



Antenatal corticosteroids and outcomes of preterm small-for-gestational-age neonates in a single medical center

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Objective

This study investigated the effect of an antenatal corticosteroid (ACS) in preterm small-for-gestational-age (SGA) neonate.

Methods

This study was a retrospective cohort study. We compared women who received ACS with unexposed controls and evaluated neonatal complications among those having a singleton SGA neonate born between 29 and 34 complete gestational weeks. The neonates born after 32 weeks of gestation were divided into subgroups. Multivariable logistic regression analysis was performed.

Results

A total 82 of the preterm infants met inclusion criteria; 57 (69.5%) were born after 32 weeks of gestation. There were no significant differences in terms of mechanical ventilation, seizure, intracranial hemorrhage, retinopathy of prematurity, necrotizing enterocolitis, feeding difficulty, and neonatal mortality between infants whose mothers received ACS and those whose mothers did not (all $P > 0.05$). However, newborns whose mothers received ACS exhibited a significantly increased risk of developing respiratory distress syndrome (RDS) (adjusted odds ratio [aOR], 3.271; 95% confidence interval [CI], 1.038-10.305; $P = 0.043$). In case of neonates born beyond 32 weeks of gestation, the risk of neonatal hypoglycemia was significantly higher in women receiving ACS after controlling for confounding factors (aOR, 5.832; 95% CI, 1.096-31.031; $P = 0.039$).

Conclusion

ACS did not improve neonatal morbidities, in SGA neonates delivered between 29 and 34 gestational weeks. Rather, ACS could increase the risk of RDS. In cases of SGA neonate delivered between 32 and 34 complete gestational weeks, the risk of hypoglycemia was significantly increased. The use of ACS in women with preterm SGA infants needs to be evaluated further, especially after 32 weeks' gestation.

Keywords: Antenatal corticosteroids; Premature birth; Infant; Fetal growth retardation; Respiratory distress syndrome, newborn

Introduction

A single course of antenatal corticosteroid (ACS) treatment has become the standard of care for women at risk of imminent or anticipated preterm delivery, particularly before 32–34 weeks' gestation [1], representing an effective therapy for respiratory distress syndrome (RDS) and improving morbidity and mortality in preterm babies. Based on a double-blind, placebo-controlled, randomized clinical trial suggesting that betamethasone can be beneficial in pregnant women at high risk of late

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preterm birth [2], the American Congress of Obstetricians and Gynecologists (ACOG) has released a practice advisory that the “administration of betamethasone may be considered in women with a singleton pregnancy between 34 and 36 complete weeks of gestation at imminent risk of preterm birth within 7 days” [3]. However, there are no randomized studies on the effect of ACS in preterm small-for-gestational-age (SGA) cases. The first randomized controlled trial of ACS in 1972 [4] not only demonstrated a reduction in RDS in preterm infants but also suggested an excess of fetal death in cases of pregnancy-related hypertension and fetal growth restriction (FGR) treated with corticosteroid. However, many of the subsequent clinical trials on the effect of ACS excluded pregnancies with such complications. In a recent meta-analysis, effects of ACS use were still inconclusive for cases with SGA [5]. In the extreme preterm birth before 29 weeks, the benefit might outweigh the possible harm, considering lung development. However, we need to consider potential risks and benefits of ACS to FGR or small-for-gestational-age (SGA) infants, especially after 32 weeks [6]. Thus, our aim was to assess the association of ACS, when administered within the ideal interval of 1–7 days before birth, with the outcomes of preterm SGA neonates. We also evaluated the effect of ACS on SGA neonates who born at 32 weeks of gestation. At this age, the level of surfactant started to increase in the amniotic fluid [7].

Materials and methods

1. Subjects

We retrospectively analyzed the medical records and perinatal database of the Department of Obstetrics and Gynecology between 2009 and 2016 for deliveries at Seoul St. Mary's Hospital. Ethics approval was obtained from the Institutional Review Boards of The Catholic University of Korea. We selected SGA (defined at birth weight less than the 10th percentile for gestational age based on sex-specific national growth charts [8]) neonates, from all consecutive singleton pregnancies resulting in a preterm neonate (gestational age between 29 and 34 complete weeks of gestation). The standard recommendation for ACS was up to 34 weeks of gestation, so the neonate born until 34 complete gestational weeks were included in this study, who exposed ACS before 34 weeks and had delivered within one weeks. Exclusion criteria for this study were stillbirths, multiple gestations, term births, and major congenital

anomalies. Major congenital anomalies were defined as life-threatening, disabling or requiring major surgery, including chromosomal trisomy. The cases of ACS within 24 hours before births or birth after 7 days were also excluded. Subgroup analysis was conducted in neonates born after 32 weeks of gestation.

