Pediatric RESEARCH

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SYSTEMATIC REVIEW

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

Johannes L. van der Merwe[1,2], Adalina Sacco[3], Jaan Toelen[1,4] and Jan Deprest[1,2,3]

BACKGROUND: Antenatal corticosteroids (ACSs) are recommended to all women at risk for preterm delivery; currently, there is controversy about the subsequent long-term neurocognitive sequelae. This systematic 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, ACSs 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.

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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 (ACSs) have been recommended to all women at risk for delivery between 24 and 34 weeks of gestation,[4] as ACSs 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 hypothalamic–pituitary–adrenal (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 ACSs, it is reasonable to reflect on animal studies to guide future research. Despite a number of preclinical studies investigating the neurocognitive effect of ACSs, the majority have reported only on direct or short-term effects.[8,9] In addition, the effects being investigated are not standardized or consistent between studies. To date, there has been no systematic 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 guidance.[10] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019119663).

[1]Department of Development and Regeneration, Cluster Woman and Child, Faculty of Medicine, KU Leuven, Leuven, Belgium; [2]Department of Obstetrics and Gynaecology, Fetal Medicine Unit, UZ Leuven, Leuven, Belgium; [3]Institute for Women's Health, University College London, London, UK and [4]Department of Pediatrics, Division Woman and Child, University Hospitals Leuven, Leuven, Belgium
Correspondence: Johannes L. van der Merwe (hannes.vandermerwe@uzleuven.be)

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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 (Supplementary Information 1). Reference lists and topic-related reviews were checked manually to identify further relevant papers. Zotero 5.0 (George Mason University, VA, USA) was used to coordinate study screening and data collection.

Inclusion and exclusion criteria
All studies reporting on the use of ACSs 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 postnatal age of ≥7 days was considered as long term. This empiric cut-off was introduced since no interspecies long-term definition exist, and we wanted to exclude studies that reported on the acute effects of ACS. Neurological outcomes were defined as any neuropathological, neurobehavioral, or neuroimaging (i.e., computed tomography (CT) and magnetic resonance imaging (MRI)) results.

Study selection
J.L.v.d.M. and A.S. 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
J.L.v.d.M. and A.S. independently extracted data and entered this into a standardized Excel (Microsoft Corp, Seattle, Washington, USA) form (Supplementary Information 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 h of each other and those administering "multiple courses" of corticosteroids, i.e., repeated doses given over >2 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. The clinical recommended intramuscularly dose for betamethasone (BM) is 24 mg in two divided doses 24 hours apart and dexamethasone (DM) 24 mg in four divided doses 12 hours apart.[11] Hence the calculated average human total dose is 0.4 mg/kg (for the average female weight of 60-80 kg) and based upon body surface area an equivalent dose in animals also comes to 0.4 mg/kg.[12] We therefore grouped the total study dosing regimens into one of the following: < 0.2 mg/kg, 0.2–0.4 mg/kg (clinical equivalent dosing), 0.41–1.0 mg/kg, and >1.0 mg/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 J.L.v.d.M. and A.S. using the Systematic Review Centre for Laboratory Animal Experimentation's tool for animal interventional studies.[13] 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 (Fig. 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 ACSs 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 the 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 (NHPs; 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 4 studies (6.3%) compared corticosteroids to no treatment. All included studies evaluated animals born at term gestations.

Risk of bias
Risk of bias of the included studies is shown in Fig. 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, DM was the most commonly studied corticosteroid (81.3%, 52/64); BM 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 0.1 to 70 mg/kg. Eighteen studies (28.1%) administered a total dose of corticosteroids which was equivalent to that used in humans (0.2–0.4 mg/kg) while the majority of studies (76.6%, 49/64) administered a total dose >0.4 mg/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 the 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 the time of harvesting, a study of NHP using a multiple-day high DM dose.[14] While 16 reported a decrease in body weight in those exposed to ACSs, herein DM was used in 13/16[15–27] and BM only in 3/16.[28–30] Furthermore, only 10.9% (7/64) reported on the brain weight or volume at the time of harvesting wherein 57.1% (4/7) reported a decrease of brain weight after the exposure of ACS.[17,30–32]

