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REVIEW

ANTENATAL CORTICOSTEROIDS - BETWEEN BEING A USEFUL DRUG AND POSING A RISK FOR FETAL AND ADULT DEVELOPMENT

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Summary

Antenatal corticosteroid therapy (ACST) is very important in reducing the sequelae of prematurity, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC). This therapy has short-term and long-term neonatal consequences that range from reduced neonatal body weight, brain growth, hypertension, hypoglycemia and obesity to delayed neurological development. In addition to undeniable importance this type of therapy has on fetal maturation, it may also impact programming of fetuses future development and health during childhood and adulthood. ACST must be personalized, as a single course, and determined by indications and assessment of the expected time of delivery, so that the exposure time of the fetus to the effects of endogenous and exogenous steroids is shortened.

Keywords: antenatal corticosteroid therapy, programming, prematurity, fetus, neonate

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INTRODUCTION

Generally, preterm delivery is the most important and unresolved problem in perinatal medicine. The global prevalence rate of preterm birth ranges from 5% to 13.3% (1). In Serbia, since 1998 the preterm birth rate of 8 % of all births has declined to 6.8% (2022), which confirmed our country in the group of countries with stable parameters of neonatal statistics (2). If a birth occurs before the completed period of gestation (37 weeks), it is defined as preterm.

According to the gestational age, there are sub-categories of preterm birth: extremely preterm – below 28 gestational weeks; very preterm – 28 to 32 weeks; and late preterm birth – after 32 to 37 weeks (3).

Preterm delivery has multifactorial etiology, and nowadays, we use the name "preterm delivery syndrome" (2). Regardless of the definition, preterm birth is related to increased maternal and perinatal morbidity and mortality as well as to the consequences on development until adulthood.

In 1972, a randomized controlled trial regarding maternal administration of betamethasone was carried out by Liggins and Howie. The results were published in a groundbreaking article that documented a decrease in cases of respiratory distress syndrome (RDS) in preterm infants and neonatal mortality. The incidence of RDS and neonatal mortality dropped from 15.6% to 10% and 11% to 6.0%, respectively (4).

Crowley and colleagues published a meta-analysis of 12 randomized controlled trials of ACST in 1990. This meta-analysis demonstrated that the ACST therapy significantly reduced not only RDS, neonatal intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC), but also the overall neonatal mortality (5). In 2021, the WHO Executive Guideline Steering Group defined recommendations for sustainable implementation of antenatal corticosteroid therapy (ACST) as one of the therapies that improved preterm birth outcomes (6) **(Table 1)**.

Today, antenatal corticosteroid administration is one of the most important and beneficial treatments used in perinatal medicine.

Regardless of the therapeutic benefits in the improvement of preterm perinatal outcomes, corticosteroids are very potent medications with a still questionable impact on fetal development and with long-term consequences related to the occurrence of chronic diseases in adulthood.

ANTENATAL CORTICOSTEROIDS FROM FETAL AND NEONATAL DEVELOPEMENT TO ADULTHOOD – *PROS AND CONS*

A) ACST and placenta: The levels of corticotropin-relising hormone (CRH) of placental origin increase during the second and third trimester. Placenta is an alternative source of adrenocorticotropin hormone (ACTH). As a result, this placental synthesis of ACTH can lead to a two- or tri-fold increase in its concentration. Total and free maternal ACTH concentrations rise gradually during pregnancy.

Placental villi are the target tissue affected by ACST in single or increased doses. There are many debates about the placental function after ACST regarding the optimal dose and interval between doses, especially when it comes to repeated doses. Some studies of increased doses of ACST demonstrated contradictory results related to placental weights, abnormalities of villous development, placental infarcts, or decreased vascular reactivity.

