Hot Articles: Practice Changing (and Sometimes Controversial) Publications in OB Research

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Disclosures

- No relevant conflicts of interest
- Investigator for CHAP and ALPS
- University of Utah site for PRAECIS

Objectives

- Describe practice-changing publications in obstetrics
- Understand study populations and limitations of available evidence
- Describe how to incorporate trial findings into practice

CHAP

- Treatment for Mild Chronic Hypertension in Pregnancy (CHAP)
- Multicenter RCT of individuals with CHTN < 23 weeks
- Randomized to
  - Active management (BP <140/90)
  - Standard treatment (BP <160/105)
- Pragmatic medication choice – labetalol or nifedipine XL

Tita et al NEJM 2022

CHAP

- Primary outcome
  - Superimposed preeclampsia with severe features
  - Medically indicated PTB < 35 weeks
  - Placental abruption
  - Fetal or neonatal death
- Secondary safety outcome
  - Fetal weight <10%ile for GA and sex at birth

Tita et al NEJM 2022

CHAP

- 2,408 participants
- Primary outcome less frequent in active management
  - 30.2% vs 37.0%, aRR 0.82 (95% CI 0.74-0.92)
- Secondary safety outcome not different between groups
  - 11.2% vs 10.4%, aRR 1.04 (95% CI 0.82-1.31)
- Treatment <140/90 improved maternal outcomes and did not increase SGA

Tita et al NEJM 2022

Should it be <130/80?

- Secondary analysis of CHAP trial
- Compared participants with mean clinic BP 130-139/80-89 vs those with BP <130/80
- Those mean clinic BP <130/80 more likely to be in active treatment arm
- <130/80 associated with lower risk of maternal composite
  - PreE with severe fxs, MIPTB < 35 wks, abruption, perinatal death
  - 16% vs 36%, aRR 0.45, 95% CI 0.38-0.54
- No difference in SGA

Bailey et al Obstet Gynecol 2023

Timing of Delivery

- Planned secondary analysis CHAP trial
  - RCT of CHTN treatment to different BP goals
  - Participants who remained pregnant at start of each gestational week were classified as planned delivery or expectant management
  - Primary maternal composite- death, serious morbidity, preE with severe fxs, blood transfusion, abruption
  - Secondary- cesarean and neonatal outcomes

Timing of Delivery- Maternal Primary Outcome

Outcome	37w0d-39w6d n=1417 aOR (95% CI)	38w0d-39w6d n=961 aOR (95% CI)	39w0d-39w6d n=460 aOR (95% CI)
Primary maternal composite outcome	1.11 (0.71-1.75)	0.90 (0.53-1.52)	1.22 (0.63-2.35)
Preeclampsia severe features	0.91 (0.54-1.53)	0.88 (0.50-1.57)	0.88 (0.43-1.80)
Hemorrhage with transfusion	1.38 (0.64-3.00)	0.87 (0.35-2.19)	---

Serious maternal morbidity and abruption could not be modeled due to low event counts

Timing of Delivery- Secondary Outcomes

Outcome	37w0d-39w6d n=1417 aOR (95% CI)	38w0d-39w6d n=961 aOR (95% CI)	39w0d-39w6d n=460 aOR (95% CI)
Primary neonatal composite	1.43 (0.96-2.14)	1.02 (0.64-1.63)	1.15 (0.66-2.01)
Cesarean birth	2.07 (1.48-2.91) **	1.25 (0.89-1.76)	1.37 (0.91-2.06)
RDS	2.58 (1.34-4.98) **	2.35 (0.86-6.42)	---
Hypoglycemia	1.87 (1.20-2.91) **	1.73 (1.02-2.92) **	0.44 (0.18-1.06)