Outcome 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

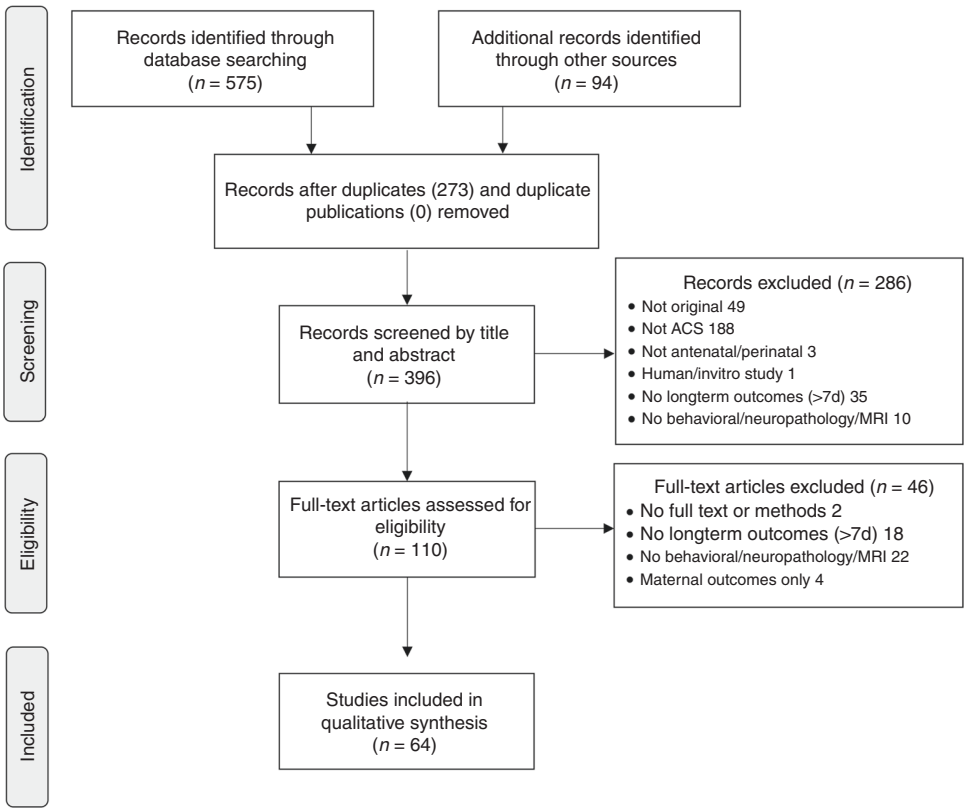

Fig. 1 Flow diagram of the study selection adapted from PRISMA 2010.[10]

(Fig. 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, DM was most commonly used (79.2%, 38/48). In addition, 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 >0.4 mg/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 3 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.[33] 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[34] and NHP.[35] In both of these studies, antenatal DM at a dose of 0.80 and 10 mg/kg, respectively, resulted in lower hippocampal volumes.

DISCUSSION

To date, there has been no systematic review summarizing the long-term neurodevelopmental outcomes after ACS therapy in preclinical models. From this review, intrauterine exposure to synthetic GCs led consistently to deleterious long-term neurocognitive effects. These outcomes may be due to the specific agents, i.e., DM, 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 ACSs 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 BM and DM in small and large animal models mainly induced an upregulation of GRs,[21,26,36–39] although four of these studies used multiple DM dosing. However, in two studies a downregulation of GR was noted although in these an oral multiple day DM dosing was used.[16,40] 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 in the risk for emotional and cognitive impairments.[41] The possible mechanisms involved are depicted in Fig. 4.

GCs are critical for normal brain development, exerting direct effects on neuronal growth, cell to cell interactions, and neuronal reorganization.[42] 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

Table 1. Characteristics of the included studies.

Publication	Species	ACS type	ACS schedule	GA of ACS exposure[a] (days)	Total dose (mg/kg)	Route	Control used	Assessment age (days)	Body weight affect	Neuropathological outcomes	Neuroimaging outcomes	Neurobehavioral outcomes
Smith[83]	Rat	DM	Multiday	1–delivery	0.85	Mat PO	Yes	60	→	No	No	Yes
Uno[35]	NHP	DM	Multiday	132–133	10.0	Mat IM	Yes	270	—	Yes	Yes	No
Holson[15]	Rat	DM	Multiday	14–21	0.80	Mat SC	No	90	↓	No	No	Yes
Muneoka[45]	Rat	DM	Multiday	17–19	0.15	Mat SC	Yes	98	→	Yes	No	Yes
Rayburn[68]	Mouse	BM/DM	Single	14	2.00	Mat SC	Yes	135	—	No	No	Yes
Brabham[16]	Rat	DM	Multiday	15–delivery	1.89	Mat PO	Yes	75	↓	Yes	No	Yes
Christensen[84]	Mouse	BM	Multiday	13–16	8.00	Mat SC	Yes	120	—	No	No	Yes
Welberg[17]	Rat	DM	Multiday	1–delivery	0.70	Mat SC	Yes	240	↓	Yes	No	Yes
Dodic[36]	Sheep	DM	Multiday	26–28	0.78	Mat IV	No	1800	—	Yes	No	No
Banjanin[37]	Guinea pig	DM	Multiday	40–41, 50–51, 60–61	6.00	Mat SC	Yes	150	→	Yes	No	No
Burlet[85]	Rat	DM	Multiday	15–19	0.50	Mat SC	Yes	18	→	No	No	Yes
Hougaard[18]	Rat	DM	Multiday	14–21	0.80	Mat SC	Yes	180	↓	No	No	Yes
McArthur[46]	Rat	DM	Multiday	16–19	0.10	Mat PO	Yes	68	→	Yes	No	No
Bruschettini[47]	Rat	BM	Two doses	20	0.34	Mat SC	Yes	21	→	Yes	No	No
Bruschettini[28]	Rat	BM	Two doses	20–21	0.34	Mat SC	Yes	150	↓	Yes	No	Yes
Hauser[19]	Rat	DM	Multiday	15–21	0.70	Mat PO	Yes	135	↓	No	No	Yes
Korzhevskii[54]	Rat	DM	Two doses	13, 19	2.00	Mat IV	No	10	—	Yes	No	No
Oliveira[20]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	1260	↓	No	No	Yes
Shoener[21]	Rat	DM	Multiday	14–19	0.78	Mat SC	Yes	21	↓	Yes	No	No
Velísek[29]	Rat	BM	Two doses	15	0.80	Mat IP	Yes	20	↓	Yes	No	Yes
Hauser[14]	NHP	DM	Multiday	42–48, 90–96	70.0	Mat PO	Yes	84	↑	No	No	Yes
Leão[55]	Rat	DM	Two doses	18–19	0.20	Mat SC	Yes	21	—	Yes	No	No
McArthur[86]	Rat	DM	Multiday	16–19	0.30	Mat PO	Yes	68	—	Yes	No	No
Owen[87]	Guinea pig	BM	Multiday	40–41, 50–51, 60–61	6.00	Mat SC	Yes	10	—	Yes	No	No
Setiawan[88]	Guinea pig	BM	Multiday	40–41, 50–51, 60–61	5.00	Mat SC	Yes	21	→	Yes	No	No
Hauser[69]	NHP	DM	Multiday	42–48, 90–96	35.0	Mat PO	Yes	360	→	No	No	Yes
Hossain[89]	Rat	DM	Multiday	14–delivery	0.70	Mat IP	Yes	180	→	Yes	No	Yes
Nagano[22]	Rat	DM	Multiday	16–21	0.25	Mat SC	Yes	70	↓	Yes	No	Yes
Noorlander[48]	Mouse	DM	Single	15, 5	0.40	Mat IP	Yes	180	→	Yes	No	Yes
Sloboda[38]	Sheep	BM	Single/ multiday	104, 111, 118, 125	0.50	Mat IM Fet IM	Yes	123	—	Yes	No	No
Hauser[23]	Rat	DM	Multiday	15–delivery	0.70	Mat PO	Yes	300	↓	No	No	Yes
Diaz[40]	NHP	DM	Multiday	42–48, 90–96	35.0	Mat PO	Yes	600	—	Yes	No	No
Kleinhaus[90]	Rat	DM	Multiday	6–8	6.00	Mat IP	Yes	29	→	No	No	Yes
Neigh[91]	Rat	DM	Multiday	14–21	0.70	Mat SC	Yes	90	—	Yes	No	Yes
Kjaer[92]	Rat	DM	Multiday	14–21	1.60	Mat SC	Yes	210	—	Yes	No	Yes