Um-Bergstorm et al. (2018) confirmed the association between multiple courses of ACST and accelerated villous maturation and preterm labor (7). Accelerated villous maturation is also observed in pregnancies complicated by chronic hypoxia. These mechanisms are very different. Wallace and Baker presumed that single-dose ACST improved villous as well as umbilical circulation (8). The possibly increased villous velocities are related to an increase in larger number of villi as well as placental perfusion and its diffusion capacity longer after the administration of ACST (9). Consequently, a single–dose of ACST improves perinatal and neonatal outcomes in preterm labor (10). Babovic et al. (2016) did not confirm the relation between a single-dose of ACST and umbilical circulation (RiAU) (11). In contrast, repeated doses of ACST are related to decreased placental weight as well as to adverse fetal or neonatal outcomes (12). Chronic hypoxic environment stimulates placental villi to secrete soluble fms-like tyrosine kinase-1 (sFlt-1). Overexpression of sFlt-1 has been linked to accelerated villous maturation, for example in preeclampsia. ACST does not change the level of sFlt-1 (13).

Finally, Leavely et al . (2017) showed that on the molecular level the accelerated villi are of advanced age, indicating that those placentas could be affected by premature activation of a normal maturational program. However, further studies that include gene expression and investigate the mechanisms and pathogenesis of preterm accelerated villous maturation are necessary(14).

B) Fetal corticosteroids Recent studies confirmed functional pituitary-adrenal axis (significant adrenal secretion of dehydroepiandrostenedion-sulphate (DHEAS) at 8-10 weeks of gestation. The fetal zone (comprising most of the adrenal cortex) is the major site of steroidogenesis before birth. Precursors of fetal steroids are placental 5-pregnenolone and 4-progesterone. Fetal cortisol is critical for placental synthesis of estrogens, and its concentrations are 5-10 times lower than maternal concentrations (14). Two placental mechanisms maintain the low glucocorticoid environment during gestation: 11β-hydroxysteroid dehydrogenase (11β-HSD)-2 conversion of active cortisol and corticos-

Table 1: WHO 2022 recommendations on antenatal corticosteroid therapy for improving preterm birth outcomes

1.0 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met: Gestational age assessment can be accurately undertaken. There is a high likelihood of preterm birth within 7 days of starting the therapy. There is no clinical evidence of maternal infection. Adequate childbirth care is available (including capacity to recognize and safely manage preterm labor and birth) The preterm newborn can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including continuous positive airway pressure [CPAP] as needed)	Context-specific recommendation
1.1 Antenatal corticosteroid therapy should be administered to women with a high likelihood of giving birth preterm in the followingt 7 days, even if it is anticipated that the full course of corticosteroids may not be completed.	Context-specific recommendation
1.2 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth, irrespective of whether single or multiple birth is anticipated.	Context-specific recommendation
1.3 Antenatal corticosteroid therapy is recommended for women with preterm prelabour rupture of membranes and no clinical signs of infection	Context-specific recommendation
1.4 Antenatal corticosteroid therapy is not recommended for women with chorioamnionitis, who are likely to give birth preterm.	Not recomended
1.5 Antenatal corticosteroid therapy is not recommended for women undergoing a planned cesarean section at 34 weeks 0 days to 36 weeks 6 days.	Not recommended
1.6 Antenatal corticosteroid therapy is recommended for women with hypertensive disorders in pregnancy, who have a high likelihood of preterm birth.	Context-specific recommendation
1.7 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth of a growth-restricted fetus	Context-specific recommendation
1.8 Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes when there is a high likelihood of preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.	Context-specific recommendation
1.9 **Either intramuscular (IM) dexamethasone or (IM) betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice.**	Recommended
1.10 A single repeat course of antenatal corticosteroids is recommended for women who have received a single course of antenatal corticosteroids at least 7 days before and, on clinical assessment, have a high likelihood of giving birth preterm in the next 7 days.	Recommended

terone into their intrinsically inert 11-keto-metabolites, and P-glycoprotein-mediated active retrograde transport of glucocorticoids from fetus to mother, maintaining the feto–maternal glucocorticoid gradient in both endogenous and exogenous glucocorticoids (15, 16). 11β-HSD2 is present in a higher concentration especially in the fetal brain during early-to-mid-gestation (17). In late gestation, there is an increased endogenous synthesis of glucocorticoids in both the mother and the fetus, while the synthesis of glucocorticoids in the placenta decreases due to a lower activity of placental 11β-HSD-2. Increased concentrations of endogenous glucocorticoids, which act via the glucocorticoid receptor (GR) to mature the fetal lungs and other organs, are important for survival in the extrauterine environment after birth (18). Finally, it is the main etiological factor of fetal programming and human development.

