Corticosteroids before late preterm and term birth: An update on the available evidence considering ongoing benefits or harms: *A summary of recently published - May 2025*

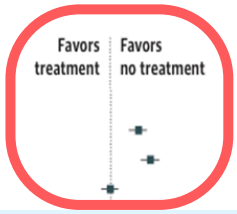
EVIDENCE FROM POPULATION-BASED STUDIES

Much of the interest and concern regarding potential harmful effects of corticosteroids is derived from population-based cohort and registry studies. Due to the nature of these studies, the ***certainty of the evidence is considered 'low' or very 'low'*** and the ability to adjust and account for the wide range of confounding factors is limited. Furthermore, it is important to note that these population-based studies do not provide information on the timing, type or dose of corticosteroids, with assumptions made that they have been given as per national guideline recommendations. These studies are therefore most likely to be assessing the longer-term impact of corticosteroids ***when given <35 weeks*** (and considered births at late preterm or term), and not the impact of corticosteroid administration for late preterm and term birth.

Räïkkönen *JAMA* 2020 doi:10.1001/jama.2020.3937

- Population-based retrospective cohort using Finnish nationwide registries 2006 -2017
- Born <37^{+0} vs ≥37^{+0} weeks, antenatal corticosteroids (ACS) yes or no (not when or how much, assumed <35 weeks)
- Primary outcome - any childhood mental and behavioural disorder from ICD-10 codes

Source	No. (%)[a] Treatment-exposed	Nonexposed	Absolute difference, % (95% CI)[b]	*P* value[c,d]	HR (95% CI)[d,e]	*P* value[c,d]
Primary outcome (any mental and behavioral disorder)						
Entire cohort	1785 (12.01)	42243 (6.45)	5.56 (5.04 to 6.19)	<.001	1.33 (1.26 to 1.41)	<.001
Term	598 (8.89)	40051 (6.31)	2.58 (1.92 to 3.29)	<.001	1.47 (1.36 to 1.60)	<.001
Preterm	1187 (14.59)	2192 (10.71)	3.88 (2.95 to 4.87)	<.001	1.00 (0.92 to 1.09)	.97

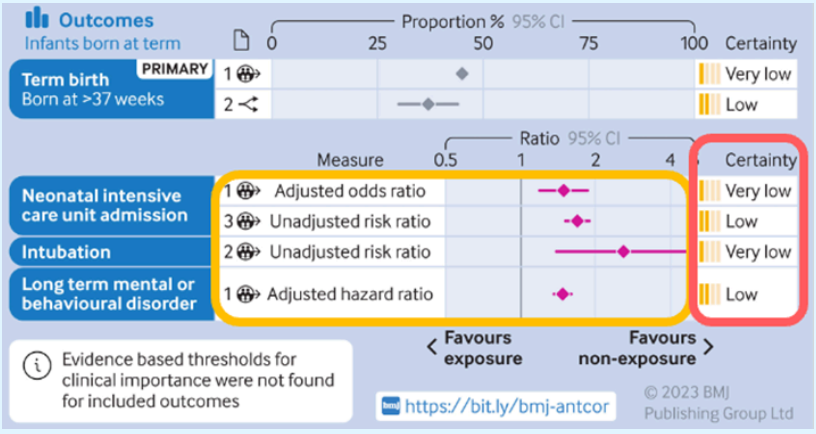


Standard practice in Finland – ACS ≤34^{+0} weeks to 2009, ≤34^{+6} weeks after 2009 with one repeat dose

This study provides evidence on the potential impact of ACS administered for early preterm birth, but when birth does not occur until term. Clinical message is to ***avoid indiscriminate use of ACS for preterm birth <35 weeks, ensure genuine concern for birth within the next 7 days.***

Ninan *BMJ* 2023 doi:10.1136/bmj-2023-076035

- Systematic review and meta-analysis
- 7 randomised controlled trials and 10 population-based cohort studies (including 1.6M births) where ACS were administered <34 weeks)
- 40% of the cohort birthed at term
- Infants whose mothers ***had ACS and birthed at term***, were more likely to have NICU admission and any long-term neurodevelopmental or behavioural disorder. The GRADE certainty of evidence is 'low' or 'very low' with no RCT evidence included in these secondary analyses



Similar to Räïkkönen study (which was included in this systematic review) evidence from this meta-analysis only includes the ***impact of ACS administered for early preterm birth, but when birth does not occur until later.***

Frier *BJOG* 2025 doi:10.1111/1471-0528.18101

- Population-based study using health reviews at 27-30 months across Scotland 2011-2017
- Analysis by gestation at birth (28-33, 34-36, 37-38, 39-41 weeks), ACS yes or no (not when or how much, assumed <35 weeks)
- Primary outcome – neurodevelopment (trained practitioner concerns and/or abnormal ASQ-3)

Gestational age at birth (weeks' gestation)	Presence of practitioner concerns about neurodevelopment: No. of children with concern/No. of children with outcome data (%) Total	Non-ACS-exposed	ACS-exposed	Model 1[a] Unadjusted OR (95% CI)	*p*	Model 2[b] Minimally adjusted OR (95% CI)	*p*	Model 3[c] Fully adjusted OR (95% CI)	*p*
28–33	977/3026 (32.3%)	137/353 (38.8%)	840/2673 (31.4%)	**0.72 (0.58; 0.91)**	**0.005**	**0.71 (0.57; 0.90)**	**0.004**	**0.79 (0.62; 0.999)**	**0.049**
34–36	2646/11 265 (23.5%)	1562/6863 (22.8%)	1084/4402 (24.6%)	**1.11 (1.02; 1.21)**	**0.02**	**1.11 (1.01; 1.21)**	**0.03**	**1.11 (1.01; 1.21)**	**0.03**
37–38	10 722/51 086 (21.0%)	10 290/48 893 (21.0%)	432/2193 (19.7%)	0.92 (0.83; 1.03)	0.13	0.94 (0.84; 1.04)	0.23	0.96 (0.85; 1.07)	0.42
39–41	35 429/210 172 (16.9%)	35 313/209 598 (16.8%)	116/574 (20.2%)	**1.25 (1.02; 1.53)**	**0.03**	**1.25 (1.02; 1.54)**	**0.03**	1.11 (0.90; 1.37)	0.33