Table 1 continued

Publication	Species	ACS type	ACS schedule	GA of ACS exposure[a] (days)	Total dose (mg/kg)	Route	Control used	Assessment age (days)	Body weight affect	Neuropathological outcomes	Neuroimaging outcomes	Neurobehavioral outcomes
Oliveira[56]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	90	—	Yes	No	Yes
Roque[93]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	90	→	No	No	Yes
Li[39]	Sheep	DM	Multiday	40–42	0.42	Mat IM	Yes	210	—	Yes	No	No
Liu[24]	Rat	DM	Multiday	14–21	1.04	Mat SC	Yes	63	↓	No	No	Yes
Nagano[62]	Rat	DM	Multiday	16–21	0.30	Mat SC	Yes	70	—	Yes	No	Yes
Oliveira[94]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	90	—	Yes	No	Yes
Rodrigues[57]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	120	—	Yes	No	Yes
Zuloaga[95]	Rat	DM	Multiday	18–22	2.00	Mat SC	Yes	60	—	Yes	No	No
Borges[58]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	98	—	No	No	Yes
Bustamante[30]	Rat	BM	Two doses	20	0.34	Mat SC	Yes	52	↓	Yes	No	Yes
Iwasa[25]	Rat	DM	Multiday	13–delivery	1.35	Mat PO	Yes	28	↓	Yes	No	No
Noorlander[49]	Mouse	DM	Single	15.5	0.40	Mat IP	Yes	180	→	Yes	No	No
Pascual[31]	Rat	BM	Two doses	20	0.34	Mat SC	Yes	52	—	Yes	No	Yes
Virdee[96]	Rat	DM	Multiday	16–19	0.20	Mat PO	Yes	90	—	Yes	No	Yes
Frahm[97]	Mouse	DM	Multiday	11–17	0.70	Mat SC	Yes	52	—	Yes	No	No
Lui[34]	Rat	DM	Multiday	14–delivery	0.80	Mat IP	Yes	120	→	Yes	Yes	Yes
Pascual[73]	Rat	BM	Two doses	20	0.34	Mat SC	Yes	82	—	Yes	No	Yes
Shende[33]	Rat	DM	Multiday	16–19	0.30	Mat PO	Yes	68	—	Yes	Yes	No
Zeng[98]	Rat	DM	Multiday	15–21	0.70	Mat SC	Yes	100	—	No	No	Yes
Hiroi[59]	Rat	DM	Multiday	18–22	2.00	Mat SC	Yes	60	—	Yes	No	Yes
McArthur[53]	Mouse	DM	Multiday	16–19	1.30	Mat PO	Yes	67	—	Yes	No	No
Pascual[50]	Rat	BM	Two doses	20	0.34	Mat SC	Yes	52	→	Yes	No	Yes
Virdee[99]	Rat	DM	Multiday	16–19	0.30	Mat PO	Yes	90	—	Yes	No	Yes
Caetano[64]	Rat	DM	Two doses	18–19	2.00	Mat SC	Yes	90	→	Yes	No	Yes
Conti[100]	Mouse	DM	Multiday	14–delivery	0.25	Mat SC	Yes	360	—	Yes	No	Yes
Tsiarli[32]	Mouse	DM	Single	14.5	0.40	Mat IP	Yes	60	—	Yes	No	Yes
Dong[26]	Rat	DM	Multiday	9–20	2.40	Mat SC	No	182	↓	Yes	No	Yes
Frahm[65]	Mouse	DM	Multiday	11–17	0.70	Mat SC	Yes	75	—	Yes	No	Yes
Liu[27]	Rat	DM	Multiday	14–21	1.04	Mat SC	Yes	28	↓	Yes	No	Yes

The average gestation period was in mice 19–20 days, rat 22–23 days, guinea pig 65–70 days, sheep 145–152 days, and non-human primates 144–166 days. Effect indicated as increased ↑, decreased ↓, or no significant difference →.
BM betamethasone, *DM* dexamethasone, *NHP* non-human primate, *Mat* maternal, *Fet* fetal, *SC* subcutaneous, *PO* per os, *IP* intraperitoneal, *IM* intramuscular, *IV* intravenous
[a]Gestational age timepoints when ACS was administered to the animals

