cervical dilation and presence of cord, and to do a vaginal swab for microscopy (wet prep for identification of trichomonas, candida) with results available within one hour. In febrile women, bacteriological confirmation of infection from blood and urine culture was available with an alert on day 2 or 3 but mostly on day 5 to 7 after taking samples. No bacteriological confirmation of cervical swabs was available. Tocolytic (nifedipine) was prescribed when indicated and avoided in cases of maternal fever. All suspected infection was treated using local protocols. Magnesium sulphate for neuroprotection was not provided.

Neonatal intensive care
The establishment and impact of a neonatal intensive care unit in this setting has been described previously[21]. Appropriate care as prescribed in high-income settings for late preterm neonates, was available in the neonatal intensive care unit *i.e.*, regular check of vital signs, regular (breast)feeding, stable body temperature, monitored oxygen saturation and intravenous antibiotics if required. Respiratory support involved

nasal or mask oxygen, apnoea mats, pulse oximetry, and intravenous aminophylline in place of oral caffeine (due to unavailability).

Staff were trained in newborn resuscitation and a study in this setting reported normal neurodevelopmental outcomes at one year of age following basic resuscitation at birth, compared to low-risk newborns who did not need resuscitation[31]. Care is guided by local protocols available and used at each SMRU site. Extreme PTB (<28 weeks) infants are provided with palliative care and parents are involved and counselled in the process[32]. Tertiary care referral is limited due to prohibitive costs.

Overall the neonatal intensive care provided was basic but was able to contend with some of the constraints of the ACT trial conducted mostly in health centres. Newborn gestational age was known, and hypoglycaemia and hypothermia were measured, prevented and treated. Suspected neonatal sepsis was a clinical diagnosis and intravenous antibiotics were available. Useful local laboratory support included haematocrit and for infection, urine sediment and malaria, neither of which are common in newborns.

Neurodevelopment

The Shoklo Developmental Test at 12–14 months of age was used to assess neurodevelopment in a sub-cohort of infants enrolled in a previously approved birth cohort being conducted during the timeframe of this study[33]. This test evaluates four different aspects of development with each item scored as pass/fail basis: coordination, speech, social interaction and milestone. Behaviour during the test (relation to the tester, interest towards the test, emotional status) was also evaluated.

Eligibility for inclusion

Birth records from 2008 were captured in real time using an application developed by Technology Sans Frontières (TSF). Further verification of the major data (registration, partogram, inpatient admissions, birth outcome, neonatal intensive care unit charts) was possible from paper-based charts, including a PTB checklist. Records from 2008–2013 were reviewed if they were: i) preterm (28 to <34 weeks), and if ii) dexamethasone administration was confirmed from clinic files; in this way capturing all possible dexamethasone eligible cases of birth from 28 weeks.

Exclusion criteria included referral to the Thai hospital for birth; and when dexamethasone was not indicated, such as *e.g.*, incidental detection of a severe congenital abnormality by ultrasound, or because there was no foetal heartbeat, or dexamethasone was given <26 weeks.

Definitions

PTB included birth from 28 to <37 weeks of life, although in this series all were early preterms <34 weeks; stillbirth included infants of 28 weeks gestation with no signs of life; early neonatal mortality was death of a liveborn infant within the first seven days of life, neonatal mortality was death of a live born infant within the first 28 days of life. Complete dexamethasone refers to three doses, and incomplete to one or two doses. Congenital abnormality included newborns with an anomaly detected by ultrasound, or on routine surface examination of the newborn including cardiac auscultation by trained staff and confirmed by a doctor.

Statistical analysis

Categorical data were reported as proportion and compared using the Chi-squared test or Fishers Exact Test for cell values <5. Median and interquartile range [IQR] described continuous data, such as gestation, and compared using the Mann-Whitney U test, with univariate associations quantified using logistic regression. To evaluate the role of dexamethasone on early neonatal and neonatal mortality, all significant risk factors for zero and three doses were combined into one logistic regression model, including congenital abnormality, gestation at birth, maternal smoking and pre-eclampsia. Pre-eclampsia was included in the multivariable model in concordance with the literature as an important risk factor, and birthweight was not included due to collinearity with gestational age. Neurodevelopmental scores for complete or any dexamethasone were compared to zero dexamethasone and adjusted for gestational age at birth. Data were analysed using IBM SPSS Statistics (RRID: SCR_016479) version 27 (IBM SPPS, Armonk, NY, USA).

Results

Of 15,829 pregnant women with singleton births between January 2008 to December 2013, 3.4% (n=544) were eligible for dexamethasone (Figure 1). The final cohort included 240 women who birthed at the clinic, at home or on the way to the clinic with 60.0% (n=144) receiving at least one dose of dexamethasone, and 40.0% (n=96) where it was indicated (estimated gestational age <34 weeks) but not received.

Baseline characteristics of the study population

The median maternal age was 22 years, almost half (43.8%, 105/240) were primigravidae (Table 1), with 47.5% (114/240) attending the first ANC visit in the first trimester and most women having ultrasound-confirmed gestational age assessment (84.4%, 204/244) (Table 2). Pre-eclampsia was significantly higher in the complete dexamethasone group (Table 1). The majority, 84.0% (121/144) birthed within seven days of receiving dexamethasone (Figure 2), with a longer interval from administration to birth in those who received a complete course (Table 1). Most women eligible for ACS arrived too late to complete three doses with 68.8% (165/240) receiving 0, 1 or 2 doses.

Birth outcomes

Overall, 78.3% (188/240) of the newborns were delivered at SMRU clinics and the majority were delivered following standard vaginal birth (88.8%, 213/240) (Table 2). There

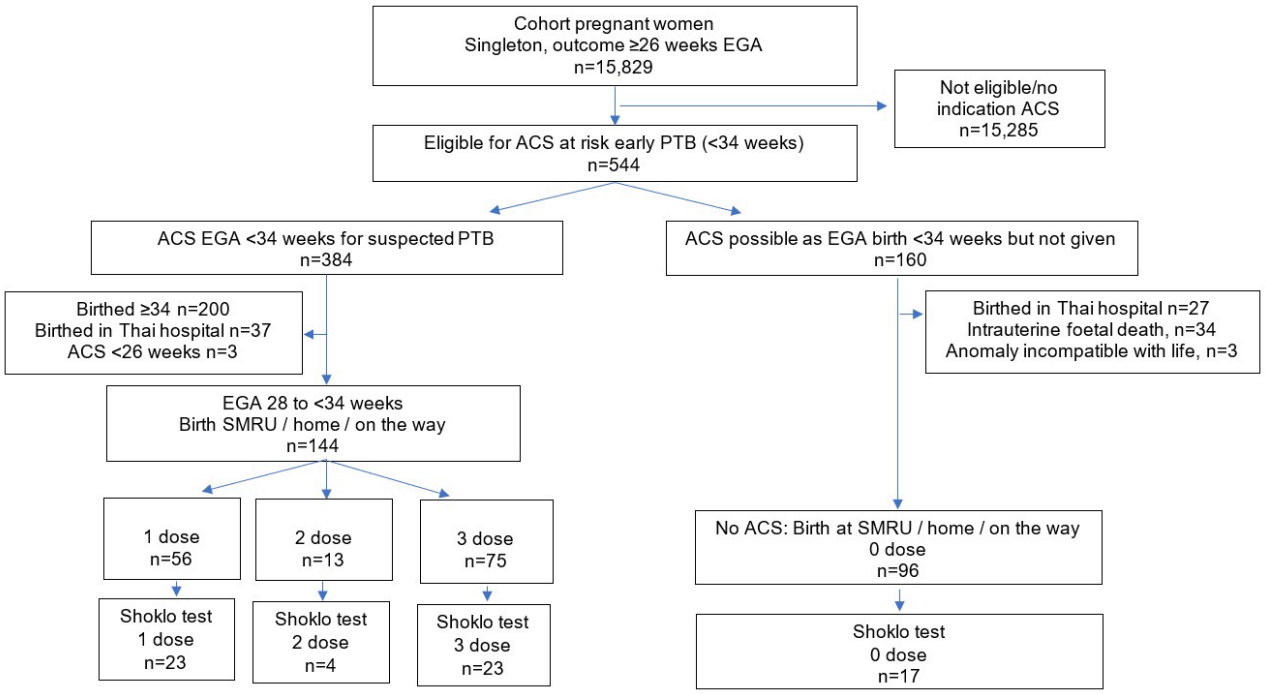

Figure 1. Study flow chart. EGA, estimated gestational age; ACS, antenatal corticosteroids; PTB, preterm birth; SMRU, Shoklo Malaria Research Unit.