2. Demographic characteristics and study outcomes

From the medical records and database, we extracted the maternal age, parity, delivery mode and gestational age at the time of delivery, without distinction among spontaneous or induced delivery, elective or emergency cesarean delivery. The medical history and diseases during pregnancy were also recorded. The gender, birthweight, placental weight and Apgar scores of the neonates were reviewed. The neonatal outcomes according to gestational week included neonatal death, intracranial hemorrhage (ICH), intraventricular hemorrhage (IVH, grade 3 or 4), sepsis, RDS, mechanical ventilation within 48 hours after birth, necrotizing enterocolitis (NEC), feeding difficulty, persistent pulmonary hypertension of newborn (PPHN), hypoglycemia (a glucose level of less than 40 mg per deciliter [2.2 mmol/L at any time]) and admission to the neonatal intensive care unit (NICU) within 48 hours after birth. Sepsis included both suspected infections (with clinical findings suggesting infection) and proved infections (as confirmed in a subgroup of neonates with positive cultures of blood, cerebrospinal fluid, or urine obtained by catheterization or suprapubic aspiration; cardiovascular collapse; or an unequivocal radiograph confirming infection in a neonate with clinical sepsis). The listed complications were selected only when diagnosed by a pediatrician. Outcomes were compared between SGA neonates who received an ACS before birth (ACS group) and those who did not receive ACSs (no ACS group). The outcomes of 2 subgroups of SGA neonates were compared according to ACS. All ACS was administration of dexamethasone-5 mg every 12 hours for 4 doses.

3. Statistical analysis

Continuous variables are described as the median and interquartile range while categorical variables are shown as numbers and percentages. Maternal baseline characteristics and neonatal outcomes were compared by the Mann-Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Logistic regression analysis was performed to demonstrate whether the adverse neonatal out-

come was reduced with ACS, when adjusted for confounding factors such as gestational age, parity, mode of delivery, maternal diabetes, gestational hypertensive disorder, and preterm premature rupture of membrane. Statistical analyses were performed using SPSS (version 18.0; IBM Corp., Chicago, IL, USA) and statistical significance was set as a *P*-value of <0.05, 2-tailed.

Results

1. Baseline characteristics

Eight hundred and thirty-two live infants were born between 29 and 34 complete weeks of gestation in our institute during the study period. A total of 82 newborns met the inclusion criteria and 57 (69.5%) of these were born after 32 weeks of gestation. The baseline characteristics are shown in Table 1. There were no significant differences in maternal age, mode of delivery, gestational diabetes, chorioamnionitis, nulliparity,

indication of delivery, and Apgar score. Infants who exposed ACS were born earlier and had lower birth weight than did those who did not received ACS (all *P*<0.05). The frequency of male infants being born was higher in the group that received ACS.

2. SGA neonates born between 29 and 34 complete weeks of gestation

The neonatal outcomes according to the use of ACS is described Table 2. In total, 45 mothers (54.8%) received ACS with dexamethasone prior to delivery. There were no significant differences in terms of RDS, mechanical ventilation, neonatal seizure, ICH, NEC, and feeding difficulty regardless of ACS (all *P*>0.05). The incidence of NICU admission, retinopathy of prematurity (ROP), PPHN, and neonatal mortality were also similar between the group that received ACS and the group that did not (NICU admission, 35 [94.5%] vs. 45 [100%]; ROP, 0 vs. 2 [4.4%]; PPHN, 0 vs. 1 [2.2%]; neonatal mortality, 1 [2.7%] vs. 1 [2.2%]; respectively; all *P*>0.05). However, after adjusting

