Corticothérapie anténatale

Thomas Schmitz

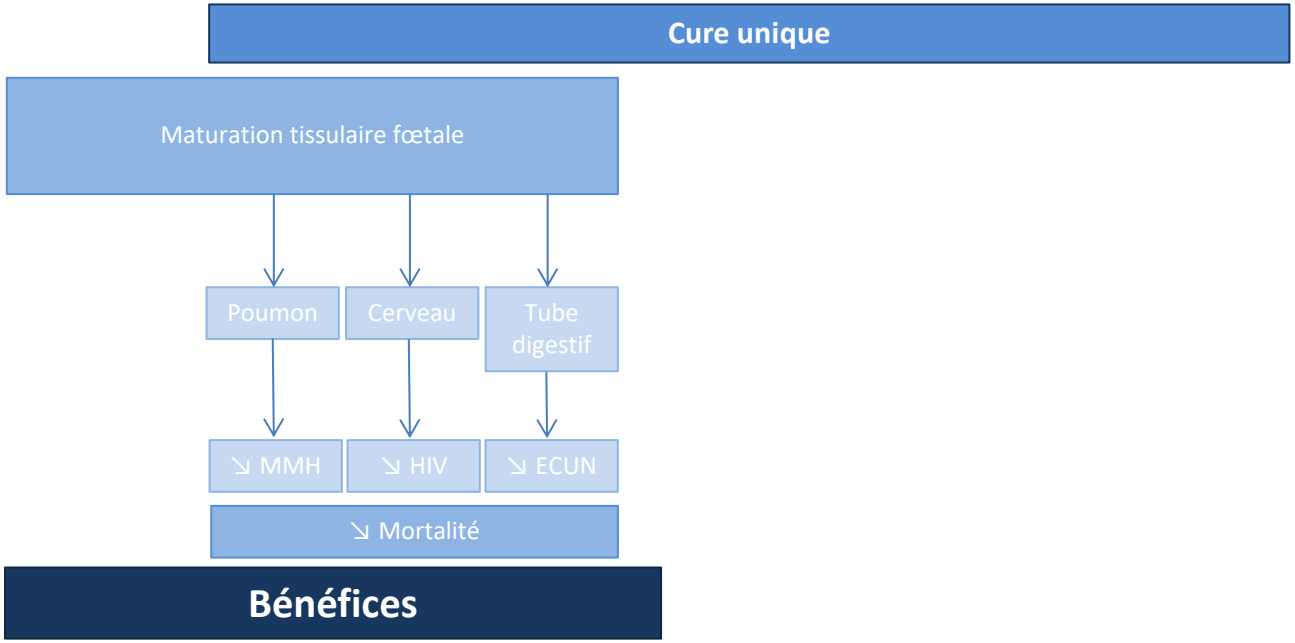
Service de Gynécologie Obstétrique
Hôpital Robert Debré

Efficacité démontrée d'une cure

- Travaux de Liggins et Howie (J Endocrinol,1969)
- Multiples essais randomisés
- Métaanalyse de Crowley (Am J Obstet Gynecol, 1995)
- Recommandations NIH et ACOG (1995)
- 2 injections IM de 12 mg de betamethasone (Celestene chronodose) à 24 h d'intervalle

Beaucoup (trop?) d'importance accordée aux résultats néonatals immédiats

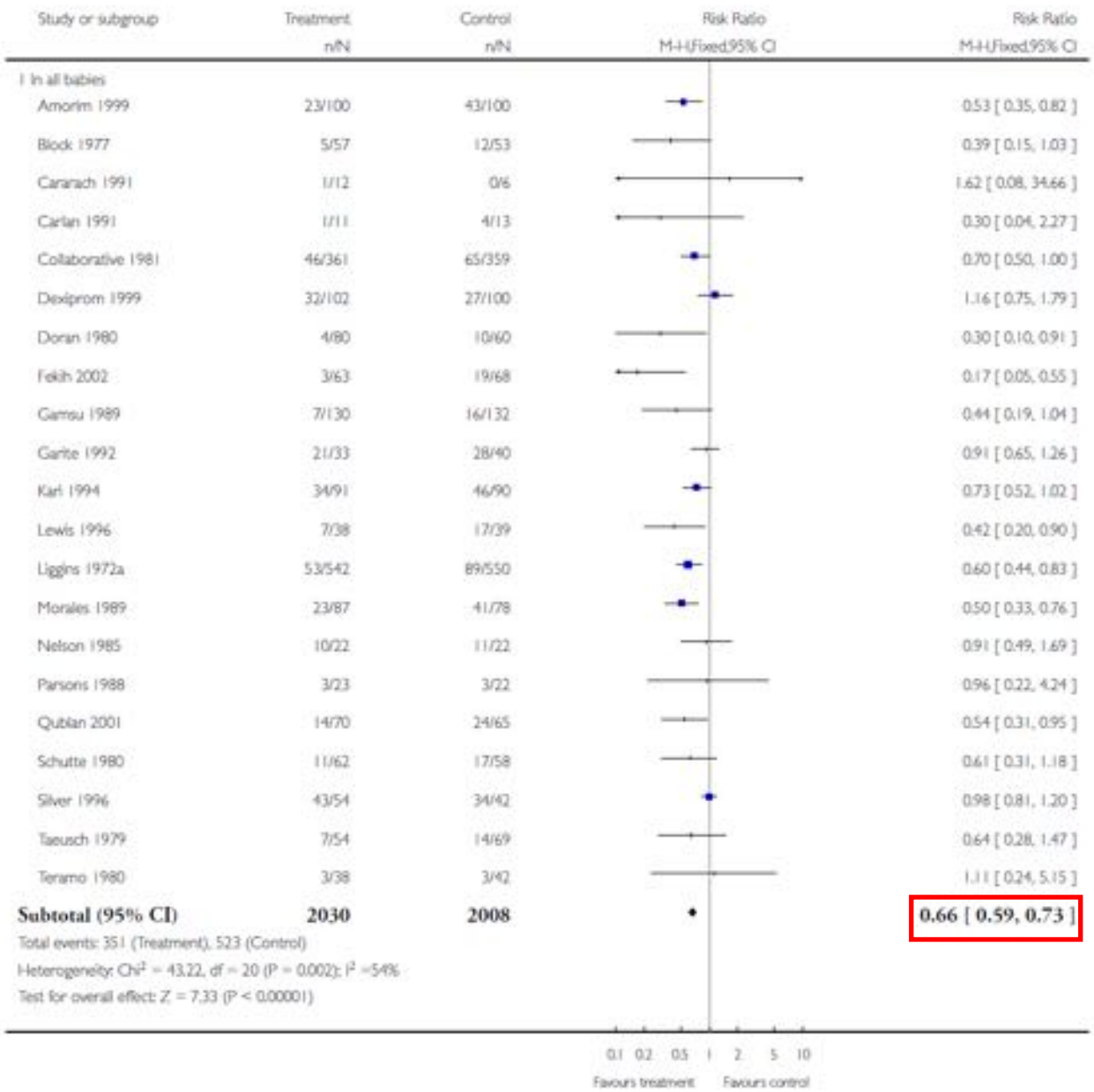
Bénéfices et risques de la corticothérapie anténatale



Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Dalziel SR

Outcome: 7 Respiratory distress syndrome

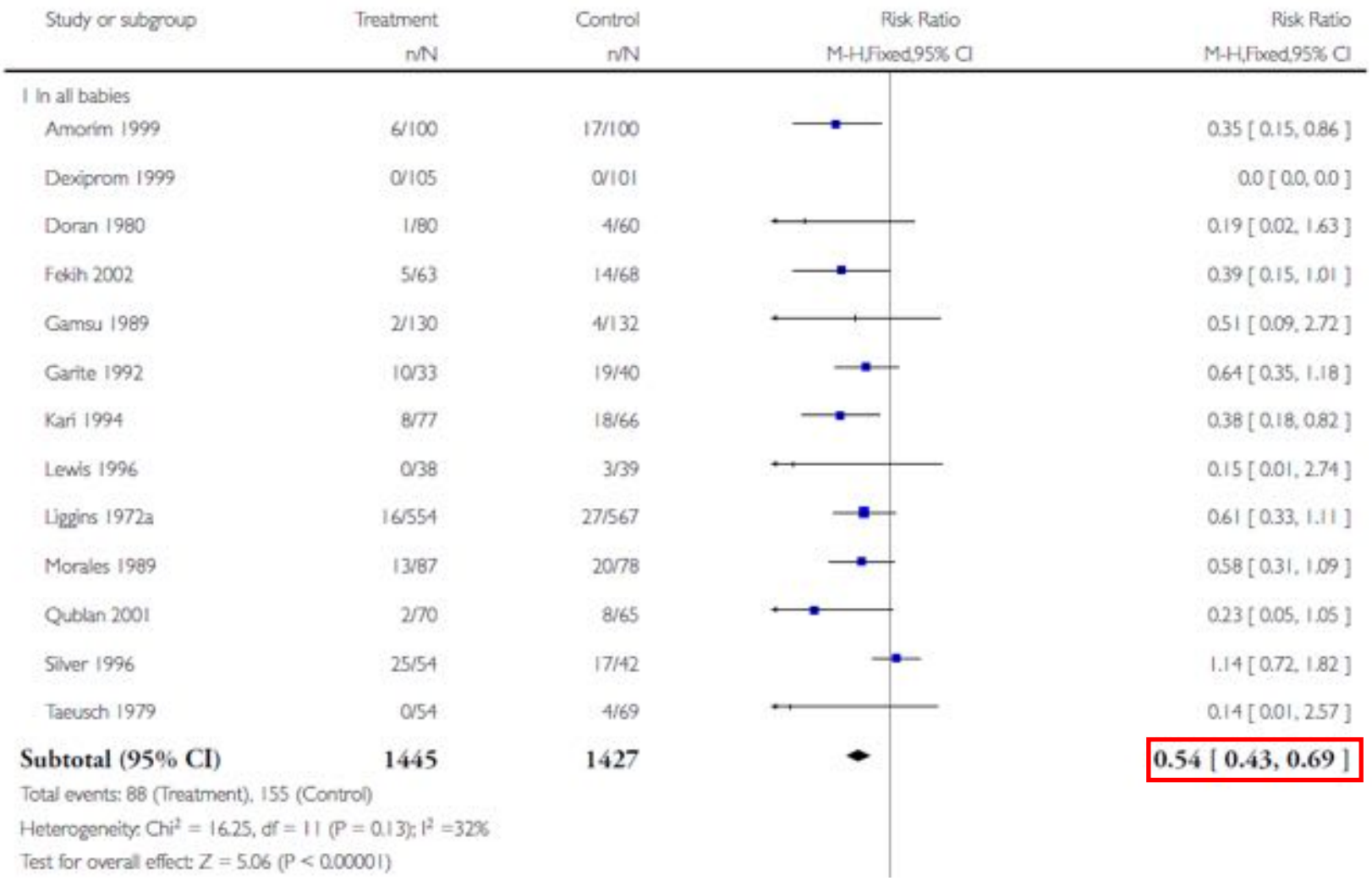


Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Dalziel SR

THE COCHRANE COLLABORATION®

Outcome: 10 Cerebroventricular haemorrhage

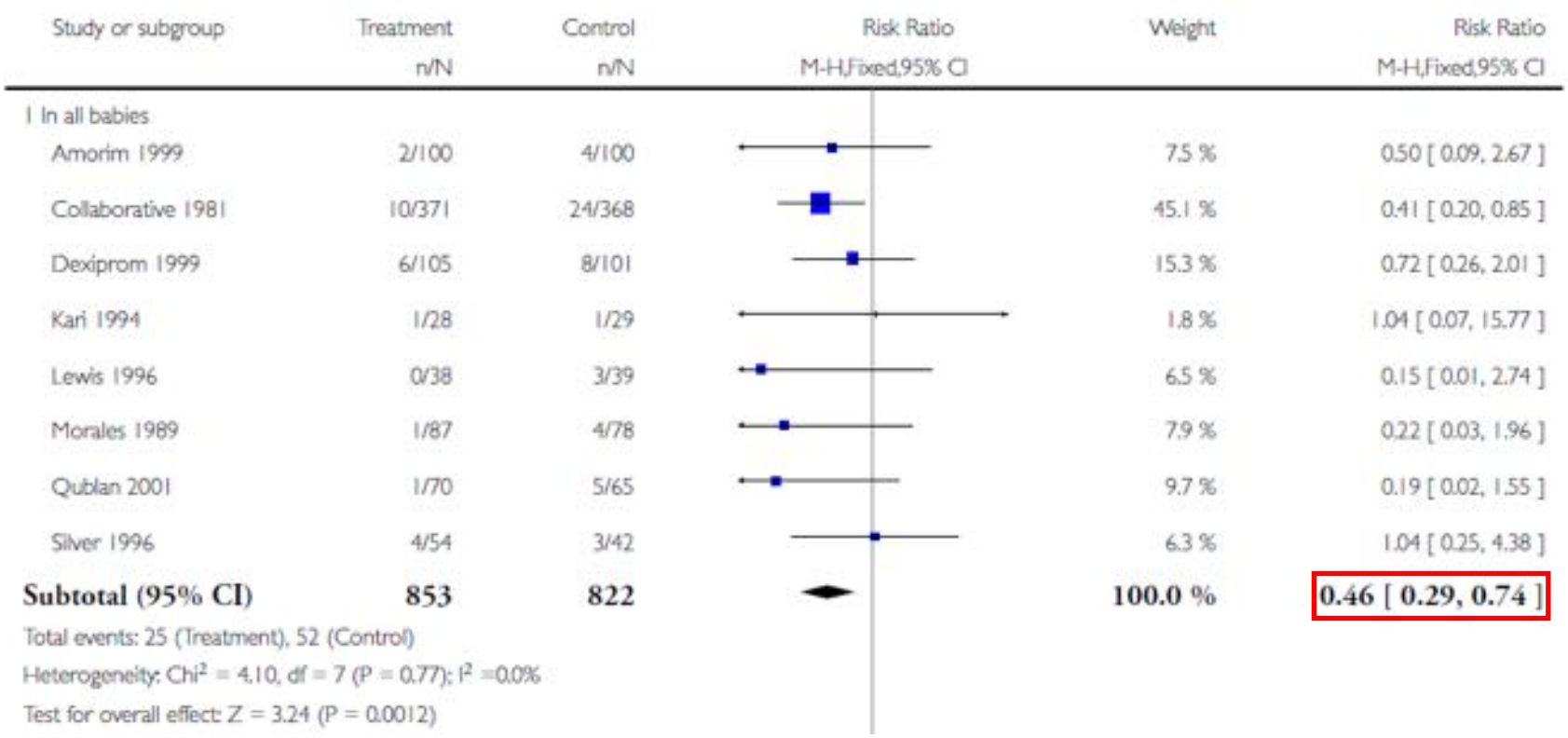


Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Dalziel SR

THE COCHRANE COLLABORATION®

Outcome: 33 Necrotising enterocolitis

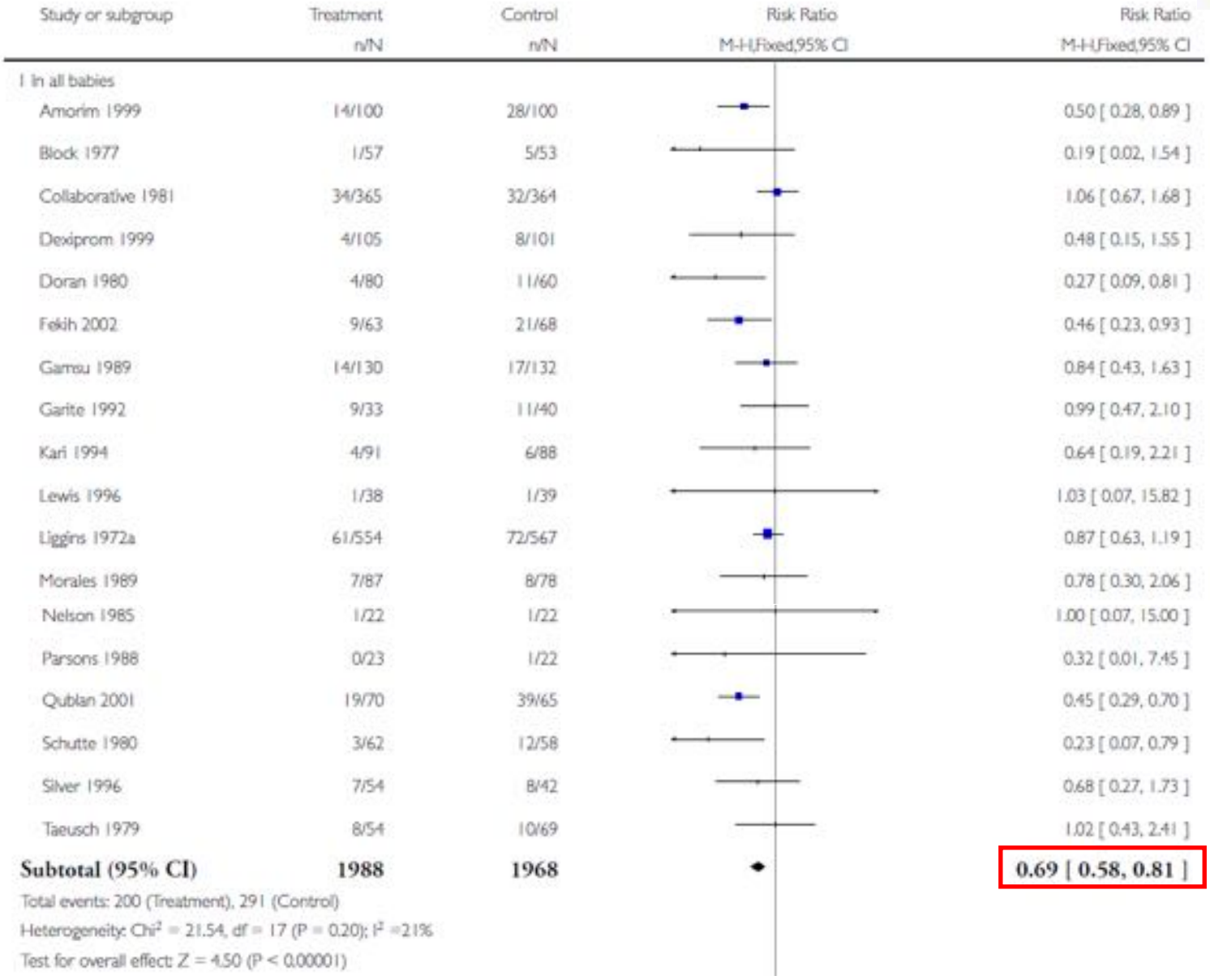


Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

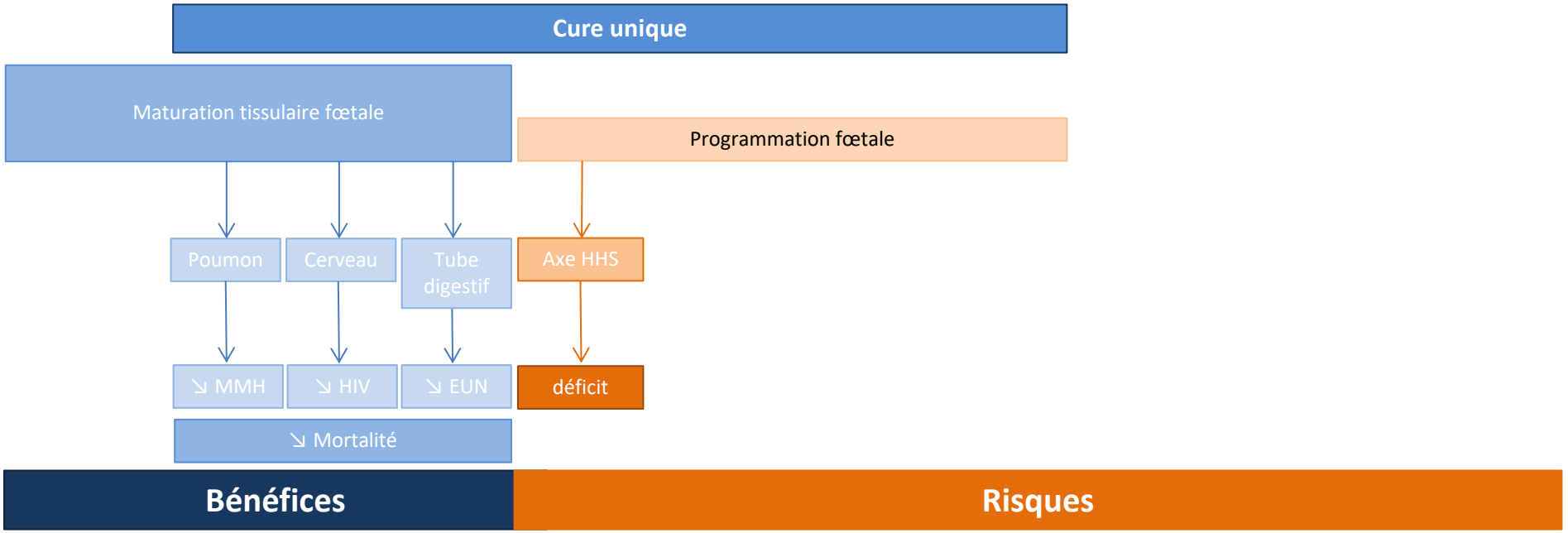
Roberts D, Dalziel SR

THE COCHRANE COLLABORATION®

Outcome: 6 Neonatal deaths



Bénéfices et risques de la corticothérapie anténatale



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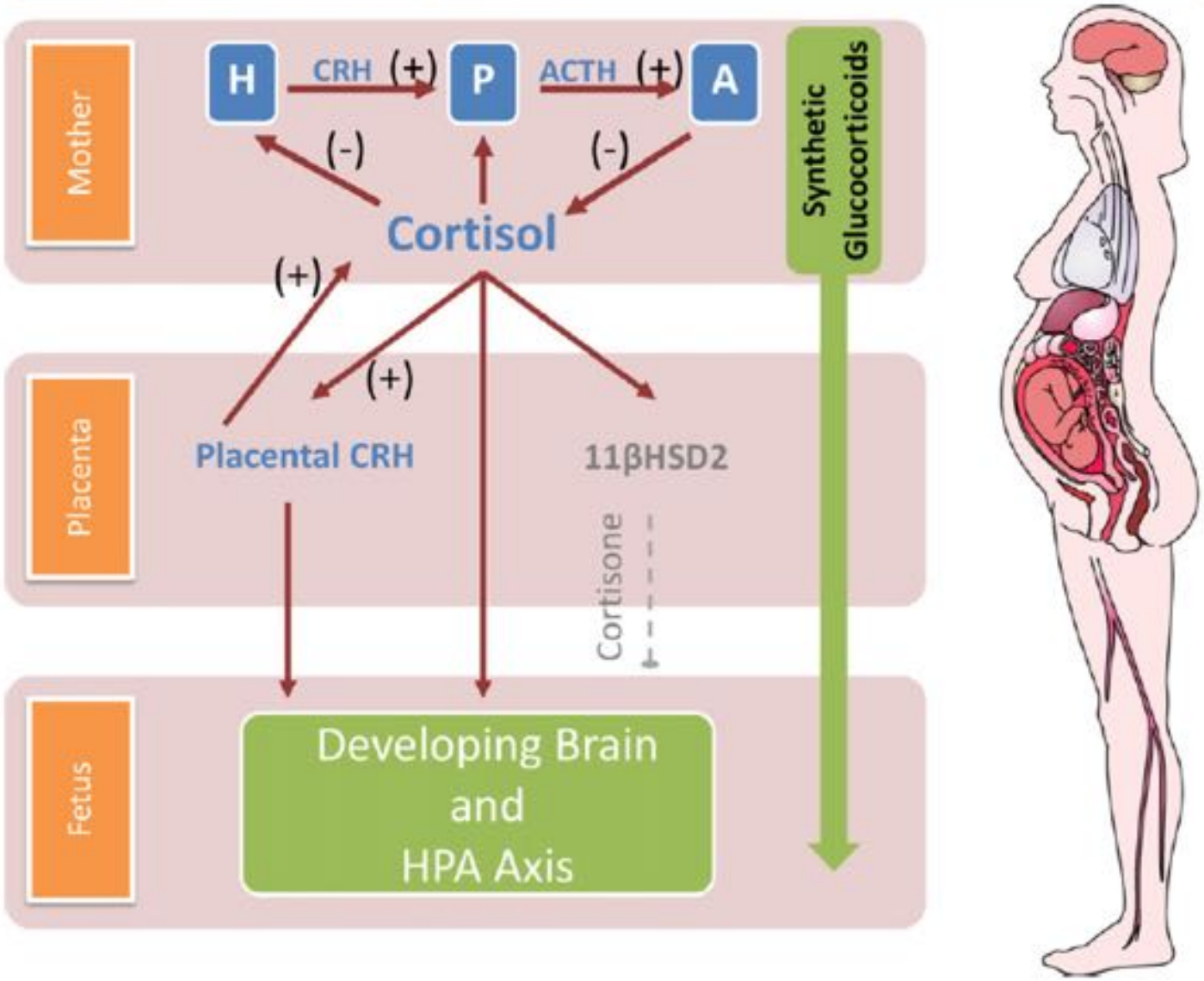
insulinR: insulino-résistance, HHS: hyphothalamo-hypophyso-surrénalien