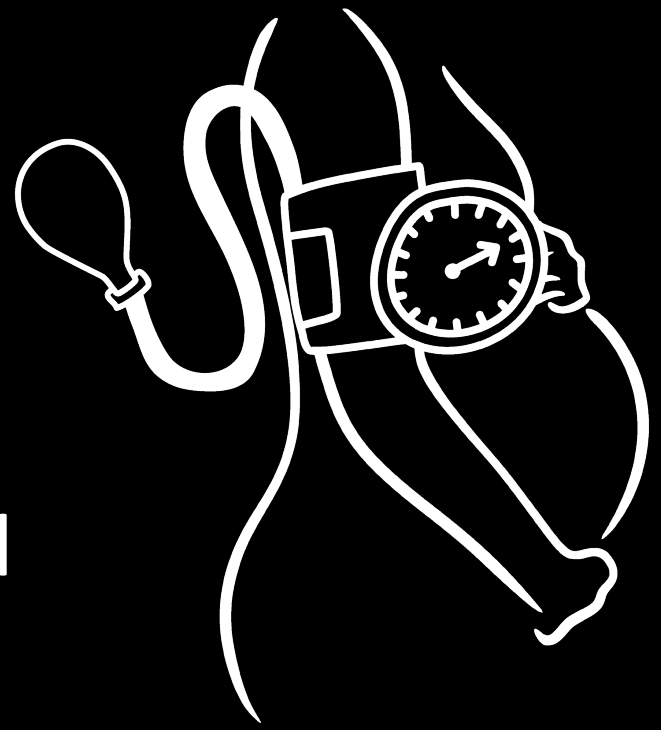
Timing of Delivery- Summary

- No association between planned delivery and primary maternal outcome
- Planned delivery in week 37 associated with cesarean
- Planned delivery in week 37 associated with RDS
- Planned delivery in week 37 and 38 associated with hypoglycemia
- No association with neonatal LOS or NICU

Integration into Practice- CHAP

- Goal BP for individuals with CHTN <140/90
  - Likely requires some home BP monitoring
  - Likely OK to dip to <130/80
- Treat with labetalol or nifedipine XL
- If well controlled, consider delivery at 39 weeks
- Cannot extrapolate to gHTN or preeclampsia

PRAECIS



- Multicenter cohort
- Evaluated predictive value of serum soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF)
- Enrolled pregnant people hospitalized between 23 and 35 weeks with hypertensive disorders of pregnancy
- Primary outcome progression to severe fxs < 2 weeks
- Other adverse outcomes were secondary outcomes