Table 1. Baseline characteristics of study population by antenatal steroid use

Characteristics	Total group (n=82)			Newborn born beyond 32 weeks of gestation (n=57)		
	No ACS (n=37)	ACS (n=45)	<i>P</i> -value	No ACS (n=30)	ACS (n=27)	<i>P</i> -value
Maternal age (yr)	33 (31–35)	34 (30–36)	0.743	34 (32–35)	34 (31–37)	0.904
Gestational age (wk)	34.1 (32.6–34.4)	32.7 (30.8–33.8)	0.002	34.1 (33.6–34.6)	33.2 (33.0–34.1)	0.005
Birth weight (g)	1,450 (1,145–1,705)	1,190 (974–1,494)	0.010	1,560 (1,371–1,721)	1,450 (1,249–1,620)	0.073
Placental weight (g)	400 (321–487)	340 (270–444)	0.067	413 (348–500)	398 (300–450)	0.127
Cesarean section	34 (91.9)	40 (88.9)	0.724	34 (91.9)	40 (88.9)	0.724
Male neonate	11 (29.7)	24 (53.3)	0.032	9 (30.3)	15 (55.6)	0.051
Gestational diabetes	2 (5.4)	2 (4.4)	0.841	2 (6.7)	1 (3.7)	0.617
Chorioamnionitis	1 (2.7)	0 (0)	0.451	1 (2.7)	0 (0)	0.526
Nulliparity	26 (70.3)	29 (64.6)	0.576	21 (70.0)	19 (70.4)	0.976
Indication of delivery						
PIH	18 (48.6)	25 (55.6)	0.533	15 (50.0)	19 (70.4)	0.118
PPROM	10 (27.0)	6 (13.3)	0.119	9 (30.0)	4 (14.8)	0.172
Preterm labor	2 (5.4)	3 (6.7)	0.817	2 (6.7)	1 (3.7)	0.617
Abnormal fetal Doppler or non-reassuring FHB ^{a)}	6 (16.2)	8 (17.8)	0.852	3 (10.0)	2 (7.4)	0.730
Oligohydramnios	1 (2.7)	3 (6.7)	0.623	1 (3.3)	1 (3.7)	0.940
1 min Apgar score less than 5	13 (35.1)	17 (37.8)	0.805	7 (23.3)	5 (18.5)	0.656
5 min Apgar score less than 7	8 (21.6)	10 (22.2)	0.948	3 (10.0)	3 (11.1)	0.999

ACS, antenatal corticosteroid; PIH, pregnancy induced hypertension; PPRM, premature preterm rupture of membrane; FHB, fetal heart beat.

^{a)}Abnormal fetal Doppler included cases of absence or reverse end-diastolic flow in umbilical artery and abnormal cerebroplacental ratio (less than 5th percentile).

for confounding factors, such as gestational age, nulliparity, neonatal sex, mode of delivery, gestational diabetes, pregnancy induced hypertension, and premature preterm rupture of membrane (PPROM), the neonates who had received ACS showed significantly higher frequencies of RDS than those who had not received ACS (adjusted odds ratio [aOR], 3.271; 95% confidence interval [CI], 1.038–10.305; $P=0.043$).

3. SGA neonate born between 32 and 34 complete weeks of gestation

Of the 57 women who delivered between 32 and 34 complete weeks of gestation, 27 (54%) women received ACS prior to delivery. Neonatal outcome showed in Table 3. There was no

significant difference in the frequency of neonatal adverse outcomes according to ACS administration (all $P<0.05$) (Table 4). After adjustment for confounding factors, neonatal hypoglycemia was significantly more prevalent in the ACS group (aOR, 5.832; 95% CI, 1.096–31.031; $P=0.039$).

4. SGA neonate born between 29 and 31 complete weeks of gestation

Of the 25 women who delivered between 29 and 31 complete weeks of gestation, 18 (72%) women received ACS prior to delivery. There were no significant differences in the frequency of neonatal adverse outcome (All $P<0.05$).