FIGURE

Neuroendocrine interactions among the maternal, placental, and fetal compartments



TABLE

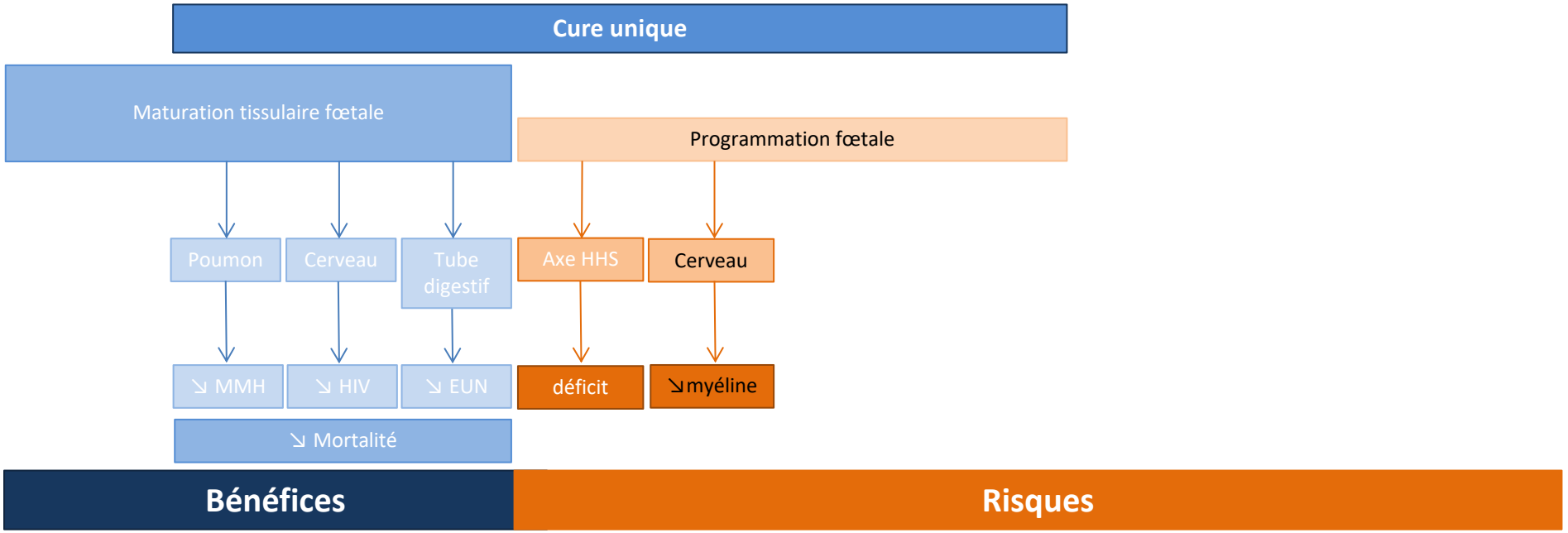
Antenatal glucocorticoid effects on neonatal stress response

Reference	Type of GC; number of courses	GA wks at GC exposure	After GC days to birth	Maturity/GA at birth	Neonatal stress challenge Cortisol response	Behavioral response	Comment/implications
Davis et al[62]	Betamethasone × 1 course	N/A	Mean 8.3 d; range, 1–21 d	Preterm only 33-34	Blunted/no cortisol response among GC-treated infants compared with no-treatment comparison group	Similar to comparison group	HPA axis function altered
Davis et al[64]	Betamethasone × 1 course	N/A	Mean 5.1 d; range, 1–9 d	Preterm only 28-30	Blunted cortisol response among GC treated as compared with no-treatment comparison group	Similar to comparison group	HPA axis function altered
Ashwood et al[66]	Betamethasone × 1 course compared with multiple courses. No control group	23-31	Unknown	Preterm only <32 and >32	Blunted cortisol response in multiple-course group compared with single-course group. Greater blunting of cortisol response at earlier gestational exposure. Baseline cortisol lower in multiple-course group at d 7 compared with single course; baseline cortisol levels were similar in the 2 groups by d 14	Not studied	Acute differences in HPA axis function in infants exposed to multiple courses vs single course
Schaffer et al[63]	Betamethasone × 1 course	29.4	Mean 60 d	Term and preterm >34 wks	Blunted cortisol and cortisone response among GC treated infants compared with the no-treatment comparison group	Not studied	HPA axis function altered
Davis et al[69]	Maternal psychosocial stress; exposed to elevated endogenous maternal cortisol in second and third trimesters	No exposure to GC treatment; prenatal endogenous maternal GCs evaluated	N/A	Term only 37-41	Larger cortisol response and slower recovery associated with elevated maternal endogenous cortisol levels	Slower recovery to baseline state	HPA axis function altered
Davis et al[65]	Betamethasone × 1 course	29.5	Mean 60.5 d; range, 28–105 d	Term only 37-41	Larger cortisol response among the GC-treated infants compared with no-treatment group; with greater response when GC exposure was at earlier GA	Similar to comparison group	HPA axis function altered

GA, gestational age; *GC*, glucocorticoids; *HPA*, hypothalamic-pituitary-adrenocortical; *N/A*, not applicable.

Wapner. Antenatal corticosteroids and HPA axis function. Am J Obstet Gynecol 2012.

Bénéfices et risques de la corticothérapie anténatale



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insulinR: insulino-résistance, HHS: hyphothalamo-hypophyso-surrénalien

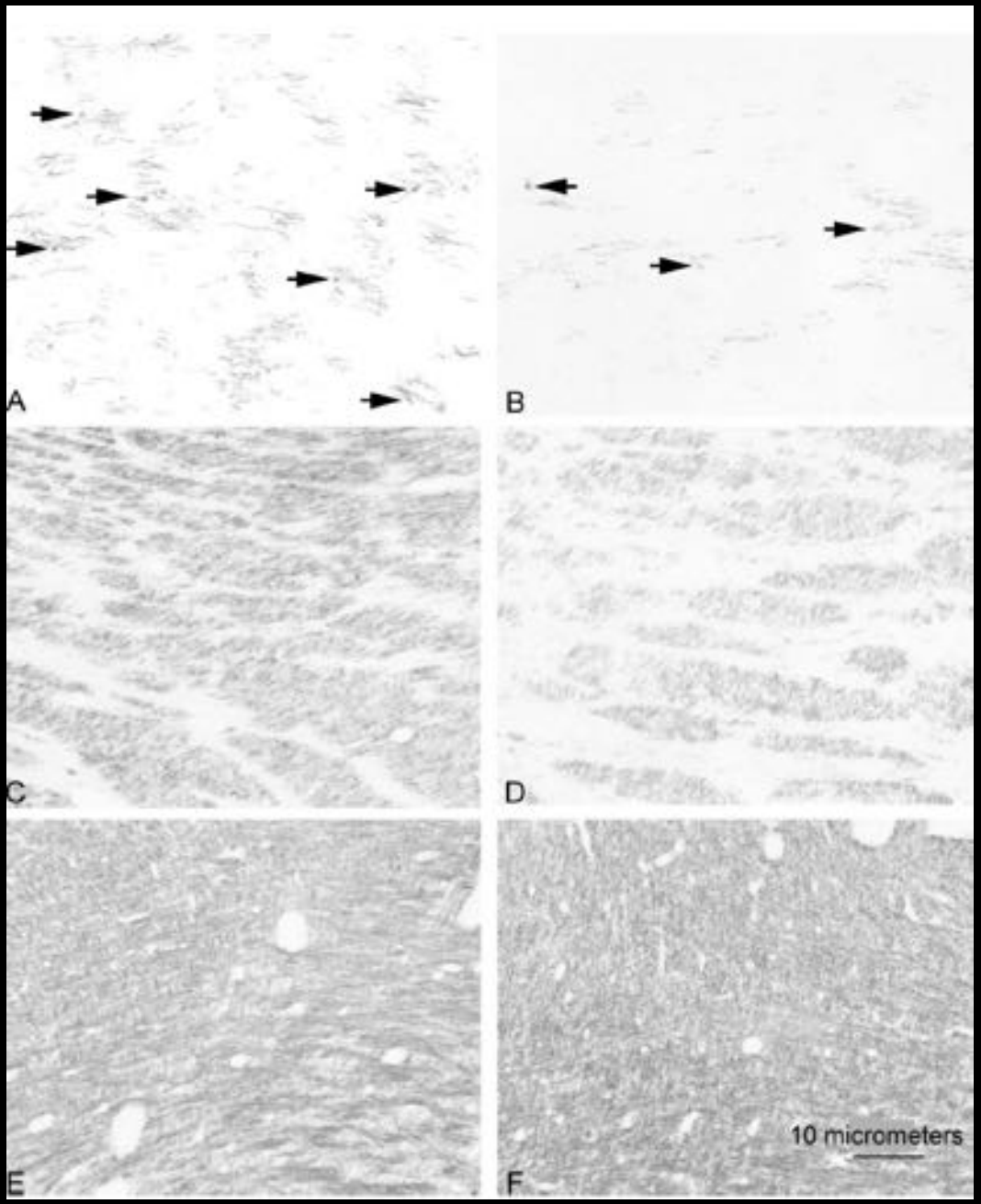
Myelin Binding Protein

Contrôle

Betaméthasone

Centre semi-ovale

- Corps calleux
- Capsule interne
- Substance blanche superficielle

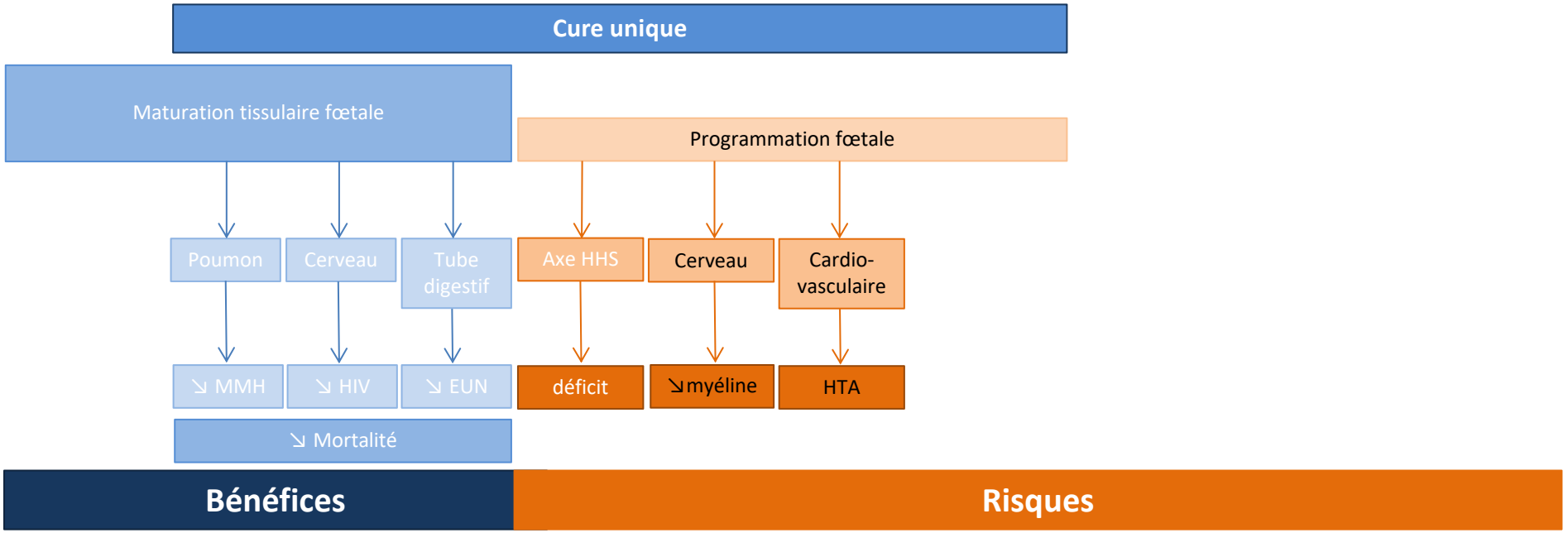


0,63

0,75

0,87

Bénéfices et risques de la corticothérapie anténatale



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Alterations in Fetal Kidney Development and Elevations in Arterial Blood Pressure in Young Adult Sheep after Clinical Doses of Antenatal Glucocorticoids

