Invest Clin 66(3): 332 - 346, 2025 https://doi.org/10.54817/IC.v66n3a09

Long-term effects of antenatal administration of corticosteroids. Where are we?

Carlos Briceño-Pérez[1], Liliana Briceño-Sanabria[2], Eduardo Reyna-Villasmil[3] and Paulino Vigil-De Gracia[4]

[1]Departamento de Obstetricia y Ginecología. Universidad del Zulia. Maracaibo, Venezuela.
[2]Bayview Surgery Center. Sarasota, Florida, United States of America.
[3]Departamento de Obstetricia y Ginecología. Hospital Central "Dr. Urquinaona, Maracaibo, Venezuela.
[4]Complejo Hospitalario "Dr. Arnulfo Arias Madrid" de la Caja de Seguro Social. Sistema Nacional de Investigación SENACYT Panamá.

Key words: corticosteroids, pregnancy; betamethasone; dexamethasone; delayed effects of medical treatment; neurologic manifestations; premature birth.

Abstract. There is increasing concern about the long-term effects of antenatal administration of corticosteroids, as some complications have been reported in neonates, adolescents and adults, which could be transmitted to subsequent generations, as it has been shown in animal and observational studies in humans. In this review, we summarize the current understanding of the long-term effects of antenatal corticosteroid administration and provide data to inform the preparation of guidelines. A literature search was performed in the PubMed database. A mechanism has been proposed as to how antenatal administration of corticosteroids could produce morbidity in neonatal neurodevelopment and lead to future diseases in adulthood. However, this hypothesis has not been proven in large randomized controlled trials. We summarize here the current data supporting and opposing the long-term effects of antenatal corticosteroid administration. Follow-up studies from randomized controlled trials have found no increased risk of neurologic impairment in children after exposure to a single course of antenatal corticosteroids. Observational and clinical trials of maternally administered antenatal corticosteroids show no evidence of increased disability on follow-up and describe associations rather than a proximate cause. Before 34 weeks of gestation, antenatal administration of corticosteroids in women at high risk for preterm birth appears to improve most neurodevelopmental outcomes. It is still recommended to administer a single course of corticosteroid treatment before preterm delivery.

Corresponding author: Carlos Briceño-Pérez. Departamento de Obstetricia y Ginecología. Universidad del Zulia. Maracaibo, Venezuela. E-mail: cabripe@hotmail.com

Efectos a largo plazo de la administración antenatal de corticosteroides. ¿Dónde estamos?

Invest Clin 2025; 66 (3): 332 – 346

Palabras clave: corticosteroides; embarazo; betametasona; dexametasona; efectos a largo plazo del tratamiento; manifestaciones neurológicas; parto pretérmino.

Resumen. Basándose en estudios en animales y observacionales en humanos, recientemente se han planteado una serie de dudas sobre los efectos a largo plazo de la administración antenatal de corticosteroides y se han notificado algunas complicaciones en neonatos, adolescentes y adultos; que incluso, podrían transmitirse a generaciones posteriores. Extenderla al periodo prematuro tardío, podría conducir a un aumento drástico del número de recién nacidos expuestos *in útero*. En esta revisión se resume el conocimiento actual de los efectos a largo plazo de la administración antenatal de corticosteroides y se aportan datos para la elaboración de guías para su uso. Para la metodología se realizó una búsqueda bibliográfica en la base de datos PubMed. Se ha propuesto un mecanismo para explicar cómo la administración antenatal de corticosteroides puede causar morbilidad en el neurodesarrollo neonatal y enfermedades programadas del adulto. Sin embargo, esta teoría no se ha demostrado en grandes pruebas controladas aleatorizadas. Aquí resumimos los efectos, a favor y en contra, a largo plazo de la administración antenatal de corticosteroides. La evidencia actual es inconsistente, los estudios de seguimiento de los ensayos controlados aleatorizados no han encontrado un mayor riesgo de deterioro neurológico en los niños, después de un solo curso antenatal de corticosteroides. Los ensayos observacionales y clínicos no muestran pruebas de aumento de discapacidad y describen asociaciones más que causas. Antes de las 34 semanas de embarazo, la administración antenatal de corticosteroides en mujeres con alto riesgo de parto pretérmino, parece mejorar la mayoría de resultados del neurodesarrollo. Antes del parto pretérmino, se recomienda un curso simple de tratamiento con corticosteroides.

Received: 10-03-2025 Accepted: 29-06-2025

INTRODUCTION

Preterm birth (PB) is a significant public health problem in the United States, with 1 in 10 infants being born before term [1]. Antenatal administration of corticosteroids (ACS) is a worldwide standard of care for preventing and reducing perinatal morbidity and mortality (PM) [2-4]. To establish the standards for ACS, after more than five decades, two NIH Consensus Conferences were held in 1994 and 2000, and numerous pronouncements from important institutions and scientific societies worldwide have been made [5,6].

Recently, some complications have been reported in neonates, adolescents and adults, which could even be transmitted to subsequent generations, and concern has been raised about the long-term effects of

ACS [7]. Recent literature suggests that the benefits of ACS may extend to late-preterm and early-term infants as well. These expanded uses may expose populations to ACS at gestational ages that have been minimally evaluated for their efficacy or risks. Researchers continue to investigate the possible associations between ACS and long-term neurodevelopmental outcomes in exposed children, given the potential implications of the overuse of ACS [8].

The objective of this review is to describe the current status of the long-term effects of ACS, based on existing evidence.

Methods/design

We conducted a narrative review of the targeted literature focusing on the long-term effects of ACS. The PubMed database was searched for literature published up from January, 01 2015 to May 26, 2024, using the following keywords: "corticosteroid", "betamethasone", "dexamethasone", "antenatal betamethasone", "antenatal dexamethasone", "antenatal corticosteroids", "late preterm antenatal corticosteroids", "at term antenatal corticosteroids", "neurodevelopmental outcomes", "neonatal outcomes", and "long-term effects". We also included studies from other sources that we considered historical or relevant to the topic. We excluded studies that were not focused on the long-term effects of ACS or that focused on the description, guidelines, and other aspects of ACS.