Table 1. Maternal characteristics and dexamethasone doses.

		Dexamethasone doses					P-value		
	Cohort	0 dose	1 dose	2 doses	1 or 2 doses	3 doses	3 doses *versus* 0 dose	1-2 doses *versus* 0 dose	3 doses *versus* 1-2 dose
Characteristics	**n=240**	**n=96**	**n=56**	**n=13**	**n=69**	**n=75**			
Age, years	22 [19-28]	23 [19-30]	21 [18-25]	21 [19-28]	21 [18-26.0]	23 [19-30]	0.628	0.060	0.033
Primigravida	105 (43.8)	34 (35.4)	34 (60.7)	6 (46.2)	40 (58.0)	31 (41.3)	0.433	0.005	0.066
Refugee (not migrant)	131 (54.6)	45 (46.9)	34 (60.7)	10(76.9)	44 (63.8)	42 (56.0)	0.281	0.040	0.396
Smoker	46 (19.2)	30 (31.3)	4 (7.1)	1 (7.7)	5 (7.2)	11 (14.7)	0.012	<0.001	0.190
Literate^	76/147 (51.7)	19/48 (39.6)	27/44 (61.4)	4/9 (44.4)	31/53 (58.5)	26/46 (56.5)	0.148	0.074	1.000
History Preterm birth	31 (12.9)	12 (12.5)	8 (14.3)	2 (15.4)	10 (14.5)	9 (12.0)	1.000	0.817	0.806
History NND	81 (33.8)	33 (34.4)	14 (25)	4 (30.8)	18 (26.1)	30 (40.0)	0.523	0.307	0.081
Anaemic 1st HCT	33 (13.8)	18 (18.8)	5 (8.9)	1 (7.7)	6 (8.7)	9 (12.0)	0.292	0.078	0.592
Pregnancy morbidity									
Malaria	33 (13.8)	19 (19.8)	6 (10.7)	0	6 (8.7)	8 (10.7)	0.139	0.077	0.782
Pre-eclampsia	11 (4.6)	1 (1.0)	2 (3.6)	0	2 (2.9)	8 (10.7)	0.006	0.378	0.064
APH	11 (4.6)	3 (3.1)	3 (5.4)	1 (7.7)	4 (5.8)	4 (5.3)	0.365	0.323	0.593
Birth ≤7 days ACS	n.a.	n.a.	56 (100.0)	13 (100.0)	69 (100.0)	52 (69.3)	n.a.	n.a.	<0.001

Data are presented as the Median, interquartile range [IQR], or n (%) unless otherwise stated; p-value- Chi-squared test or Fisher's exact test if cell count<5, medians by Mann-Whitney U test

Abbreviations: ACS antenatal corticosteroids, ANC antenatal care, APH antepartum haemorrhage, HCT haematocrit, n.a. not applicable, NND neonatal death.
^Literacy (self-reported) routinely collected from 2010.

Table 2. **Neonatal characteristics and dexamethasone doses.**

Variables		Dexamethasone doses					P-value		
	Cohort	0 dose	1 dose	2 dose	1 or 2 doses	3 doses	3 *versus* 0 dose	1-2 *versus* 0 dose	3 *versus* 1-2 dose
	n=240	n=96	n=56	n=13	n=69	n=75			
Place of birth									
SMRU clinic	188 (78.3)	50 (52.1)	56 (100)	13 (100)	69 (100)	69 (92.0)			
Home	45 (18.8)	40 (41.7)	0	0	0	5 (6.7)			
On the way to clinic	7 (2.9)	6 (6.3)	0	0	0	1 (1.3)	<0.001	<0.001	0.056
Male	146/237 (61.6)	55/93 (59.1)	39 (69.6)	10 (76.9)	49 (71.0)	42 (56.0)	0.754	0.137	0.083
Congenital Abnormality	13/237 (5.5)	6/93 (6.5)	3 (5.4)	n.a.	3 (4.3)	4 (5.3)	1.000	0.415	0.546
EGA birth, weeks, Median [IQR]	32.1 [30.4-33.2]	32.3 [30.3-33.2]	32.1 [30.5-33.3]	31.5 [29.7-32.3]	31.6 [30.4-33.0]	32.2 [30.2-33.2]	0.616	0.420	0.714
EGA by US, n (%)	206 (85.8)	83 (86.5)	49 (87.5)	12 (92.3)	61 (88.4)	62 (82.7)	0.525	0.815	0.355
PTB group									
PTB 28–29 weeks	43 (17.9)	16 (16.7)	9 (16.1)	3 (23.1)	12 (17.4)	15 (20.0)			
PTB 30–31 weeks	62 (25.8)	23 (24.0)	18 (32.1)	5 (38.5)	23 (33.3)	16 (21.3)			
PTB 32–33 weeks	135 (56.3)	57 (59.4)	29 (51.8)	5 (38.5)	34 (49.3)	44 (58.7)	0.823	0.364	0.269
Type of delivery									
Cephalic vaginal birth	213 (88.8)	87 (90.6)	47 (83.9)	12 (92.3)	59 (85.5)	67 (89.3)			
Breech/Face^	26 (10.8)	8 (8.3)	9 (16.1)	1 (7.7)	10 (14.5)	8 (9.7)			
Forceps	1 (0.4)	1 (0.4)	0	0	0	0	0.548	0.327	0.409
Weighed in 72 hrs	225/231 (97.4)	83/88 (94.3)	56 (100)	13 (100)	69 (100)	73/74 (98.6)	0.221	0.053	0.517
Birth weight*, kg Median [IQR]	1.65 [1.36-1.90] n=206	1.66 [1.30-1.95] n=77	1.72 [1.47-1.95] n=51	1.66 [1.22-1.85] n=12	1.72 [1.42-1.91] n=63	1.66 [1.30-1.88] n=66	0.729	0.629	0.372
Apgar < 7 at 5 min	14/182 (7.7)	6/51 (11.8)	2/53 (3.8%)	0	2/65 (3.1)	6/66 (9.1)	0.761	0.072	0.142
Stillbirth	7 (2.9)	0	2 (3.6)	1 (7.7)	3 (4.3)	4 (5.3)	0.035	0.071	0.546
Early Neonatal death	56/233 (24.0)	28/96 (29.2)	13/54 (24.1)	5/12 (41.7)	18/66 (27.3)	10/71 (14.1)	0.025	0.860	0.061
Neonatal death**	69/168 (41.1)	37/71 (52.1)	13/40 (32.5)	5/11 (41.5)	18/51 (35.3)	14/46 (30.4)	0.023	0.096	0.669

Data are presented as the Median, interquartile range [IQR], (min-max); n (%) unless otherwise stated; p-value- Chi-squared test or Fisher's exact test is cell count<5, median by Mann-Whitney U test.

Abbreviations: SMRU Shoklo malaria research unit, ACS antenatal corticosteroids-dexamethasone, EGA estimated gestational age, US ultrasound, PTB preterm birth, n.a not applicable.

^ 1 face presentation in 3 dose group, *Birthweight in live-born normal singletons weighed in 72 hours of life. **Neonatal death in live-born infants followed up for the first 28 days of life.