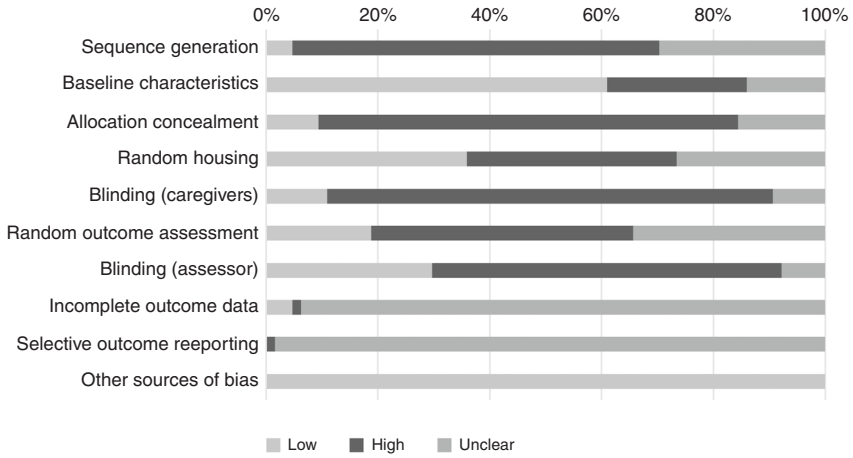

Fig. 2 Risk of bias assessment using SYRCLE's risk of bias tool for animal studies.[13]

Table 2. Details of the reported antenatal corticosteroid regimes.

		Mouse, $n = 9$	Rat, $n = 45$	Guinea pig, $n = 3$	Sheep, $n = 3$	NHP, $n = 4$
Corticosteroid used, *n* (%)	BM	1 (11.1)	7 (15.6)	2 (66.7)	1 (33.3)	—
	DM	7 (77.8)	38 (84.4)	1 (33.3)	2 (66.7)	4 (100)
	Both	1 (11.1)	—	—	—	—
Single course, *n* (%)		4 (44.4)	16 (35.6)	—	1 (33.3)	—
Total dose (mg/kg), median (IQR)		0.70 (0.4–1.3)	0.78 (0.34–2.0)	6.00 (5.00–6.00)	0.50 (0.42–0.78)	35.00 (22.5–52.5)
Total dose (mg/kg), number of studies per steroid type BM/DM	<0,2	—	—/2	—	—	—
	0.2–0.4	—/4	7/7	—	—	—
	0.41–1.0	—/2	1/14	—	2/2	—
	>1.0	1/2	0/18	2/1	—	—/4
Route, *n* (%)	SC	5 (55.6)	30 (66.7)	3 (100)	—	—
	PO	1 (11.1)	10 (22.2)	—	—	3 (75)
	IP	3 (5.9)	4 (8.9)	—	—	—
	IM	—	—	—	2 (66.7)	1 (25)
	IV	—	1 (2.2)	—	1 (33.3)	—
Control group used, *n* (%)		9 (100)	42 (93.3)	3 (100)	2 (66.7)	4 (100)
Oldest outcome age (days)		120 (67–180)	82 (52–100)	21 (10–150)	210 (122–1800)	315 (177–480)

Results given as number (*n*) and percentage (%) or median with IQR
NHP non-human primate, *BM* betamethasone, *DM* dexamethasone, *SC* subcutaneous, *PO* per os, *IP* intraperitoneal, *IM* intramuscular, *IV* intravenous

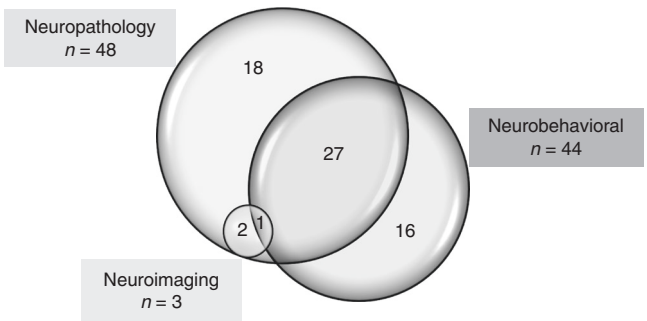

Fig. 3 Venn diagram: break down of studies by reported outcome categories.

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 ≥0.4 mg/kg. 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.[43,44] 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 ≤0.4 mg/kg, ACS exposure was *not* associated with a reduction of long-term body or brain weight.[45–50] However, in one study a single course of BM exposure led to a significant reduction in both body and brain weights.[30] In sheep, fetal exposure to repeated doses of maternal BM results in significant reductions in fetal brain weight that persist until 3 years of age.[51]

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 BM treatments and reductions in brain weight persist until at least 3 weeks of postnatal age.[47] As with prenatal stress exposure, ACS can also influence fetal brain development by changing neuronal migration, synaptic plasticity, and neurotransmitter activity.[52] In this review, some studies observed altered neuronal states that lead to persistent lower neuron densities especially in the hippocampus[26,35] with ongoing amplified apoptosis[53] and decreased

Table 3. Neuropathological outcome measures reported in the selected studies with specific staining used.