Antenatal administration of corticosteroids

ACS has led to its demonstration of efficacy and safety, making it a worldwide standard of care for the prevention and reduction of fetal morbidity and PM (Tables 1 and 2) [1,2-4,5,6,9,10].

Additionally, there is evidence supporting the recommendation of a "rescue" course of corticosteroids if seven days have passed after the initial course [2,11-13].

ACS in late preterm pregnancy

Recently, ACS has been extended beyond 34 weeks of gestation (34.0 to 36.6 weeks of gestation) because studies demonstrate modest benefits from ACS for late preterm and term elective cesarean deliveries [3]. In 2016, a great multicenter, randomized trial [14] involved women with a singleton pregnancy at late preterm pregnancy who were at high risk for delivery. Participants received two injections of betamethasone phosphate/acetate or a matching placebo 24 hours apart. The primary outcome was a neonatal composite of treatment in the first 72 hours or stillbirth or neonatal death within 72 hours after delivery. Primary outcome occurred in 165 of 1427 infants (11.6%) in the betamethasone group and 202 of 1400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval [CI], 0.66 to 0.97; p= 0.02). In the betamethasone group, neonatal hypoglycemia was more common (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; p<0.001). ACS (betamethasone) significantly reduced the rate of neonatal respiratory complications in women at risk for late preterm delivery [14].

The Society for Maternal-Fetal Medicine (SMFM), in march 2016 [15], in the "Implementation of the use of ACS in the late PB period in women at risk for preterm delivery", recommended the treatment with a betamethasone phosphate/acetate single course, in women with late preterm gestation, with a singleton pregnancy, who are at high risk for PB within the next seven days, [15]. In October 2016, the American College of Obstetricians and Gynecologists (ACOG) [11], recommended the administration of betamethasone phosphate/acetate in late preterm gestations, in pregnant women who have not received a previous course of ACS and are at risk of PB within seven days [11].

Two trials of antenatal dexamethasone in preventing mortality and severe morbidity among late preterm newborns, in low-income

Table 1. Recommendations of scientific institutions on ACS in early preterm, late preterm and term gestation.

Gestation	SMFM [16]	ACOG [11,12]	RCOG [13,20]	FIGO [21]	WHO [17,22]	WAPM-PMF [10]	EGPC [19]
Early preterm	ACS prior to 34 weeks is standard practice for women at high risk for delivery in the next 7 days.	For pregnant women between 24 0/7 and 33 6/7 weeks at risk of PB within 7 days. Also for pregnant women starting at 23 0/7 at risk of PB within 7 days.	Should be offered to women between 24^{+0} and 34^{+6} weeks' gestation in whom imminent PB is anticipated	For whom PB is anticipated between 24 and 34 weeks, one course of ACS should ideally be offered, 18 to 72 before PB is expected.	ACS is recommended for women with a high likelihood of PB from 24 weeks to 34 weeks.	A single course of ACS should be administered bet-ween 24+0 and 33+6 weeks of gestation in women at high-risk of PB within the next 7 days.	ACS should be administered to women between 24 and 33weeks, when PB is anticipated in the next seven days.
Late preterm	To patients who meet the inclusion criteria of the Antenatal Late Preterm Steroids trial.	ACS may be considered in pregnant women between 34 0/7 and 36 6/7 weeks who are at risk of PB Within 7 days and who have not received a previous course of ACS.	In very late preterm women, ACS should be considered in light of the balance of risks and benefits.	ACS should not be offered routinely to women in whom late preterm birth between 34 and 36 weeks is anticipated.	ACS is not recommended for women undergoing planned caesarean section at 34 weeks 0 days to 36 weeks 6 days.	ACS is not routinely recommendded between 34+0 and 36+6 weeks in women at high-risk of PB within the next 7 days because of the current uncertainty regarding the benefit to risk ratio.	ACS between 34,0 and 34,6 weeks should only be offered to a few selected cases (Expert opinion). ACS between 35 and 36 weeks should be restricted to prospective randomized trials.
Term	–	–	For women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion about the potential risks and benefits of ACS. Although ACS may reduce admission to the NICU for respiratory morbidity, it is uncertain if there is any reduction in RDS, transient tachypnoea or NICU admission, and may result in hypoglycaemia and potential developmental delay morbidity.	ACS should not be given routinely before cesarean delivery at term.	–	ACS is not routinely recommended before scheduled cesarean section at term because of the current uncertainty regarding the benefit to risk ratio. In the absence of other indications, a scheduled cesarean section should not be performed before 39+0 weeks.	ACS in pregnancies beyond 37weeks is not indicated, even for scheduled cesarean delivery.

SMFM: society of maternal fetal medicine ACOG: American college of obstetricians and gynecologists RCOG: royal college of obstetricians and gynecologists FIGO: federation international of obstetrics and gynecology WHO: world health organization WAPM-PMF: world association of perinatal medicine-perinatal medicine foundation EGPC: European guide of perinatal care ACS: antenatal administration of corticosteroids PB: preterm birth.

Table 2. Benefits and risk of ACS.

– ACS before 34 weeks presents an undeniable benefit for the unborn child if born prematurely.
– Identifying patients who will actually deliver within 7 days following the treatment is difficult and further studies need to be conducted.
– After 34 weeks of gestation the benefit/risk balance is against ACS.
– Studies should be conducted on reducing ACS.

ACS: antenatal administration of corticosteroids.

countries, did not show adverse childhood neurodevelopmental outcomes and proved safe and efficacious [16,17]. In the ALPS follow-up study of a Randomized Controlled Trial (RCT) 16, ACS initially showed improvement in short-term neonatal respiratory outcomes at age six years or older, without adverse childhood neurodevelopmental outcomes, but with an increased rate of hypoglycemia [16]. In a multicenter, two-arm, parallel, double-blind, placebo-controlled, randomized trial[17]; antenatal dexamethasone for late preterm birth did not result in a reduction in neonatal death, stillbirth, or severe neonatal respiratory distress [17].

