

The association between antenatal corticosteroid use in late-preterm and early-term pregnancy and nonreassuring fetal status

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This study aimed to compare perinatal outcomes, including nonreassuring fetal status, according to antenatal corticosteroid therapy (ACT) use during late-preterm and early-term pregnancies. This was a retrospective cohort study of women with singleton pregnancies who were at risk of late-preterm (34-36⁺⁶ weeks) birth or early-term (37-38⁺⁶ weeks) scheduled cesarean section from August 2017-July 2019. ACT was administered until June 2018, after which a policy was implemented such that ACT was not used for pregnant women in the above circumstances. Women were grouped based on whether they delivered before or after the policy change and were subdivided into late-preterm birth and early-term scheduled cesarean section groups to reduce variations in newborn outcomes. Multivariable logistic regression was used to determine whether the use of antenatal corticosteroids increased the odds of perinatal outcomes. In total, 216 women (215 neonates, 1 stillborn) were included. In the late-preterm delivery group, the rate of nonreassuring fetal status was significantly higher in the antenatal corticosteroid group than in the non-corticosteroid group (33.3% vs 12.0%, $P = 0.017$). In the early-term delivery group, the rate was non-significantly higher in the antenatal corticosteroid use group (19.0% vs 6.3%, $P = 0.091$). In the multivariable logistic regression, ACT was associated with an increased risk of nonreassuring fetal status ($P = 0.025$) and a reduced incidence of transient tachypnea of the newborn (TTN) ($P = 0.011$). We determined for the first time that ACT in late-preterm and early-term pregnancy is associated with nonreassuring fetal status. Here, ACT in late-preterm and early-term pregnancy had no benefit beyond decreasing the TTN rate.

Keywords

Antenatal corticosteroid; Late-preterm pregnancy; Early-term pregnancy; Nonreassuring fetal status; Transient tachypnea of the newborn

1. Introduction

Since its first description by Liggins and Howie in 1972 [1], antenatal corticosteroid therapy (ACT) in pregnant women at risk of preterm birth has been an important and standard obstetric intervention to reduce neonatal mortality and morbidity, especially respiratory complications. Re-

cently, ACT has been reported to significantly reduce the neonatal respiratory morbidity rate even among those at high risk of late-preterm birth, who are between 34 + 0/7 weeks and 36 + 6/7 weeks of gestation [2]. Accordingly, the American College of Obstetricians and Gynecologists (ACOG) recommends ACT for women with imminent late-preterm birth after 34 weeks of gestation as well as imminent preterm birth before 34 weeks of gestation [3]. Selective cesarean section is also considered an important cause of neonatal respiratory morbidity. In particular, the risk of respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN) increases at the time of elective cesarean section before 39 weeks. The Royal College of Obstetricians and Gynecologists recommends that all women planning to undergo elective cesarean delivery before 39 weeks of gestation be given antenatal corticosteroids [4].

However, whether the benefits of the use of standardized ACT in late-preterm or early-term pregnancy outweigh the side effects remains unknown. A high incidence of hypoglycemia has been reported in neonates whose mothers received ACT [2], and an association between ACT and reduced fetal thymic growth has also been reported [5]. Studies on the long-term effects of exposure to antenatal corticosteroid use are lacking. In addition, there is a lack of discriminatory results on the role of antenatal corticosteroids in special populations, such as women with diabetes or multiple pregnancies.

It has been reported that the administration of antenatal corticosteroids is associated with temporal suppression of indicators of fetal wellbeing, including fetal heart rate acceleration, heart rate variability, breathing and response to vibroacoustic stimulation [6, 7]. There is concern that antenatal corticosteroid use may lead to a misdiagnosis of fetal distress and the unnecessary delivery of premature neonates. However, to the best of our knowledge, there have been no studies on differences in perinatal outcomes, including indicators

for evaluating fetal wellbeing, other than neonatal respiratory morbidity according to antenatal corticosteroid use in late-preterm and early-term pregnancy.