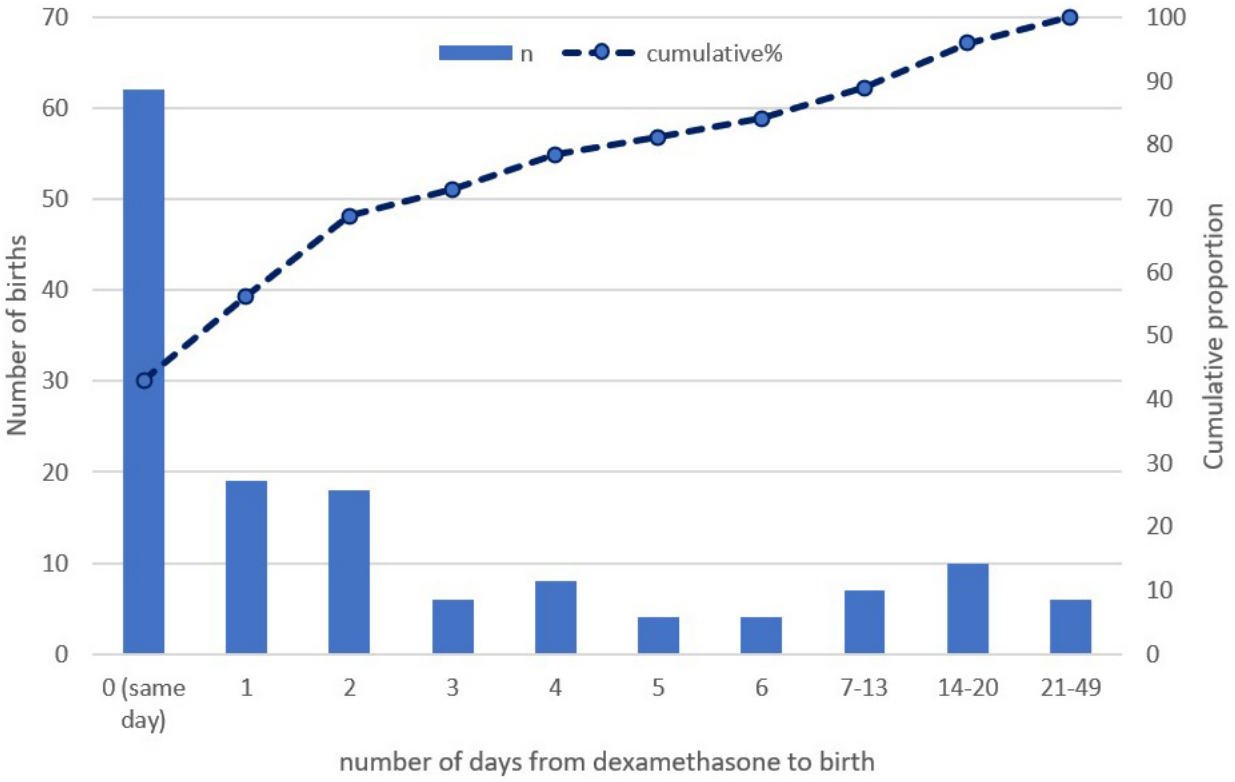

Figure 2. Dexamethasone to delivery interval (n=144).

were 2.9%, (7/240) of infants that were stillborn but had a foetal heartbeat present before dexamethasone was prescribed (Table 2).

Early neonatal and neonatal mortality and associated risk factors

The proportion of early neonatal death was 24.0% (56/233) and neonatal death was 41.1% (69/168) (Table 2). After retaining factors significant on univariate analysis, in multivariable logistic regression models, compared to complete dosing, there was no evidence of benefit of incomplete and no dosing of dexamethasone on early neonatal mortality, as both were associated with elevated early neonatal mortality: adjusted ORs 4.09 (1.39 to 12.00) and 3.13 (1.14 to 8.63), respectively (Table 3). By contrast, for neonatal death, while there was clear evidence that no dosing was associated with higher mortality, adjusted OR 3.82 (1.42 to 10.27), the benefit of incomplete dosing was uncertain (adjusted OR 1.75 (0.63 to 4.81)) (Table 3). Congenital abnormality, earlier gestation at birth and pre-eclampsia were significantly and independently associated with an increased risk of early neonatal death and neonatal death (Table 3).

Crude early neonatal and neonatal mortality

There were a different number of neonates available for analysis in the early neonatal period (n=233) and by day 28 (n=168). Including only infants followed up to day 28, the early neonatal and neonatal mortality rates per 1,000 live births were 333 (95% CI, 266-408) and 411 (95% CI, 339-486), respectively (Table 4, Panel A). The largest crude reductions in early neonatal and neonatal deaths were observed comparing three to zero doses of dexamethasone: 44.9% (95 % CI, 43.4 to 46.3) and 41.6% (95% CI, 40.3 to 43.0), respectively (Table 4, Panel B).

Neurodevelopmental score

There was no difference observed between the median total score (or separate components including coordination, social, speech and motor milestones) of the Shoklo Developmental test in the sub-cohort (Figure 1), 28.8% (67/233) of unselected infants at 12 months of age (Table 5).

Maternal febrile morbidity

Among the 138 women who gave birth <7 days from ACS there were 19 (13.8%, 95% CI 8.5-20.7) with fever within 72 hours of birth, while 8 of the 96 (8.3%, 95% CI 3.7-15.8) who did not receive ACS had fever; with a similar time distribution of fever onset (Figure 3); and the two main causes of fever were chorioamnionitis (n=11 (n=8 ACS, n=3 no ACS) and malaria (n=4, n=3 ACS, n=1 no ACS).

Discussion

In women who gave birth before 34 weeks, early neonatal (24%) and neonatal mortality (41%) were high. The proportion

Table 3. Risk factors associated with early neonatal and neonatal mortality multivariable model.

	Yes	No	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Yes	No	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
	n=56	n=177	P-value	P-value	n=69	n=99	P-value	P-value
Congenital abnormality								
No	45/53 (84.9)	173(97.7)	ref	ref	57/66 (86.4)	98/99 (99.0)	ref	ref
Yes	8 (15.1)	4 (2.3)	7.69 (2.22-26.68)	5.34 (1.09-25.99)	9 /66(13.6)	1/99 (1.0)	15.47 (1.91-125.31)	14.55 (1.39-152.07)
			0.001	0.038			0.01	0.025
Preterm birth (weeks)								
28-29	22 (39.3)	17 (9.6)	10.91 (4.70-25.30)	19.36 (7.19-52.14)	25 (36.2)	12 (12.1)	7.02 (2.98-16.55)	11.27 (4.21-30.17)
			<0.001	<0.001			<0.001	<0.001
30-31	20 (35.7)	42 (23.7)	4.01 (1.86-8.66)	4.37 (1.79-10.66)	25 (36.2)	23 (23.2)	3.66 (1.71-7.86)	5.03 (2.06-12.27)
			<0.001	<0.001			<0.001	<0.001
32-33	14 (25.0)	118 (66.7)	ref	ref	19 (27.5)	64 (64.6)	ref	ref
Dexamethasone Doses								
Complete	10 (17.9)	61 (43.5)	ref	ref	14 (20.3)	32 (32.3)	ref	ref
Incomplete	18 (32.1)	48 (27.1)	2.29 (0.97-5.41)	4.09 (1.39-12.00)	18 (26.1)	33 (33.3)	1.25 (0.53-2.92)	1.75 (0.63-4.81)
			0.059	0.01			0.612	0.281
No dose	28 (50.0)	68 (38.4)	2.51 (1.13-5.59))	3.13 (1.14-8.63)	37 (53.6)	34 (34.3)	2.48 (1.14-5.44)	3.82 (1.42-10.27)
			0.024	0.027			0.022	0.008
Smoker								
No	37 (66.1)	150 (84.7)	ref	ref	49 (71.0)	86 (86.9)	ref	ref
Yes	19 (33.9)	27 (15.3)	2.85 (1.43-5.68)	3.36 (1.32-8.53)	20 (29.0)	13 (13.1)	2.70 (1.24-5.89)	1.94 (0.73-5.17)
			0.003	0.011			0.013	0.187
Pre-eclampsia								
No	52 (92.9)	173 (97.7)	ref	ref	65 (94.2)	97 (98.0)	ref	ref
Yes	4 (7.1)	4 (2.3)	3.33 (0.80-13.77)	13.77 (2.38-79.62)	4 (5.8)	2 (2.0)	1.86(0.48-7.18)	9.21 (1.9-71.59)
			0.097	0.003			0.37	0.034

Data are presented as n (%) unless otherwise stated.

