REFERENCES

1 Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;**70:**1–25.
2 Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. *Lancet* 2012;**380:**2197–223.
3 India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: The global burden of disease study 1990–2016. *Lancet Glob Health* 2018;**6:**e1339–51.
4 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;**326:**1419.
5 Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, *et al*. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: The UMPIRE randomized clinical trial. *JAMA* 2013;**310:**918–29.
6 Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, *et al*. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): A pragmatic, cluster-randomised trial. *Lancet* 2019;**394:**672–83.
7 Roy A, Naik N, Srinath Reddy K. Strengths and limitations of using the polypill in cardiovascular prevention. *Curr Cardiol Rep* 2017;**19:**45.
8 Grodzinsky A, Arnold SV, Jacob D, Draznin B, Kosiborod M. The impact of cardio-vascular drugs on glycemic control: A review. *Endocr Pract* 2017;**23:**363–71.
9 Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; **109:**1101–7.

SATYAVIR YADAV
AMBUJ ROY
Department of Cardiology
All India Institute of Medical Sciences
New Delhi
India
drambujroy@gmail.com

Antenatal dexamethasone for early preterm birth in low-resource countries

Oladapo OT, Vogel JP, Piaggio G, Nguyen M-H, Althabe F, Gülmezoglu AM, Bahl R, Rao SPN, De Costa A, Gupta S, Baqui AH, Khanam R, Shahidullah M, Chowdhury SB, Ahmed S, Begum N, Roy AD, Shahed MA, Jaben IA, Yasmin F, Rahman MM, Ara A, Khatoon S, Ara G, Akter S, Akhter N, Dey PR, Sabur MA, Azad MT, Choudhury SF, Matin MA, Goudar SS, Dhaded SM, Metgud MC, Pujar YV, Somannavar MS, Vernekar SS, Herekar VR, Bidri SR, Mathapati SS, Patil PG, Patil MM, Gudadinni MR, Bijapure HR, Mallapur AA, Katageri GM, Chikkamath SB, Yelamali BC, Pol RR, Misra SS, Das L, Nanda S, Nayak RB, Singh B, Qureshi Z, Were F, Osoti A, Gwako G, Laving A, Kinuthia J, Mohamed H, Aliyan N, Barassa A, Kibaru E, Mbuga M, Thuranira L, Githua NJ, Lusweti B, Ayede AI, Falade AG, Adesina OA, Agunloye AM, Iyiola OO, Sanni W, Ejinkeonye IK, Idris HA, Okoli V, Irinyenikan TA, Olubosede OA, Bello O, Omololu OM, Olutekunbi OA, Akintan AL, Owa OO, Oluwafemi RO, Eniowo IP, Fabamwo AO, Disu EA, Agbara JO, Adejuyigbe EA, Kuti O, Anyabolu HC, Awowole IO, Fehintola AO, Kuti BP, Isah AD, Olateju EK, Abiodun O, Dedeke OF, Akinkunmi FB, Oyeneyin L, Adesiyun O, Raji HO, Ande ABA, Okonkwo I, Ariff S, Soofi SB, Sheikh L, Zulfiqar S, Omer S, Sikandar R, Sheikh S, Giordano D, Gamerro H, Carroli G, Carvalho J, Neilson J, Molyneux E, Yunis K, Mugerwa K, Chellani HK. (Department of Maternal, Newborn, Child, Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland; Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; Bangabandhu Sheikh Mujib Medical University, Projahnmo Research Foundation, Institute of Child and Mother Health, Center for Woman and Child Health, and Enam Medical College and Hospital, Dhaka, and Sylhet Muhammad Ataul Gani Osmani Medical College Hospital, Jalalabad Ragib–Rabeya Medical College Hospital, and Sylhet Women's Medical College Hospital, Sylhet—both in Bangladesh; KLE Academy of Higher Education and Research, Jawaharlal Nehru Medical College, Belagavi, Shri B.M. Patil Medical College, Vijayapura, S. Nijalingappa Medical College, Bagalkot, Srirama Chandra Bhanja Medical College, Cuttack, and Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi—all in India; University of Nairobi and Kenyatta National Hospital, Nairobi, Coast Provincial General Hospital, Mombasa, Nakuru Level 5 Hospital, Nakuru, Kiambu Level 5 Hospital, Kiambu, and Thika Level 5 Hospital, Thika—all in Kenya; the College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Kubwa General Hospital, Kubwa, Nyanya General Hospital, Nyanya, State Specialist Hospital and Mother and Child Hospital, Akure, Lagos Island Maternity Hospital, and Lagos State University Teaching Hospital, Lagos, Obafemi Awolowo University, Ile-Ife, University of Abuja, Abuja, Sacred Heart Hospital, Abeokuta, Mother and Child Hospital, Ondo, University of Ilorin, Ilorin, and University of Benin, Benin City—all in Nigeria; Aga Khan University, Karachi, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, and Liaquat University Hospital, Hyderabad—all in Pakistan; Centro Rosarino de Estudios Perinatales, Rosario, Argentina; Statistika Consultoria, Campinas, Brazil; University of Liverpool, Liverpool, United Kingdom; College of Medicine, University of Malawi, Blantyre; American University of Beirut, Beirut, Lebanon; and the Makerere University College of Health Sciences, Kampala, Uganda.) Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med* 2020;**383:**2514–25.