At the study institution, antenatal corticosteroids were administered to women at risk of late-preterm birth or who were planning to undergo early-term scheduled cesarean section without labor. One case of intrauterine fetal death occurred after two doses of betamethasone in a woman who had no underlying disease or other obstetric risk factors and was admitted for the administration of antenatal corticosteroids in early-term pregnancy, with the intent to undergo scheduled cesarean section. Based on that experience, our institution changed its policy to not use ACT in cases of late-preterm birth or of women who were planning to undergo early-term scheduled cesarean sections without labor.

The purpose of this study was to investigate differences in perinatal outcomes according to the use of antenatal corticosteroids in late-preterm and early-term pregnancy.

2. Materials and methods

This was a retrospective cohort study of women with singleton pregnancies who were at risk of late-preterm ($34-36^{+6}$ weeks) birth or early-term ($37-38^{+6}$ weeks) cesarean section without labor signs, and the study was conducted at Gyeongsang National University Changwon Hospital, Changwon, Gyeongsangnam-do, Korea, from August 2017 to July 2019.

During the study period, betamethasone was administered to the cohort of women until June 2018. The women received the contents of the two syringes intramuscularly 24 hours apart, each containing betamethasone 12 mg (as betamethasone sodium phosphate 15.7 mg). Since June 2018, a policy not to use betamethasone has been implemented for pregnant women in the above situation.

Women at risk for late-preterm delivery who were at $34 + 0/7$ weeks to $36 + 6/7$ weeks of gestation were enrolled. The risk for late-preterm delivery included preterm labor with cervical change, preterm premature rupture of membranes, or maternal-fetal indications that require preterm delivery (maternal: hypertensive disorder, placenta previa bleeding, and maternal underlying diseases; fetal: oligohydramnios). Women with early-term scheduled cesarean section, birth between $37^{+0/7}$ weeks to $38^{+6/7}$ weeks of gestation, placenta previa, a history of cesarean section or myomectomy and maternal request were also enrolled. Women with fetuses with major fetal malformations or with severe intrauterine growth retardation (estimated fetal weight < 3 rd percentile) were excluded from the cohort.

Maternal charts were reviewed, and the following data were collected: maternal age, height, time of steroid administration, gestational age at delivery, method of delivery, diabetes, reasons for late-preterm birth or early-term scheduled cesarean birth, and antepartum complications, including nonreassuring fetal status on cardiotocography (CTG) and meconium staining. Nonreassuring fetal status was based

on abnormal fetal heart rate tracing. Fetal heart monitoring was carried out, and tracings were classified as normal, suspicious, or pathologic, according to 1) the presence, type, and length of decelerations, 2) the presence of bradycardia, and 3) the assessment of variability, as reported by the International Federation of Gynecology and Obstetrics (FIGO) in 2015 [8]. According to this criterion, pathological patterns were either baseline heart rate below 100 bpm or reduced variability; increased variability; sinusoidal pattern or repetitive late or prolonged decelerations during > 30 min or 20 min if reduced variability; or one prolonged deceleration with > 5 min. In cases with pathologic pattern, two attending physicians who were experienced obstetricians were consulted to determine nonreassuring fetal status.

Neonatal charts were linked to maternal charts. Neonatal charts were reviewed for the following data: birth weight, one-minute and five-minute Apgar scores, umbilical artery pH, blood glucose concentration within the first 24 hours of life, neonatal hypoglycemia (< 50 mg/dL), neonatal intensive care unit (NICU) admission, hospital days and neonatal morbidity, including TTN, RDS, meconium aspiration syndrome (MAS) and the use of surfactants. TTN was defined as the presence of tachypnea within 6 hours after birth; RDS was defined per the presence of clinical signs, such as grunting, flaring, tachypnea, retractions, requirement for respiratory support (supplemental oxygen requirement and/or non-invasive or invasive ventilation) and admission to a neonatal intensive care unit (NICU) for respiratory support. Typical radiological findings of respiratory distress (radiological features and required oxygen therapy) were reticulogranular patterns, air bronchograms and ground glass appearance. MAS was defined as the presence of meconium below the vocal cords, suggesting previous aspiration.

The primary outcome was to compare the differences in perinatal outcomes according to ACT use, namely, nonreassuring fetal status, NICU admission, and the presence of TTN. Furthermore, the outcomes of the newborns were suspected to be influenced by the number of gestational weeks, so the outcomes were stratified by late-preterm and early-term birth. In addition, in the clinical situation, factors affecting nonreassuring fetal status were identified to further explore the circumstances in which predelivery attention should be paid for favorable newborn outcomes.

