# Long-term neuropathological and/or neurobehavioral effects of antenatal corticosteroid therapy in animal models: a systematic review

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Systematic Review

**Abstract:**

**Background**

Antenatal corticosteroids (ACS) are recommended to all women at risk for preterm delivery, currently there is controversy about the subsequent long-term neurocognitive sequelae. This systemic review summarizes the long-term neurodevelopmental outcomes after ACS therapy in animal models.

**Methods**

An electronic search strategy incorporating MeSH and keywords was performed using all known literature databases and in accordance with PRISMA guidance. (PROSPERO CRD42019119663).

**Results**

Of the 669 studies identified eventually 64 were included. The majority of studies utilized dexamethasone at relative high dosages and primarily involved rodents. There was a high risk of bias, mostly due to lack of randomization, allocation concealment and blinding. The main outcomes reported on was neuropathological, particularly glucocorticoid receptor expression and neuron densities, and neurobehavior. Overall there was an upregulation of glucocorticoid receptors with lower neuron densities and a dysregulation of the dopaminergic and serotonergic systems. This coincided with various adverse neurobehavioral outcomes.

**Conclusions**

In animal models ACS consistently lead to deleterious long-term neurocognitive effects. This may be due to the specific agents, i.e. dexamethasone, or the repetitive/higher total dosing used. ACS administration varied significantly between studies and there was a high risk of bias. Future research should be standardized in well characterized models.

## Background

Glucocorticoids (GCs) are essential in the biological processes required for the transition from intrauterine to extrauterine life. The overall action of endogenous GCs is to trigger organ maturation, thereby enabling the lungs, liver, gastrointestinal tract, thyroid, adrenals and kidneys to function and sustain life outside the uterine environment (1). GCs are also crucial for normal brain maturation, as they initiate terminal maturation, remodel axons and dendrites and affect cell survival (2). Both suppressed and elevated GC levels can impair brain development and functioning (3).

Since 1994, antenatal corticosteroids (ACS) have been recommended to all women at risk for delivery between 24 and 34 weeks of gestation (4). As ACS are effective not only in reducing perinatal morbidity, i.e. respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and sepsis but also the mortality that is associated with prematurity (5). Although the beneficial short-term outcomes of ACS therapy were evident from an early stage, longer-term outcomes, including neurodevelopment, have been less extensively studied. A systematic review of maternal ACS administration in pregnancy reported improved neurodevelopmental outcomes in these children. However, this systematic review consisted mostly of nonrandomized studies and reported on crude neurodevelopmental outcomes (6). Therefore, although ACS therapy appears safe and effective, current clinical data cannot define the precise effect of ACS therapy on future neurodevelopment. Long-term effects of ACS therapy have recently been described in a longitudinal study suggesting that ACS therapy yields persistent changes in HPA-axis reactivity into late adolescence and may confer increased vulnerability for developing stress-related disorders (7).

In view of the unclear long-term outcomes in clinical studies and the widespread use of ACS, it is reasonable to reflect on animal studies to guide future research. Despite a number of preclinical studies investigating the neurocognitive effect of ACS, the majority have reported only on direct or short-term effects (8,9). Additionally, the effects being investigated are not standardized or consistent between studies. To date there has been no systemic review summarizing the long-term neurodevelopmental outcomes after ACS therapy in preclinical models.

## Methods

*Protocol and Registration*

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidance (10) . The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019119663)

*Literature search strategy*

A literature search was conducted in PubMed, MEDLINE, EMBASE, Scopus, Web of Science and the Cochrane Library. The electronic search strategy included both Medical Subject Headings (MeSH) and keywords (Supplement 1). Reference lists and topic-related reviews were checked manually to identify further relevant papers. Zotero 5.0 (George Mason University, Virginia, US) was used to coordinate study screening and data collection.

*Inclusion and exclusion criteria*

All randomized, cohort, case-controlled studies and case series reporting on the use of ACS in animals were considered eligible. No date or language restrictions were applied. Systematic reviews, narrative review articles and editorials were excluded. Studies were excluded if corticosteroids were administered postnatally and if no long-term or neurological outcomes were reported in the offspring. For the purposes of this study, a post-natal age of seven days or more was considered as long term. Neurological outcomes were defined as any neuropathological, neurobehavioral or neuroimaging (i.e. CT and MRI) results.