Thadhani et al NEJM Evidence 2022

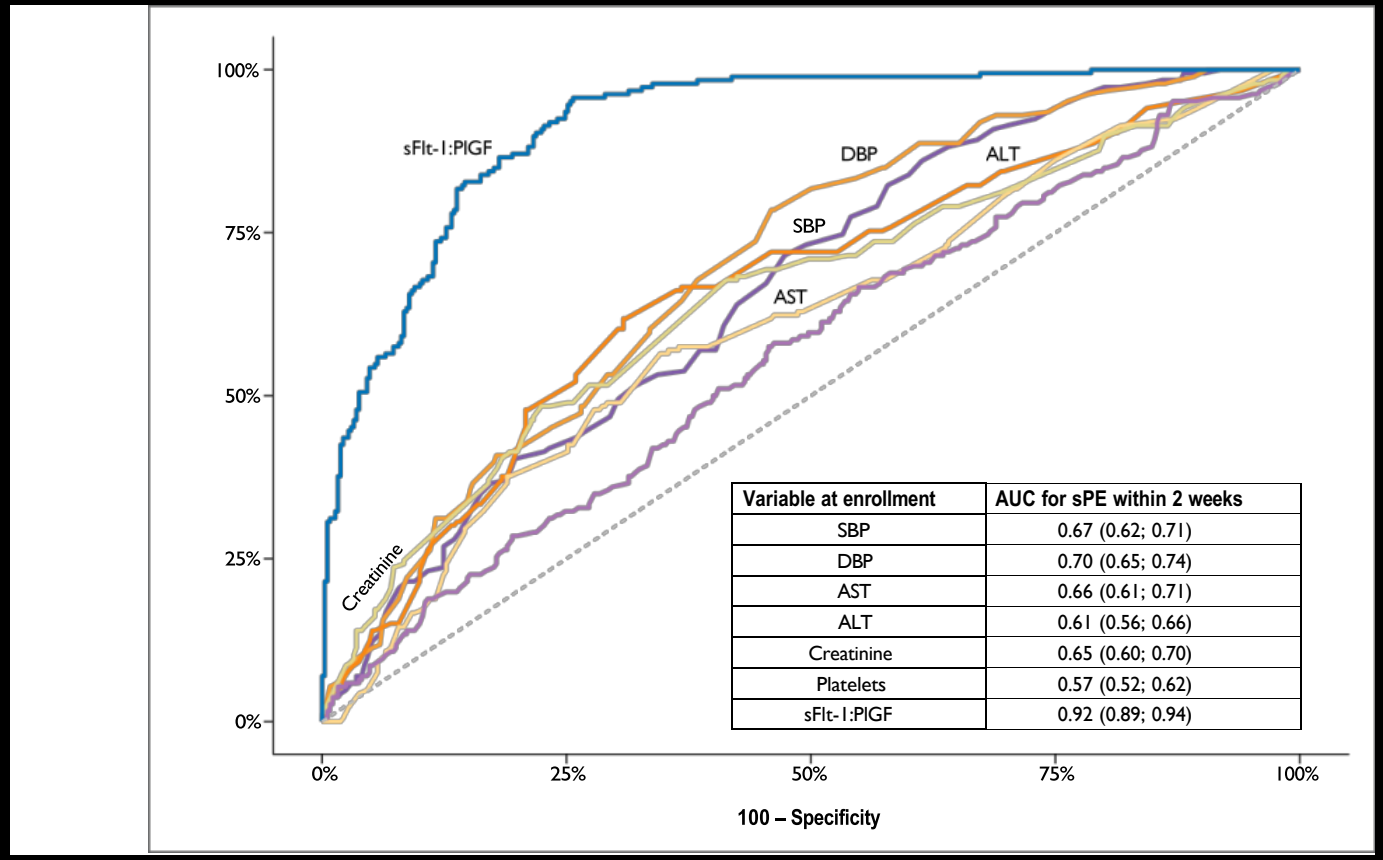
PRAECIS

- Preeclampsia Risk Assessment: Evaluation of Cut-Offs to Improve Stratification (PRAECIS)
- 1014 enrolled
  - 299 derivation cohort
  - 715 validation cohort
- Derivation cohort median sFlt-1:PlGF 200 among those who developed severe features
  - sFlt-1:PlGF 6 among those who did not develop severe fxs
- Based on AUC, used ratio ≥ 40 as potentially predictive of progression to severe features within 2 weeks

Thadhani et al NEJM Evidence 2022

PRAECIS- Validation Cohort

- Using ratio ≥ 40
- NPV 96%
- PPV 65%
- AUC 0.92
- Risk adverse maternal outcomes (16% vs 3%, RR 5.8)



Variable at enrollment	AUC for sPE within 2 weeks
SBP	0.67 (0.62; 0.71)
DBP	0.70 (0.65; 0.74)
AST	0.66 (0.61; 0.71)
ALT	0.61 (0.56; 0.66)
Creatinine	0.65 (0.60; 0.70)
Platelets	0.57 (0.52; 0.62)
sFlt-1:PlGF	0.92 (0.89; 0.94)

Thadhani et al NEJM Evidence 2022

History of Assays

- sFlt-1:PlGF assay approved in Europe 2009
- NICE recommends assay used in conjunction with standard clinical assessment for preE
- Used widely in Canada, Asia, Australia, New Zealand
- Approved by FDA (KRYPTOR Test System)