The included women were grouped for analysis according to whether they delivered before or after the antenatal corticosteroid use policy change that occurred in June 2018. Differences in maternal characteristics and neonatal outcomes were compared according to the use of antenatal corticosteroids and late-preterm or early-term birth. In the statistical analysis, the chi-squared test or Fisher's exact test was used for categorical variables, and Student's *t*-test or the Wilcoxon rank-sum test was used for continuous variables. To evaluate the associations between perinatal outcomes and the use of ACT, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. A logistic regression

model with Firth's penalized likelihood approach was carried out to identify the mutually adjusted effects among outcomes and the independent variables chosen on the basis of statistical significance (univariate analysis, P -value < 0.05); maternal age, BMI, gestational age at delivery, oligohydramnios, preterm labor, and preterm premature rupture of membranes were used as adjusting variables. A P -value ≤ 0.05 was considered significant. Univariate and multivariable logistic regression analyses were conducted to determine the independent prognostic factors for nonreassuring fetal status. Factors identified in the univariate analysis as associated with nonreassuring fetal status at a level less than 0.2 were included in this stepwise procedure. Statistical significance was defined as a P -value < 0.05 . Statistical analyses were performed using SAS (Ver. 9.4, SAS Institute, Cary, NC, USA).

The study protocol was approved by the Institutional Review Board (IRB) of Gyeongsang National University Changwon Hospital, and the requirement for informed consent was waived (serial number: GNUCH 2020-07-017). All methods were performed in accordance with the relevant guidelines and regulations of the institution.

3. Results

A total of 216 women (215 with live newborns, 1 with a stillbirth) were included in the study. In our hospital, the policy for ACT was changed in June 2018; 103 women (47%) were included before the discontinuation of ACT and 113 women (53%) were included after the discontinuation of ACT. The mean gestational age was 36.7 (± 1.2) weeks. There were 110 cases of late-preterm birth and 106 cases of early-term birth. In the late-preterm birth group, suspected fetal distress rates were high in the antenatal corticosteroid group (33.3% vs 12.0%, $P = 0.017$). Among the early-term birth groups, birth weights were slightly lower in the antenatal corticosteroid group than in the nonantenatal corticosteroid group (2875.7 ± 348.0 g vs 3087.9 ± 394.7 g, $P = 0.006$). However, there were no significant differences among the groups according to the presence or absence of ACT in the NICU admission rate, length of hospital stay, presence of hypoglycemia or neonatal morbidity rate (Table 1).

The overall outcomes are shown in Table 2. After multivariable logistic regression, exposure to antenatal corticosteroids was associated with an increased risk of nonreassuring fetal status (adjusted OR 2.61, 95% CI 1.13-6.04) and a reduced incidence of TTN (adjusted OR 0.36, 95% CI 0.16-0.79). Antenatal corticosteroids were not associated with the need for NICU admission (adjusted OR 1.02, 95% CI 0.45-2.30).

We performed a categorized analysis to detect any differences in the effect of corticosteroid use according to gestational age at delivery. The results are depicted in Table 3. In the late-preterm birth group, exposure to antenatal corticosteroids was associated with an increased risk of nonreassuring fetal status (adjusted OR 3.29, 95% CI 1.20-8.99),

but there was no significantly increased risk in the early-term birth group. In a categorized analysis to detect differences in antenatal corticosteroid effects by gestational age at delivery, ACT did not significantly reduce the incidence of TTN (adjusted OR 0.15, 95% CI 0.01-2.75) or the need for NICU admission.

Factors found to affect nonreassuring fetal status in the logistic multivariate analysis were the presence of preeclampsia (adjusted OR 4.72, 95% CI 1.22-18.33), oligohydramnios (adjusted OR 3.90, 95% CI 1.74-8.75) and ACT (adjusted OR 2.96, 95% CI 1.29-6.79), as shown in Fig. 1.