*Study selection*

JvdM and AS independently screened titles and abstracts and thereafter performed a full text review of all studies. Disagreements were resolved by consensus. A low threshold for full-text retrieval and review was used.

*Data extraction*

JvdM and AS independently extracted data and entered this into a standardized Excel (Microsoft Corp, Seattle, Washington, US) form (Supplement 2). Disagreements were resolved by consensus. Information noted included study design, animal species, number of animals and gestation for that model. Treatment data recorded included type of corticosteroid, route of administration, number of doses and gestational age of treatment. Treatment regimens were grouped into those administering a "single course" of corticosteroids i.e. a single or two doses given within 48 hours of each other and those administering "multiple courses" of corticosteroids i.e. repeated doses given over more than two days. The dose of corticosteroids given was noted and converted into mg/kg based on information provided in the study, if not already given as such. This was then multiplied by the number of doses given in order to give a total administered dose in mg/kg. We calculated the average human total dose of antenatal corticosteroids to be 0.4mg/kg (12mg betamethasone or dexamethasone given twice, with an average female weight of 60-80kg). We therefore empirically grouped the total study dosing regimens into one of the following: <0.2mg/kg, 0.2-0.4mg/kg (clinical equivalent dosing), 0.41-1.0mg/kg, and >1.0mg/kg. Outcome data recorded included age of animals at assessment, neuropathology parameters, neurobehavioral and neuroimaging outcomes, as well as the overall effect of ACS in that study.

*Risk of bias*

Risk of bias was independently assessed by JvdM and AS using the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE's) tool for animal interventional studies (11). Study quality was noted on a standardized Excel form. Disagreements were resolved by consensus.

*Data synthesis and statistical methods*

Meta-analysis and comparative statistics were not planned as it was anticipated that the data would be difficult to collate or compare. Therefore, heterogeneity between studies was not calculated and narrative results and descriptive statistics were produced.

## Results

*Study selection*

The electronic search identified 575 studies published until October 2018 (Figure 1); hand-searching of reference lists identified a further 94 studies. Following removal of duplicate studies (273), 396 studies were screened by title and abstract and a further 286 were excluded as irrelevant. Full text review of the remaining 110 studies was conducted, and 46 were excluded. The main reasons for study exclusion at any stage were: no antenatal corticosteroids given (56.6%, 188/332), no long-term outcomes (16.0%, 53/332), reviews and editorials (14.8%, 49/332) and no neuropathological, neurobehavioral or neuroimaging outcomes (9.6%, 32/332). After exclusions, 64 studies were included for systematic review.

*Study characteristics*

Characteristics of included studies are shown in Table 1. The majority of studies were in the rat (70.3%, 45/64); other animal models included the mouse (14.1%, 9/64), non-human primates (6.25%, 4/64) the sheep (4.7%, 3/64), and the guinea pig (4.7%, 3/64). Most studies (93.8%, 60/64) compared corticosteroids to a non-active control (e.g. saline), although four studies (6.3%) compared corticosteroids to no treatment. All included studies evaluated animals born at term gestations.

*Risk of bias*

Risk of bias of included studies is shown in Figure 2. Most studies had a high risk of bias due to the lack of random sequence generation (65.7%, 42/64), allocation concealment performed (75%, 48/64) and blinding of caregivers (10.9%, 7/64) or assessors (29.7%, 19/64).

*ACS treatment*

Details of ACS treatment is shown in Table 2. Overall, dexamethasone was the most commonly studied corticosteroid (81.3%, 52/64); betamethasone was used in 17.2% of studies (11/64) and both corticosteroids were used in one mouse study. Two thirds of studies administered multiple courses of corticosteroids (67.2%, 43/64) with the total administered dose varying from 0.1mg/kg to 70mg/kg. Eighteen studies (28.1%) administered a total dose of corticosteroids which was equivalent to that used in humans (0.2-0.4mg/kg) while the majority of studies (76.6%, 49/64) administered a total dose higher than 0.4mg/kg. In two studies (3.1%, 2/64) the effects of a brief low dosage ACS exposure was also explored.

*Growth – body weight*

There was no routine reporting on the general health of the animals at time of assessment or harvesting. Though, 50.0% (32/64) of the studies did report on the body weight at the time of the last assessment. Only one study reported an increased weight at time of harvesting, a study of NHP using a multiple day high DM dose (32). While 16 reported a decrease in bodyweight in those exposed to ACS, herein DM was used in 13/16 (14,17,19,23,27,29,30,39,42,50,57,73,75)and BM only in 3/16 (26,31,56). Furthermore, only 10.9% (7/64) reported on the brain weight or volume at time of harvesting wherein 57.1% (4/7) reported a decrease of brain weight after the exposure of ACS (19,56,59,72).