Neuropathological outcome	Reported studies per species (*n*)	Corticosteroid	Total dose (mg/kg)	Effect per outcome assessed and region of interest
Mineralocorticoid and/or glucocorticoid receptor quantification ($n = 14$)	Rat ($n = 7$)			
	Brabham[16]	DM	1.89	GR[a]—Hippocampus ↓
	Welberg[17]	DM	0.70	GR and MR[a]—Hippocampus ↓, amygdala ↑
	Shoener[21]	DM	0.78	GR and MR[a]—Hippocampus ↓, hypothalamus NS
	Hossain[89]	DM	0.70	GR[a]—Paraventricular nucleus NS
	Nagano[22]	DM	0.25	GR[a,b]—Amygdala ↓, hippocampus NS, hypothalamus NS
	Kjaer[92]	DM	1.60	GR and MR[a]—Hippocampus NS
	Dong[26]	DM	2.40	GR[a]—Hippocampus ↑
	Guinea pig ($n = 3$)			
	Banjanin[37]	DM	6.00	MR[a]—Hippocampus ↑; GR—Hippocampus NS
	Owen[87]	BM	6.00	GR and MR[a]—Hippocampus NS, hypothalamus NS
	Setiawan[88]	BM	5.00	GR and MR[b]—Hippocampus ↑ (females)
	Sheep ($n = 3$)			
	Dodic[36]	DM	0.78	GR and MR[a]—Hippocampus NS, hypothalamus NS
	Sloboda[38]	BM	0.50	GR[a]—Hippocampus NS; MR[a]—Hippocampus ↑
	Li[39]	DM	0.42	GR and MR[a]—Hypothalamus ↑, Hippocampus ↑ (males)
	NHP ($n = 1$)			
	Diaz[40]	DM	35	GR and MR[a]—Prefrontal cortex NS
Neuron density or quantification ($n = 8$)	Rat ($n = 4$)			
	Korzhevskii[54]	DM	2.00	Nissl—Paraventricular zone ↑
	Hossain[89]	DM	0.70	NeuN[c]—Paraventricular nucleus NS
	Shende[33]	DM	0.30	Hematoxylin—Hippocampus NS, amygdala NS, nucleus accumbens NS
	Dong[26]	DM	2.40	Nissl—Hippocampus ↓
	Mouse ($n = 3$)			
	Noorlander[48]	DM	0.40	Nissl—Hippocampus NS
	Noorlander[49]	DM	0.4	Nissl—Hippocampus CA ↑, hippocampus dentate gyrus NS
	Conti[100]	DM	0.25	NeuN[c]—Hippocampus DG ↓
	NHP ($n = 1$)			
	Uno[35]	DM	10	Nissl—Hippocampus ↓, frontal cortex ↓
Dendrite or Golgi quantification ($n = 9$)	Rat ($n = 8$)			
	Bruschettini[28]	BM	0.34	Synaptophysin[c]—Hippocampus NS; MAP2[c]—Hippocampus ↓
	Oliveira[94]	DM	2.00	Golgi-Cox[c]—Stria terminalis ↑; amygdala ↓
	Rodrigues[57]	DM	2.00	Golgi-Cox[c]—Nucleus accumbens ↓
	Bustamante[30]	BM	0.34	Golgi-Cox[c]—Hippocampus↓, dendrite length
	Pascual[31]	BM	0.34	Golgi-Cox[c]—Cerebellum, vermis ↓
	Pascual[73]	BM	0.34	MAP2[c]—ND; ↓ dendrite— cerebellum NS, Vermis NS
	Pascual[50]	BM	0.34	mGluR1[c]—Cerebellum NS
	Dong[26]	DM	2.40	Syn I[b]—Hippocampus NS
	Mouse ($n = 1$)			
	Conti[100]	DM	0.25	GFP[c]—Hippocampus DG ↓
Proliferation assessment ($n = 6$)	Rat ($n = 4$)			
	Bruschettini[28]	BM	0.34	^{3}H-Thy—↑ Hippocampus, SVZ
	Leão[55]	DM	0.20	BrdU[c]—Ventral tegmental area ↓, nucleus accumbens ↓
	Korzhevskii[54]	DM	2.00	PCNA[c]—Paraventricular zone ↓
	Dong[26]	DM	2.40	Cyclin A, Ki67[c]—Hippocampus ↓
	Mouse ($n = 2$)			
	Noorlander[48]	DM	0.40	Ki67[c]—Hippocampus DG ↓
	Noorlander[49]	DM	0.40	Ki67[c]—Hippocampus ↓
Astrocyte or microglia quantification ($n = 4$)	Rat ($n = 2$)			
	Shende[33]	DM	0.30	GFAP[c]—Hippocampus NS, amygdala NS (↓ processes)
	Caetano[64]	DM	2.00	Iba1[c]—Prefrontal cortex ↓
	Mouse ($n = 2$)			
	McArthur[53]	DM	1.30	Glutamine synthetase[c]—Substantia nigra ↑, ventral tegmental area ↑
	Frahm[65]	DM	0.70	GFAP[c]—Paraventricular nucleus ↓ females ↑ males
Apoptosis assessment ($n = 3$)	Rat ($n = 1$)			
	Dong[26]	DM	2.40	Caspace 3[c]—Hippocampus ↑
	Mouse ($n = 2$)			
	Noorlander[49]	DM	0.40	Caspace 3[c]—Hippocampus NS
	McArthur[53]	DM	1.30	Caspace 3[c]—Substantia nigra, ventral tegmental area ↑
Dopaminergic neuron quantification ($n = 11$)	Rat ($n = 10$)			
	Muneoka[45]	DM	0.15	Dopamine/DOPAC[d]—Hypothalamus ↓, striatum, neocortex ↓
	McArthur[46]	DM	0.10	Tyrosine hydroxylase[c]—Substantia nigra ↑, ventral tegmental area ↑
	McArthur[86]	DM	0.30	Tyrosine hydroxylase[c]—Substantia nigra ↑, ventral tegmental area ↑