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Table 4. Crude early neonatal and neonatal mortality per 1,000 live births (95%CI) in 168 neonates followed to day 28 (1 Jan 2008 to 31 Dec 2013).

Panel A. Early neonatal and neonatal mortality per 1,000 live births.

Outcomes	Cohort	No dose	Complete (3) doses	Incomplete dose	Any dose
Early Neonatal Death (ENND)	333	394	217	353	289
95% CI	(266-408)	(289-511)	(121-358)	(236-491)	(208-386)
Neonatal Death (NND)	411	521	304	353	330
95% CI	(339-486)	(407-633)	(190-449)	(236-491)	(244-429)

Panel B. Crude % reduction in death (95% CI) by dexamethasone groups.

Outcomes	Any doses vs. No dose	Complete (3) dose *vs.* No dose	Complete (3) dose *vs.* Incomplete dose
Early Neonatal Death (ENND)	26.8	44.9	38.4
95% CI	(25.4-28.2)	(43.3-46.3)	(36.8-40.0)
Neonatal Death (NND)	36.7	41.6	13.8
95% CI	(35.4-38.0)	(40.3-43.0)	(12.7-15.0)

Table 5. Comparison of Shoklo Neurological Developmental test at different dexamethasone doses: Panel A, and Panel B.

Panel A. Complete *vs.* no dose of dexamethasone.

Neurological score item	Complete dexamethasone 3 Doses	No Dose	p-value*
	n=23	n=17	
Total Score (n=40)	52.5 [49.0-56.5] (17.0-60.0)	55.0 [49.0-60.0] (42.0-64.0)	0.321
Coordination score	24.0 [22.0-28.0] (8.0-30.0)	26.0 [23.0-30.0] (17.0-35.0)	0.100
Social score	5.0 [5.0-5.5] (1.0-7.0)	5.0 [5.0-6.0] (3.0-7.0)	0.476
Speech score	4.0 [3.0-5.0] (2.0-5.0)	4.0 [4.0-5.0] (2.0-6.0)	0.866
Motor milestones score	19.0 [17.5-20.0] (6.0-23.0)	18.5 [16.0-21.0] (14.0-22.0)	0.931
Total behaviour score^	14.0 [14.0-15.0] (12.0-15.0)	14.0 [13.0-15.0] (12.0-15.0)	0.813

Panel B. Any number of doses *vs.* no dose of dexamethasone.

Neurological score item	Any number of dexamethasone Doses,	No Dose	p-value*
	n=50	n=17	
Total Score (n=67)	55.0 [51.0-58.0] (17.0-66.0)	55.0 [49.0-60.0] (42.0-64.0)	0.758
Coordination score	26.0 [24.0-29.0] (8.0-33.0)	26.0 [23.0-30.0] (17.0-35.0)	0.394
Social score	5.0 [5.0-6.0] (1.0-7.0)	5.0 [5.0-6.0] (3.0-7.0)	0.843
Speech score	4.0 [4.0-5.0] (2.0-5.0)	4.0 [4.0-5.0] (2.0-6.0)	0.964
Motor milestones score	19.0 [17.5-20.0] (6.0-23.0)	18.5 [16.0-21.0] (14.0-22.0)	0.718
Total behaviour score^	14.0 [14.0-15.0] (12.0-15.0)	14.0 [14.0-15.0] (12.0-15.0)	0.665

Data are presented as the median [IQR] and (min-max); *p-value adjusted for gestation at birth; ^The total behaviour score is not counted towards the total score but provides an indication of the test 'scene'.

A score of 15 (top score) indicates that at the time of the test, the infant was interested and not crying or asleep (state of consciousness), in a positive emotional state (happy, smiling) and not afraid of the tester accepting their approach to interact with the tests.

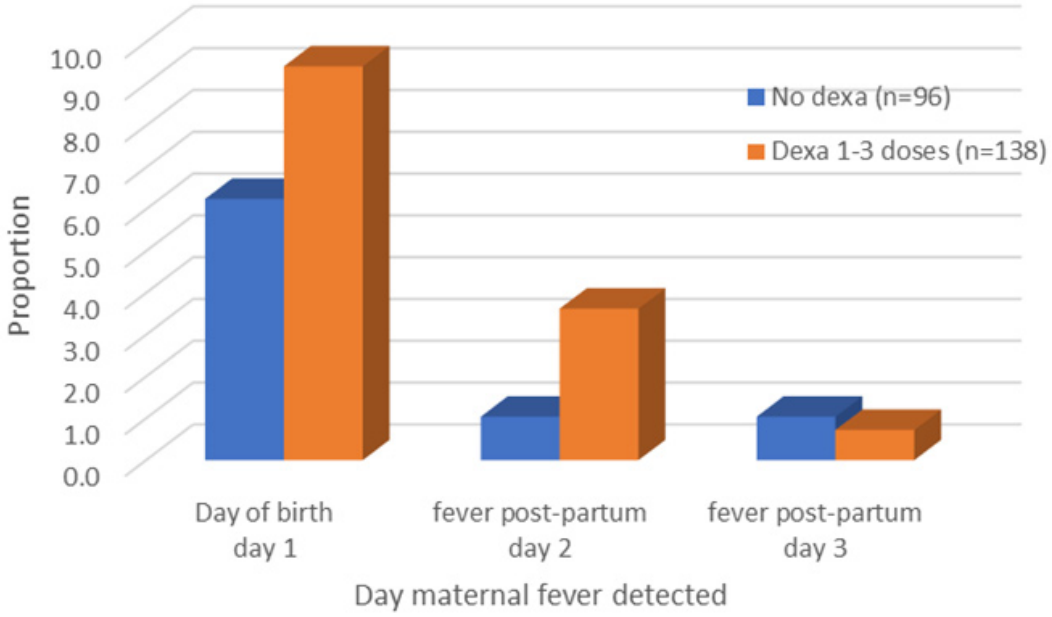

Figure 3. Timing of maternal febrile morbidity from birth.

of neonatal deaths, 30.4% (14 of 46), in the complete dexamethasone group in this setting was higher than observed in the ACTION trial: 19.6% (278 of 1417) in the treatment group and 23.5% (331 of 1406) in the placebo (normal saline) group, where approximately one in five newborns were provided CPAP and a further one in 14 mechanical ventilation[13]. Context is important to neonatal survival. In this study we have portrayed the clinics as low-resource clinics as CPAP and mechanical ventilation are unavailable however locally trained staff were able to provide services such as ultrasound and microscopy, and mother and newborn care with basic equipment and drugs, so the higher mortality is not unexpected. Overall, the setting is probably somewhat better than health centres described in the ACT trial but less sophisticated than hospitals in the ACTION trial.

In multivariable analysis, zero or incomplete dosing (compared with complete dosing), lower gestation at birth (28–29 or 30–31 weeks compared with 32–33 weeks), congenital abnormality and pre-eclampsia were associated with a significantly increased risk of neonatal death. In this setting and with cautious regard for the retrospective nature of the data, a lower number, estimated at one in five women with a risk of PTB need to receive a complete dexamethasone course to prevent one neonatal death, when compared with one in 25 in the ACTION trial (which included the more vulnerable gestational aged neonates from 26 weeks)[13]. The role of incomplete dosing remains uncertain. As dexamethasone is one of the only low-cost and available tools in conflict-affected and fragile states, or amongst marginalized populations where healthcare can be associated with catastrophic expenditure[34], this study suggests the benefit in terms of neonatal mortality outweigh potential risks in terms of maternal infection, which is common in tropical South East Asia[35,36]. As two in three eligible women arrived too late for effective dosing (completing the 3 injections) efforts towards ensuring all women recognize symptoms of preterm labour and the need to access care as soon as possible, may be a low cost method to reduce mortality rates.