JORGE P. FIGUEROA, JAMES C. ROSE, G. ANGELA MASSMANN, JIE ZHANG, AND GONZALO ACUÑA

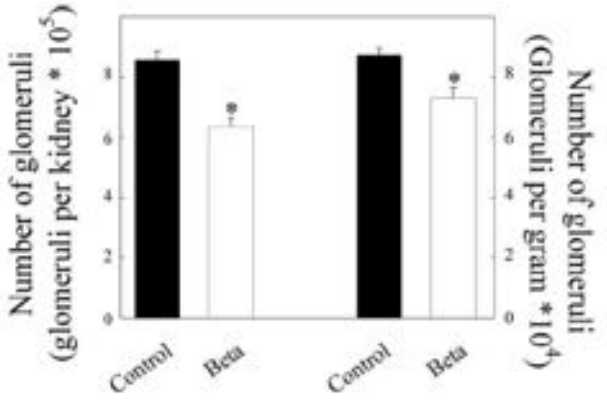


Figure 2. Glomeruli number per kidney and per gram of kidney at 135 dGA. Fetuses were exposed to either vehicle (Control; $n = 21$) or betamethasone (Beta; $n = 14$) *via* maternal injection of 0.17 mg/kg at 80 and 81 dGA. A significant decrease in nephron number was observed (*$p < 0.01$ by t test).

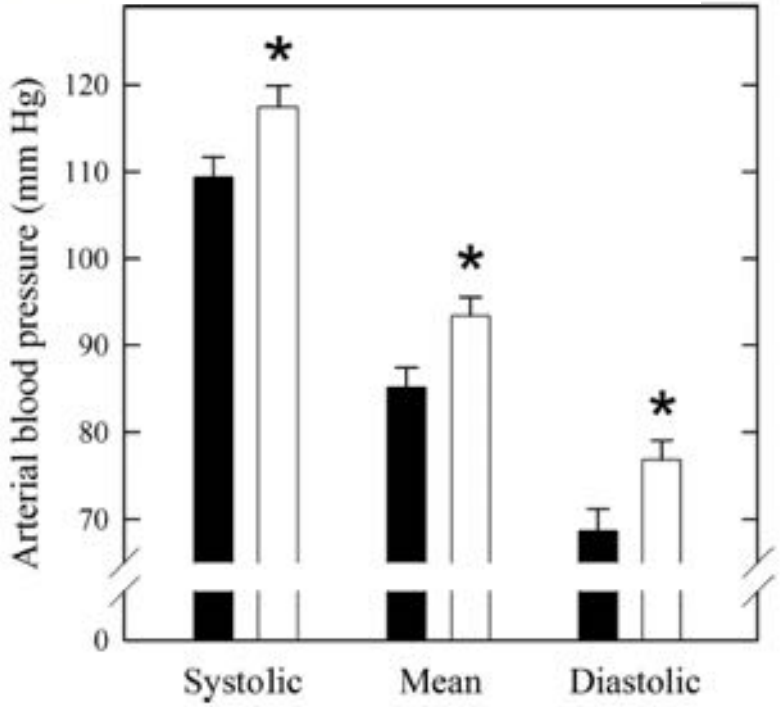
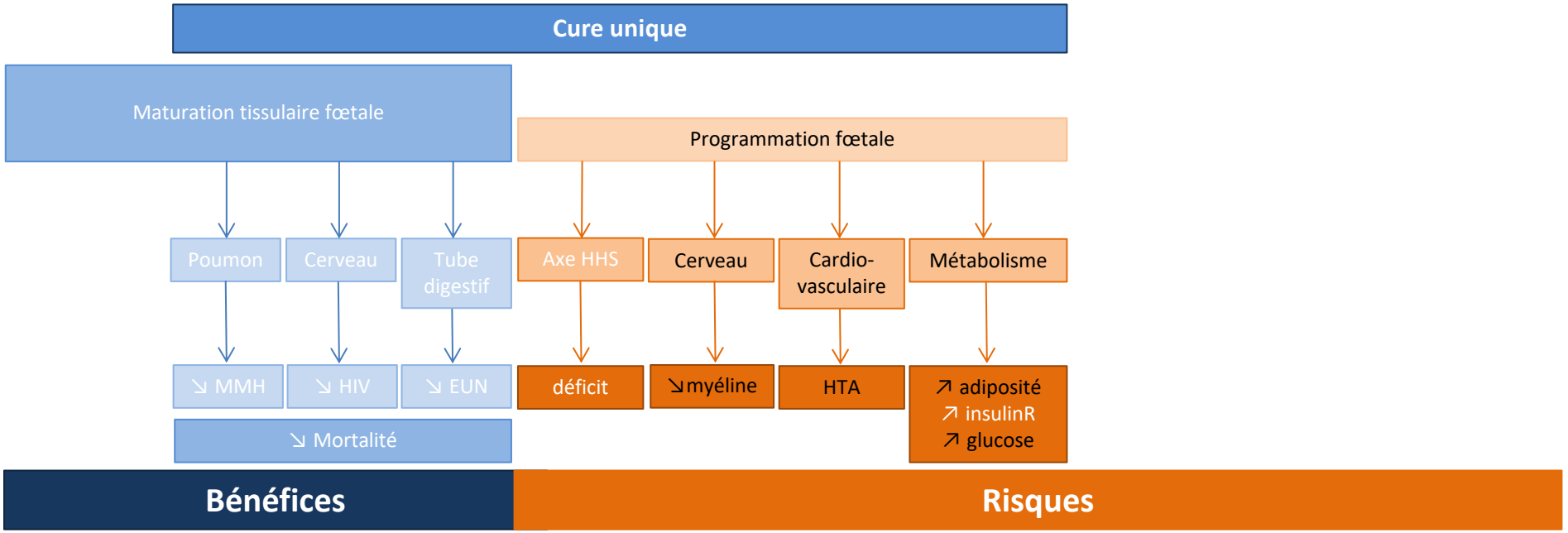


Figure 3. Arterial BP in 6-mo-old sheep that were exposed to either vehicle (Control; $n = 11$; ■) or betamethasone (Beta; $n = 15$; □) *via* maternal injection of 0.17 mg/kg at 80 and 81 dGA. Pressures represent the overall average of 2400 1-min pressure averages over 2 d. A significant increase in BP was observed in the betamethasone group (*$p < 0.05$ by two-sample t test).

Bénéfices et risques de la corticothérapie anténatale



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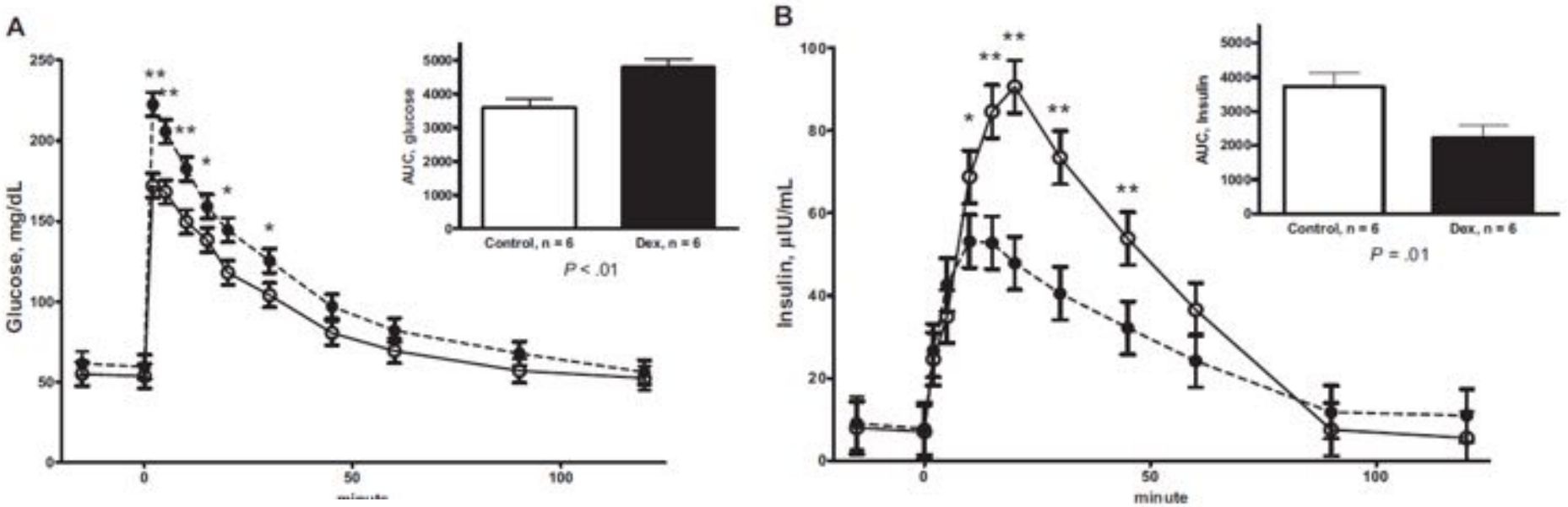
Growth and insulin dynamics in two generations of female offspring of mothers receiving a single course of synthetic glucocorticoids

Nathan M. Long, PhD; Desiree R. Shasa; Stephen P. Ford, PhD; Peter W. Nathanielsz, MD, PhD, ScD

F1



Growth and insulin dynamics in two generations of female offspring of mothers receiving a single course of synthetic glucocorticoids