Table 2. Neonatal outcomes related to antenatal corticosteroid use between 29 and 34 weeks of gestation

Characteristics	No ACS (n=37)	ACS (n=45)	P-value	OR (95% CI)	aOR (95% CI) ^{a)}
RDS	11 (29.7)	22 (48.9)	0.078	2.261 (0.905–5.649)	3.271 (1.038–10.305) ^{b)}
Mechanical ventilation	14 (37.8)	23 (51.1)	0.229	1.718 (0.709–4.161)	1.970 (0.712–5.449)
Sepsis	3 (8.1)	9 (20.0)	0.129	2.833 (0.707–11.355)	3.090 (0.694–13.761)
Neonatal seizure	4 (10.8)	4 (8.9)	0.770	0.805 (0.187–3.465)	0.946 (0.191–4.682)
Any ICH	14 (37.8)	20 (44.4)	0.654	1.314 (0.541–3.192)	1.432 (0.539–3.805)
IVH (\geq grade 3)	1 (2.7)	4 (8.7)	0.372	3.512 (0.375–32.878)	2.411 (0.237–24.561)
NEC	2 (5.4)	5 (11.1)	0.449	2.188 (0.399–11.991)	1.904 (0.336–10.789)
Feeding difficulties	5 (13.5)	7 (15.6)	0.795	1.179 (0.341–4.075)	0.901 (0.229–3.535)
Hypoglycemia	8 (21.6)	17 (37.8)	0.114	2.833 (0.707–11.355)	2.454 (0.813–7.405)

ACS, antenatal corticosteroid; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; RDS, respiratory distress syndrome; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

^{a)}Adjusted by as gestational age, nulliparity, neonatal sex, mode of delivery, gestational diabetes, pregnancy induced hypertension, and premature preterm rupture of membrane; ^{b)} $P<0.05$.

Table 3. Neonatal outcomes related to antenatal corticosteroid use in newborn born beyond 32 weeks of gestation

Characteristics	No ACS (n=30)	ACS (n=27)	P-value	OR (95% CI) ^{a)}	aOR (95% CI) ^{a)}
RDS	5 (16.7)	6 (22.2)	0.596	1.429 (0.381–5.353)	4.993 (0.595–41.910)
Mechanical ventilation	7 (23.3)	7 (25.9)	0.820	1.150 (0.344–3.845)	1.597 (0.387–6.584)
Sepsis	1 (3.3)	3 (11.1)	0.336	3.625 (0.354–37.142)	3.387 (0.285–40.240)
Neonatal seizure	4 (13.3)	3 (11.1)	0.799	0.813 (0.165–4.010)	1.124 (0.193–6.542)
Any ICH	10 (33.3)	10 (37.0)	0.770	1.176 (0.396–3.496)	1.457 (0.409–5.191)
IVH (\geq grade 3)	1 (3.3)	2 (7.4)	0.599	2.320 (0.198–27.137)	1.256 (0.078–20.159)
Feeding difficulties	4 (13.3)	4 (14.8)	0.872	1.130 (0.253–5.042)	0.851 (0.151–4.781)
Hypoglycemia	4 (13.3)	9 (33.3)	0.072	3.250 (0.866–12.194)	5.832 (1.096–31.031) ^{b)}

ACS, antenatal corticosteroid; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; RDS, respiratory distress syndrome; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

^{a)}Adjusted by as gestational age, nulliparity, neonatal sex, mode of delivery, gestational diabetes, pregnancy induced hypertension, and premature preterm rupture of membrane; ^{b)} $P<0.05$.

Table 4. Crude and adjusted odds ratios of each outcome related to antenatal corticosteroid uses in neonate who delivered beyond 32 weeks of gestation

Characteristics	OR (95% CI)	P-value	Adjusted OR (95% CI) ^{a)}	P-value
RDS	0.923 (0.305–2.788)	0.755	2.432 (0.463–12.764)	0.294
Mechanical ventilation	4.875 (0.479–49.586)	0.877	0.708 (0.184–2.729)	0.616
Sepsis	1.125 (0.231–5.481)	0.295	1.988 (0.136–29.051)	0.615
Seizure	0.929 (0.331–2.603)	0.884	1.461 (0.172–12.385)	0.728
Feeding difficulties	0.708 (0.161–3.115)	0.647	0.562 (0.094–3.369)	0.528
Hypoglycemia	4.500 (1.218–16.622)	0.018	13.111 (1.943–88.494)	0.008

OR, odds ratio; CI, confidence interval; RDS, respiratory distress syndrome.

^{a)}Adjusted by gestational age, nulliparity, cesarean section rate, gestational diabetes mellitus, pregnancy induced hypertension, and premature preterm rupture of membrane.