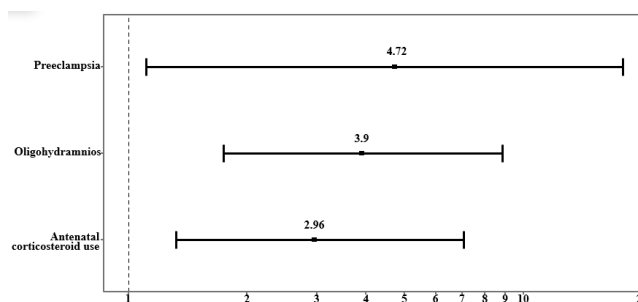


Fig. 1. Plot of odds ratios of factors associated with nonreassuring fetal status. Factors found to affect the nonreassuring fetal status in the multivariate stepwise backward logistic regression model were preeclampsia, oligohydramnios and antenatal corticosteroid use. The increased odds of the presence of nonreassuring fetal status were significantly associated with preeclampsia (adjusted OR 4.72, 95% CI 1.22-18.33), oligohydramnios (adjusted OR 3.90, 95% CI 1.74-8.75) and ACT (adjusted OR 2.96, 95% CI 1.29-6.79).

4. Discussion

In this study, ACT in late-preterm and early-term pregnancy was associated with an increased risk of perinatal nonreassuring fetal status and a decreased prevalence of TTN in neonates. A decreased prevalence of TTN in neonates after antenatal corticosteroid use has already been demonstrated in a large randomized controlled trial [2]. However, to the best of our knowledge, this is the first study on the relationship between the use of antenatal corticosteroids in late-preterm or early-term pregnancy and negative perinatal outcomes, such as nonreassuring fetal status. Furthermore, our study suggests that in addition to antenatal corticosteroid use, the presence of preeclampsia and oligohydramnios also increases the risk of nonreassuring fetal status. There is a common consensus that preeclampsia and oligohydramnios are associated with perinatal morbidity [9]. Therefore, antenatal corticosteroid administration in the presence of preeclampsia and oligohydramnios should be decided cautiously, and additional attention should be given to interpreting reassuring signs of fetal wellbeing.

In our study, there was a statistically significant difference in the rate of TTN between the group treated with antenatal corticosteroids and the control group. This is in accor-

Table 1. Demographic, obstetric and neonatal characteristics.