C) *ACST-- drugs and treatment:* Two main synthetic corticosteroids used in clinical practice are betamethasone-acetate and dexamethasone sodium phosphate (Table 1). They are not inactivated by endogenous dehydrogenase enzymes. These agents have minimal mineralocorticoid and weak immunosuppressive activity with short-term administration. However, betamethasone is more potent than dexamethasone (19). ACST has been administered in a variety of ways including orally, intramuscularly, intravenously, intraamniotically, and as a direct intramuscular injection into the fetus. The most common way of administration is the Liggins method – intramuscular injection into the mother's muscle tissue (4). ACST treatment includes two 12-mg doses of betamethasone given i.m 24 hours/four 6-mg doses of dexamethasone administered i.m every 12 hours (Table 1). The benefit of ACST administration is greatest 2–7 days after the initial dose.

D) *Fetal lung and ACST* Endogenous as well as exogenous glucocorticoids induce the production of lipid and protein surfactant components. The production of lipid surfactant components include the induction of lipogenic enzymes (phosphocholine transferase, methyl transferase) necessary for phospholipid synthesis, and the conversion of unsaturated to disaturated phosphatidylcholine. Glucocorticoids via thyroid transcription factor-1 (TTF-1), which is vital for normal lung development and is primarily expressed by type II alveolar epithelial cells in the fetal lung at term and in postnatal life, induce pro-

tein surfactant production. TTF-1 plays a role in the synthesis of SP-A, B and C proteins at gene level. Pulmonary surfactant is produced by type II pneumocytes (20). It decreases the surface tension of terminal alveoli, promotes lung expansion during inspiration, prevents alveolar collapse and loss of lung volume at the end of expiration, and facilitates the recruitment of the collapsed alveoli. Finally, more than 20 years ago, Ballard (1995) documented that antenatal corticosteroids increase tissue and alveolar surfactant production, lung compliance, clearance of fluid from the lungs, maturation of parenchymal structure, and they reduce vascular permeability (21).

E) Fetal brain, behavior and ACST Miller SR et al. observed increased cerebral vascular resistance, decreased fetal cerebral blood flow and oxygen delivery, and impaired hippocampus region-specific cerebral oxygen delivery (22). In contrast, Vafaei et al. (2021) documented that antenatal corticosteroid administration increased fetal middle cerebral artery pulsatile index (MCA PI), as an autoregulation mechanism (to stabilize cerebral perfusion) (23). Finally, Babovic et al. observed no changes in resistant indices in cerebral circulation after direct fetal intramuscular corticosteroid therapy (23). These findings depend on the mode of corticosteroid administration. The CST receptors are expressed in the hippocampus. Exposure to antenatal glucocorticoids in utero, via CST receptors, has widespread acute effects on neuronal structure and synapses that induce alteration morphology and the function of the hippocampal area. These effects may induce neuronal death. Treatment with antenatal dexamethasone caused dose-dependent neuronal degeneration of hippocampal neurons and reduced hippocampal volume. These effects persisted in rhesus monkeys until they were about 20 months old. Fetuses receiving multiple lower-dose ACST injections were more severely affected than those receiving a single large injection. As Seckl cited, human and animal studies have demonstrated that disrupting normal patterns of myelinization, reduction of neuronal cell number, and interneuronal signal pathways in the fetal brain may be associated with several consequences on fetal behavior and neonatal memory (24). Our study demonstrated that maternal corticosteroid therapy interfered with the diurnal rhythm in fetal movements, with ~50% decreased movements for 24-48 hours as well as a decreased number of breathing movements (11). On the other hand, direct fetal intramuscular corticosteroid therapy induces increased fetal breathing movements and fetal biophysical profile (25).