Currently, there is no agreement on the use of ACS in the late preterm period, as the SMFM [18] and ACOG [12] recommend its use in the United States, whereas many institutions and scientific societies worldwide do not [10,13,19-22].

The expanded use of ACS in late preterm pregnancy

Literature suggests that the benefits of ACS may extend to late-preterm and early-term infants as well [2,11,12,14,18]. This expanded use exposes populations to ACS at gestational ages that have been minimally evaluated for efficacy or risk. Extending the use of ACS to the late preterm period may lead to a dramatic increase in the number of infants exposed *in utero* to ACS (nearly 10% of fetuses) and an even greater increase in the proportion of fetuses exposed to ACS, which will eventually be born at term. As treatments expand, benefits decrease and risks increase[3,23-27].

ACS in a term pregnancy

In 2005, the multicenter RCT study ASTECS (Antenatal Steroids for Term Elective Cesarean Section) included 998 women with term pregnancies, of whom 503 received a single course of betamethasone phosphate/acetate in the 48 hours preceding a cesarean section. The primary outcome was admission to the special care baby unit with respiratory distress. Of the 35 children admitted to the special baby units with respiratory distress, 24 babies were in the control group and 11 in the intervention group, a statistically significant difference ($p = 0.02$). The incidence of admission with respiratory distress in the control group was 0.051, and in the treatment group, was 0.024 (relative risk 0.46, 95% confidence interval 0.23 to 0.93). In this study, both ACS and delaying delivery until 39 weeks reduce admissions to special care baby units with respiratory distress after elective cesarean section at term[28]. In 2009, a Cochrane systematic review [29,] concluded that results from the single trial are promising, but more studies with larger samples were needed.

Additionally, more data and a longer follow-up would be needed to assess potential harms and complications. In October 2010, the Royal College of Obstetricians and Gynecologists of the United Kingdom [13] established that there is a lack of evidence available regarding the safety of ACS in babies born after 36+0 weeks of gestation. Elective lower-segment cesarean section should not typically be performed until 39+0 weeks of gestation, rather than the ACS [13].

ACS and long-term effects

The increased use of ACS during the late prenatal period and prior to cesarean sections at term, due to their proven efficacy and safety, has resulted in a significant rise in the number of infants exposed to ACS in utero. Approximately three-fourths of all PB occur in the late preterm period [16]. Currently, almost 10% of fetuses are exposed *in utero* to ACS, and >50% of women given ACS for presumed PB will not deliver within the optimal exposure window of seven days [3,7,24,30]. The net effect is that a substantial fraction of the delivery population will be exposed to ACS, and more fetuses exposed to ACS are delivered at term (most recipients deliver after 35 weeks' gestation and 44% to 50% deliver at term) [3,7,24].

The New Zealand Group followed children who received betamethasone *in utero* during the study of Liggins study [4] for many years, 2005-2007, establishing that [2]: 1. ACS with a single course of betamethasone do not alter psychological, pulmonary and cardiovascular functions at 30-31 years of follow-up. 2. Adults who were born moderately preterm have increased blood pressure and insulin resistance at 30 years of age; 3. PB, and not poor fetal growth, is the primary determinant of this association; 4. Obstetricians should continue to use a *single course* of ACS for the prevention of neonatal respiratory distress syndrome (RDS).

Based on animal and observational studies in humans, several concerns have recently been raised about the long-term effects of ACS, and some complications have been reported in neonates, adolescents, and adults, which could even be transmitted to subsequent generations [7,18]. Although the long-term risks associated with ACS use (such as neonatal neurodevelopmental issues and adult program diseases) remain uncertain, several observations have been reported on the likely long-term effects of ACS. Late effects of ACS suggest caution for the expanded use of ACS beyond at-risk pregnancies at 24-34 weeks [2,24].

ACS and the hypothalamic-pituitary-adrenal axis

In animal studies, exposure to exogenous ACS has been associated with a delay in brain growth and development, as well as increased activity and persistent changes in the hypothalamic-pituitary-adrenal (HPA) axis and endogenous corticosteroid production. At the molecular level, transcriptional changes occur in metabolic and growth pathways. Epigenetic mechanisms participate in transgenerational inheritance, not genomic[7,25]. Exposures that alter the methylation status of the 11β-hydroxysteroid dehydrogenase type 2 enzyme in the placenta can lead to transcriptional repression of the gene, resulting in the fetus being exposed to higher levels of cortisol. Such an adaptation to an intrauterine insult is thought to be beneficial in the short term and is linked to an increased chance of offspring survival to reproductive age. In adults, activation of the HPA axis has been linked to increased likelihood of cardiovascular risk factors comprising the metabolic syndrome, including higher glucose, blood pressure, and triglycerides, as well as ischemic heart disease, cognitive decline, and depression in later life[25]. It remains to be determined whether the HPA axis hyperactivity contributes to such effects [7,25,26].

Evidence on the long-term effects of ACS

Let us now review some recent animal and human evidence on the long-term effects of ACS (Table 3).

Animal studies

In utero exposure to single doses of exogenous corticosteroids may affect fetal brain development and neurological outcomes, as suggested by some animal studies. The hypothesis proposed by Seckl in 2004 [31] was recognized in an editorial by Reynolds and Seckl [25], indicating that rats and lambs exposed to an adverse in utero environment during development can experience long-term effects on physiology and an increased risk of adult disease. Overall, the

Table 3. Evidences on the long-term effects.