*Outcomes assessment*

Neuropathology was the commonest outcome reported, either alone (28.1%, 18/64) or in combination with neurobehavioral assessment (42.2%, 27/64) or neuroimaging (3.1%, 2/64).

Neurobehavioral assessment alone was assessed in 25.0% of studies (16/64), and one study (1.6%) assessed all three outcomes (Figure 3). The average age at final assessment was 157 days (range 10 - 1800 days)

*Neuropathological assessments performed*

In the 48 studies that reported on a neuropathological outcomes, dexamethasone was most commonly used (79.2%, 38/48). Additionally, in a third (35.4%, 17/48) of the neuropathological outcome studies, ACS was used at a clinical equivalent dose while the majority of studies (60.4%, 29/48) used an accumulative dose higher than 0,4mg/kg. The commonest neuropathological outcomes reported was glucocorticoid receptor (GR) quantification (29.2%, 14/48), neuron density (16.7%, 8/48) or a form of dendritic assessment (16.7%, 8/48). The complete breakdown of reported neuropathological outcomes are displayed in Table 3.

*Neurobehavioral assessments performed*

Neurobehavioral assessments were reported in 44 studies in only three of the species. As noted above, most studies reported on the effects of DM and used almost exclusively rat and mice species. Neurobehavioral outcomes assessed are summarized in Table 4.

*Neuroimaging assessments performed*

In one study CT imaging was used to quantify total brain volumes in rats (64). Herein, antenatal DM did not lead to any difference in brain volumes at 3 months of ages. A further two studies utilized MRI to quantify the hippocampal volumes and T2-signal intensities in the

rat (62) and NHP (13). In both of these studies antenatal DM at a dose of 0,80mg/kg and 10mg/kg respectively, resulted in lower hippocampal volumes.

## Discussion

To date there has been no systemic review summarizing the long-term neurodevelopmental outcomes after ACS therapy in preclinical models. From this review, intrauterine exposure to synthetic GCs lead consistently to deleterious long-term neurocognitive effects. These outcomes may be due to the specific agents, i.e. dexamethasone, or the repetitive or higher total dosing used. ACS administration varied significantly between studies and most studies suffered from a high risk of bias. Neuropathological outcomes were most commonly reported, specifically the expression of GR, while reduced neurobehavioral functioning was reported in mainly rodent species.

Synthetic GCs are agonists of the GR and predominantly act via genomic effects mediated by the GR, a nuclear transcription factor. Because of its marked GR expression, the fetal lung is one of the primary targets of synthetic GCs administered to expedite fetal development. The effects of ACS on the fetal and neonatal lung have been reviewed elsewhere (5), but their impact on other organ systems with high GR expression including the brain and kidney have mostly been assessed in short-term outcomes (9). In this review, the commonest long-term neuropathological outcome reported on was the expression of GR in mostly the hippocampus and hypothalamus. Herein, both with BM and DM, in small and large animal models mainly induced an upregulation of GRs (20,21,30,41,49,73) although four of these studies used multiple DM dosing. However, in two studies a down regulation of GR was noted although in these an oral multiple day DM dosing was used (17,43). The ultimate effect of this dysregulation on the GR can have a significant inhibitory downstream effect on the developing fetal brain and HPA axis, leading to profound programming influences on the

nervous system and henceforth an increase the risk for emotional and cognitive impairments (76). The possible mechanisms involved are depicted in Figure 4.

GCs are critical for normal brain development, exerting direct effects on neuronal growth, cell to cell interactions and neuronal reorganization (79). The mechanisms regulating the maturational effects of GCs on various fetal organs are complex. However, exposure of the developing brain to inappropriate levels of GCs at critical developmental time windows can modify both the structure and function of neuronal cells. The majority of studies used multiple or repetitive doses over multiple days, consequently in most studies there were a high total dose exposure of 0.4mg/kg or more. Previously in small animal studies, ACS was associated with delayed growth of the whole body and brain, as well as altered behavior studies at birth (80,81). From this review, there was an inconsistent long-term impact on brain and/or body weight and size. In those studies that used a total dose of ≤ 0.4mg/kg, ACS exposure was *not* associated with a reduction of long-term body or brain weight (15,24,25,40,58,68). However, in one study a single course of BM exposure lead to a significant reduction in both body and brain weights (56). In sheep, fetal exposure to repeated doses of maternal betamethasone results in significant reductions in fetal brain weight that persist until 3 years of age (82).