Discussion

In this study, we observed that the exposure of preterm SGA fetuses to ACSs between 29 and 34 weeks of gestation was not associated with a significant decrease or increase in the odds of NICU admission, mechanical ventilation, sepsis, seizure, IVH, ROP, NEC, PPHN, feeding difficulties, neonatal death, or hypoglycemia. However, the frequency of RDS was notably increased in the group that received ACS. Although this result was adjusted with gestational age and birth weight, it is thought that the group that received ACS included more newborns that were born earlier and weighed less. And exposure of preterm SGA fetuses to ACSs before birth between 32 and 34 weeks of gestation was associated with neonatal hypoglycemia.

Retarded fetal growth is associated with chronic hypoxia and acidosis. Because SGA fetuses might be already exposed to elevated endogenous corticosteroid levels, ACS can cause too much burden including fetal hemodynamics and neurologic development [9]. There are many evidences from basic science and observational studies for potential fetal harms [6]. It has been reported that restricted fetal growth is related with adult hypertension, atherosclerosis, type 2 diabetes, and metabolic derangement [10,11], although the degree to which low birth weight mediates adult disease is controversial. Also, it was reported that ACS was associated with increased cortisol reactivity to acute psychosocial stress in 6–11 years old [12]. The effect of ACS on the developing brain is controversial [6]. Multiple courses of ACS have been associated with decreased weight, length, and fetal head circumference at birth, and increased risk of neurodevelopmental and neurosensory impairment by 5 years of age [13,14]. A recent meta-analysis sug-

gested that a single course of ACSs in women at high risk for preterm birth appears to improve most neurodevelopmental outcomes in offspring born before 34 weeks of gestation [15]. Growth restricted fetal brain might be more vulnerable to oxidative damage, as an experimental sheep model of FGR has demonstrated the relationship between betamethasone and disturbed neuronal integrity and enhanced cell death in the brain due to increased cerebral oxidative stress [9]. However, the effects of ACS on the brain of human growth-restricted fetuses remain largely understudied. The effects of ACS on the hemodynamics of the growth restricted fetuses were evaluated with end-diastolic flow of umbilical artery after ACS, using Doppler ultrasonography. While there were higher risks of neonatal morbidity associated with lack of return of end-diastolic flow after ACS in growth-restricted fetuses, the mechanisms and the long-term impact are still unknown [16,17]. The only data available about long-term neurocognitive outcomes after late preterm administration of ACSs vs. placebo come from the initial corticosteroids study [4], which showed no difference between exposure groups, in cognitive functioning, working memory and attention, and other neurocognitive assessments. Considering the proven mechanisms and effects of ACS on developing brain, we should be cautious when we give ACS in the premature FGR cases [18]. There are 2 recent retrospective studies reporting that ACS significantly reduced mortality and severe morbidities among preterm SGA neonates [19,20]. However, one study included SGA neonates within 24–31 weeks' gestation, while the other study included SGA neonates from 24 to 33 weeks' gestation. The present study included SGA neonates from 29 to 34 weeks' gestation, which might present less mortality and severe morbidities. Low incidence of mortality and morbidity might be the reason

that we could not find the benefit of ACS. The gestational age and birth weight of the group that did not receive ACS were significantly higher than those of the group that received ACS, which could act as a selection bias. However, even after the adjustment by gestational age, birth weight including other clinical confounding factors, there was no significant difference between ACS group and no ACS group. In addition, the risk of neonatal hypoglycemia was significantly higher in the ACS group, between 32 and 34 weeks' gestation, in logistic regression analysis. Also, small sample size of this study is our limitation. A previous study from Japan showed that ACS does not affect short- or long-term outcome in SGA infants when the birth weight is less than 1,500 g [21]. These similar results can be related with ethnic difference. So, data on the efficacy and safety of ACS in pregnancies complicated by FGR or SGA are limited and conflicting. SGA includes growth restricted and constitutionally small fetuses. Our study has limitation in that it cannot distinguish between FGR and constitutionally small fetuses. Therefore, it is needed to evaluate the effects of ACS on the severe FGR cases, which have abnormal flow patterns in umbilical and middle cerebral arteries.