  May 18, 2023

Burwick et al Obstet Gynecol 2024

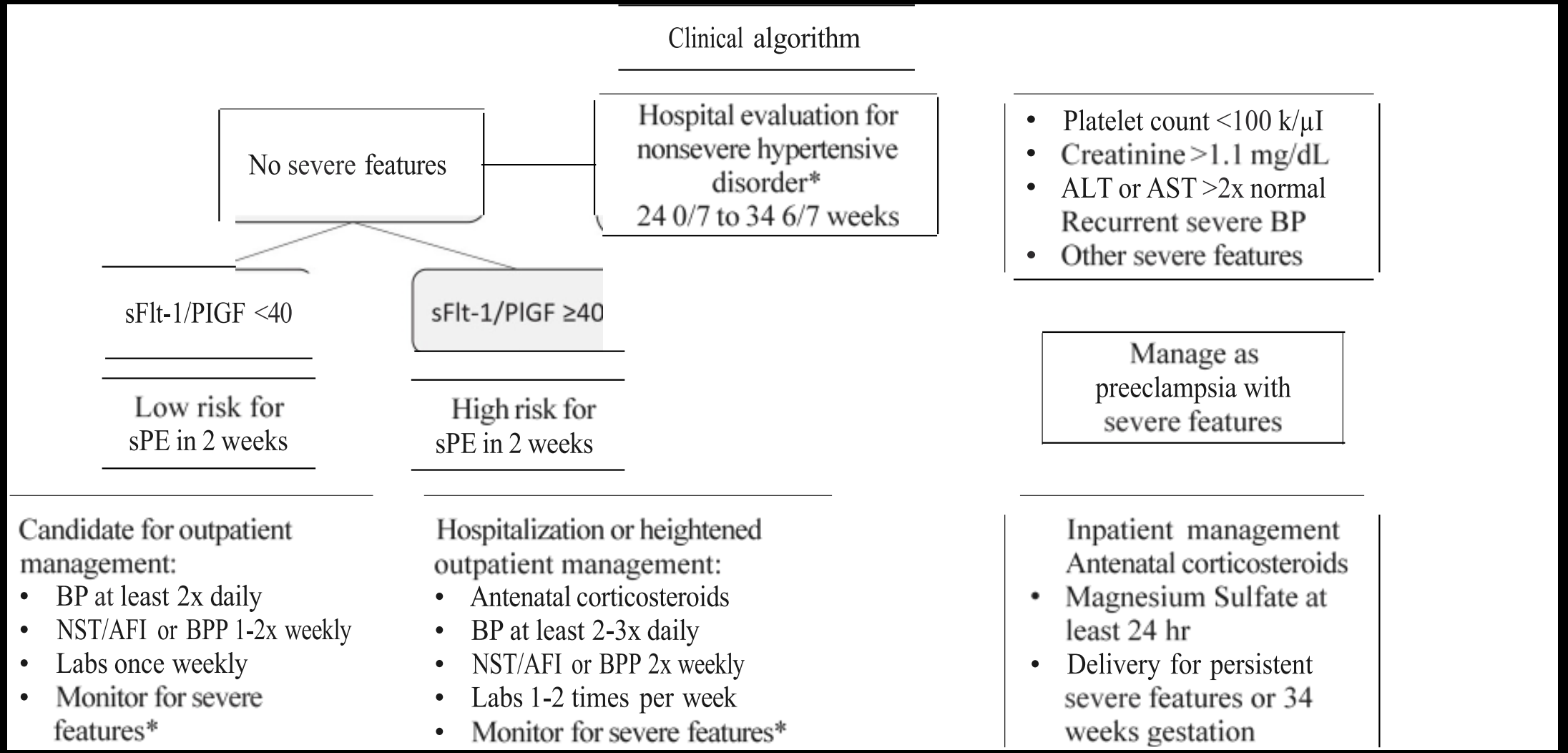
Other sFlt-1/PlGF Studies

Table 1. Clinical Studies Evaluating the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio for Prediction of Preeclampsia