Authors	Year	Type of evidence	Results/Conclusions/Comments
			Evidence in animals
Reynolds, Seckl [25]	2012	Editorial	Recognize the hypothesis of Seckl [31], in 2004.
Seckl [31]	2004	Review	Hypothesized that prenatal exposure to excess glucocorticoids or stress might represent a mechanism linking fetal growth with adult pathophysiology. The data suggest that both pharmacological and physiological exposure prenatally to excess glucocorticoids, programmes cardiovascular, metabolic and neuroendocrine disorders in adult life. It was published in 2004, i.e. 19 years ago. It was based on a majority of animal studies. Most of the cited animal studies, in which weight reduction was obtained, were conducted between 1978-2001, and used multiple courses of ACS, characterized because they do not enhance the beneficial effects of single courses and because produce fetal injury. Multiple courses of ACS are not recommended since 2000 [6].
Jobe, Goldenberg [3]	2018	Clinical opinion	Noted that cardiovascular and metabolic abnormalities have been identified in large animal models and cohorts of children exposed to ACS, that are consistent with fetal programming for adult diseases.
			Evidence in humans
			A single course of ACS
Smolder et al. [33]	1990	RCT	ACS does not alter lung function or the prevalence of wheeze and asthma at age 30. Found no difference in neurologic and ophthalmologic examination results.
Dalziel et al., cited by [2]	2006	Longitudinal by 30 years	ACS of a single course of betamethasone, found no increased risk of impairment in cognitive functioning, working memory, attention, psychiatric morbidity, or health-related quality of life.
Stutchfield et al. [34]	2013	Multicenter RCT (ASTECS trial),	No difference in behavioral, cognitive, or developmental outcomes among children aged 8-15 years whose mothers received a single course of ACS before elective cesarean delivery at 37-38 weeks of gestation.
Sotiriadis et al. [35]	2015	Systematic review	A single course of ACS in women at high risk for PB appears to improve most neurodevelopmental outcomes in offspring born before 34 weeks of gestation.
Alexander et al. [36]	2016	Cross-sectional study	A single course of ACS does not aggravate long-term cognitive deficits. Our data indicated that conditions related to a threatening PB rather than ACS per se, were associated with long-term decreases in the child's intelligence.
Melamed et al. [27]	2019	Retrospective cohort study	Children exposed to ACS were more likely to have suspected neurocognitive disorders.
Raikkönen et al. [8]	2020	Retrospective cohort study	Siblings exposed to ACS were more likely to exhibit any childhood mental or behavioral disorder.
Ninan et al. [37]	2022	Systematic review	A single course of ACS, was associated with a significant decrease in the adjusted odds of neurodevelopmental impairment in children with extremely preterm birth..
Hutcheon et al. [38]	2022	Regression discontinuity design	Found little evidence that children with higher probability of exposure to ACS have higher rates of ADHD prescriptions in childhood, supporting the safety of ACS for this neurodevelopmental outcome.
			Multiple course of ACS
Asztalos et al. [42]	2014	Secondary analysis of the RCT MACS (MACS-5 trial)	Children born ≥ 37 weeks and exposed to multiple ACS therapy may have an increased risk of neurodevelopmental/neurosensory impairment by 5 years of age.

ACS: Antenatal administration of corticosteroids RCT: Randomized controlled trials ASTECS: Antenatal betamethasone for term caesarean section PB: Preterm birth ADHD: Attention deficit/hyperactivity disorder MACS: Multiple antenatal courses of steroids.

data suggest that both pharmacological and physiological exposure prenatally to excess glucocorticoids can lead to cardiovascular, metabolic and neuroendocrine disorders in adult life [31].

Concerning the Seckl's study [31], it should be noted that: 1. It was published in 2004, i.e. 20 years ago. 2. It was based on a majority of animal studies. 3. Most of the cited animal studies, in which weight reduction was obtained used multiple courses of ACS (defined as the use of ACS multiple courses: three, four, five, six or more courses), characterized because they do not enhance the beneficial effects of single courses and because produce fetal injuries and were conducted between 1978 and 2001 [2]. For these reasons, they have not been recommended since 2000. The four extensive studies worldwide, using multiple ACS courses, reported fetal injuries (TEAMS, NIH, ACTORDS, and MACS) [2,6]. On multiple courses, in the section "Human Clinical Observations," Seckl[31] notes that a single course of ACS is associated with a significant reduction in the incidence of intraventricular hemorrhage and a trend toward fewer neurodevelopmental disabilities. However, a survey by the British Obstetric Departments showed that 98% of participants were prescribing multiple courses of ACS. There is little evidence of the safety and efficacy of such a regime. Recent overviews suggest that there is no evidence of additional benefits from multiple courses of glucocorticoid therapy during pregnancy, but that clear conclusions are prevented by the lack of prospective RCTs and by variations in the protocols employed. ACS has also been linked with higher blood pressure in adolescence and subtle effects on neurological function, including reduced visual closure and visual memory. In 2018, Jobe and Goldenberg [3] noted in a clinical opinion article that cardiovascular and metabolic abnormalities have been identified in large animal models and cohorts of children exposed to ACS, which are consistent with fetal programming for adult diseases [3]. After 34 weeks of gestation, when rapid brain growth occurs, theoretically, these effects could be more pronounced [32].

Human studies:

A single course of ACS

In children born after exposure to a single course of ACS, follow-up studies from RCTs of ACS have found no increased risk of neurologic impairment. Their precise assessment of neurodevelopmental outcomes was a strength of these studies [16]. However, findings are mixed, in observational studies.