Our study demonstrated that ACS could not decrease neonatal mortality and morbidities, in SGA neonates delivered between 29 and 34 weeks of gestation. And the risk of neonatal hypoglycemia was increased in ACS group, in SGA neonates delivered between 32 and 34 weeks of gestation. Although a single course of ACS has become the standard of care in most high-income countries for cases of imminent or anticipated preterm delivery, particularly before 32–34 weeks' gestation and ACOG expanded a recommendation of ACS to women with a singleton pregnancy between 34 and 36 weeks of gestation at imminent risk of preterm birth within 7 days, ACS in women at preterm FGR need to be further evaluated, especially after 32 weeks' gestation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Effect of corticosteroids for fetal maturation on perinatal

outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. *JAMA* 1995;273:413-8.

2. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med* 2016;374:1311-20.

3. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice; Society for Maternal/Fetal Medicine. Committee opinion no.677: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2016;128:e187-94.

4. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;50:515-25.

5. Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. *PLoS One* 2016;11:e0147604.

6. Vidaeff AC, Blackwell SC. Potential risks and benefits of antenatal corticosteroid therapy prior to preterm birth in pregnancies complicated by severe fetal growth restriction. *Obstet Gynecol Clin North Am* 2011;38:205-14, ix.

7. Snyder JM, Mendelson CR, Johnston JM. The morphology of lung development in the human fetus. In: Nelson GH, editor. *Pulmonary development: transition from intrauterine to extrauterine life*. New York (NY): Marcel Dekker; 1985. p.19-46.

8. Lee JK, Jang HL, Kang BH, Lee KS, Choi YS, Shim KS, et al. Percentile distributions of birth weight according to gestational ages in Korea (2010-2012). *J Korean Med Sci* 2016;31:939-49.

9. Miller SL, Chai M, Loose J, Castillo-Meléndez M, Walker DW, Jenkin G, et al. The effects of maternal betamethasone administration on the intrauterine growth-restricted fetus. *Endocrinology* 2007;148:1288-95.

10. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004;305:1733-6.

11. Lillycrop KA, Burdge GC. Epigenetic changes in early life and future risk of obesity. *Int J Obes (Lond)* 2011;35:72-83.

12. Alexander N, Rosenlöcher F, Stalder T, Linke J, Distler W,

- Morgner J, et al. Impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term-born children. *J Clin Endocrinol Metab* 2012;97:3538-44.
13. Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, et al. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. *Lancet* 2008;372:2143-51.
 14. Asztalos E, Willan A, Murphy K, Matthews S, Ohlsson A, Saigal S, et al. Association between gestational age at birth, antenatal corticosteroids, and outcomes at 5 years: multiple courses of antenatal corticosteroids for preterm birth study at 5 years of age (MACS-5). *BMC Pregnancy Childbirth* 2014;14:272.
 15. Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. *Obstet Gynecol* 2015;125:1385-96.
 16. Simchen MJ, Alkazaleh F, Adamson SL, Windrim R, Telford J, Beyene J, et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. *Am J Obstet Gynecol* 2004;190:296-304.
 17. Robertson MC, Murila F, Tong S, Baker LS, Yu VY, Wallace EM. Predicting perinatal outcome through changes in umbilical artery Doppler studies after antenatal corticosteroids in the growth-restricted fetus. *Obstet Gynecol* 2009;113:636-40.
 18. Malaeb SN, Stonestreet BS. Steroids and injury to the developing brain: net harm or net benefit? *Clin Perinatol* 2014;41:191-208.
 19. Riskin-Mashiah S, Riskin A, Bader D, Kugelman A, Boyko V, Lerner-Geva L, et al. Antenatal corticosteroid treatment in singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-based study. *BJOG* 2016;123:1779-86.
 20. Melamed N, Pittini A, Barrett J, Shah J, Yoon EW, Lemyre B, et al. Antenatal corticosteroids and outcomes of small-for-gestational-age neonates. *Obstet Gynecol* 2016;128:1001-8.
 21. Ishikawa H, Miyazaki K, Ikeda T, Murabayashi N, Hayashi K, Kai A, et al. The effects of antenatal corticosteroids on short- and long-term outcomes in small-for-gestational-age infants. *Int J Med Sci* 2015;12:295-300.