Study	Study Location, Type	Study Group	n	Primary Outcome	sFlt-1/PlGF Ratio Threshold*		NPV (%)	PPV (%)
					Low Risk	High Risk		
PROGNOSIS[14]	Multicentert	Suspected PE 24 0/7-36 6/7 wk	1,050	PE within 1 wk	38 or less	Greater than 38	99	17
		Suspected PE 24 0/7-36 6/7 wk	1,050	PE within 4 wk'	38 or less	Greater than 38	95	39
PROGNOSIS[21]	Asia, multicenter§	Suspected PE 20 0/7-36 6/7 wk	700	PE within 1 wk'	38 or less	Greater than 38	99	18
		Suspected PE 20 0/7-36 6/7 wk	700	PE within 4 wk'	38 or less	Greater than 38	95	30
ROPE Study[40]	Boston, Massachusetts, single-center	Suspected PE before 34 wk	199	sPE within 2 wk	38 or less	Greater than 38	98	65
		Suspected PE before 34 wk	199	sPE within 2 wk	85 or less	Greater than 85	91	74
PRAECIS[10]	United States, multicenter	GHTN, PE, CHTN±PE at 23 0/7-34 6/7 wk	715	sPE within 2 wk	Less than 40	40 or greater	96	65
ROPE Study[15,7,7,4]o	Boston, Massachusetts, single-center	Confirmed PE 20 0/7-34 6/7 wk	459	sPE within 2 wk	38 or less	Greater than 38	94	66
		Confirmed PE 20 0/7-34 6/7 wk	459	sPE within 2 wk	85 or less	Greater than 85	85	77

Burwick et al Obstet Gynecol 2024

Proposed algorithm if integrated into care



Burwick et al Obstet Gynecol 2024

Integration into Clinical Practice

- FDA approved (KRYPTOR Test System)
- Can be considered for use as risk stratification tool
- CANNOT replace standard clinical management and decision making
- May add to our tools when risk stratifying patients for need for hospitalization and BMZ administration

ALPS

- Multicenter RCT enrolled individuals between 34w0d and 36w5d at risk for preterm delivery
- Received 2 doses betamethasone 24 hrs apart or placebo
- Primary outcome neonatal composite within 72 hrs of birth
  - Use of CPAP or HFNC for ≥ 2 hours
  - Supplemental oxygen with FiO2 ≥ 0.30 for ≥4 hours
  - ECMO or mechanical ventilation
  - Stillbirth or neonatal death

Gyamfi-Bannerman et al NEJM 2016

ALPS

- Primary outcome less frequent in BMZ group

Outcome	Betamethasone	Placebo	RR (95% CI)
Primary Outcome	11.6%	14.4%	0.80 (0.66-0.97)
CPAP for ≥ 2 hrs	10.2%	13.1%	0.77 (0.63-0.95)
FiO2 ≥ 0.30 for ≥ 4 hrs	3.4%	4.4%	0.77 (0.53-1.12)
Mechanical ventilation	2.4%	3.1%	0.78 (0.50-1.21)
ECMO	0	0	N/A
Stillbirth or NND	0	0	N/A

Gyamfi-Bannerman et al NEJM 2016

ALPS

- Neonatal hypoglycemia more frequent BMZ group
  - 24.0% vs 15.0%, RR 1.60 (95% CI 1.37-1.87)
  - Individuals with diabetes excluded from trial

ALPS Implementation

- Cross sectional study U.S. births
- Liveborn singleton gestation born 34 to 36 weeks without pre-existing maternal diabetes
- Adjusted rate of steroid use increased from 5% to 12%
- Assisted ventilation use decreased after dissemination period
  - 8.9% vs 8.2% (adjusted incidence rate ratio 0.91, 95% CI 0.85-0.98)
- No change assisted ventilation > 6 hours

Clapp et al JAMA Network Open 2022

ALPS and Neurodevelopment

- Some animal data suggest adverse effects on fetal brain
- Rhesus macaques decreased number of pyramidal neurons in hippocampus and degeneration of axodendritic synaptic terminals
  - Effect was dose dependent
- Rat models demonstrate changes in transcription factors involved in cell differentiation with dexamethasone exposure
- Repetitive doses of BMZ had adverse effects in humans