Gestational age at delivery (weeks)	Late preterm			Early term		
	Steroids (N = 60)	No steroids (N = 50)	P	Steroids (N = 43)	No steroids (N = 63)	P
Antenatal corticosteroid						
Maternal age (years)	32.6 ± 5.2	33.6 ± 4.3	0.260	34.6 ± 3.6	34.4 ± 4.4	0.874
Height (cm)	161.7 ± 4.5	160.6 ± 5.0	0.234	161.5 ± 4.8	160.7 ± 4.5	0.406
BMI (kg/m ²)	24.9 ± 4.7	28.7 ± 5.3	< 0.001	22.4 ± 4.1	26.9 ± 3.9	< 0.001
Normal weight (18.5-24.9)	35 (58.3%)	15 (30.0%)	0.005	35 (83.3%)	20 (31.7%)	< 0.001
Overweight (25.0-29.9)	16 (26.7%)	16 (32.0%)		6 (14.3%)	31 (49.2%)	
Obese (≥ 30 kg/m ²)	9 (15.0%)	19 (38.0%)		1 (2.4%)	12 (19.0%)	
Gestational diabetes	7 (11.7%)	14 (28.0%)	0.054	9 (20.9%)	5 (7.9%)	0.099
Gestational age at delivery (weeks)	35.6 ± 0.8	35.9 ± 0.7	0.113	37.5 ± 0.5	37.9 ± 0.5	< 0.001
Major indication for antenatal corticosteroids						
Scheduled cesarean delivery	4 (6.7%)	4 (8.0%)	1.000	43 (100%)	63 (100.0%)	
Placenta previa	4 (6.7%)	3 (6.0%)	1.000	8 (18.6%)	1 (1.6%)	0.006
Preeclampsia	3 (5.0%)	7 (14.0%)	0.193	2 (4.7%)	0 (0.0%)	0.317
Oligohydramnios	22 (36.7%)	14 (28.0%)	0.447	16 (37.2%)	0 (0.0%)	< 0.001
Preterm labor	22 (36.7%)	12 (24.0%)	0.221	0 (0.0%)	0 (0.0%)	
Preterm PROM	8 (13.3%)	13 (26.0%)	0.150	1 (2.3%)	0 (0.0%)	0.847
Perinatal events						
Nonreassuring fetal status	20 (33.3%)	6 (12.0%)	0.017	8 (19.0%)	4 (6.3%)	0.091
Meconium stained AF	1 (1.7%)	0 (0.0%)	1.000	1 (1.7%)	0 (0.0%)	0.704
Stillbirth	0 (0.0%)	0 (0.0%)		1 (2.3%)	0 (0.0%)	0.847
Neonatal outcome						
pHUA	7.3 ± 0.1	7.3 ± 0.1	0.675	7.3 ± 0.1	7.3 ± 0.1	0.093
Birth weight (g)	2623.4 ± 67.2	2681.8 ± 67.6	0.516	2875.7 ± 348.0	3087.9 ± 394.7	0.006
NICU admission	41 (68.3%)	33 (66.0%)	0.956	8 (19.0%)	13 (20.6%)	1.000
Duration of admission (days)	7.7 ± 8.4	8.2 ± 7.4	0.728	2.6 ± 7.0	1.4 ± 3.6	0.325
Glucose	72.6 ± 15.0	72.6 ± 18.4	0.995	70.9 ± 17.5	68.3 ± 8.9	0.395
Hypoglycemia (< 50 mg/dL)	3 (5.3%)	2 (4.0%)	1.000	2 (5.4%)	1 (1.8%)	0.725
Respiratory distress syndrome	5 (8.3%)	1 (2.0%)	0.301	1 (2.4%)	0 (0.0%)	0.837
Transient tachypnea of the newborn	19 (31.7%)	21 (42.0%)	0.356	0 (0.0%)	7 (11.1%)	0.066
Meconium aspiration syndrome	0 (0.0%)	0 (0.0%)		1 (2.4%)	0 (0.0%)	0.837
Surfactant use	5 (8.3%)	2 (4.0%)	0.593	1 (2.4%)	1 (1.6%)	1.000
Apgar score at 1 min	6.9 ± 1.3	6.8 ± 1.5	0.779	7.3 ± 0.9	7.5 ± 0.9	0.112
Apgar score at 5 min	8.2 ± 0.9	8.1 ± 1.1	0.729	8.4 ± 0.6	8.7 ± 0.7	0.008

Data are shown as the mean ± SD or n (%). SE, standard error.

dance with a study published by Gyamfi-Bannerman *et al.* [2]. When the incidence rate of TTN was divided by 37 weeks of gestation to reduce the differences in neonatal outcomes according to variations in gestational age, there was no significant reduction in either group. Porto *et al.* [10] also found that antenatal corticosteroid use did not reduce respiratory morbidity among late-preterm newborns. Furthermore, in our study, the use of antenatal corticosteroids was not associated with NICU admission rates, and neonatal prognoses, such as Apgar scores, did not differ between the antenatal corticosteroid groups.

In our study, the birth weight of newborns was lower in the steroid group than in the nonsteroid group (2875 ± 348.0 vs 3087.9 ± 394.7 g; $P = 0.006$) among early-term births. Additionally, the incidence of oligohydramnios was overwhelmingly high in the steroid group (37.2% vs 0.0%, $P \leq 0.001$). Our finding is consistent with medical interventions that increased oligohydramnios and/or fetal growth restric-

tion. However, since the birth weight of the fetus is influenced by multiple factors and because it is also necessary to consider the association with maternal weight in some cases (maternal BMI 22.4 ± 4.1 vs 26.9 ± 3.9; $P \leq 0.001$), further studies on the relationship between steroid use and fetal weight should be conducted.

Our finding is consistent with a recent population cohort study that showed that neonates who were exposed to antenatal corticosteroids were smaller in size at birth than unexposed neonates [11]. In addition, the study reported an increased rate of medical interventions in neonates exposed to antenatal corticosteroids. The growth and wellbeing of the fetus is multifactorial, and the degree to which antenatal corticosteroid use affects the fetus is unknown. However, these findings should be considered when administering antenatal corticosteroids in clinical practice.