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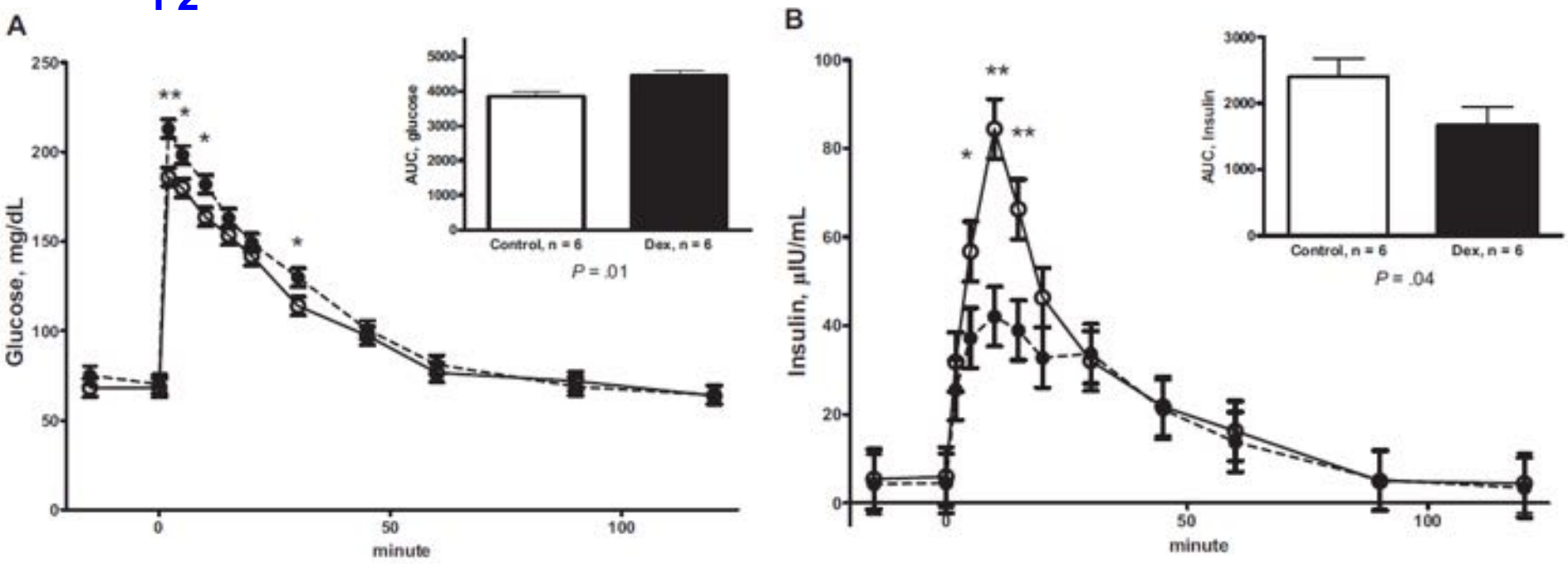
F2



Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial

Lancet 2005; 365: 1856–62

Stuart R Dalziel, Natalie K Walker, Varsha Parag, Colin Mantell, Harold H Rea, Anthony Rodgers, Jane E Harding

Clinical Trials Research Unit (S R Dalziel MBChB, N K Walker PhD, V Parag MSc, A Rodgers FAFPHM), Liggins Institute (S R Dalziel, Prof J E Harding FRACP), Division of Maori and Pacific Health (Prof C Mantell FRANZCOG), and Department of Medicine (Prof H H Rea FRACP), University of Auckland, Auckland, New Zealand

Correspondence to: Prof Jane Harding, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand
j.harding@auckland.ac.nz

Summary

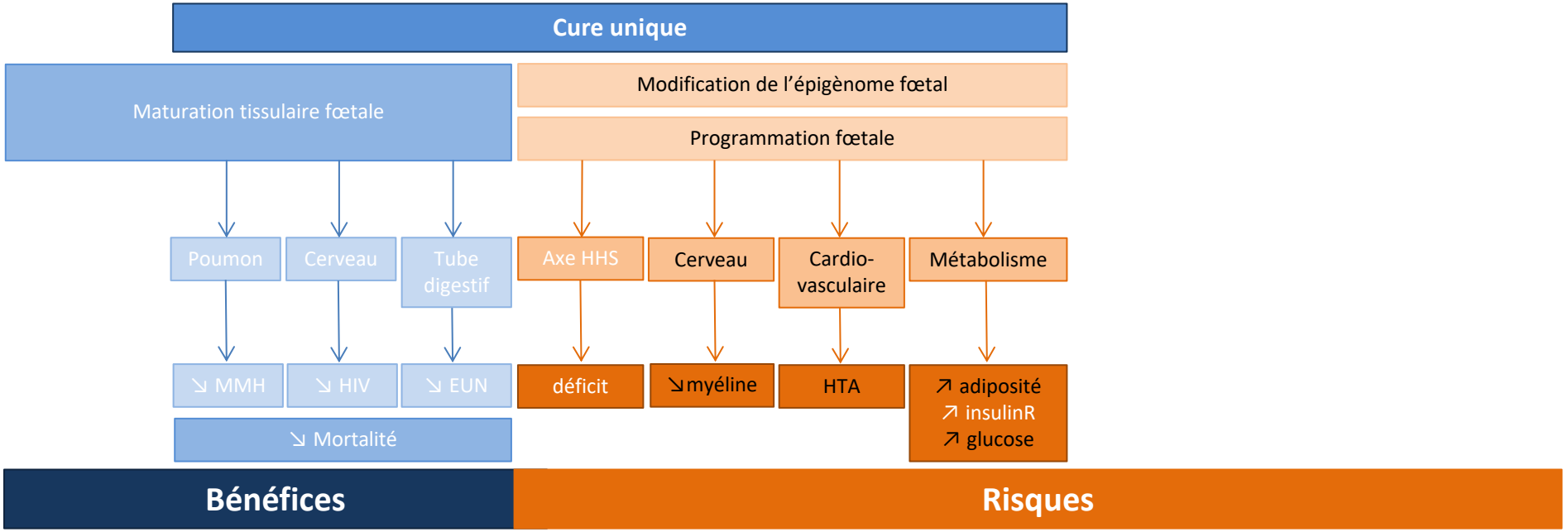
Background Antenatal betamethasone treatment is widely used for the prevention of neonatal respiratory distress syndrome in preterm infants and substantially reduces neonatal mortality and morbidity. Fetal exposure to excess glucocorticoids has been proposed as one of the core mechanisms of the fetal origins of adult disease hypothesis. We assessed whether antenatal exposure to betamethasone for the prevention of neonatal respiratory distress syndrome affects cardiovascular risk factors at 30 years of age.

Methods We followed up at age 30 years 534 individuals whose mothers participated in a double-blind, placebo-controlled, randomised trial of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome. Mothers received two doses of betamethasone or placebo given by intramuscular injection 24 h apart. Follow-up assessments included anthropometry; measurement of blood pressure, blood lipids (after overnight fasting), and early morning cortisol levels; and a 75 g oral glucose tolerance test.

Findings There were no differences between those exposed to betamethasone and to placebo in body size, blood lipids, blood pressure, plasma cortisol, prevalence of diabetes, or history of cardiovascular disease. After a 75 g oral glucose tolerance test, participants exposed to betamethasone had higher plasma insulin concentrations at 30 min (60·5 *vs* 52·0 mIU/L; ratio of geometric means 1·16 [95% CI 1·03 to 1·31], p=0·02) and lower glucose concentrations at 120 min (4·8 *vs* 5·1 mmol/L; difference –0·26 mmol/L [–0·53 to 0·00], p=0·05) than did those exposed to placebo.

Interpretation Antenatal exposure to betamethasone might result in insulin resistance in adult offspring, but has no clinical effect on cardiovascular risk factors at 30 years of age. Thus, obstetricians should continue to use a single course of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome.

Bénéfices et risques de la corticothérapie anténatale



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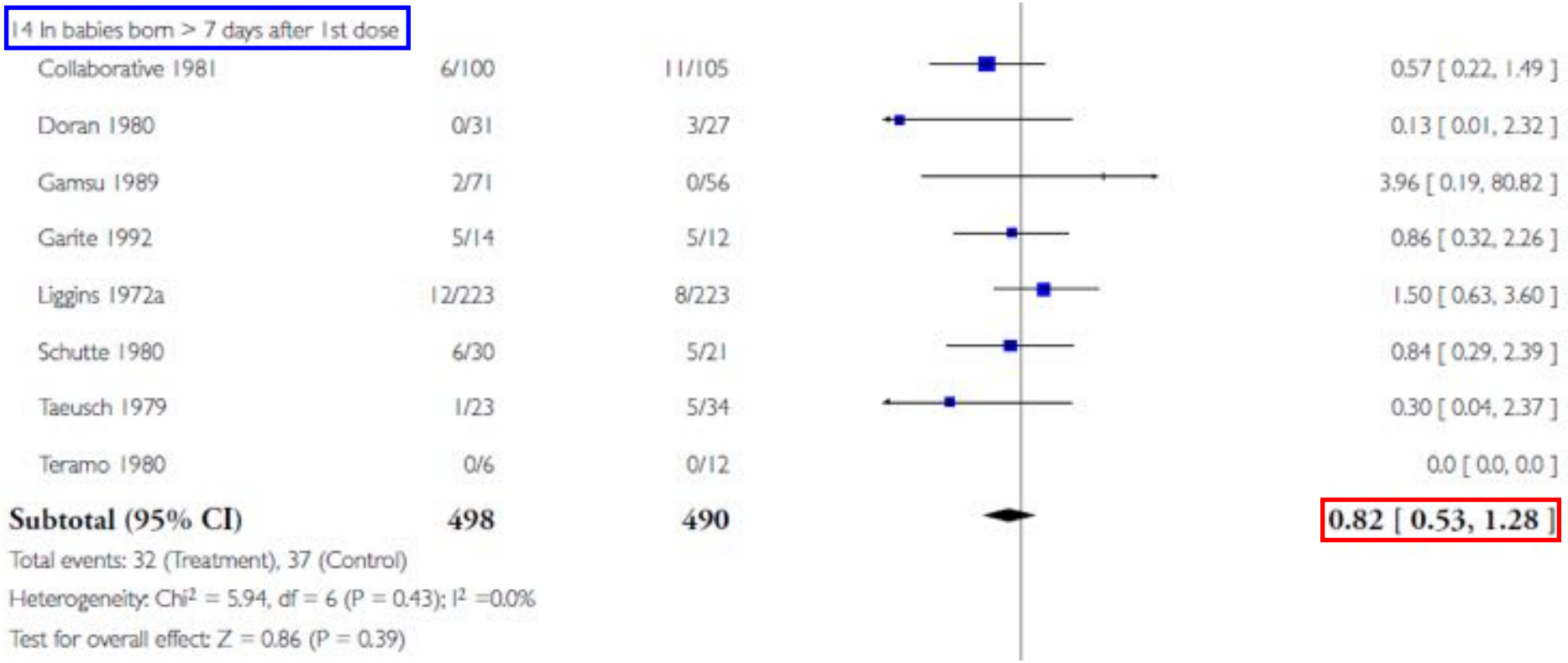
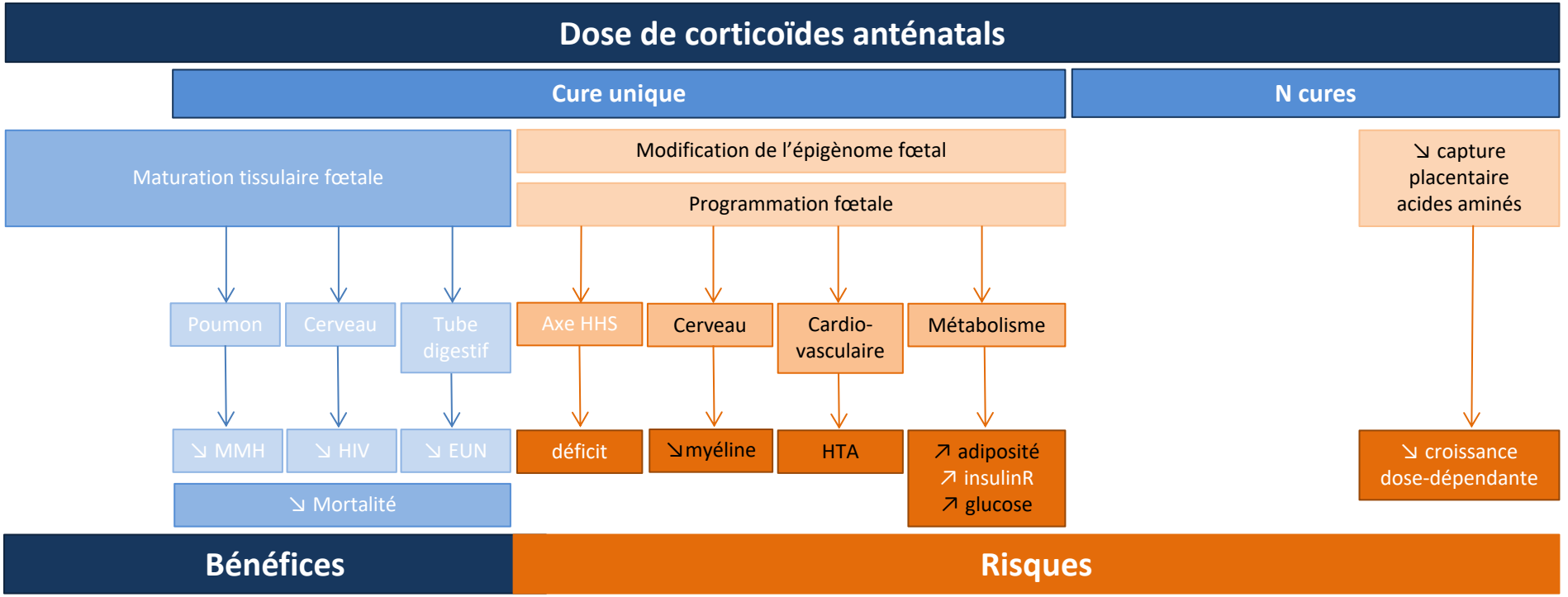
Problème de la durée d'action d'une cure unique