SUMMARY

The WHO Antenatal Corticosteroids for Improving Outcomes in preterm Newborns (ACTION-I) trial is a randomized study that investigated the safety and efficacy of antenatal steroid, dexamethasone, among women at risk of preterm birth in low- and middle-income countries (LMICs). A total of 2852 women between 26 weeks 0 days and 33 weeks 6 days of gestation from 29 secondary- and tertiary-level hospitals across five LMICs—Bangladesh, India, Kenya, Nigeria and Pakistan—were randomized to receive intramuscular dexamethasone at a dose of 6 mg every 12 hours for four doses or an identical placebo if preterm birth was expected in the next 48 hours. Eligible women were assessed by obstetric care providers and gestational age was confirmed using ultrasonographic examination performed in early gestation or at presentation. Women with clinical signs of severe infection, major congenital foetal anomalies and those with previous use or contraindication to systemic glucocorticoids were excluded from the study. One repeat course (identical to initial

assignment) was permitted if women had not given birth after 7 completed days but still met the inclusion criteria. The participants, physicians and investigators were blinded to the study assignment and mother–infant dyads were followed up until 28 days after delivery or until death, whichever was earlier.

The three primary outcomes of the study were neonatal death, stillbirth or neonatal death and possible maternal bacterial infection. The trial was terminated after the second interim analysis showed significant perinatal and neonatal mortality benefits in the dexamethasone arm and keeping in mind the existing evidence in favour of antenatal steroids. About half of all women in both arms received four doses of dexamethasone or placebo, and 90% delivered before 37 weeks of gestation. The risk of neonatal death was lower in the dexamethasone arm (19.6% *v.* 23.5%; relative risk 0.84; 95% CI 0.72–0.97; p=0.03). The combined outcome of stillbirth or neonatal death was also lower and the incidence of maternal bacterial infection had not increased in the dexamethasone arm. Among the various pre-specified secondary analyses, the incidence of early neonatal death, severe respiratory distress at 24 hours of birth, neonatal hypoglycaemia at 6 hours after birth, need for major resuscitation at birth, the use of continuous positive airway pressure (CPAP) and the duration of oxygen therapy were lower among neonates exposed to antenatal dexamethasone.

COMMENT

Antenatal corticosteroids (ACS) are considered a magic bullet to decrease neonatal mortality and morbidity among preterm infants. However, the Antenatal Corticosteroids Trial (ACT, cluster randomized trial)[1] done in the community settings of LMICs challenged this and created a controversy when the trial results revealed a 12% increase in neonatal mortality among all live-born infants, 11% increase in stillbirth rates and higher odds of maternal infection in the intervention clusters. This was in sharp contrast to the results of the earlier trials that enrolled a total of 7774 women and 8158 infants and included in the Cochrane systematic review.[2] The ACTION-I trial was designed to address the knowledge gap created by the uncertainty of whether ACS use is effective and safe in LMICs.[3]

Before delving into the implications of the ACTION-I study results, a brief understanding of the characteristics of earlier trials and the ACT is mandatory. The Cochrane review[2] included 30 trials, mostly conducted in hospital settings of high-income countries (HICs) except six trials from five LMICs (Brazil, Colombia, Jordan, South Africa and Tunisia). Betamethasone was used in 21 trials. Dexamethasone, the preparation that is cheaper, is easily available and does not require refrigeration for storage, was used only in seven trials. While a majority of the trials were conducted before 2000, nine trials contributed to 50% of the data and strengthened the evidence that ACS reduces the risk of perinatal death, neonatal death and morbidities such as respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, need for respiratory support and intensive care admission, even with advances in neonatal care.

Despite the benefits of ACS, its uptake across LMICs for at-risk women has been uniformly poor (10%) compared to 90% coverage in HICs.[4,5] The ACT in 2015 was designed to investigate the feasibility, effectiveness and safety of implementing the use of ACS in LMIC settings.[1] It was a community-based, cluster-randomized trial done in 101 rural and semi-urban clusters in six countries. Birth attendants in health facilities (clinics, primary health centres as well as hospitals) in intervention clusters were trained to identify at-risk women, and to assess gestational age with the help of pregnancy discs based on the date of last menstrual period or by measuring uterine height using a colour-coded tape. They were also trained to administer dexamethasone injection using ready-to-use preterm kits. In the intervention clusters, 80% of women identified to be at risk of preterm delivery received the first dose of dexamethasone in the community or at the primary health centre. Since the gestational age could not be accurately assessed, birth weight less than the 5th percentile was used as a proxy for preterm births. The use of ACS increased from 10% to 45% in the intervention clusters for women with a less-than-5th-percentile infant. The increased neonatal mortality especially among newborns with greater weight centile, more stillbirths and maternal infections in the intervention clusters in the ACT was unanticipated.