No differences between the corticoid and the placebo groups were found in 1990, in one RCT of betamethasone, when Smolder et al. [33] studied potential side effects of ACS to prevent neonatal RDS, in 10- to 12-year-old children (N: 84). The lung function as assessed by the presence of wheeze and asthma at age 30, was not altered by ACS. This study found no difference in neurologic and ophthalmologic examination results [33]. These findings were similar to those of a longitudinal study conducted in 2006, which followed 534 30-year-old adults[33]. ACS by a single course of betamethasone did not increase the risk of impairment in lung function, cognitive functioning, working memory, attention, psychiatric morbidity, or health-related quality of life between the betamethasone and placebo groups [2]. In a questionnaire-based follow-up of a multicenter RCT (ASTECS Trial), Stutchfield et al. [34] demonstrated no difference in behavioral, cognitive, or developmental outcomes among children aged 8 to 15 years whose mothers received a single course of ACS before elective cesarean at 37 to 38 weeks of gestation [34]. In 2015, Sotiriadis et al. [35], concluded that a single course of ACS in women at high risk for PB appears to improve most neurodevelopmental outcomes in offspring born before 34 weeks of gestation as showed by reduced risk for cerebral palsy (seven studies; treated: 390 of 5,199, untreated: 146 of 1,379; RR 0.678, 95% confidence interval [CI] 0.564-0.815), psycho-

motor development index less than 70 (two studies; treated: 783 of 3,049, untreated: 258 of 969; RR 0.829, 95% CI 0.737-0.933), and severe disability (five studies; treated: 1,567 of 4,840, untreated: 475 of 1,211; RR 0.787, 95% CI 0.729-0.850); in a systematic review, included RCT and non RCT, reporting on the neurodevelopmental outcomes of children whose mothers were administered a single course of ACS for threatened PB [35]. In a cross-sectional study of a mixed-sex cohort of 222 term-born children (aged 6-11 years), Alexander et al. [36] concluded that their data indicated that ACS does not aggravate long-term cognitive deficits [36].

In 2019, a retrospective cohort study (2006-2011), by Melamed et al. [27], examined outcomes at five years of age in 5432 children exposed to ACS compared with 523,782 children not exposed. Children exposed to ACS were more likely to have suspected neurocognitive disorders (exposure to ACS vs no exposure: 25.8% vs 21.6%; p<0.001; adjusted hazard ratio [aHR] 1.16, 95% CI 1.10 to 1.21) [27]. In 2020, Raikkönen et al. [8] conducted a population-based retrospective cohort study using nationwide registries of all singleton live births in Finland that survived until one year, along with a within-sib-pair comparison among term siblings. They found that siblings exposed to ACS were more likely to exhibit any childhood mental or behavioral disorder and concluded that ACS was significantly associated with mental and behavioral disorders in term-born children (12.01% among those exposed to ACS vs 6.45% among those not exposed; absolute difference, 5.56% [95% CI, 5.04%-6.19%]; p<.001) [8]. In 2022, in another systematic review and meta-analysis of 30 studies involving more than 1.25 million children, Ninan et al. [37] noted that exposure to a single course of ACS was associated with a significant decrease in the adjusted odds of neurodevelopmental impairment in children with extremely high PB. ACS exposure was associated with increased adjusted risks of neurocognitive and/or psychological impairment in children with late-preterm and full-term birth [37]. Furthermore, in 2022, Hutcheon et al. [38], found little evidence that children with a higher probability of exposure to ACS have higher rates of attention-deficit/hyperactivity disorder (ADHD) prescriptions in childhood, supporting the safety of ACS for this neurodevelopmental outcome. They used a regression discontinuity design, over a median follow-up period of nine years, 892 (5.5%) children had one or more dispensations of ADHD [38]. In 2022, Sarid et al. [39], synthesized the association between ACS exposure and the risk of preterm birth and brain development in infants ultimately born at late preterm and term. Their protocol included 27 observational studies (12 retrospective cohort studies, 11 prospective cohort studies and four cross-sectional studies). In 14 studies, a single course of ACS was administered; in two studies, two or more courses of ACS were administered. In seven studies, the number of courses of ACS varied among study participants and in four studies, the regimen was not specified. The most common adverse outcomes were reduced neonatal head circumference, structural cortical differences on magnetic resonance images, increased prevalence of psychiatric problems, and increased risk of neurodevelopmental delays, in ACS-exposed late preterm and term infants. Further research, such as preterm labor, maternal stress, and the number of ACS courses, is needed to establish better the long-term neurological effects of ACS on late preterm and term infants, given that the existing research was at serious risk for bias [39]. In 2023, Yao et al. [40], investigated the associations between ACS and serious infections in children during the first 3, 6, and 12 months of life. This nationwide cohort study found that children exposed to one course of ACS were significantly more likely to have an increased risk of serious infection during the first 12 months of life. The study cohort consisted of 1,960,545 singleton children: 45,232 children were exposed to one course of ACS, and 1,915,313 children were not ex-

posed. The adjusted hazard ratios for overall serious infections, sepsis, pneumonia, and acute gastroenteritis, among children exposed to ACS, were significantly higher than those not exposed. The adjusted hazard ratios for overall serious infection ($p<0.001$), sepsis ($p = 0.02$), pneumonia ($p<0.001$), and acute gastroenteritis ($p<0.001$) were significantly higher from birth to 12 months of life [40]. In 2023, Weiss et al. [41] determined if ACS exposure was associated with infant cortisol levels. One hundred eighty-one women and their infants participated in the study. Infants whose mothers received ACS had significantly lower resting-state (B = -2.47, CI: -3.691; to 0.0484) and post-stressor (B = 0.51, CI: -4.283, to -0.4276) cortisol levels across the first year of life than infants whose mothers did not receive ACS. Results indicate a state of dampened HPA activation and cortisol hypo-arousal that persists across the first year of life among infants who were exposed to ACS in utero. They concluded that further research is needed to examine the mechanisms responsible for any alterations that occur during the development of the fetal HPA axis, including epigenetic and biochemical factors [41].

Multiple, repeat or weekly courses of ACS:

In 2000, studies examining multiple courses of ACS, were reserved for patients enrolled in clinical trials [2,6]. However, we will point out that after multiple courses of ACS, different outcomes have been observed. In 2014, in the trial MACS-5, Asztalos et al. [42] concluded that children born ≥ 37 weeks and exposed to multiple ACS therapy may have an increased risk of neurodevelopmental/neurosensory impairment by five years of age [42]; they studied the association between gestational age at birth, multiple courses of ACS and outcomes at five years, In the previously cited 2022, Sarid et al.´s trial [39], two or more courses of ACS were administered.