Table 3 continued

Neuropathological outcome	Reported studies per species (*n*)	Corticosteroid	Total dose (mg/kg)	Effect per outcome assessed and region of interest
	Leão[55]	DM	0.20	Tyrosine hydroxylase[c]—Ventral tegmental area ↓, nucleus accumbens ↓
	Oliveira[56]	DM	2.00	Dopamine[a,d]—Hypothalamus, nucleus accumbens ↓
	Rodrigues[57]	DM	2.00	Tyrosine hydroxylase[c]—Nucleus accumbens ↓
	Oliveira[94]	DM	2.00	Dopamine[a]—Amygdala ↓
	Borges[58]	DM	2.00	Dopamine[d]—Amygdala, nucleus accumbens ↓
	Virdee[96]	DM	0.20	Tyrosine hydroxylase[c]—Substantia nigra ↑, ventral tegmental area, striatum ↑
	Virdee[99]	DM	0.30	Dopamine[d]—Prefrontal cortex NS, striatum NS
	Mouse ($n = 1$)			
	McArthur[53]	DM	1.30	Tyrosine hydroxylase[c]—Substantia nigra↑, ventral tegmental area ↑
Serotonergic neuron quantification ($n = 5$)	Rat ($n = 5$)			
	Muneoka[45]	DM	0.15	5-HT[d]—Hypothalamus ↓
	Oliveira[56]	DM	2.00	5-HT[d]—Hypothalamus, nucleus accumbens ↓
	Nagano[62]	DM	0.30	5-HT[a]—Prefrontal cortex, hippocampus ↓
	Hiroi[59]	DM	2.00	TpH2[a]—Dorsal raphe nucleus ↓ (females)
	Virdee[99]	DM	0.30	5-HT[d]—Prefrontal cortex NS, striatum NS
GABAergic interneurons ($n = 2$)	Rat ($n = 2$)			
	Zuloaga[95]	DM	2.00	Calretinin[c]—Amygdala ↓ (females)
	Lui[34]	DM	0.80	Reelin[a]—Hippocampus ↓
Neurotransmitter ($n = 2$)	Rat ($n = 2$)			
	Velísek[29]	BM	0.80	Neuropeptide Y[c]—Hippocampus ↑
	Iwasa[25]	DM	1.35	Neuropeptide Y[a]—Hypothalamus ↓
Other ($n = 3$)	Rat ($n = 3$)			
	Neigh[91]	DM	0.70	von Willebrand factor[c]—Hippocampus ↓, amygdala NS
	Frahm[97]	DM	0.70	Desmin[c]—Paraventricular nucleus ↑
	Liu[27]	DM	1.04	O-GlcNAc transferase[a,b]—Hippocampus ↓

Results given as number (*n*) with statistically significant effect indicated as increased ↑, decreased ↓, or not significant NS
BM betamethasone, *DM* dexamethasone
[a]Polymerase chain reaction or in situ hybridization
[b]Western blot
[c]Immunocytochemistry
[d]Chromatography

proliferation[48,49,54,55] 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[45,55–59] that also has an effect on the central norepinephrine and peripheral activation of the sympathetic nervous system.[60] 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.[61] 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.[45,58,62] The serotoninergic system, a neurotransmitter system implicated in stress regulation and etiology of affective disorders is therefore another target for ACS exposure.[59] This review confirms the alterations in serotonin receptors (5-HT1A and 5-HT2A) and transporters secondary to hippocampal and hypothalamus GR programming.

In addition, 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.[63] 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.[53,64,65]

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.[66,67] 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,[22,31,45] sex-specific alterations in motor activity and sexual behavior,[15,59] and impaired spatial memory.[17,20] While in mice, maternal administration of ACS resulted in delayed development and impaired motoric function in the offspring.[68] Even a single course of ACS resulted in affecting anxiety, memory, and socialization behaviors.[32,65] In NHP, there was reduced sociability and increased motivation reward behavior[69] with dramatic differences in the hippocampal structure and developmental as quantified by MRI.[35]

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.[70] 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.[68] BM and DM differ only in the configuration of a single methyl group with subsequent

Table 4. Neurobehavioral assessments reported in the selected studies, per species and type of antenatal corticosteroid used including the reported significant outcomes.