Experts cautioned physicians and policy-makers that large-scale implementation of ACS at all levels of healthcare in LMIC settings may be harmful.[6] In this trial, only 16% of the women who received ACS ultimately gave birth to a less-than-5th-percentile newborn, implying substantial overdiagnosis of imminent preterm birth and overtreatment. While the lack of accurate gestational age assessment, lack of trained obstetric providers and sub-optimal health facilities in the community settings are possible reasons for the poor outcome,[6] other epidemiological factors (overall higher risk of malnutrition, susceptibility to sepsis and microbiological factors) could have contributed too.

In 2015, the WHO recommended that ACS be offered to women between 24 and 34 weeks of gestation only if certain criteria are met including imminent preterm birth within 1–7 days, accurate assessment of gestational age, no evidence of maternal infection and facilities for maternal and newborn care are available.[7] Thus, the WHO ACTION trials were designed; ACTION-I (testing ACS use among those with <34 weeks' gestation) and ACTION-II (among late preterm births; 34–36 weeks). It also addressed the limitations of earlier trials through accurate assessment of gestational age using ultrasonographic examination and assessment of at-risk women by obstetricians. This ensured appropriate selection of subjects, leading to treatment being received only by those who needed it. The trial sites were selected after a standardized assessment of maternal and neonatal services in the facility. Clinical training and access to oxygen, pulse oximetry and CPAP equipment were provided.

The ACTION-I trial is also the largest placebo-controlled trial on ACS to be conducted in a low-resource setting that used dexamethasone, and more than 90% of those exposed to ACS delivered preterm infants in contrast to just 16% in the ACT trial who delivered a less-than-5th-percentile newborn. The follow-up of mother–infant dyads in the ACTION-1 trial was continued in the community and the follow-up rate was 99%. The trial was more inclusive and enrolled women with multiple pregnancies, previous preterm birth and comorbid conditions such as hypertensive disorders, growth-restricted foetus and diabetes. The study had great methodological rigor and low risk of bias for all key criteria and the data safety monitoring board terminated the study timely when the benefit of ACS was clear.

The trial had a few limitations: the investigators used ultrasonography for accurate dating of gestation age, however two-thirds of the women had ultrasonography done in the third trimester when accuracy could vary by 14 days or more. All the participating sites reasonably met the minimum standards for facility readiness, but maternal and neonatal care and availability of surfactant varied across sites.

In summary, the ACTION -I trial results reaffirm the beneficial

effects of ACS in reducing perinatal and neonatal mortality without any adverse maternal effects in low-resource hospital settings. For policy-makers, the trial results inform that appropriate identification of at-risk women and a minimum standard of healthcare facilities is essential before scaling up implementation of ACS. For LMICs aiming to reduce neonatal mortality below 12/1000 live births to achieve Sustainable Development Goal-3 by 2030, the ACTION trial results give hope with an impact of saving 140 000–200 000 neonatal deaths annually, if ACS coverage is 100%.

Conflicts of interest. None declared

REFERENCES

1 Althabe F, Belizan JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, *et al.* A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: The ACT cluster-randomised trial. *Lancet* 2015;**385:**629–39.

2 Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017;**3:**CD004454.

3 McClure EM, Goldenberg RL, Jobe AH, Miodovnik M, Koso-Thomas M, Buekens P, *et al.* Reducing neonatal mortality associated with preterm birth: Gaps in knowledge of the impact of antenatal corticosteroids on preterm birth outcomes in low-middle income countries. *Reprod Health* 2016;**13:**61.

4 McClure EM, de Graft-Johnson J, Jobe AH, Wall S, Koblinsky M, Moran A, *et al.* A conference report on prenatal corticosteroid use in low- and middle-income countries. *Int J Gynaecol Obstet* 2011;**115:**215–19.

5 Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, *et al.* Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;**126:**443–56.

6 Azad K, Costello A. Extreme caution is needed before scale-up of antenatal corticosteroids to reduce preterm deaths in low-income settings. *Lancet Glob Health* 2014;**2:**e191–2.

7 World Health Organization. WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization; 2015. Available from: *https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/pregnancy-complications/preterm-birth/who-recommendation-antenatal-corticosteroid-therapy-women-risk-preterm-birth-24-weeks-34-weeks* (accessed on 24 Nov 2020).

SINDHU SIVANANDAN
Department of Neonatology
Jawaharlal Institute of Postgraduate Medical Education and Research
Puducherry
India

ASHOK DEORARI
Department of Paediatrics
WHO Collaborating Centre for Training and Research in Newborn Care
All India Institute of Medical Sciences
New Delhi
India
ashokdeorari_56@hotmail.com