Limitations of previous studies

Some limitations have been identified in previous studies (Table 4) [18,24,42,43]. Data from RCT on the long-term effects of ACS on the fetal brain are limited [22].

Table 4. Limitations to evidences on the long-term effects of ACS [18,24,42,43].

- Many of these studies either were from small samples or used population-based registry data, from which the severity of illness may be difficult to discern.
- Given the retrospective, observational study designs, the authors did not account for the admission or delivery indication or other antenatal complications (such as fetal growth restriction, oligohydramnios, infections during pregnancy, red blood cell alloimmunization, hydrops, or congenital anomalies) that may substantially influence long-term neurologic outcomes.
- Previous studies have suggested that it is not, in fact, the ACS* itself but rather the condition leading to a threat of PB† that is associated with neurologic impairment in exposed children.
- Information regarding steroid type, dosing, frequency, and timing of exposure in most studies is unknown.
- There is a potential bias related to differential referral or diagnosis of subjects exposed to ACS with abnormal development
- The lack of standardized evaluations by trained professionals blinded to exposure status, along with the absence of defined diagnostic criteria, leaves room for bias and subjectivity in diagnosis.

ACS: Antenatal administration of corticosteroids PB: Preterm birth.

To answer the question of where we stand, we summarize the current data for and against the long-term effects of ACS.

Evidence for and against the long-term effects of ACS

In recent years, there has been much evidence for and against the long-term effects of ACS (Table 5) [2,3,7-9,18,23-27,29,35-37,42,43].

Summary and conclusions

Animal studies have found that ACS affect many organs. Observational and clinical trials of maternal ACS show no evidence of increased disability on follow-up and describe associations rather than a proximate cause.

ACS in women at high risk for PB appears to improve most neurodevelopmental

Table 5. Evidence for and against long-term effects of ACS [2,3,7-9,18,23-27,29,35-37,42,43]

FOR

– Several concerns have been raised on the potential long-term effects of ACS* on cerebral function and neonatal growth.
– It is now well recognized that exposure to an adverse in utero environment during development has long-term effects on physiology and later risk of adult disease.
– Large observational studies have reported reduced neonatal weight and length in children exposed to ACS.
– Cardiovascular and metabolic abnormalities have been identified in large animal models and cohorts of children exposed to ACS that are consistent with fetal programming for adult diseases.
– There are observational data linking exposure to multiple courses of ACS to increased rates of aggressive, destructive, distractible and hyperkinetic behavior at both ages of 3 and 6 years.
– Siblings exposed to ACS were more likely to exhibit any childhood mental or behavioral disorder.
– The RCT data also do not strongly support the optimal interval from ACS to delivery of 1-7 days.
– Epidemiology-based studies using large cohorts with >85% of at-risk pregnancies treated with ACS, probably overestimate the benefits of ACS.
– Although most of the prematurity-associated mortality is in low-resource environments, the efficacy and safety of ACS in those environments remain to be evaluated.

AGAINST

– The long-term outcomes in human children are not well understood. Animal studies have found that ACS affect many organs across multiple stages of life.
– Data from RCT on the long-term effects of ACS on the fetal brain are limited. Another important factor is that many of the included infants were born prematurely and it is likely that the immediate benefits of ACS compensate for the potential long-term adverse effects of ACS.
– Observational reports describe associations rather than proximate cause and are subject to bias from undetected and undetectable confounders.
– These high evidence level randomized data will allow us to reframe the late preterm ACS discussion around the uncertain risk of developmental delay.
– ACS-exposed children born extremely preterm had a markedly lower risk of neurodevelopmental impairment and/or psychological outcomes when compared with unexposed children.
– ACS in women at high risk for PB appears to improve most neurodevelopmental outcomes in offspring born before 34 weeks of gestation and is significantly associated with reduced mortality before 3 years of age in very low birth weight infants with chorioamnionitis (do not alter neurodevelopmental outcomes).
– Other studies either found no difference in neurodevelopmental outcomes or attributed the increased observed risk for adverse neurologic outcomes among term-born children to receiving multiple courses (rather than a single course) of ACS or to the underlying condition threatening preterm delivery rather than the steroid exposure itself.
– The short-term benefits of ACS for high-risk pregnancies in high-resource environments certainly justify ACS. Single course ACS treatment before preterm delivery must still be recommended as life-saving and cost effective intervention. Late effects of ACS suggest caution for the expanded use of ACS beyond at-risk pregnancies at 24-34 weeks
– Multiple ACS courses are not recommended since 2000.

ACS: Antenatal administration of corticosteroids RCT: Randomized controlled trials PB: Preterm birth.

outcomes before 34 weeks of gestation, and reduces mortality before three years of age in very low birth weight infants with chorioamnionitis.

Other studies either found no difference in neurodevelopmental outcomes or attributed the increased observed risk for adverse neurologic outcomes among term-born children to receiving multiple courses of ACS or to the underlying condition threatening PB rather than the steroid exposure itself.

On the long-term effects of ACS on the fetal brain, there are limited data from RCTs. The interpretation of available RCT data is further hampered by both the lack of an unexposed control group and insufficient power to detect significant differences in rare events. Additionally, many of the included infants were born prematurely, which is another important factor.

In high-resource environments, the short-term benefits of ACS for high-risk pregnancies certainly justify ACS. Single-course ACS treatment before preterm delivery must still be recommended as a life-saving and cost-effective intervention.

Cautioning against the expanded use of ACS beyond at-risk pregnancies at 24-34 weeks suggests late effects of ACS.

Multiple ACS courses are not recommended since 2000.

The long-term outcomes in human children are not well understood. Therefore, the possible association between ACS and long-term neurodevelopmental outcomes in exposed children should be further investigated. Specifically, longitudinal studies and large RCTs are needed to provide more insight into this topic.