Standard practice in UK - ACS ≤34^{+6} weeks to 2015, ≤33^{+6} weeks after 2015

There was no difference in ASQ-3 neurodevelopment scores across any gestational age group once adjusted for confounders - *child sex, child age at review and maternal age, maternal BMI, smoking status, parity, maternal diabetes, year of birth and neighbourhood deprivation.*

Frier BJOG 2025 continued:

The authors noted: Effect sizes of associations were small. Small effects of limited clinical relevance can potentially become statistically significant in sufficiently large study samples. There was a lack of information on ACS: gestation, administration, formulation, dosage and indications. Also lacking information on underlying causes of preterm birth, including infection and antibiotic use, and other confounding effects, including fetal growth restriction, congenital anomalies, genetic disorders, and maternal hypertensive disorders were not assessed.

EVIDENCE FROM RANDOMISED CONTROLLED TRIALS

Long-term outcomes after ACS use for preterm birth

Walters *PLOS Medicine* 2024 doi:10.1371/journal.pmed.1004378 cardiometabolic and respiratory outcomes, others presented/pending publication

- 50-year follow-up of the original Liggins RCT of ACS
- ACS for preterm birth <37 weeks, some of the cohort birthed preterm and some at term
- 424 (46% alive) traced and consented to health questionnaire and data linkage
- Primary outcome - cardiometabolic, secondary outcomes across health and wellbeing

Outcome	Betamethasone	Placebo	Adj. RR (95% CI)
Cardiometabolic risk factor composite, n/N	159/229 (69.4%)	131/195 (67.2%)	1.02 (0.89, 1.18)
Composite of obstructive airways disease, n/N	77/229 (41.5%)	66/195 (38.5%)	1.01 (0.76, 1.35)
Diagnosis or treatment of mental health disorder*, n/N	96/229 (41.9%)	84/195 (43.1%)	1.00 (0.79, 1.26)
Proportion with highest level of education tertiary*, n/N	126/223 (56.5%)	113/193 (58.6%)	0.97 (0.81, 1.16)
Any criminal conviction*, n/N	7/191 (3.7%)	4/166 (2.4%)	1.28 (0.34, 4.79)
Proportion not in paid work, retired, full time student or caregiver*, n/N	24/220 (10.9%)	25/189 (13.2%)	0.87 (0.48, 1.56)

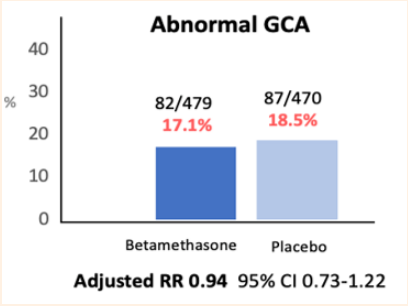
* Results presented in *Paediatric Academic Societies,* Washington DC 2023, and *PSANZ* Melbourne 2023

This study provides ***reassuring evidence on the longer-term impacts of ACS across a wide variety of health and wellbeing outcomes*** when administered for preterm birth at any gestation <37 weeks.

Long-term outcomes after ACS use for late preterm birth

Gyamfi-Bannerman *JAMA* 2024 doi:10.1001/jama.2024.4303

- Follow-up of cohort of children whose mothers participated in the ALPS trial (RCT for ACS prior to anticipated preterm birth 34^{+0} to 36^{+6} weeks for all modes of birth, which demonstrated respiratory benefit but an unanticipated finding of higher rates of neonatal hypoglycaemia)
  [Gyamfi-Bannerman NEJM 2016 doi:10.1056/NEJMoa1516783]
- Includes 949 children assessed for primary outcome of General Conceptual Ability (GCA) score as a measure of cognition/neurodevelopment
- Similar rates of hypoglycaemia in corticosteroid and placebo groups as in original trial
- No difference in mean GCA scores
- No difference in any component of the GCA score or behaviour and motor assessments
- Similar findings when analyses restricted to births >37 weeks



This study provides evidence that ***late preterm corticosteroid use has no impact on neurodevelopmental outcomes by early school age*** (despite an increase in neonatal hypoglycaemia).

Outcomes after ACS use for planned CS

Sotiriadis *Cochrane Database of Systematic Reviews* 2021 doi:10.1002/14651858.CD006614.pub4

Three of the trials included in the 2018 Cochrane Review of ACS prior to planned CS at term were removed in the 2021 Review due to concerns about trustworthiness. The trend towards reduced respiratory morbidity persists at $<38^{+0}$ weeks, 38^{+0} - 38^{+6}, and $\geq 39^{+0}$ weeks but is no longer statistically significant, with only one trial (the ASTECS Trial) included in the analysis. However, a reduction in neonatal special care for respiratory complications remains significant (RR 0.45, 95% CI 0.22 – 0.90). No trials of ACS prior to planned CS to date have reported data on neonatal hypoglycaemia.
Longer-term follow-up is limited to a single questionnaire-based study of the ASTECS Trial, published in 2013. It included only 37% of the original cohort at the age of 8-15 years. There were ***no differences in all measures on the strengths and difficulties subscales*** (relating to behaviour). The study reported a higher chance of children born to mothers who received ACS prior to their planned CS, being in the ***lower quartile for academic ability at school***. The study was not designed or powered for this analysis.

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