Mouse studies have suggested that exogenous steroids may have different effects, particularly with regard to brain

Table 2. Overall perinatal outcomes according to maternal use of antenatal corticosteroids.

Variable	Steroids (n = 102)	No steroids (n = 113)	Adjusted ^a OR (95% CI)	P
Nonreassuring fetal status	28 (73.7%)	10 (26.3%)	2.61 (1.13-6.04)	0.025
NICU admission	49 (51.6%)	46 (48.4%)	1.02 (0.45-2.30)	0.965
Transient tachypnea of the newborn	19 (40.4%)	28 (59.6%)	0.36 (0.16-0.79)	0.011

CI, confidence interval; NICU, neonatal intensive care unit. ^a Adjustments for maternal age, BMI, gestational age at delivery, oligohydramnios, preterm labor, and preterm premature rupture of membranes.

Table 3. Categorized analysis: Perinatal outcomes according to gestational age and antenatal corticosteroid exposure.

Gestational age at delivery (weeks)	Late preterm		Early term	
	Adjusted ^a OR (95% CI)	P	Adjusted ^a OR (95% CI)	P
Nonreassuring fetal status	3.29 (1.20-8.99)	0.017	1.86 (0.40-8.61)	0.185
NICU admission	1.53 (0.62-3.76)	0.332	1.53 (0.62-3.76)	0.424
Transient tachypnea of the newborn	0.55 (0.24-1.27)	0.146	0.15 (0.01-2.75)	0.996

CI, confidence interval; NICU, neonatal intensive care unit. ^a Adjustments for maternal age, BMI, gestational age at delivery, oligohydramnios, preterm labor, and preterm premature rupture of membranes.

development, at different gestational ages and according to glucocorticoid receptor-mediated responses [12]. In this regard, few studies have been conducted on the long-term effects of antenatal corticosteroid exposure in late-preterm or term newborns, so the effects on neurodevelopment in newborns are uncertain to date.

There are limitations to this study. First, because not all suspected nonreassuring fetal status cases resulted in birth asphyxia, low pH on umbilical cord blood gas analysis or low Apgar scores, it is difficult to conclude that ACT is a decisive factor in a poor outcome of an actual newborn. However, our results showing that the use of antenatal corticosteroids in late-preterm pregnancy is associated with an abnormal fetal heart rate parameter, which may mimic fetal distress, is worth considering in clinical practice. Second, the effects of tocolytics for antenatal corticosteroid administration in late preterm pregnancy and medication for maternal comorbidities were not considered. Third, since this study is a retrospective study conducted by a single institution, influencing variables other than the use of antenatal steroids may not be the same.

Nevertheless, this study is the first report of a case of still-birth after antenatal corticosteroid administration in a low-risk term pregnancy without other obstetrical risk factors. Furthermore, the results of this study are important in raising the possibility of negative effects associated with the universal adoption of antenatal corticosteroids in pregnant women at risk of late-preterm birth or early-term birth, despite the lack of research on the negative short- and long-term outcomes.

5. Conclusions

Our study showed that ACT in late-preterm pregnancy was associated with nonreassuring fetal status and that the use of ACT in late-preterm and early-term pregnancy resulted in a decreased incidence of TTN. Among the perinatal outcomes examined in this study, except for TTN, there was no benefit from the use of antenatal corticosteroids. In addition,

the factors that increase the likelihood of a nonreassuring fetal heart rate were preeclampsia and oligohydramnios, as well as antenatal corticosteroid use. Additional attention should be given to the use of antenatal steroids to identify benefits in these clinical situations.

Abbreviations

ACT, antenatal corticosteroid therapy; CI, confidence intervals; OR, odds ratio; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

Author contributions

JEP contributed to the conception and design of the study, the acquisition, analysis, and interpretation of the data, review of the literature, and writing and revision of the manuscript. JKP contributed to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and writing and revision of the manuscript. HCJ, IAC and JCB contributed to the acquisition of the data and revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of Gyeongsang National University Changwon Hospital, and the requirement for informed consent was waived (approval number: GNUCH 2020-07-017). All methods were performed in accordance with the relevant guidelines and regulations of the institution.

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Conflict of interest

The authors declare that they have no competing interests.

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