➔ **Répétition des cures**

Bénéfices et risques de la corticothérapie anténatale



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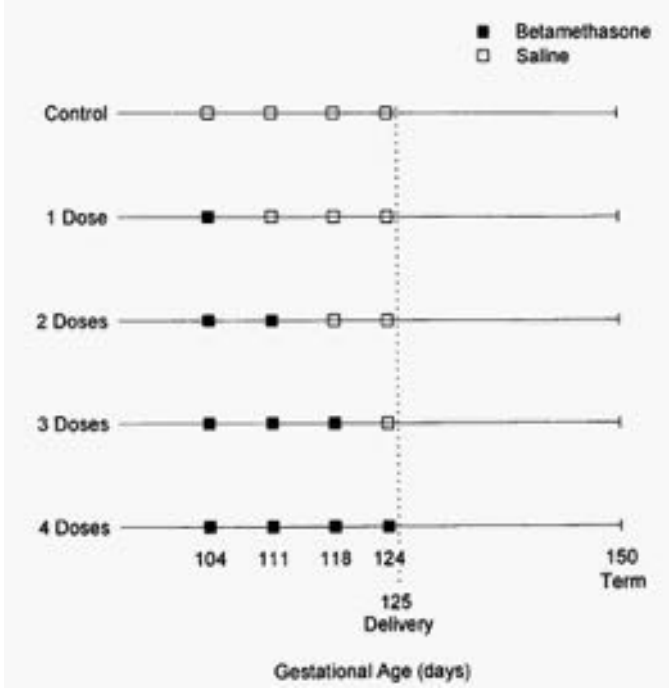
Repetitive Prenatal Glucocorticoids Improve Lung Function and Decrease Growth in Preterm Lambs

MACHIKO IKEGAMI, ALAN H. JOBE, JOHN NEWNHAM, DANIEL H. POLK, KAREN E. WILLET, and PETER SLY

Perinatal Research Laboratories, Harbor-UCLA Medical Center, Torrance, California; King Edward Memorial Hospital, Subiaco; Institute for Child Health Research, Perth, Western Australia, Australia



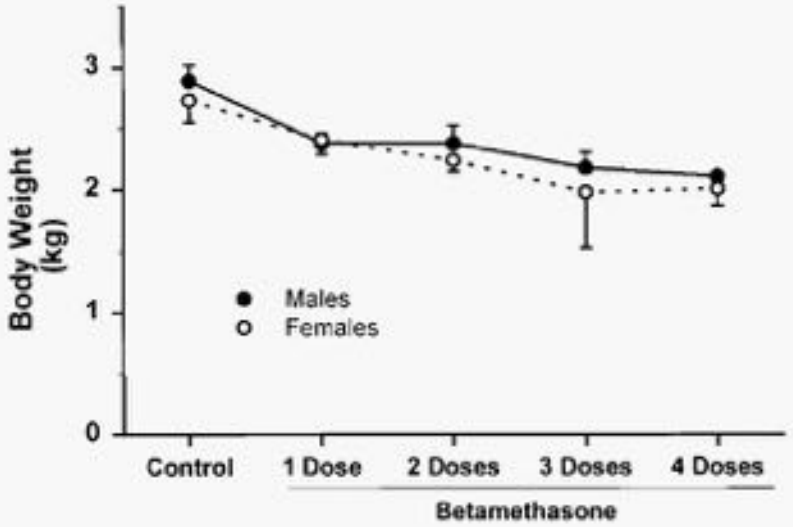


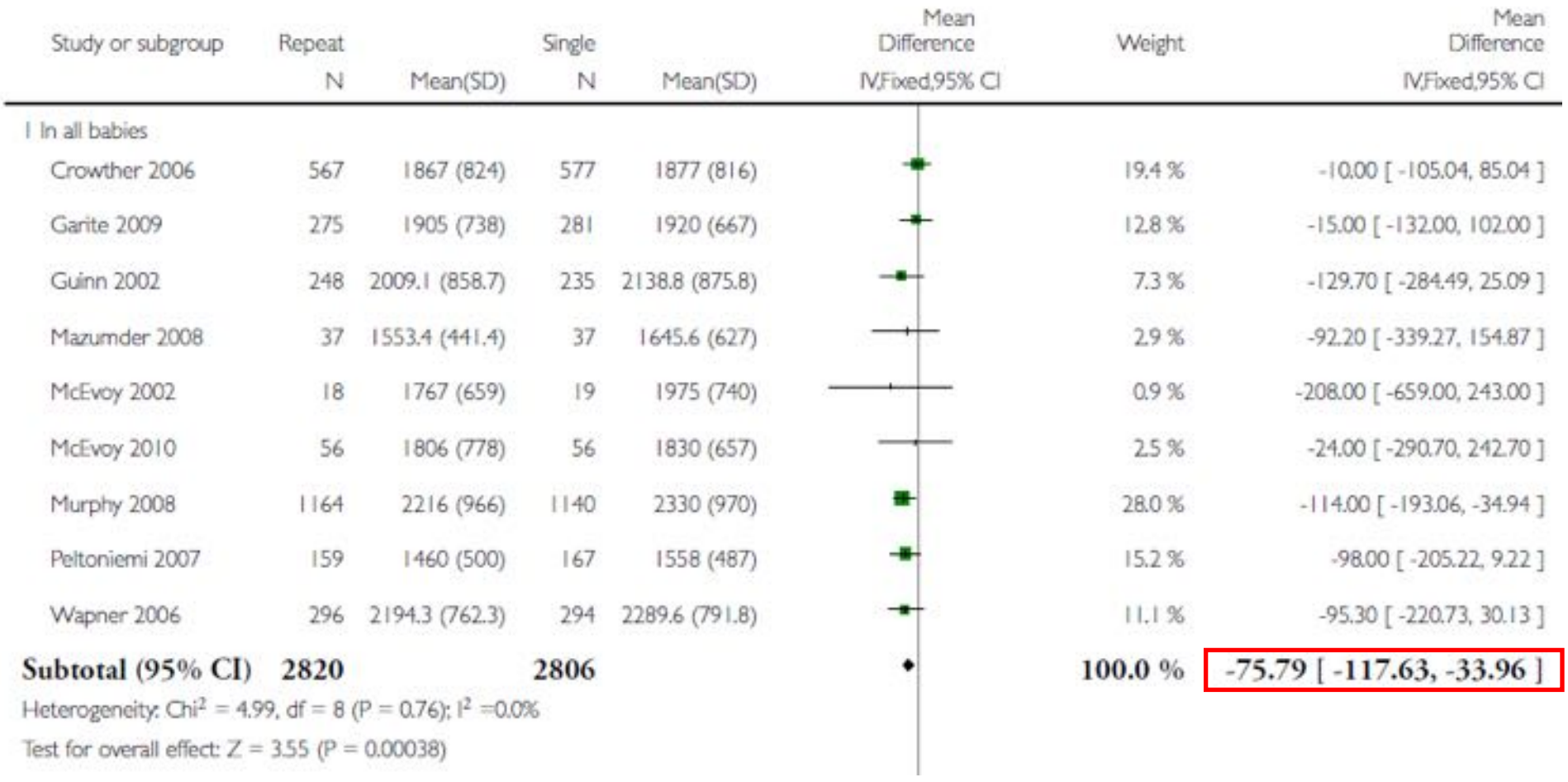
Figure 2. Birth weights of male and female lambs. Mean body weights decreased after betamethasone exposure for both males and females, and there were no consistent diferences between the male and female lambs.

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

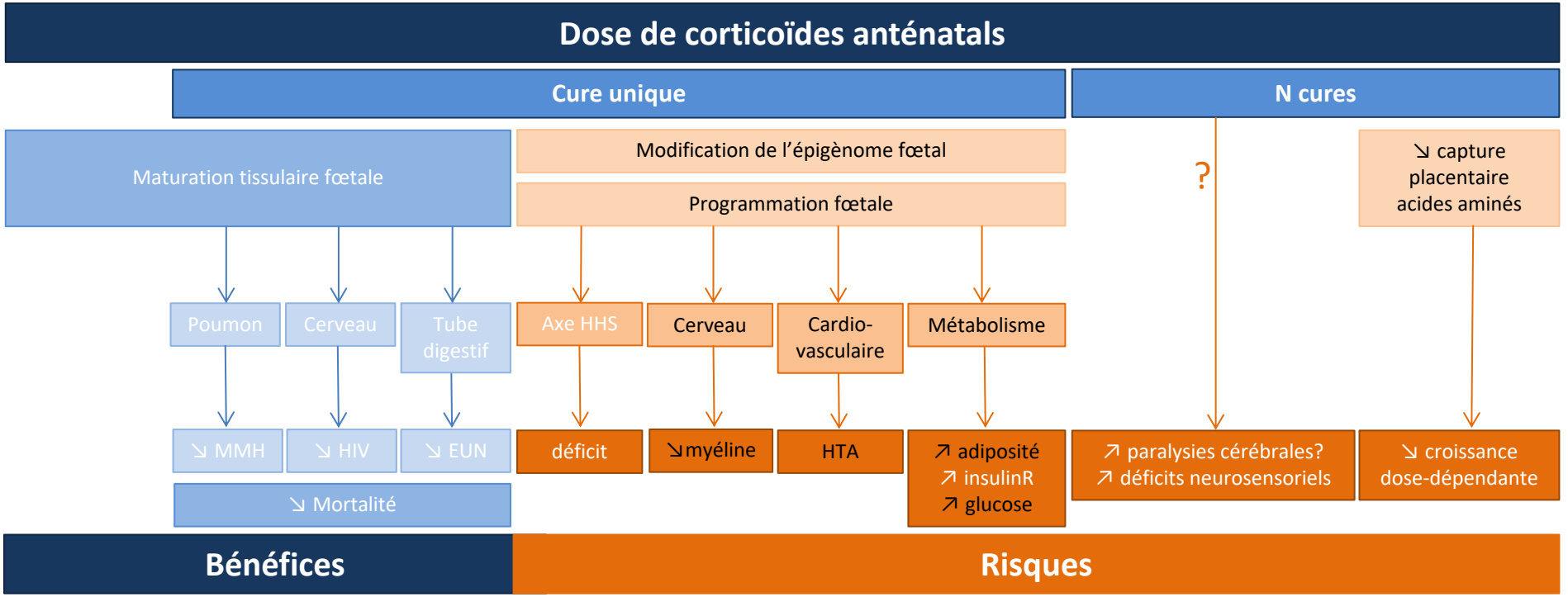
THE COCHRANE COLLABORATION®

Crowther CA, McKinlay CJD, Middleton P, Harding JE

Outcome: 4 Mean birthweight (g)