The ACT Trial suggested upscaling of interventions, including ACS administration in low-resource settings, was harmful to preterm neonates in contrast to reports from high-income settings[11]. The ACT trial relied on fundal height and birth weight as a proxy for gestational age, while an obvious strength in this study was that all women had ultrasound: 84% before 24 weeks of gestational age, nearly half in the first trimester. As a result, in the ACT trial, ACS exposure occurred in pregnancies where it was not warranted, as the pregnancy was not preterm. Gestation is the single most significant factor to influence neonatal death and is reflected in the multivariable analysis presented here. Obstetricians and gynaecologists should take an active leadership role in ensuring the implementation of ultrasound to accurately date pregnancies, therefore supporting a reduction in health disparities[37]. Ultrasound is mobile and technically easier than CPAP to reach more women and can be purposed for roles beyond gestational age assessment, such as identification of multiple pregnancy and placenta praevia, and commencing timely antimalarial prophylaxis. It is not only the availability of the ultrasound machine and trained staff (we trained local staff who had finished school at 16 years of age) but also the affordability and acceptability of women to attend ANC at least before 24 weeks gestation.

The ACTION trial[13] and a Cochrane systematic review of three cluster-randomized trials, including the ACT trial, suggested a cautious approach to clinical protocols for low-resource settings; one that accounts for both established efficacy and the possibility of adverse effects when certain conditions are not met[38]. Consequently, WHO has updated its 2015 recommendations on Antenatal corticosteroids considering new evidence from the ACTION trial. While ACS is still recommended between 24 to 34 weeks gestation for women at risk of PTB to improve outcomes, the 2022 update includes CPAP when needed for neonatal respiratory support as a condition[39]. However, access to assisted ventilation is a frequent unmet need for low-resource settings. Hence this study, unlike the review by Pattanittum *et al.*,[16] excluded infants born in hospital to maintain a focus on those likely to derive benefit from dexamethasone. Given the challenges in scaling up even bubble CPAP use in low resource settings[40], this study is novel as it demonstrates that a complete course of dexamethasone with no assisted ventilation reduced neonatal mortality in early PTB.

In addition, in the cost-effectiveness analysis of the ACTION Trial, dexamethasone was cost-saving compared with no intervention. Furthermore, sensitivity analysis showed dexamethasone to be cost-saving or highly cost-effective despite the use of ultrasound to confirm gestational age before receiving dexamethasone[14]. While findings such as these are reassuring, there is a need for further research on the cost-effectiveness of dexamethasone for early PTB in settings such as ours without CPAP or mechanical ventilation.

Our study has some limitations. First, due to the retrospective nature of the study, there might be a risk of bias. We cannot rule out unmeasured confounding. However, the partial effect we found with an incomplete dose does suggest that our findings are not influenced by bias. The main limitation of this study is that not all infants could be followed up to day 28 and only a sub-cohort of infants had neurodevelopmental testing at one year of age. Nevertheless, the findings from the Thailand-Myanmar border are consistent with the main outcomes of a Cochrane systematic review of 27 clinical ACS trials published in 2020 and partially fill a gap in knowledge for ACS in understudied and low-resource groups[9]. Another limitation is that the data are from 2008 to 2013, however, the current level of neonatal care available to this marginalized population is unchanged. The overall health situation is deteriorating given the current problems with COVID and the *coup d'état* in Myanmar, emphasizing the need to make the most of the very few tools that can make a difference in these situations.

Conclusions

A complete course of dexamethasone for early PTB, in well-dated pregnancies with basic screening and treatment for maternal infection, in a setting with appropriate newborn care without assisted ventilation, was associated with a significant reduction in early neonatal and neonatal mortality in a dose-dependent manner. Dexamethasone did not appear to be associated with adverse infant neurodevelopmental scores nor an increased risk of morbidity from maternal infection. Efforts to help women recognize symptoms of preterm birth and access care as soon as possible to achieve complete ACS dosing may reduce neonatal mortality.

Data availability

Data cannot be shared publicly as this is a population of undocumented refugees and migrants, and they have not given their permission to share data. Data are available from the Mahidol-Oxford Research Unit Institutional Data Access Committee (contact Rita Chanviriyavuth, email: datasharing@tropmedres.ac) for researchers who meet the criteria for access to confidential data. Applicants complete an Application Form and a Data Access agreement. Applications are considered by the DAC on a case-by-case basis informed by an assessment criterion, defined in the DAC terms of reference. The type of agreement that applicants are asked to complete will be determined by the DAC. Consideration will involve consultation with PIs, relevant collaborators and other experts. More details are available at https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing/moru-tropical-network-policy-on-sharing-data-and-other-outputs.

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References

1. Howson CP, Kinney MV, McDougall L, *et al.*: **Born too soon: preterm birth matters.** *Reprod Health.* 2013; **10 Suppl 1**(Suppl 1): (S1). PubMed Abstract | Publisher Full Text | Free Full Text

2. Chawanpaiboon S, Vogel JP, Moller AB, *et al.*: **Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis.** *Lancet Glob Health.* 2019; **7**(1): e37–e46. PubMed Abstract | Publisher Full Text | Free Full Text

3. Egesa WI, Waibi WM: **Bubble Nasal Continuous Positive Airway Pressure**

(bNCPAP): An Effective Low-Cost Intervention for Resource-Constrained Settings. *Int J Pediatr.* 2020; **2020**: 8871980.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Kleinhout MY, Stevens MM, Osman KA, *et al.*: **Evidence-based interventions to reduce mortality among preterm and low-birthweight neonates in low-income and middle-income countries: a systematic review and meta-analysis.** *BMJ Glob Health.* 2021; **6**(2): e003618.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Dalziel SR, Crowther CA, Harding JE: **Antenatal corticosteroids 40 years on: we can do better.** *Lancet.* 2014; **384**(9957): 1829–1831.
PubMed Abstract | Publisher Full Text

6. Brownfoot FC, Crowther CA, Middleton P: **Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth.** *Cochrane Database Syst Rev.* 2008; (4): CD006764.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Crowther CA, Harding J: **Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease.** *Cochrane Database Syst Rev.* 2003; (3): CD003935.
PubMed Abstract | Publisher Full Text

8. Jacobsson B, Simpson JL, FIGO Working Group for Preterm Birth: **FIGO good practice recommendations for reducing preterm birth and improving child outcomes.** *Int J Gynaecol Obstet.* 2021; **155**(1): 1–4.
PubMed Abstract | Publisher Full Text

9. McGoldrick E, Stewart F, Parker R, *et al.*: **Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth.** *Cochrane Database Syst Rev.* 2020; **12**(12): CD004454.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Jobe AH, Kemp MW, Kamath-Rayne B, *et al.*: **Antenatal corticosteroids for low and middle income countries.** *Semin Perinatol.* 2019; **43**(5): 241–246.
PubMed Abstract | Publisher Full Text

11. Althabe F, Belizán JM, Buekens P, *et al.*: **Antenatal corticosteroids to reduce preterm deaths in low-income settings.** *Lancet Glob Health.* 2014; **2**(8): e444.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Althabe F, Thorsten V, Klein K, *et al.*: **The Antenatal Corticosteroids Trial (ACT)'s explanations for neonatal mortality - a secondary analysis.** *Reprod Health.* 2016; **13**(1): 62.
PubMed Abstract | Publisher Full Text | Free Full Text

13. WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, *et al.*: **Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries.** *N Engl J Med.* 2020; **383**(26): 2514–2525.
PubMed Abstract | Publisher Full Text | Free Full Text

14. WHO ACTION Trial Collaborators: **Antenatal dexamethasone for improving preterm newborn outcomes in low-resource countries: a cost-effectiveness analysis of the WHO ACTION-I trial.** *Lancet Glob Health.* 2022; **10**(10): e1523–33.
PubMed Abstract | Publisher Full Text