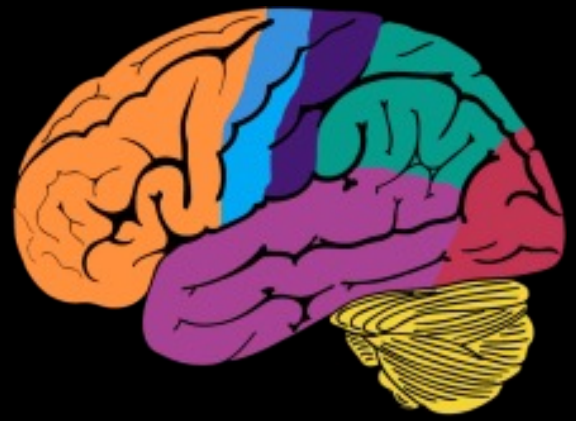
Uno Brain Res Dev Brain Res 1990; Slotkin Brain Res Dev Brain Res 1998; Wapner NEJM 2007

Finnish Data

- Population-based retrospective cohort using nationwide registries in Finland
- 674,877 children included
  - 14,868 steroid-exposed
- Increased frequency of mental and behavioral disorder with exposure
  - 12% vs 6%, aHR 1.33 (95% CI 1.26-1.41)
- Among preterm born children, no statistically significant difference when comparing exposed vs unexposed
- No data on indication, deaths or GA at administration

Raikkonnen et al JAMA 2020

ALPS and Neurodevelopment



- China National Birth Cohort study
- 1759 participants
  - 710 exposed to antenatal corticosteroids (dex or prednisone at any gestational age)
- Increased risk of being “non-competent” cognitive development of Bayley scales at 1 year of age
- Exposure to dexamethasone aRR 1.62 (95% CI 1.10-2.38) of non-competent neurodevo compared with unexposed

Tao et al Am J Obstet Gynecol 2022

JAMA Peds Systematic Review and Meta-Analysis

- Included 30 cohort studies
  - 26 focused on neurodevo and/or psych outcomes
- Duration of participant follow-up 1-3 years
- Examined exposure to corticosteroids during pregnancy
- Primary outcome any adverse neurologic or psychologic disorder
- Assessed both overall and by timing of exposure

Ninan et al JAMA Peds 2022

JAMA Peds Systematic Review and Meta-Analysis

- Single course among extremely preterm birth significant reduction in risk of neurodevelopmental impairment
  - aOR 0.69, 95% CI 0.57-0.84
- Children with late preterm birth exposure associated with higher risk of neuro disorder
  - aHR 1.12, 95% CI 1.05-1.20
- Children with term birth exposure associated with higher risk of psychiatric or behavioral disorder
  - aHR 1.47, 95% CI 1.36-1.60

Ninan et al JAMA Peds 2022

RCT Follow-Up Studies

- Follow-up study of RCT of BMZ vs placebo
- Initially enrolled 24w0d to 36w6d
  - Majority in late preterm period
- No differences in measures of cognitive testing at 6 years of age
- No differences in cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health-related quality of life at 30 yrs

MacArthur et al Pediatrics 1982

SMFM 2023 ALPS Neurodevelopment

- Prospective follow-up study of participants MFMU ALPS trial
- Of 2,831 in parent trial, 1026 enrolled
- Children ≥ 6 years of age completed Differential Ability Scales, 2nd Edition (DAS-II)
- Primary outcome general conceptual ability score (GCA) <85 or 1 SD less than mean
- No difference 17% BMZ group and 19% placebo group
  - aRR 0.94 (95% CI 0.73-1.22)

Gyamfi-Bannerman AJOG SMFM abstracts 2023

Integrating into Clinical Practice

- ALPS offered between 34w0d and 36w5d
- Restrict to those anticipated to deliver preterm but more than 12 hours from first dose
- Withhold from those with pre-existing diabetes
- Discuss evolving long term safety data
- Shared decision-making

Thank you!

- Questions and Discussion