Statement of ethics

This study was approved by the University of Zulia Ethics Committee (number 21-2024) on March 21, 2024. It adhered to the laws and national ethical guidelines of Venezuela, as well as the COPE guidelines and the Declaration of Helsinki.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding Sources

The authors did not receive support from any organization for the submitted work.

ORCID number of authors

- Carlos Briceño-Perez (CBP): 0000-0002-3270-8236
- Liliana Briceño-Sanabria (LBS): 0000-0002-5045-0072
- Eduardo Reyna-Villasmil (ERV): 0000-0002-5433-7149
- Paulino Vigil-De Gracia (PVDG): 0000-0002-1494-3654

Author contributions

CBP contributed to the study conception. CBP, LBS, ERV and PVDG contributed to the design, researched literature, analized it and design the protocol, manuscript revision and approved final version.

REFERENCES

1. **American College of Obstetricians Gynecologists' Committee on Practice Bulletins—Obstetrics.** Practice bulletin number 171: Management of preterm labor. 2016. Obstet Gynecol 2016;128 (4):e155-164. *https://doi.org/10.1097/AOG.0000000000001711.*
2. **Briceño-Pérez C**. Maduración pulmonar fetal. Prevención exitosa de complicaciones y muertes perinatales. 1ª Edición. Caracas. AMOLCA; 2008. Disponible en: https://www.researchgate.net/publication/263967080_Maduracion_Pulmonar_Fetal.
3. **Jobe A, Goldenberg R**. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. Am J Obstet

Gynecol 2018;219(1):62-74. *https://doi.org/10.1016/j.ajog.2018.04.007*

4. **Liggins GC, Howie R.** A controlled trial of antepartum corticosteroid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50(4): 515-525. PMID: 4561295.
5. **NIH Consensus Statement**. Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. 1994;12(2):1-24. PMID: 7728157.
6. **National Institutes of Health Consensus Development Panel.** Antenatal corticosteroids revisited: repeat courses. National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. Obstet Gynecol 2001;98(1)144-150. *https://doi.org/10.1016/s0029-7844(01) 01410-7.*
7. **Briceño-Pérez C, Briceño-Sanabria L, Briceño-Sanabria C, Reyna-Villasmil E**. Early life corticosteroid overexposure: epigenetic and fetal origins of adult diseases. Int J Obstet Gynecol. 2024; 164(1):40-46. *https://doi.org/10.1002/ijgo.14914.*
8. **Raikkönen K, Gissler M, Kajantie E**. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. JAMA 2020;323(19):1924-1933. *https://doi.org/10.1001/jama.2020.3937.*
9. **Briceño-Pérez C, Reyna-Villasmil E, Vigil-De Gracia P**. Antenatal corticosteroid therapy: historical and scientific basis to improve preterm birth management. Eur J Obstet Gynecol Reprod Biol 2019; 234: 32-37. *https://doi.org/10.1016/j.ejogrb.2018.12.025*
10. **Dagklis T, Sen C, Tsakiridis I, Villalaín C, Allegaert K, Wellmann S, et al.** The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation. J Perinat Med 2022; 50(4):375-385; *https://doi.org/10.1515/jpm-2022-0066.*
11. **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(4): e187-194. *https://doi.org/10.1097/AOG.0000000000001715.*
12. **Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation.** Obstet Gynecol 2017; 130(2): e102-109. *https://doi.org/10.1097/AOG.0000000000002237.*
13. **Royal College of Obstetricians and Gynaecologist.** Antenatal corticosteroids to reduce neonatal morbidity and mortality. Green top guideline N° 7. 2010. Disponible en: https://www.glowm.com/pdf/Antenatal%20Corticosteroids%20to%20Reduce%20Neonatal%20Morbidity.pdf
14. **Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, NICHD Maternal-Fetal Medicine Units Network.** Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016; 374(14):1311-1320. Erratum in: N Engl J Med 2023;388(18):1728. *https://doi.org/10.1056/NEJMx220010.*
15. **Society for Maternal-Fetal Medicine (SMFM) Publications Committee.** Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol 2016; 215 (2) B13-5. *https://doi.org/10.1016/j.ajog.2016.11.1032.*
16. **Gyamfi-Bannerman C, Clifton RG, Tita ATN, Blackwell SC, Longo M, de Voest JA, O'Shea TM, et al.** Neurodevelopmental Outcomes After Late Preterm Antenatal Corticosteroids. The ALPS follow-up study. JAMA 2024;331(19):1629-1637. *https://doi.org/10.1001/jama.2024.4303.*
17. **WHO ACTION Trials Collaborators**. Antenatal dexamethasone for late preterm birth: a multi-centre, two-arm, parallel, double-blind, placebo-controlled, randomized trial. EClinicalMedicine. 2022;44:101285. *https://doi.org/10.1016/j.eclinm.2022.101285*
18. **Society for Maternal-Fetal Medicine (SMFM), Reddy U, Deshmukh U, Dude A, Harper L, Osmundson SS.** Society for Ma-

ternal-Fetal Medicine Consult Series #58: Use of antenatal corticosteroids for individuals at risk for late preterm delivery. Am J Obstet Gynecol 2021; 225(5):B36-B42. *https://doi.org/10.1016/j.ajog.2021.07.023.*