15. Massawe A, Kidanto HL, Moshiro R, *et al.*: **A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country.** *PLoS One.* 2018; **13**(3): e0193146.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Pattanittum P, Ewens MR, Laopaiboon M, *et al.*: **Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project.** *BMC Pregnancy Childbirth.* 2008; **8**: 47.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Cavallin F, Trevisanuto D, Thein A, *et al.*: **Birthplace is a risk factor for exchange transfusion in outborn infants admitted for jaundice in Myanmar: a case-control study.** *J Matern Fetal Neonatal Med.* 2020; **33**(9): 1526–1531.
PubMed Abstract | Publisher Full Text

18. Milkowska-Shibata MA, Aye TT, Yi SM, *et al.*: **Understanding Barriers and Facilitators of Maternal Health Care Utilization in Central Myanmar.** *Int J Environ Res Public Health.* 2020; **17**(5): 1464.
PubMed Abstract | Publisher Full Text | Free Full Text

19. McGready R, Boel M, Rijken MJ, *et al.*: **Effect of early detection and treatment on malaria related maternal mortality on the north-western border of Thailand 1986-2010.** *PLoS One.* 2012; **7**(7): e40244.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Turner C, Carrara V, Aye Mya Thein N, *et al.*: **Neonatal intensive care in a Karen refugee camp: a 4 year descriptive study.** *PLoS One.* 2013; **8**(8): e72721.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Hoogenboom G, Thwin MM, Velink K, *et al.*: **Quality of intrapartum care by skilled birth attendants in a refugee clinic on the Thai-Myanmar border: a survey using WHO Safe Motherhood Needs Assessment.** *BMC Pregnancy Childbirth.* 2015; **15**: 17.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Moore KA, Simpson JA, Wiladphaingern J, *et al.*: **Influence of the number and timing of malaria episodes during pregnancy on prematurity and small-for-gestational-age in an area of low transmission.** *BMC Med.* 2017; **15**(1): 117.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Moore KA, Fowkes FJI, Wiladphaingern J, *et al.*: **Mediation of the effect of malaria in pregnancy on stillbirth and neonatal death in an area of low transmission: observational data analysis.** *BMC Med.* 2017; **15**(1): 98.
PubMed Abstract | Publisher Full Text | Free Full Text

24. McGready R, Kang J, Watts I, *et al.*: **Audit of antenatal screening for syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study [version 2; peer review: 2 approved].** *F1000Res.* 2014; **3**: 123.
PubMed Abstract | Publisher Full Text | Free Full Text

25. McGready R, Rijken MJ, Turner C, *et al.*: **A mixed methods evaluation of Advanced Life Support in Obstetrics (ALSO) and Basic Life Support in Obstetrics (BLSO) in a resource-limited setting on the Thailand-Myanmar border [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2021; **6**: 94.
PubMed Abstract | Publisher Full Text | Free Full Text

26. WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, *et al.*: **Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries.** *N Engl J Med.* Supplementary appendix.Table S1,Characteristics of ACTION-I trial hospitals;p20, 2020; **383**(26): 2514–2525.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Rijken MJ, Gilder ME, Thwin MM, *et al.*: **Refugee and migrant women's views of antenatal ultrasound on the Thai Burmese border: a mixed methods study.** *PLoS One.* 2012; **7**(4): e34018.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Rijken MJ, Mulder EJH, Papageorghiou AT, *et al.*: **Quality of ultrasound biometry obtained by local health workers in a refugee camp on the Thai-Burmese border.** *Ultrasound Obstet Gynecol.* 2012; **40**(2): 151–7.
PubMed Abstract | Publisher Full Text | Free Full Text

29. Rijken MJ, Lee SJ, Boel ME, *et al.*: **Obstetric ultrasound scanning by local health workers in a refugee camp on the Thai-Burmese border.** *Ultrasound Obstet Gynecol.* 2009; **34**(4): 395–403.
PubMed Abstract | Publisher Full Text | Free Full Text

30. Moore KA, Simpson JA, Thomas KH, *et al.*: **Estimating Gestational Age in Late Presenters to Antenatal Care in a Resource-Limited Setting on the Thai-Myanmar Border.** *PLoS One.* 2015; **10**(6): e0131025.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Janet S, Carrara VI, Simpson JA, *et al.*: **Early neonatal mortality and neurological outcomes of neonatal resuscitation in a resource-limited setting on the Thailand-Myanmar border: A descriptive study.** *PLoS One.* 2018; **13**(1): e0190419.
PubMed Abstract | Publisher Full Text | Free Full Text

32. McGready R, Paw MK, Wiladphaingern J, *et al.*: **The overlap between miscarriage and extreme preterm birth in a limited-resource setting on the Thailand-Myanmar border: a population cohort study [version 1; peer review: 2 approved with reservations].** *Wellcome Open Res.* 2016; **1**: 32.
PubMed Abstract | Publisher Full Text | Free Full Text

33. Haataja L, McGready R, Arunjerdja R, *et al.*: **A new approach for neurological evaluation of infants in resource-poor settings.** *Ann Trop Paediatr.* 2002; **22**(4): 355–68.
PubMed Abstract | Publisher Full Text

34. Myint CY, Pavlova M, Groot W: **Catastrophic health care expenditure in Myanmar: policy implications in leading progress towards universal health coverage.** *Int J Equity Health.* 2019; **18**(1): 118.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Chansamouth V, Thammasack S, Phetsouvanh R, *et al.*: **The Aetiologies and Impact of Fever in Pregnant Inpatients in Vientiane, Laos.** *PLoS Negl Trop Dis.* 2016; **10**(4): e0004577.
PubMed Abstract | Publisher Full Text | Free Full Text

36. McGready R, Ashley EA, Wuthiekanun V, *et al.*: **Arthropod borne disease: the leading cause of fever in pregnancy on the Thai-Burmese border.** *PLoS Negl Trop Dis.* 2010; **4**(11): e888.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Giudice LC, Llamas-Clark EF, DeNicola N, *et al.*: **Climate change, women's health, and the role of obstetricians and gynecologists in leadership.** *Int J Gynaecol Obstet.* 2021; **155**(3): 345–356.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Rohwer AC, Oladapo OT, Hofmeyr GJ: **Strategies for optimising antenatal corticosteroid administration for women with anticipated preterm birth.** *Cochrane Database Syst Rev.* 2020; **5**(5): CD013633.
PubMed Abstract | Publisher Full Text | Free Full Text

39. World Health Organization: **WHO recommendations on: antenatal corticosteroids for improving preterm birth outcomes.** Geneva; 2022.
PubMed Abstract

40. Tayler A, Ashworth H, Bou Saba G, *et al.*: **Feasibility of a novel ultra-low-cost bubble CPAP (bCPAP) System for neonatal respiratory support at Muhimbili National Hospital, Tanzania.** *PLoS One.* 2022; **17**(12): e0269147.
PubMed Abstract | Publisher Full Text | Free Full Text

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✓ **Elizabeth Asztalos**
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada

This manuscript is version 2 of a previously reviewed manuscript. Reviewing the previous comments made by earlier reviewers, the authors have addressed all of the issues adequately.

The only comment I would like to make is that conclusions made based on the follow-up of a subset of the children need to viewed with caution and this should be stated as such in the limitation. Also, ongoing concerns about fetal exposure to antenatal steroids may not be evident at 12-14 months of age as some of the large population based studies have eluded to but that there were no significant challenges noted is reassuring. Consequently, the wording in the abstract on this issue should be rephrased to reflect this.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a neonatologist with a primary interest in neurodevelopment follow-up of NICU infants. I have done work related to antenatal corticosteroids

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 May 2024

https://doi.org/10.21956/wellcomeopenres.23481.r80809

Kathryn Maitland
Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme, Kilifi, Kenya

The authors have satisfactorily addressed the two other reviewers comments. Whilst I agree with both that a limitation of the work presented in the retrospective nature of the design, their findings align with the conclusions of a published Cochrane review on the subject. It is an important step in hypothesis generation in the case for support for a large Phase III trial.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Paediatrician, global health, clinical trials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 23 October 2023

https://doi.org/10.21956/wellcomeopenres.21484.r68134

Lamidi Isah Audu
[1] Department of Paediatrics, Kaduna State University, Kaduna, Nigeria
[2] Paediatrics, Federal University Health Sciences Azare, Azare, Bauchi, Nigeria

This manuscript addresses the impact of antenatal corticosteroid on early neonatal and neonatal mortality in a low resource setting and specifically where neonatal respiratory support beyond intranasal oxygen supplementation is not available. It is a retrospective analysis of available records on 240 preterm babies (GA 28-<34 weeks) out of which mothers of 144 received Dexamethasone (1,2 or 3 doses). The data collection and analysis are clearly and explicitly written. The findings suggest that only full-dose (12mg, 8hrly X 3) is associated with reduction in neonatal mortality.