Reported studies per species (*n*)	Neurobehavioral assessment (*n*)	Corticosteroid	Total dose (mg/kg)	Reported significant outcome
Open field behavior ($n = 22$)	Rat ($n = 20$)			
	Smith[83]	DM	0.85	↑ Stress
	Muneoka[45]	DM	0.15	↓ Ambulation, ↓ rearing
	Welberg[17]	DM	0.70	↓ Ambulation, ↓ rearing
	Bruschettini[28]	BM	0.34	No difference
	Oliveira[20]	DM	2.00	↓ Locomotion, ↓ explore
	Velísek[29]	BM	0.80	↓ Rearing
	Nagano[22]	DM	0.25	↓ Ambulation, ↓ rearing
	Hauser[23]	DM	0.70	No difference
	Neigh[91]	DM	0.70	↓ Locomotion
	Liu[24]	DM	1.04	↓ Ambulation, ↓rearing
	Nagano[62]	DM	0.30	↓ Ambulation, ↓ rearing
	Rodrigues[57]	DM	2.00	↓ Ambulation
	Pascual[31]	BM	0.34	↓ Locomotion, ↓ explore
	Virdee[96]	DM	0.20	No difference
	Zeng[98]	DM	0.70	No difference
	Hiroi[59]	DM	2.00	↓ Locomotion, ↓ center time
	Virdee[99]	DM	0.30	No difference
	Caetano[64]	DM	2.00	No difference
	Dong[26]	DM	2.40	No difference
	Liu[27]	DM	1.04	↓ Ambulation, ↓ rearing
	Mouse ($n = 2$)			
	Tsiarli[32]	DM	0.40	No difference,↑ center time
	Frahm[65]	DM	0.70	No difference
Elevated plus maze ($n = 13$)	Rat ($n = 11$)			
	Welberg[17]	DM	0.70	↓ Open arm entries
	Oliveira[20]	DM	2.00	↑ Anxiety
	Velísek[29]	BM	0.80	↑ Latency
	Hossain[89]	DM	0.70	↓ Open arm entries (males)
	Hauser[23]	DM	0.70	No difference
	Oliveira[94]	DM	2.00	↓ Open arm entries
	Pascual[73]	BM	0.34	↓ Open arm entries
	Zeng[98]	DM	0.70	No difference
	Pascual[50]	BM	0.34	No difference
	Caetano[64]	DM	2.00	↓ Time open arms
	Dong[26]	DM	2.40	No difference
	Mouse ($n = 2$)			
	Rayburn[68]	BM+DM	2.00	↑ Time open arms (BM only)
	Tsiarli[32]	DM	0.40	↑ Time open arms
Forced swim test ($n = 13$)	Rat ($n = 10$)			
	Welberg[17]	DM	0.70	↑ Immobile
	Burlet[85]	DM	0.50	No difference
	Oliveira[20]	DM	2.00	↑ Immobile
	Nagano[22]	DM	0.25	No difference
	Hauser[23]	DM	0.70	↑ Female floating time
	Roque[93]	DM	2.00	↑ Immobile
	Borges[58]	DM	2.00	↑ Immobile, ↓ climbing
	Hiroi[59]	DM	2.00	↑ Immobile
	Caetano[64]	DM	2.00	No difference
	Liu[27]	DM	1.04	↑ Immobile
	Mouse ($n = 3$)			
	Rayburn[68]	BM+DM	2.00	No difference
	Conti[100]	DM	0.25	↑ Immobile
	Tsiarli[32]	DM	0.40	↓ Immobile
Morris water maze ($n = 9$)	Rat ($n = 7$)			
	Brabham[16]	DM	1.89	↑ Trial blocks
	Bruschettini[28]	BM	0.34	No difference
	Oliveira[20]	DM	2.00	No difference
	Hauser[23]	DM	0.70	No difference
	Lui[34]	DM	0.80	No difference
	Zeng[98]	DM	0.70	No difference
	Dong[26]	DM	2.40	↑ Latency, ↑ distance
	Mouse ($n = 2$)			
	Christensen[84]	BM	8.00	No difference
	Noorlander[48]	DM	0.40	↑ Latency, ↑ distance
Acoustic startle ($n = 7$)	Rat ($n = 6$)			
	Hougaard[18]	DM	0.80	↑ Response
	Hossain[89]	DM	0.70	↑ Startle amplitude

Table 4 continued

Reported studies per species (*n*)	Neurobehavioral assessment (*n*)	Corticosteroid	Total dose (mg/kg)	Reported significant outcome
	Kleinhaus[90]	DM	6.00	↓ Startle amplitude
	Kjaer[92]	DM	1.60	↑ Startle amplitude
	Oliveira[94]	DM	2.00	↑ Startle amplitude
	Virdee[96]	DM	0.20	No difference
	Mouse ($n = 1$)			
	Rayburn[68]	BM+DM	2.00	↓ Response (DM only)
Prepulse inhibition ($n = 6$)	Rat ($n = 6$)			
	Hougaard[18]	DM	0.80	No difference
	Hauser[19]	DM	0.70	No difference
	Kleinhaus[90]	DM	6.00	↑ Level, ↑ efficiency
	Kjaer[92]	DM	1.60	No difference
	Oliveira[94]	DM	2.00	No difference
	Virdee[96]	DM	0.20	↑ Response in males
Sucrose preference test ($n = 5$)	Rat ($n = 5$)			
	Neigh[91]	DM	0.70	↓ Preference
	Roque[93]	DM	2.00	↓ Preference
	Liu[24]	DM	1.04	↓ Preference
	Borges[58]	DM	2.00	↓ Preference
	Liu[27]	DM	1.04	↓ Preference
T-maze ($n = 2$)	Rat ($n = 1$)			
	Virdee[99]	DM	0.30	No difference
	Mouse ($n = 1$)			
	Rayburn[68]	BM+DM	2.00	No difference
Light dark choice ($n = 3$)	Rat ($n = 3$)			
	Nagano[22]	DM	0.25	↓ Time in light box
	Nagano[62]	DM	0.30	↓ Transitions
	Hiroi[59]	DM	2.00	No difference
Tube runway ($n = 2$)	Mouse ($n = 2$)			
	Rayburn[68]	BM+DM	2.00	No difference
	Christensen[84]	BM	8.00	No difference
Social play ($n = 2$)	Rat ($n = 2$)			
	Kleinhaus[90]	DM	6.00	↓ Walkovers
	Borges[58]	DM	2.00	Neg
Tail suspension ($n = 2$)	Rat ($n = 1$)			
	Liu[27]	DM	1.04	↑ Immobile
	Mouse ($n = 1$)			
	Frahm[65]	DM	0.70	↓ Immobile
Sexual behavior analysis ($n = 2$)	Rat ($n = 2$)			
	Holson[15]	DM	0.80	No difference
	Oliveira[56]	DM	2.00	↓ Mounts, latency, ejaculations
Object recognition test ($n = 1$)	Rat ($n = 1$)			
	Bruschettini[28]	BM	0.34	No difference
Y-maze ($n = 1$)	Rat ($n = 1$)			
	Bustamante[30]	BM	0.34	↓ Novel arm entries
Marble burying ($n = 1$)	Rat ($n = 1$)			
	Pascual[73]	BM	0.34	Increased
Grasping test ($n = 1$)	Rat ($n = 1$)			
	Burlet[85]	DM	0.50	↓ Grasping time
Ultrasound vocalization ($n = 1$)	Rat ($n = 1$)			
	Borges[58]	DM	2.00	No difference
Righting reflex ($n = 1$)	Rat ($n = 1$)			
	Burlet[85]	DM	0.50	↑ Duration
Horizontal bar ($n = 1$)	Rat ($n = 1$)			
	Velísek[29]	BM	0.80	No difference
Radial 8 arm ($n = 1$)	Mouse ($n = 1$)			
	Rayburn[68]	BM+DM	2.00	No difference
Negative geotaxis ($n = 1$)	Mouse ($n = 1$)			
	Rayburn[68]	BM+DM	2.00	No difference
Ethanol consumption ($n = 1$)	Rat ($n = 1$)			
	Rodrigues[57]	DM	2.00	↑ Consumption
Home cage behavior ($n = 3$)	Rat ($n = 1$)			
	Borges[58]	DM	2.00	↓ Social behavior
	Non-human primate ($n = 2$)			
	Hauser[14]	DM	70.00	↑ Mobile, solitary play
	Hauser[69]	DM	35.00	↑ Mobile, ↓ social play, ↓ exploration
Cambridge Neuropsychological Test Automated Battery ($n = 1$)	Non-human primate ($n = 1$)			
	Hauser[69]	DM	35.00	↑ Responses, ↑ rewards (females)