19. **Daskalakis G, Pergialiotis V, Domellöf M, Ehrhardt H, Di Renzo GC, Koç E, et al.** European guidelines on perinatal care: Corticosteroids for women at risk of preterm birth. J Mat Fetl Med 2023; 36(1): 2160628. *https://doi.org/10.1080/14767058.2022.2160628.*
20. **Stock SJ, Thomson AJ, Papworth S; Royal College of Obstetricians and Gynaecologists.** Antenatal corticosteroids to reduce neonatal morbidity and mortality. BJOG 2022; 129(8):e35-e60. *doi: https://doi.org/10.1111/1471-0528.17027.*
21. **Norman J, Shennan A, Jacobsson B, Stock SJ, FIGO Working Group for Preterm Birth.** FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm. Int J Gynecol Obstet. 2021;155 (1):26-30. *https://doi.org/10.1002/ijgo.13836.*
22. **World Health Organization. WHO recommendations on Antenatal corticosteroids for improving preterm birth outcomes.** World Health Organization 2022. Licence: CC BY-NC-SA 3.0 IGO. PMID: 36279381.
23. **Jobe A**. Antenatal Corticosteroids. A concern for lifelong outcomes. J Pediatr 2020; 217:184-188. *https://doi.org/10.1016/j.jpeds.2019.09.015.*
24. **Vidaeff A, Belford M, Kemp M, Saade GR, Caughey AB, Wapner RJ, et al.** Updating the balance between benefits and harms of antenatal corticosteroids requires appropriate causal inference: a reply. Am J Obstet Gynecol 2023; 228(2):129-132. *https://doi.org/10.1016/j.ajog.2022.10.002.*
25. **Reynolds RM, Seckl JR.** Antenatal glucocorticoid treatment: are we doing harm to term babies? J Clin Endocrinol Metab 2012;97(10):3457-3459. *https://doi.org/10.1210/jc.2012-3201.*
26. **Rizzo G, Mappa I.** Antenatal corticosteroids and fetal growth: do we need more evidence? Am J Obstet Gynecol 2023;228(3):353. *https://doi.org/10.1016/j.ajog.2022.09.038.*
27. **Melamed N, Asztalos E, Murphy K, Zaltz A, Redelmeier D, Shah BR, Barrett J**. Neurodevelopmental disorders among term infants exposed to antenatal corticosteroids during pregnancy: a population-based Study. BMJ Open 2019;9(9):e031197. *https://doi.org/10.1136/bmjopen-2019-031197.*
28. **Stutchfield P, Whitaker R, Russell I, Antenatal Steroid for Term Elective Caesarean Section (ASTECS) Research Team.** Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomized trial. BMJ 2005;331: (7518): 662. *https://doi.org/10.1136/bmj.38547.416493.06.*
29. **Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis J.** Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev 2009; (4):CD006614. *https://doi.org/10.1002/14651858.CD006614.pub2.*
30. **di Donato E, Guerby P, Guyard Boileau B, Vayssiere C, Allouche M**. A nomogram to optimize the timing of antenatal corticosteroids in threatened preterm delivery. Am J Obstet Gynecol MFM 2023;5(7):100955. *https://doi.org/10.1016/j.ajogmf.2023.100955.*
31. **Seckl JR**. Prenatal glucocorticoids and long-term programming. Eur J Endocrinol 2004;151(Suppl 3):U49-U62. *https://doi.org/10.1530/eje.0.151u049.*
32. **Kugelman A, Colin AA.** Late preterm infants: near term but still in a critical developmental time period. Pediatrics 2013;132(4):741-751. *https://doi.org/10.1542/peds.2013-1131.*
33. **Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J**. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12-year follow-up. Pediatrics 1990;86(1):65-70. PMID: 2193304.

34. **Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJ**. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed 2013;98(3):F195-200. *https://doi.org/10.1136/archdischild-2012-303157.*
35. **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 metaanalysis. Obstet Gynecol 2015;125(6):1385-1396. *https://doi.org/10.1097/AOG.0000000000000748.*
36. **Alexander N, Rosenlöcher F, Dettenborn L, Stalder T, Linke J, Distler W, et al**. Impact of antenatal glucocorticoid therapy and risk of preterm delivery on intelligence in term-born children. J Clin Endocrinol Metab 2016;101(2): 581-589. *https://doi.org/10.1210/jc.2015-2453.*
37. **Ninan K, Livanage SK, Murphy KE, Asztalos E, McDonald SD.** Evaluation of long-term outcomes associated with preterm exposure to antenatal corticosteroids. A systematic review and meta-analysis. JAMA Pediatr 2022;176(6):e220483. *https://doi.org/10.1001/jamapediatrics.2022.0483.*
38. **Hutcheon JA, Strumpf EC, Liauw J, Skoll MA, Socha P, Srour M, et al.** Antenatal corticosteroid administration and attention-deficit/hyperactivity disorder in childhood: a regression discontinuity study. CMAJ 2022;194(7):E235-E241. *https://doi.org/10.1503/cmaj.211491.*
39. **Sarid EB, Stooper ML, MorencyAM, Garfinkle J.** Neurological implications of antenatal corticosteroids on late preterm and term infants: a scoping review. Pediatr Res 2022; 92(5):1225-1239. *https://doi.org/10.1038/s41390-022-02135-3.*
40. **Yao TC, Chang SM, Wu CS, Tsai YF, Sheen KH, Hong X, et al**. Association between antenatal corticosteroids and risk of serious infection in children: nationwide cohort study. BMJ 2023;382:e075835. *https://doi.org/10.1136/bmj-2023-075835.*
41. **Weiss SJ, Keeton V, Richoux S, Cooper B, Niemann S.** Exposure to antenatal corticosteroids and infant cortisol regulation. Psychoneuroendocrinology 2023; 147:105960. *https://doi.org/10.1016/j.psyneuen.2022.105960.*
42. **Asztalos E, Willan A, Murphy K, Matthews S, Ohlsson A, et al., and MACS-5 Collaborative Group.** Association between gestational age at birth, antenatal corticosteroids, and outcomes at 5 years: multiple courses of antenatal corticosteroids for PB study at 5 years of age (MACS-5). BMC Pregnancy Childbirth 2014;14:272. *https://doi.org/10.1186/1471-2393-14-272.*
43. **Raikkönen K, Gissler M, Tapiainen T, Kajantie E**. Associations between maternal antenatal corticosteroid treatment and psychological developmental and neurosensory disorders in children. JAMA Net Open 2022;5(8):e2228518. *https://doi.org/10.1001/jamanetworkopen.2022.28518.*