The following observations noted would require further comments by the authors:

1. Mothers who received a full dose of Dexamethasone had significantly higher incidence of febrile illness. What was the impact of this on the mothers. This finding is not discussed,

2. Presence of congenital anomaly was a criterion for exclusion but the results show that babies with congenital anomalies were analysed and neonatal mortality was reportedly significantly higher in babies with congenital anomalies. This contradiction should be explained.

3. One of the stated study limitations was the inability to follow up all infants to 28 days, but this information was not stated in the body of the manuscript. it is important to know how many babies were followed up to 28 days as this will unequivocally define the denominator for the determination of the neonatal mortality rate.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a Neonatologist and a clinical research expert.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Mar 2024

Humayra Aisha Bashir

This manuscript addresses the impact of antenatal corticosteroid on early neonatal and neonatal mortality in a low resource setting and specifically where neonatal respiratory support beyond intranasal oxygen supplementation is not available. It is a retrospective analysis of available records on 240 preterm babies (GA 28-<34 weeks) out of which mothers of 144 received Dexamethasone (1,2 or 3 doses). The data collection and analysis are clearly and explicitly written. The findings suggest that only full-dose (12mg, 8hrly X 3) is associated with reduction in neonatal mortality. We thank the reviewer for their time and helpful suggestions. The following observations noted would require further comments by the authors:

1. Mothers who received a full dose of Dexamethasone had significantly higher incidence of febrile illness. What was the impact of this on the mothers. This finding is not discussed,

The section on maternal fever was reviewed with the data presented in a more logical format given the comments from reviewer 1 and 2. Please see the revised section on Maternal febrile morbidity; no significant difference.

1. Presence of congenital anomaly was a criterion for exclusion but the results show that babies with congenital anomalies were analysed and neonatal mortality was reportedly significantly higher in babies with congenital anomalies. This contradiction should be explained.

Thank you. We have clarified it and now stated instead ‘incidental detection of severe congenital anomaly’ under Exclusion criteria. Under the ultrasound section, we have also made it clearer that experienced sonographers can notice some congenital anomalies.

1. One of the stated study limitations was the inability to follow up all infants to 28 days, but this information was not stated in the body of the manuscript. it is important to know how many babies were followed up to 28 days as this will unequivocally define the denominator for the determination of the neonatal mortality rate.

Amended. In Table 2, the variable Neonatal Mortality is 69/168. We have stated that 168 infants were followed up for the first 28 days of life. We have also amended table 4 to that effect.

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 October 2023

https://doi.org/10.21956/wellcomeopenres.21484.r68132

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Rob Mooji
[1] OBS/GYN, Erasmus University Rotterdam, Rotterdam, South Holland, The Netherlands
[2] Ndala Hospital, Ndala, Tanzania

Dear authors,

Congratulations on this article.

The exact role of ACT in LMICs is still unclear and this article will help to determine in what settings ACT is beneficial.

The article is well written with a clear methodology.

My biggest concern about the article is that is a retrospective cohort study with inherent risk of (selection) bias and you present your results with a degree of certainty which is not supported by this design. So I would advise to formulate your conclusions with more uncertainty and note this in your limitations.

It is not uncommon in medical research that findings from cohort studies suggest an effect which cannot be confirmed in RCTs. And in this case a selection bias does not seem unlikely: in women with signs of infection doctors might have refrained from ACT. And maybe infected children were born too quick to start or complete ACT.

On the other hand there seems to be a dosing effect which supports your conclusion that ACT is effective in your setting. And as your setting resembles more the ACTION trial setting than the Althabe trial setting I would expect a positive effect. So your conclusion is probably right, but with this design you can't state it for certain. You can only conclude that these findings support a

positive effect in a setting which has a bit poorer resources than the ACTION trial.

Introduction

The first sentence is a bit confusing, I would add a comma and maybe repeat birth (preterm birth, birth before 37 weeks).

The 2nd sentence is also a bit confusing. 1 million of 15 preterm newborns die.

The third sentence I can't find any support for this statement in your references. Of course IRDS is important since it often cannot be treated or prevented (by ACT), but in really poor resource settings I will assume that hypothermia, feeding problems, hypoglycemia and infection are also important, maybe even more (depending on the gestational age). And I feel a lot attention goes to IRDS (and ACT) while more basic aspects of preterm newborn life support are neglected.

I think IRDS get's a lot of attention and is assumed to be important, but this is only the case of the level of care is at least enough to treat more simple problems like above.

3rd paragraph: why is via in italics?

In this paragraph I would make a bit more clear that the Althabe ACT trial was conducted mostly in health centres. In your discussion you rightly say that early ultrasound makes a big difference, but the difference in obstetric and neonatal care was very big in these 2 settings. In the Althabe trial, besides that the GA was unclear, also infection could often not be ruled out (by laboratory confirmation) and hypoglycemia and hypothermia were not measured, prevented or treated. The ACTION trial was done in LMICs, but the hospitals were much better equipped (I would say not representing 90% of LIC hospitals). So the challenge is to determine what care is essential to allow safety of ACT and it is probably somewhere in between. The WHO was a bit strict in their first prerequisites but this needs to be finetuned. In Tanzania they tried combining ACT with antibiotics, and showed some effect although this was also in a well-equipped teriary centre, so not clear if this would work in health centres as well.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0193146

Methods

Since the important thing of this article is to determine in which setting ACT is beneficial, you should be very specific about what is and is not possible.

Page 4: paragraph dexamethasone: did you indicate tocolytics when you suspected infection? What did you use to real this out?
Results

I don't fancy the word "birthed", but maybe that's my non-native English.

2nd paragraph: you refer to table 1 that 84,4% of women had ultrasound confirmed GA, bit I think this is Table 2.

In your discussion you state 84% is US confirmed and add that half is in the 1st trimester, but I

couldn't find this in your results section.

Maternal febrile mortality

I am a bit confused by the way you present this. Why bother with the febrile morbidity before the admission of dexamethasone. This should be with the baseline comparison (Table 1) to check if there is any bias (women with fever getting more of less often dexamthason). Febrile morbidity after dexamethasone is relevant, but why not simple state fever after dexamethasone vs after admission (in the non-dexamethasone group)

Discussion

You start by saying you work in a low resource setting. This is of course true, but exactly how low is a bit in the eye of the beholder and a lot of hospitals in LMICs have less resources.

Like I said before, with a retrospective design be careful to state your results like it is certain, for example when you say NNT of 5.

I fully agree with the paragraph that probably the most effective modality which can help in making hospitals ready to make safe use of ACT is a ultrasound (more than incubators, ventilators, etc.). You might want to add that in the Althabe trial there was a lot of incorrect use of ACT which diluted the positive effects and exposed more women to the risks. You could also add it is not only availability of the machine, but also affordability of the service, acceptability of the women to attend ANC early.

The paragraph about ACTION is also nice, and I agree with your idea that probably more children die when thermal care and feeding support are not available than if ventilators are not around. So this a nice thing your study gives information about.
Can you say something about the 2 outcomes: early and total neonatal death? I can imagine early neonatal death is more related to prematurity and total neonatal death includes more often other causes which explains why only early neonatal mortality is significant. Do you agree, or do you think another reason? It is a finding which is worth mentioning in this section. And why measure the 2 endpoints? Does it say anything about your neonatal care setting that the children who die later are in both groups?