Gross changes in brain growth are the result of specific alterations in neuronal development and cell death. It has previously been noted that the cellular proliferation in the brain of neonatal rats is acutely decreased by betamethasone treatments and reductions in brain weight persist until at least 3 weeks of postnatal age (25). As with prenatal stress exposure, ACS can also influence fetal brain development by changing neuronal migration, synaptic

plasticity, and neurotransmitter activity (83). In this review some studies observed altered neuronal states that lead to persistent lower neuron densities especially in the hippocampus (13,73) with ongoing amplified apoptosis (67) and decreased proliferation (28,33,40,58) being reported. Furthermore, the protective negative feedback loop of the HPA axis is mediated by cortisol binding to receptors in especially the hypothalamus, hippocampus and prefrontal cortex. It was foreseeable that most studies in this review noted alterations in these specific regions.

Inhibiting or turning off the HPA response axis can lead to a direct effect on the dopaminergic and serotonergic systems. Studies noted that ACS exposure was associated with less dopaminergic cells in multiple brain regions including the amygdala and hypothalamus (15,33,47,53,55,66) that also has an effect on the central norepinephrine and peripheral activation of the sympathetic nervous system (84). The meso-cortico-limbic system, mediated by dopamine release especially from the nucleus accumbens and ventral tegmental area, encodes the rewarding and reinforcing properties of natural reward behavior (85). Evidently any dysfunction of this system could lead to multiple neuropsychiatric conditions.

Moreover, the reprogramming of the HPA axis by ACS is also associated with lower neuron expression in the serotonergic system especially in the hypothalamus, hippocampus and frontal cortex (15,51,55). The serotoninergic system, a neurotransmitter system implicated in stress regulation and etiology of affective disorders is therefore another target for ACS exposure (66). This review confirms the alterations in serotonin receptors (5-HT1A and 5-HT2A) and transporters secondary to hippocampal and hypothalamus GR programming.

Additionally, ACS can also lead to altered glial astrocyte function. Astrocytes assume multiple roles in maintaining an optimally suited milieu for neuronal function from the production of trophic factors, regulation of neurotransmitters and ion concentrations, to the removal of toxins and debris from the cerebrospinal fluid (CSF) (86). Impairments in these and other functions, as well as physiological reactions of astrocytes to injury, can trigger or exacerbate neuronal dysfunction. In this review multiple studies noted the long-term dysregulation of neuroglia especially astrocytes (67,70,74).

So far, it is clear that the developing brain, with the meso-cortico-limbic system as a focus point, is particularly sensitive to exogenous GCs. The hippocampus, which plays a central role in this system, has a myriad of complex functions within the brain. These include cognition, behavior, memory, coordination of the autonomic activity, and regulation of a number of endocrine systems (87,88). Given this wide spectrum of regulatory roles it is apparent that it will have a profound impact in postnatal and adult life. In rats, prenatal DM exposure, resulted in more anxiety like behavior (15,39,59), sex-specific alterations in motor activity and sexual behavior (14,66), and impaired spatial memory (19,29). While in mice, maternal administration ACS resulted in delayed development and impaired motoric function in the offspring (16) Even a single course of ACS resulted in affecting anxiety, memory and socialization behaviors (72,74). In NHP, there was reduced sociability and increased motivation reward behavior (37) with dramatic differences in the hippocampal structure and developmental as quantified by MRI (13).

These results indicate that both DM and BM interfere with the developing brain but it remains unclear from clinical trials whether one corticosteroid (or one particular regimen) has

advantages over another (89). Both cross the placenta in their active form, and both have similar biologic activity with neither acting as a mineralocorticoid and both having weak immunosuppressive short-term effects (16). BM and DM differ only in the configuration of a single methyl group with subsequent different pharmacokinetics; BM has a larger volume of distribution and decreased clearance and thus a longer half-life. (90) In addition, the commonly available DM preparation contains a sodium metabisulfite preservative, and sulfite is neurotoxic. However, prenatal exposure to sulfite is likely to be low (because it is administered to the mother and may not reach the fetus at the same dose) (91). From this review both BM and DM resulted in long-term sequelae, with no clear benefit of one over another. As previously stated, most investigations used DM and mostly multiple dosing or courses, but even low dose or single courses of BM (25,26,56,59,63,68)and DM (33,40,58,72) resulted in clear neuropathological and neurobehavioral deficits.