Bénéfices et risques de la corticothérapie anténatale



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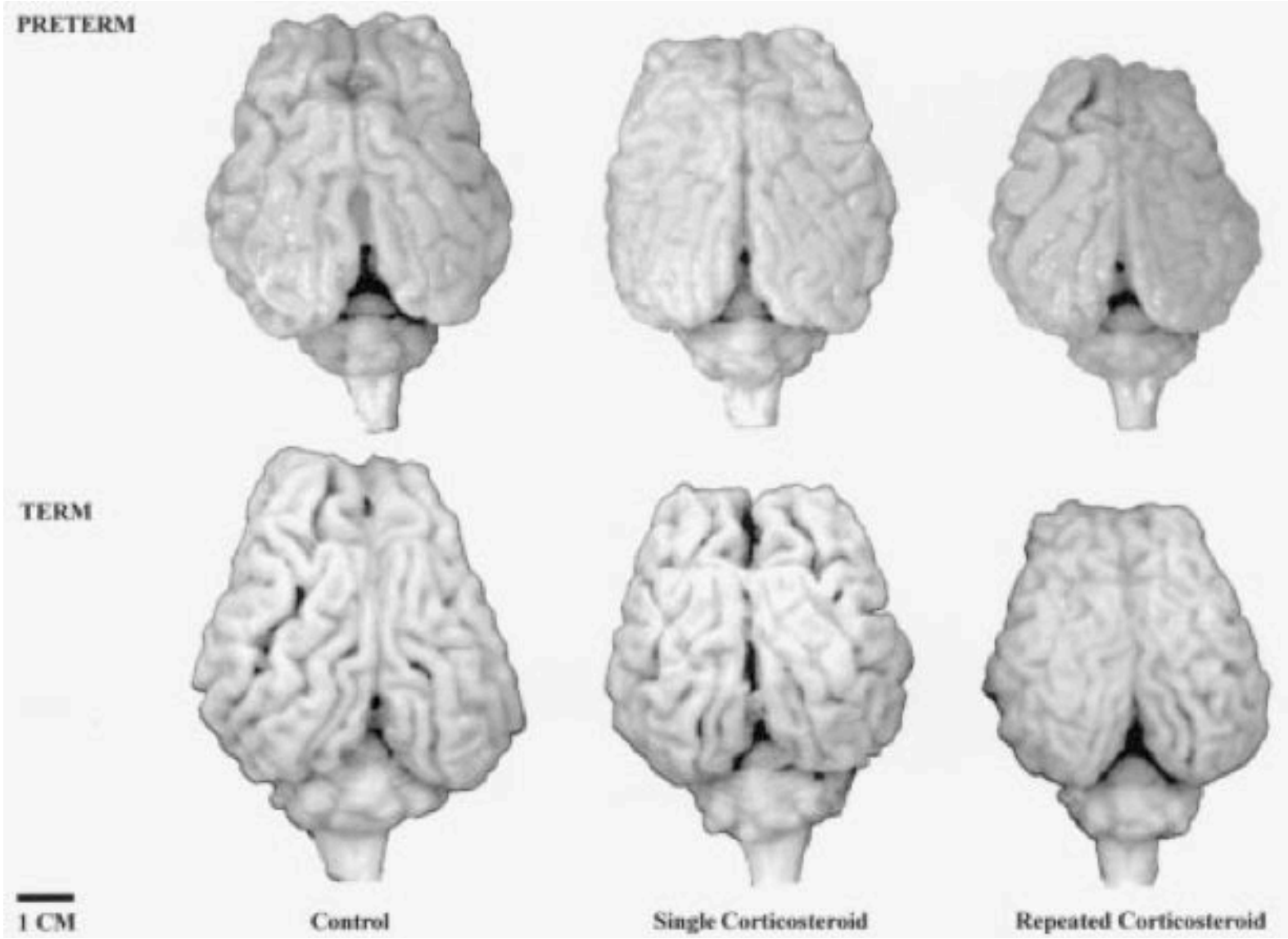


- Diminution du volume cérébral (Huang, Obstet Gynecol, 1999)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes after Repeat Doses of Antenatal Corticosteroids

Ronald J. Wapner, M.D., Yoram Sorokin, M.D., Lisa Mele, Sc.M., Francee Johnson, R.N., B.S.N., Donald J. Dudley, M.D., Catherine Y. Spong, M.D., Alan M. Peaceman, M.D., Kenneth J. Leveno, M.D., Fergal Malone, M.D., Steve N. Caritis, M.D., Brian Mercer, M.D., Margaret Harper, M.D., Dwight J. Rouse, M.D., John M. Thorp, M.D., Susan Ramin, M.D., Marshall W. Carpenter, M.D., and Steven G. Gabbe, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

CONCLUSIONS

Children who had been exposed to repeat as compared with single courses of antenatal corticosteroids did not differ significantly in physical or neurocognitive measures. Although the difference was not statistically significant, the higher rate of cerebral palsy among children who had been exposed to repeat doses of corticosteroids is of concern and warrants further study. (ClinicalTrials.gov number, NCT00015002.)

Table 2. Outcomes of the Children at Follow-up.*

Outcome	Repeat Corticosteroids (N = 206 Pregnancies and 248 Children)	Placebo (N = 195 Pregnancies and 238 Children)	Relative Risk (95% CI)	Difference (95% CI)	P Value
Age at neurologic examination — mo	29.9±6.1	30.1±5.7		−0.2 (−1.3 to 0.9)	0.47
Hospital readmission after discharge — %†	31.6	36.4	0.9 (0.7 to 1.1)		0.30
Asthma — %†	8.3	14.4	0.6 (0.3 to 1.0)		0.05
Seizures — %†	3.4	4.6	0.7 (0.3 to 1.9)		0.53
Pneumonia after discharge — %†	12.1	13.9	0.9 (0.5 to 1.5)		0.61
Blood pressure — mm Hg					
Systolic	91.7±13.2	94.6±14.8		−2.9 (−5.5 to −0.2)	0.16
Diastolic	57.5±9.9	58.5±11.0		−1.0 (−3.0 to 0.9)	0.32
Anthropometric measurements					
Weight — kg	13.5±2.7	13.7±2.6		−0.2 (−0.7 to 0.2)	0.19
Height — cm	90.5±6.4	91.1±5.7		−0.6 (−1.7 to 0.5)	0.26
Head circumference — cm	49.0±1.9	49.1±1.8		−0.1 (−0.4 to 0.2)	0.84
Weight percentile‡	49.5±31.8	54.1±33.1		−4.6 (−10.4 to 1.2)	0.16
Height percentile‡	48.6±30.5	52.3±29.2		−3.8 (−9.1 to 1.6)	0.24
Head circumference percentile‡	51.2±32.6	51.7±31.6		−0.5 (−6.2 to 5.3)	0.79
Weight <10th percentile — %‡	13.7	12.0	1.1 (0.7 to 1.9)		0.62
Height <10th percentile — %‡	11.7	7.3	1.6 (0.9 to 3.0)		0.14
Head circumference <10th percentile — %‡	19.5	14.0	1.4 (0.9 to 2.2)		0.14
Bayley PDI score — median (range)	99.0 (<50 to 138)	96.0 (<50 to 133)		2 (−1 to 5)	0.32
Bayley PDI score <85 — %†	24.9	28.5	0.9 (0.6 to 1.2)		0.43
Bayley PDI score <70 — %†	12.4	11.8	1.1 (0.6 to 1.8)		0.86
Bayley MDI score — median (range)	88.0 (<50 to 125)	87.0 (<50 to 126)		0 (−3 to 4)	0.87
Bayley MDI score <85 — %†	43.0	44.9	1.0 (0.8 to 1.2)		0.71
Bayley MDI score <70 — %†	18.7	16.0	1.2 (0.7 to 1.8)		0.50
Cerebral palsy — no./total no. (%)†	6/206 (2.9)	1/195 (0.5)	5.7 (0.7 to 46.7)		0.12
Cerebral palsy in pregnancies with ≥4 treatment courses — no./total no. (%)†	5/139 (3.6)	1/124 (0.8)	4.5 (0.5 to 37.7)		0.22
Cerebral palsy or death in pregnancies with ≥4 treatment courses — no./total no. (%)†	9/161 (5.6)	2/143 (1.4)	4.0 (0.9 to 18.2)		0.05

Table 3. Details of the Seven Children with a Diagnosis of Cerebral Palsy.*

Treatment Group and Child	Gestational Age at Birth	Birth Weight	Medical Complications	Severity of Cerebral Palsy	Type of Cerebral Palsy	No. of Courses of Study Treatment	Small for Gestational Age†	Twin	Neonatal Ultrasound Examination of the Head
	wk	*g*							
Repeat corticosteroids									
1	38.7	3200	None	Mild	Diplegic	4	No	No	Normal
2	36.4	1600	None	Mild	Diplegic	4	Yes	Yes	Normal
3	35.9	2200	None	Mild	Unclassified	4	No	Yes	Normal
4	34.6	2400	Respiratory distress	Mild	Diplegic	3	No	No	Normal
5	34.1	1610	Perinatal stroke	Mild	Hemiplegic	4	Yes	No	Slit ventricles
6	30.9	1149	Respiratory distress and IVH	Mild	Hemiplegic	4	No	Yes	Grade I IVH
Placebo									
1	33.3	1985	Respiratory distress	Severe	Quadriplegic	4	No	No	Normal

Original Investigation | COMPARATIVE EFFECTIVENESS RESEARCH

Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study

Outcomes in Children at 5 Years of Age (MACS-5)

Elizabeth V. Asztalos, MD; Kellie E. Murphy, MD; Andrew R. Willan, PhD; Stephen G. Matthews, PhD; Arne Ohlsson, MD; Saroj Saigal, MD; B. Anthony Armson, MD; Edmond N. Kelly, MB; Marie-France Delisle, MD; Amiram Gafni, DSc; Shoo K. Lee, MBBS; Renee Sananes, PhD; Joanne Rovet, PhD; Patricia Guselle, MIR; Kofi Amankwah, MD; Mariam Saleem, MIPH; Johanna Sanchez, MIPH; for the MACS-5 Collaborative Group

MAIN OUTCOMES AND MEASURES The primary outcome was death or survival with a neurodevelopmental disability in 1 of the following domains: neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual/hearing aids), or neurocognitive/neurobehavioral function (abnormal attention, memory, or behavior).

RESULTS There was no significant difference between the groups in the risk of death or neurodevelopmental disability: 217 of 871 children (24.9%) in the multiple-courses group vs 210 of 848 children (24.8%) in the single-course group (odds ratio, 1.02 [95% CI, 0.81 to 1.29]; $P = .84$).

CONCLUSIONS AND RELEVANCE Multiple courses, compared with a single course, of antenatal corticosteroid therapy did not increase or decrease the risk of death or disability at 5 years of age. Because of a lack of strong conclusive evidence of short-term or long-term benefits, it remains our opinion that multiple courses not be recommended in women with ongoing risk of preterm birth.

Table 3. Treatment Comparisons (Multiple Courses vs Single Course of ACS) of Primary Outcome and Components by Gestational Age at Birth (Preterm vs Term)

Outcome (N = 1719)	OR (95% CI); *P* Value		*P* Value for Interaction[a]
	Preterm Infants (<37 wk) (n = 1257)	Term Infants (≥37 wk) (n = 462)	
Primary composite	0.87 (0.67-1.14); .32	1.69 (1.04-2.77); .04	.02
Death[b]	0.91 (0.58-1.41); .66	0.58 (0.52, 6.47); .65	.72
Neuromotor disability	No convergence	No convergence	No convergence
Neurosensory disability	0.84 (0.55-1.29); .43	3.70 (1.57-8.75); .004	.005
Neurocognitive disability	0.89 (0.62-1.28); .53	1.31 (0.75-2.29); .35	.31

Comment s'intègrent ces données dans la pratique clinique?