Limitations

Here you really need to say something about the design (retrospective), but you can also say that the partial effect with an incomplete dose suggest your findings are not influenced by bias. And you can say that you think other factors in neonatal care are more relevant than airway support.

References

1. Massawe A, Kidanto HL, Moshiro R, Majaliwa E, et al.: A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country.*PLoS One*. 2018; **13** (3): e0193146 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: International maternal health and obstetrics, ACT

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Mar 2024

Humayra Aisha Bashir

Dear authors,

Congratulations on this article.

The exact role of ACT in LMICs is still unclear and this article will help to determine in what settings ACT is beneficial.

The article is well written with a clear methodology.

My biggest concern about the article is that is a retrospective cohort study with inherent risk of (selection) bias and you present your results with a degree of certainty which is not supported by this design. So I would advise to formulate your conclusions with more uncertainty and note this in your limitations.

We have amended the limitations and conclusion with more uncertainty.

It is not uncommon in medical research that findings from cohort studies suggest an effect which cannot be confirmed in RCTs. And in this case a selection bias does not seem unlikely: in women

with signs of infection doctors might have refrained from ACT. And maybe infected children were born too quick to start or complete ACT.
On the other hand there seems to be a dosing effect which supports your conclusion that ACT is effective in your setting. And as your setting resembles more the ACTION trial setting than the Althabe trial setting I would expect a positive effect. So your conclusion is probably right, but with this design you can't state it for certain. You can only conclude that these findings support a positive effect in a setting which has a bit poorer resources than the ACTION trial.

We appreciate these comments to define the setting and context better. They are a helpful perspective and we have tried to address the deficiencies in the first submitted version to better clarify the resources and how the setting compares with ACTION sites in the revised manuscript. See the last paragraph of 'Settings' and 'Neonatal intensive care' in the methods.

Introduction

The first sentence is a bit confusing, I would add a comma and maybe repeat birth (preterm birth, birth before 37 weeks).

Amended as suggested.

The 2nd sentence is also a bit confusing. 1 million of 15 preterm newborns die.

Amended as suggested.

The third sentence I can't find any support for this statement in your references.

Thank you for noting this. We have amended the sentence retaining reference 4 (and removed references 3 and 5).

Of course IRDS is important since it often cannot be treated or prevented (by ACT), but in really poor resource settings I will assume that hypothermia, feeding problems, hypoglycemia and infection are also important, maybe even more (depending on the gestational age). And I feel a lot attention goes to IRDS (and ACT) while more basic aspects of preterm newborn life support are neglected.
I think IRDS get's a lot of attention and is assumed to be important, but this is only the case of the level of care is at least enough to treat more simple problems like above.

Agreed and modified.

3rd paragraph: why is via in italics?

No reason, amended.

In this paragraph I would make a bit more clear that the Althabe ACT trial was conducted mostly in health centres. In your discussion you rightly say that early ultrasound makes a big difference, but the difference in obstetric and neonatal care was very big in these 2 settings. In the Althabe

trial, besides that the GA was unclear, also infection could often not be ruled out (by laboratory confirmation) and hypoglycemia and hypothermia were not measured, prevented or treated. The ACTION trial was done in LMICs, but the hospitals were much better equipped (I would say not representing 90% of LIC hospitals). So the challenge is to determine what care is essential to allow safety of ACT and it is probably somewhere in between. The WHO was a bit strict in their first prerequisites but this needs to be finetuned. In Tanzania they tried combining ACT with antibiotics, and showed some effect although this was also in a well-equipped teriary centre, so not clear if this would work in health centres as well.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0193146

We have amended the introduction and methods with the help of these comments (and added the reference into the introduction).

Methods

Since the important thing of this article is to determine in which setting ACT is beneficial, you should be very specific about what is and is not possible.

We have clarified the setting further in the methods.

Page 4: paragraph dexamethasone: did you indicate tocolytics when you suspected infection? What did you use to real this out?

We have amended the section on page 4 in the methods about tocolytics and investigation of maternal fever.

Results

I don't fancy the word "birthed", but maybe that's my non-native English.

And we have frequently received the opposite comment for delivered. One reviewer (not this manuscript) suggested that 'delivered' sounds more like getting a letter or a parcel. If the reviewer does not mind we prefer to continue with "birthed".

2nd paragraph: you refer to table 1 that 84,4% of women had ultrasound confirmed GA, bit I think this is Table 2.

Amended and thank you for pointing it out.

In your discussion you state 84% is US confirmed and add that half is in the 1st trimester, but I couldn't find this in your results section.

It is in the section here: "The median maternal age was 22 years, almost half (43.8%, 105/240) were primigravidae, 47.5% (114/240) attended first ANC visit in first trimester and most women had ultrasound confirmed gestation (84.4%, 204/244) (Table 2).

Maternal febrile mortality

I am a bit confused by the way you present this. Why bother with the febrile morbidity before the admission of dexamethasone. This should be with the baseline comparison (Table 1) to check if there is any bias (women with fever getting more of less often dexamethasone). Febrile morbidity after dexamethasone is relevant, but why not simple state fever after dexamethasone vs after admission (in the non-dexamethasone group)

We agree that the clarity of this section needs to improve. We have taken your suggestions to examine fever in the first 72 hours from birth. We have deleted Figure 5.

Discussion

You start by saying you work in a low resource setting. This is of course true, but exactly how low is a bit in the eye of the beholder and a lot of hospitals in LMICs have less resources.

Agree and we have amended the last paragraph of the "settings" in the methods and rephrased the discussion.

Like I said before, with a retrospective design be careful to state your results like it is certain, for example when you say NNT of 5.

Agree and we have amended the statement.

I fully agree with the paragraph that probably the most effective modality which can help in making hospitals ready to make safe use of ACT is a ultrasound (more than incubators, ventilators, etc.). You might want to add that in the Althabe trial there was a lot of incorrect use of ACT which diluted the positive effects and exposed more women to the risks. You could also add it is not only availability of the machine, but also affordability of the service, acceptability of the women to attend ANC early.

Agree and amended.

The paragraph about ACTION is also nice, and I agree with your idea that probably more children die when thermal care and feeding support are not available than if ventilators are not around. So this a nice thing your study gives information about.

Thank you.

Can you say something about the 2 outcomes: early and total neonatal death? I can imagine early neonatal death is more related to prematurity and total neonatal death includes more often other causes which explains why only early neonatal mortality is significant. Do you agree, or do you think another reason? It is a finding which is worth mentioning in this section. And why measure the 2 endpoints? Does it say anything about your neonatal care setting that the children who die later are in both groups?

Again we thank you for the care you have taken as a reviewer. In the first submission, we used all infants followed to day 7 for early neonatal death (n=233) and all followed to day 28

for neonatal death (n=168) – so we were not comparing the same population. Table 5 has been replaced so the denominator is the same i.e. infants followed to day 28. We were interested to understand if ACS helped survival in terms of acute RDS (Early NND) but infants just died later (NND) but this does not appear to be the case.

Limitations

Here you really need to say something about the design (retrospective), but you can also say that the partial effect with an incomplete dose suggest your findings are not influenced by bias. And you can say that you think other factors in neonatal care are more relevant than airway support.

Agree and amended.

Is the work clearly and accurately presented and does it cite the current literature? Yes Is the study design appropriate and is the work technically sound? Yes Are sufficient details of methods and analysis provided to allow replication by others? Yes If applicable, is the statistical analysis and its interpretation appropriate? Yes Are all the source data underlying the results available to ensure full reproducibility? Yes Are the conclusions drawn adequately supported by the results? Partly
References 1. Massawe A, Kidanto HL, Moshiro R, et al.: A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country. PLoS One. 2018; 13 (3): e0193146 PubMed Abstract | Publisher Full Text

Competing Interests: No competing interests were disclosed.