This systematic review and the assimilated research have limitations mostly due to the administration regimes chosen, the lack of stringent methodological approach and non-standardized reporting. The dosing regimens are not clearly “clinical equivalent” using mostly multiple dosages over multiple days. The true fetal exposure is not quantified and therefore the differences that each species metabolism bring is not addressed. Most of the studies investigate DM while BM is more in clinical use. Also, the high bias risk due the lack of randomization, allocational and treatment concealment, and selective/incomplete outcome reporting limit the interpretation of these results. As with all translational research there is inherent risk that the risk or benefit can be overestimated due to publication bias. Ultimately, there is always the problem of species-specific factors that influence the translational value of the relevant research.

To grasp the effect of ACS on the neuroendocrine maturation, the timing of maturation of the HPA axis relative to birth needs to be clearly comprehended. In animals that give birth to mature young (sheep, guinea pigs, and primates) maximal brain growth and a large proportion of neuroendocrine maturation (including corticosteroid receptor development) takes place *in utero* (92,93). In contrast, in species that give birth to immature young (rats, rabbits, and mice), much neuroendocrine development occurs in the postnatal period (94). Therefore, maternal GC treatment in late gestation will impact on different stages of brain and HPA development depending on the species studied. Another important consideration when extrapolating among different studies and species is that of receptor sensitivity. Mice and rats are corticosensitive (high receptor affinity for GCs) compared with other species, such as guinea pigs and primates, which are considered corticoresistant (95).

*Conclusion*

In conclusion, many animal models have been used to highlight the efficacy and potential adverse effects of ACS. In this review, a general pattern is observed of consistent neurocognitive sequelae that ultimately lead to modulated fetal programming, the so-called Developmental Origins of Health and Disease hypothesis. The mechanistic view of an intrauterine factor mediating brain growth and neurocognitive development at a vulnerable time in gestation while subsequently resulting in permanent alterations is one that has been included in many neurocognitive and psychiatric conditions. Current research pertaining to the neurocognitive effects of ACS consisted mostly of DM using repetitive and high dosages in rodent species. There is a new focus on ACS since the role and indication for ACS has

recently rapidly expanded to include rescue and repeated dosages, and late pre-term birth. (96–98)

Preclinical research could help in defining the efficacy and long-term outcomes in future ACS research, but models needs to be standardized to help address the barriers in translational neuroscience research. Principles that could be followed are:

1. Adequate and appropriate dosages that could include dose-response curves
2. Define the time and gestational age window of exposure in a well-characterized model
3. Blinded, physiologically controlled reproducible studies
4. Histological and functional outcomes assessed acutely and long-term

Furthermore imaging, especially MRI, could help characterize the insults even better especially in a longitudinal models where the long-term impact needs to be defined. So far this has been underutilized in this area.

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**Figure 1.** Flow diagram of study selection adapted from PRISMA 2010 (10)

**Figure 2.** Risk of bias assessment using SYRCLE's risk of bias tool for animal studies (11)

**Figure 3.** Venn Diagram: break down of studies by reported outcome categories

**Figure 4.** The regulation of the maternal and fetal HPA axis during pregnancy. The human placenta expresses the genes for proopiomelanocortin and the major stress hormone, corticotropin-releasing hormone (CRH). As pregnancy progresses, these stress hormones including maternal cortisol, increase dramatically. Because of the positive feedback between GCs and placental CRH, the effects of excess endogenous or synthetic GCs may be amplified with potentially negative consequences for the developing fetus. The consequences of prenatal treatment with BM or DM may be more profound as they cross the placenta more easily because they are not readily metabolized by the placental enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), that protects the fetus from maternal cortisol (77,78). These synthetic GCs can gain direct access to glucocorticoid receptors without significant reduction in their circulating or tissue levels due to local oxidation. These endocrine changes are important for fetal maturation, but if the levels are altered (e.g., ACS exposure), they influence (program) the fetal nervous system, especially the meso-cortico-limbic system with long-term consequences.