BM betamethasone, *DM* dexamethasone

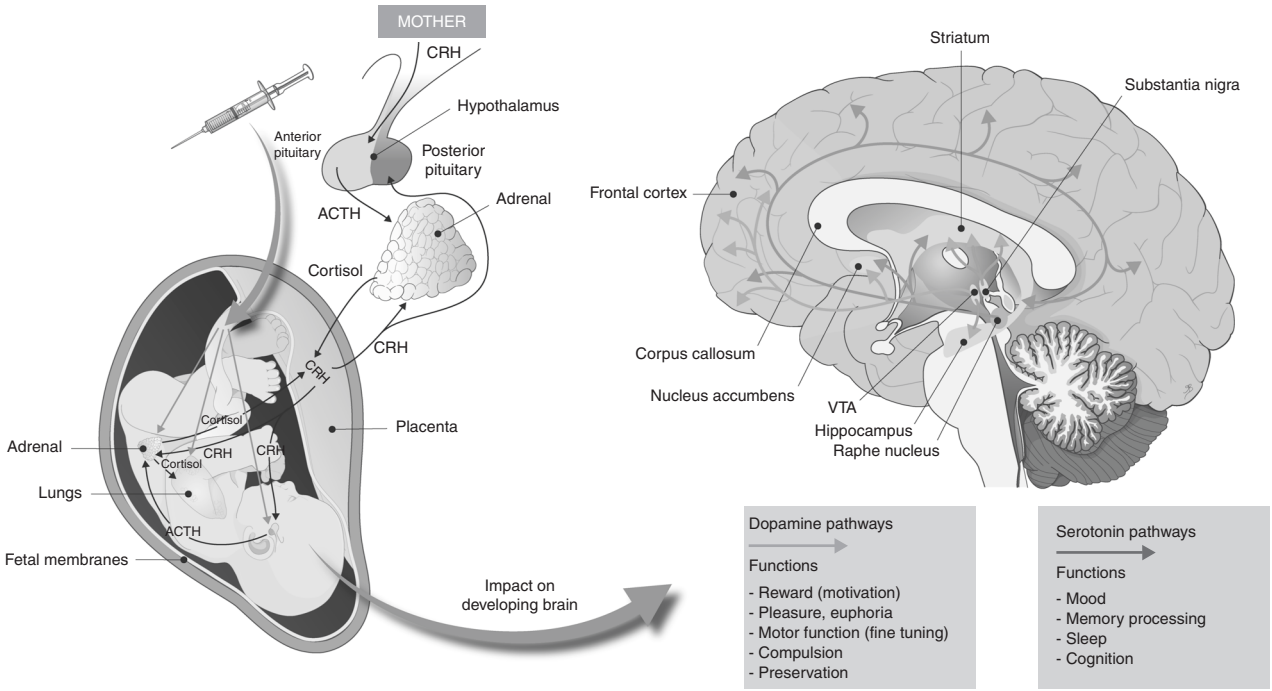

Fig. 4 The regulation of the maternal and fetal HPA axis during pregnancy. The human placenta expresses the genes for proopiomelanocortin and the major stress hormone, corticotropin-releasing hormone (CRH). As pregnancy progresses, these stress hormones including maternal cortisol, increase dramatically. 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.[81,82] 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.

different pharmacokinetics; BM has a larger volume of distribution and decreased clearance and thus a longer half-life.[71] 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).[72] 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[28,30,31,47,50,73] and DM[32,48,49,55] 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. There was also a high bias risk due the lack of randomization, allocational and treatment concealment, and ultimately selective/incomplete outcome reporting limit the interpretation of these results. Pseudoreplication is another critical methodological issue in animal behavioral research. Although many articles controlled for baseline characteristics, at least in some part, very few clearly stated how litter allocation was managed in their study. 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.[74,75] In contrast, in species that give birth to immature young (rats, rabbits, and mice), much neuroendocrine development occurs in the postnatal period.[76] 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.[77]

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 preterm birth.[78–80]

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 studies; and
4. Histological and functional outcomes assessed acutely and long term.

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

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All authors have contributed to the writing of this paper. J.L.v.d.M. and A.S. performed the search and extracted the data. J.T. and J.D. guided the results and merged and corrected the work.

ADDITIONAL INFORMATION

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