F) Fetal cardiovascular system and ACST Glucocorticoids act via intracellular receptors in fetal myocard: the glucocorticoid receptor (GR or type II receptor) and the high-affinity mineralocorticoid receptor (MR or type I receptor). These receptors are activitated by ligand- binding, which further triggers the transcription factors of specific genes in the cellular nucleus (26). Endogenous glucocorticoids, through receptors, promote structural, functional, and metabolic remodeling in fetal cardiomyocytes. The systolic and diastolic ratio (E/A wave ratio), as a marker of cardiac maturity, is reduced. Our study did not confirm significant changes in the systolic function of the fetal heart after ACST (11). Early systolic and diastolic function is impaired, similar to the preterm neonates. This functional immaturity is related to the structural immaturity of the fetal heart: as shortened and disorganized myofibrils, a lack of cardiomyocyte alignment, and biochemical immaturity (in terms of calcium handling) (27). Recent studies observed that ACST reduces fetal capillary length and volume as well as placental vascularisation (28,29). These observations are associated with increased resistance in placental and umbilical circulation. In support of this observation, ACST can induce abnormal cardiac maturation, with impaired heart function in late gestation in the third trimester of pregnancy (30). After ACST, the transient increase in peripheral vascular resistance raises blood pressure resulting in increased human fetal cardiac output. Dexamethasone rapidly induces the regulation of cardiac mitochondrial capacity as a marker for the functional and metabolic maturation of the fetal heart in both in-vivo and in-vitro studies. The key point of that regulation is the abolition of glucocorticoid effects on mitochondrial oxygen consumption and its relation to the maturation of myofibril structure (27). Dexamethasone alone is ineffective in the induction of human maturation of cardiomyocytes. But when dexamethasone acts together with the thyroid hormone (T3), it induces maturation and improves the contractile force of cardiomyocytes (31) This inter-dependent relationship of T3 and glucocorticoids in cardiac maturation is an important confirmation of ACST, where only glucocorticoid is administered. If glucocorticoid receptors are activated before the HPA axis has started to produce circulating fetal T3 in any substantial amount, the maturation of fetal organs induced by glucocorticoids could be limited. ACST decreases or increases the basal fetal heart rate (BFHR), but all changes are less than 10 bpm. The changes are suggestive of sympathetic suppression (11). Long-term heart rate variability is reduced with fewer accelerations (32). The transient deterioration in the heart rate pattern may lead to a misdiagnosis of fetal distress (11).

ANTENATAL CORTICOSTEROIDS PROGRAMMING NEONATAL DEVELOPMENT AND ADULTHOOD

The concept of early-life physiological 'programming' or 'imprinting' implies the relationship between prenatal environmental events, altered fetal growth and development, and later pathophysiology (33). Exposure to antenatal corticosteroid therapy by single or repeated courses in utero at critical developmental stages can alter the functioning of many organ systems that extend into adult life.

A) Short-term neonatal effects of a single-course ACST are *transient neonatal tachypnea/apnea after 34 gw, hypoglycemia, reduced risk of neonatal RDS, reduced risk of neonatal intraventricular hemorrhage (IVH), and reduced risk of necrotizing enterocolitis (NEC)* (6).

B) **Long-term neonatal effects** are principally related to repeated ACST courses:

- ***decreased birth weight*** Bloom et al. observed the link between low neonatal birth weight and repeated maternal ACST course in the third trimester of gestation. (34). This birth weight reduction presumably reflected the catabolic actions of exogenous steroids (33).
- ***decreased neonatal length*** Rodriguez et al. (2019) observed a significant correlation between decreased neonatal birth length and adult height as well as a risk of death from several major chronic diseases in adulthood (35).
- ***decreased brain growth*** The majority of cells in the developing brain originate from the neural stem or progenitor cells. Many nuclear receptors, including thyroid hormone receptors and the glucocorticoid receptor (GR) that are expressed in these cells, are pivotal for the development of the brain (36). In the developing brain, the classical genomic GR signaling pathway is important for the stabilization of vascular endothelial cells. The stabilization of vascular endothelial cells by GR plays an important role in decreasing the risk of IVH after preterm birth. Neurogenesis, gliogenesis as well as the production of neural stem or progenitor cells all depend on whether ACST was given in a single dose or repeatedly. This process indirectly contributes to the cognitive and behavioural impairments observed in infants exposed to ACST in utero. (37) This hypothesis explains that the timing of neurogenesis and gliogenesis is controlled and regulated by the formation of oligodendrocytes and astrocytes before and after birth in humans (38).
- ***deleterious effects on the fetal/neonatal cerebral myelination*** Aszatols et al. (2013) observed a spectrum of neurodevelopmental disabilities such as neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual or hearing aids), or neurocognitive or neurobehavioral function (abnormal attention, memory, or behavior) of 2141 preterm survival children at 18-24 months of age, linked to maternal exposure to multiple courses of corticosteroids. She suggests that neuromotor disability is a consequence of interference in the developing brain or nerve and potential exposure to antenatal corticosteroids. It is extremely important that the preterm fetus is exposed not only to the exogenous corticosteroid treatment, but also to the natural endogenous fetal surge of cortisol in late pregnancy, which is critical for normal fetal growth and development (39). In contrast, our study investigates the fact that a single course of ACST could impact neurological conditions, as assessed through the muscular tone of 82 prematurely born infants (31-33 gw) over the first 12 months after birth. During this period, a significantly greater number of infants from the ACST group had good muscular tone when compared to those from the control group without therapy (40).
- ***increased blood pressure and human newborns*** Mudler (2004) observed increased blood pressure within 24 hours after maternal administration of one course of betamethasone (41). This was ascribed to the baroreceptor reflex, in which an increase in blood pressure very rapidly triggers a decrease in heart rate, causing blood pressure to fall, but not in very early fetuses. Babovic et al. (2016) did not support these findings after maternal administration of one course of dexamethasone (11). Excess endogenous or exogenous cortisol directly elevates blood pressure at birth in humans. But, ACST affects fetal/neonatal blood pressure during organogenesis, growth, or maturation depending on gestational age and the stage of organ development at the time of fetal exposure to glucocorticoids (42). Exposure to glucocorticoids during the final week of pregnancy in rats is sufficient to produce permanent adult hypertension. This effect may be primarily due to the complex species-specific patterns of expression of glucocorticoid receptors and specific enzyme 11b-HSD, which regulates maternal glucocorticoid transfer to the fetus and modulates glucocorticoid action in individual tissues (43).

CONCLUSION

Antenatal corticosteroid therapy is a gold standard in the prevention of short-term and long-term sequels of prematurity. Our knowledge is limited concerning the relation between an excess of exogenous steroids and fetal, neonatal, and childhood development. In addition to the undeniable importance of fetal maturation, this type of therapy also implies the influence on the programming of future development and health during childhood and adulthood. ACST must be personalized, as a single course, determined by the indications and the assessment of the expected time of delivery, so as to shorten the exposure time of the fetus to the effects of endogenous and exogenous steroids.

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Authors' contributions

IB, RS, MJ, and NKO contributed to the conceptualisation. IB, JB,VP and JP contributed to the methodology and investigation. JB and JM contributed to the resources. JM contributed to data curation. IB, JB and JM contributed to writing and original draft preparation. RS contributed to writing, reviewing and editing. VP, JP and MA contributed to visualisation. IB contributed to supervision. IB and NKO contributed to project administration.

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ANTENATALNI KORTIKOSTEROIDI - IZMEĐU LEKA I RIZIKA ZA RAZVOJ FETUSA I PROGRAMIRANJA ODRASTANJA

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Sažetak

Antenatalna kortikosteroidna terapija (ACST) je veoma značajna u redukciji sekvela prematuriteta respiratornog distres sindroma (RDS), intraventrikularne hemoragije (IVH) kao i nekrotizirajućeg enterokolitisa (NEC). Ova terapija ima kratkotrajne i dugotrajne neonatalne posledice, počev od smanjenja telesne mase neonatusa na rođenju, rasta mozga, hipertenzije i hipoglikemije i gojaznosti, do odloženog neurološkog razvoja. Pored nesumnjivog značaja u maturaciji ploda, ova vrsta terapije podrazumeva i uticaj na programiranje budućeg razvoja i zdravlja tokom detinjstva i zrelog doba. ACST mora biti personalizovana, u vidu jednog kursa, određena indikacijama i procenom očekivanog vremena završavanja porođaja, kako bi se skratilo vreme ekspozicije fetusa delovanju endogenih i egzogenih steroida.

Ključne reči: antenatalna kortikosteroidna terapija, programiranje, prematuritet, fetus, neonatus

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