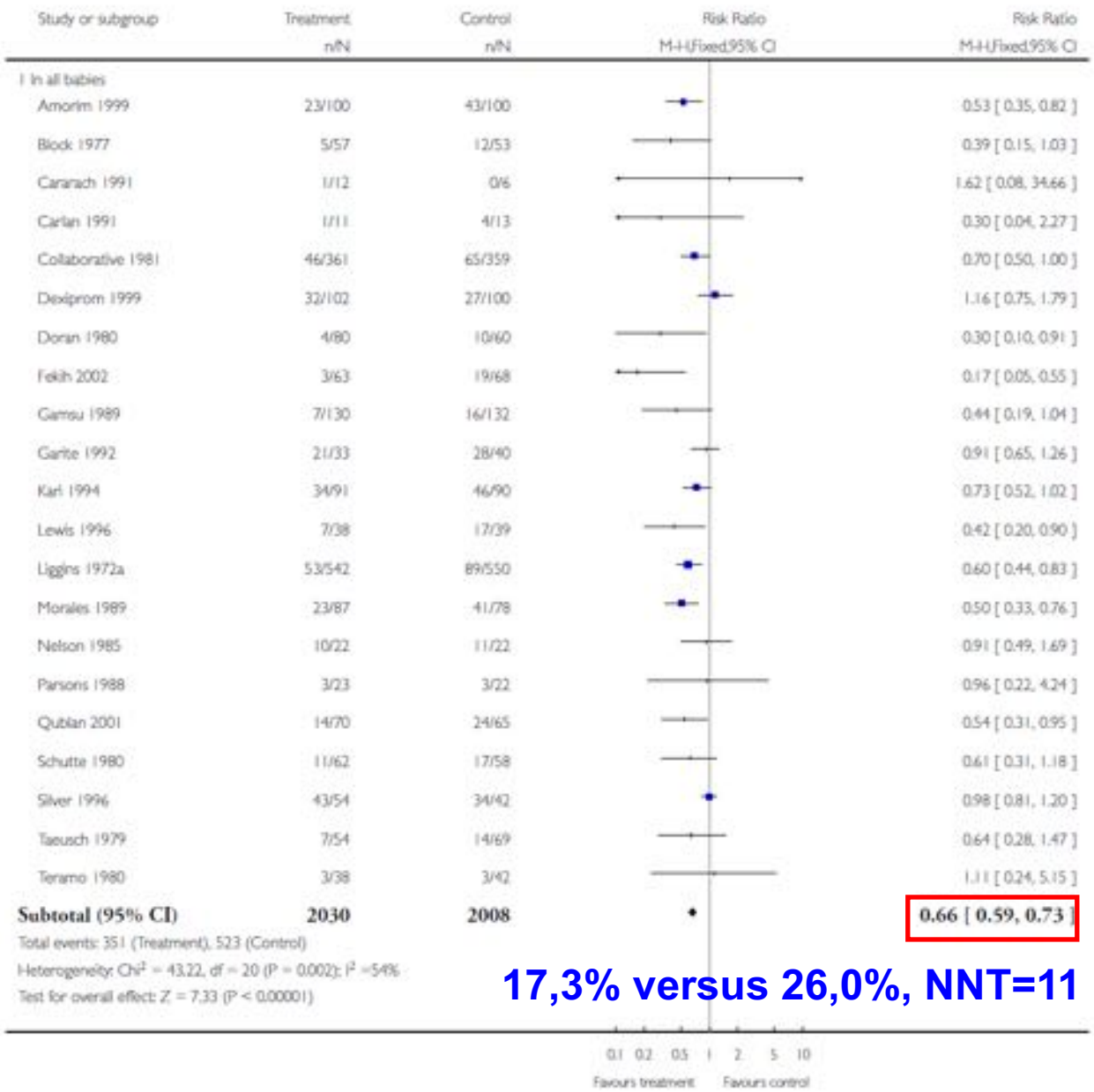
- Risque d'accouchement prématuré < 34 SA
- Cures répétées systématiques
- Cures de sauvetage
- Risque d'accouchement prématuré ≥ 34 SA

Risque d’accouchement prématuré < 34 SA

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Dalziel SR

Outcome: 7 Respiratory distress syndrome



17,3% versus 26,0%, NNT=11

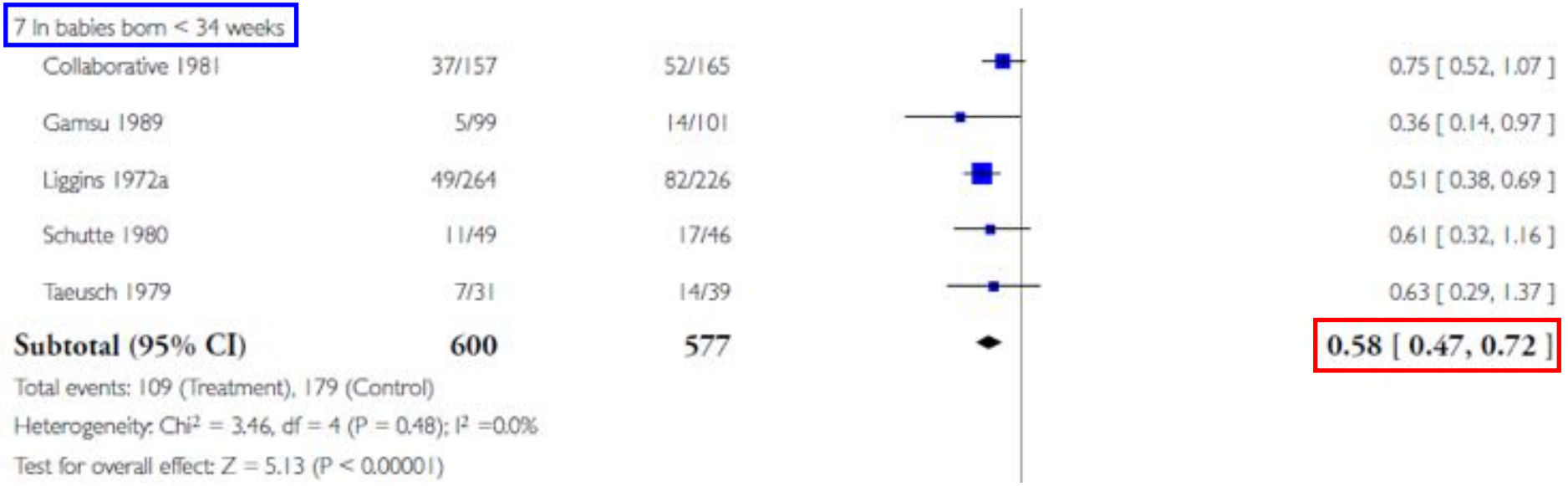
THE COCHRANE COLLABORATION®

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Dalziel SR

THE COCHRANE COLLABORATION®

7 In babies born < 34 weeks



Collaborative 1981	37/157	52/165	0.75 [0.52, 1.07]
Gamsu 1989	5/99	14/101	0.36 [0.14, 0.97]
Liggins 1972a	49/264	82/226	0.51 [0.38, 0.69]
Schutte 1980	11/49	17/46	0.61 [0.32, 1.16]
Taeusch 1979	7/31	14/39	0.63 [0.29, 1.37]
Subtotal (95% CI)	**600**	**577**	**0.58 [0.47, 0.72]**

Total events: 109 (Treatment), 179 (Control)

Heterogeneity: $Chi^2 = 3.46$, $df = 4$ ($P = 0.48$); $I^2 = 0.0\%$

Test for overall effect: $Z = 5.13$ ($P < 0.00001$)

18,2% versus 31,0%, NNT=8

8<NNT<11 pour prévenir 1 RDS
Bénéfices aussi neurologiques et digestifs
Réduction de la mortalité néonatale

Risques à long terme modérés

Journal de Gynécologie Obstétrique et Biologie de la Reproduction (2016) 45, 1399—1417

PRÉMATURITÉ SPONTANÉE

Prévention des complications de la prématurité par l'administration anténatale de corticoïdes

Prevention of preterm birth complications by antenatal corticosteroid administration

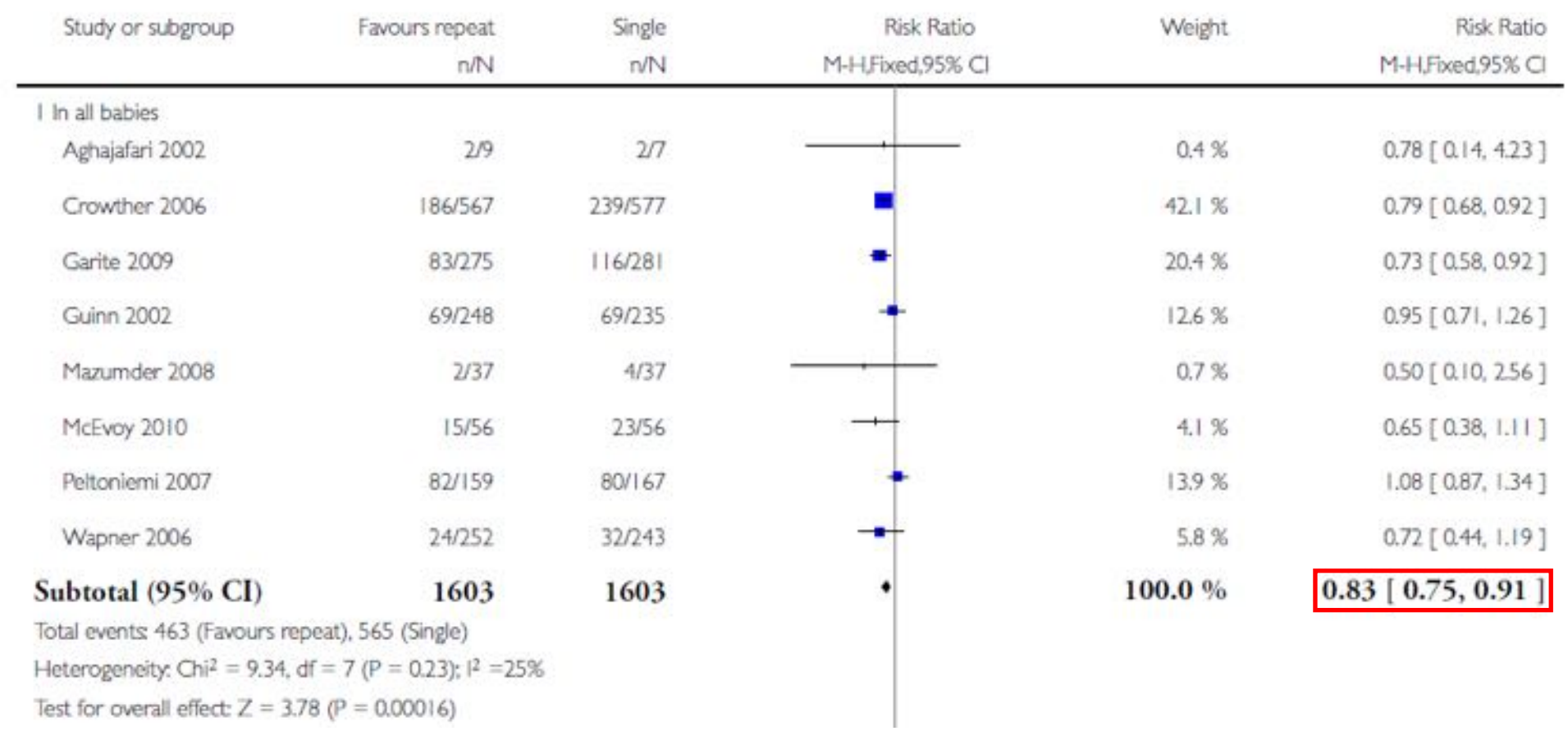
En conclusion, en raison d'une balance bénéfices/risques très favorable, l'administration anténatale d'une cure de corticoïdes est recommandée à toutes les patientes à risque d'accouchement prématuré avant 34 SA (grade A). L'âge gestationnel à partir duquel débuter les corticoïdes anténatals sera fonction des seuils choisis pour entreprendre des soins de réanimation néonatale au sein des maternités et des réseaux périnatals (accord professionnel).

Cures répétées systématiques

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

Crowther CA, McKinlay CJD, Middleton P, Harding JE

Outcome: 1 Respiratory distress syndrome



Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

Crowther CA, McKinlay CJD, Middleton P, Harding JE

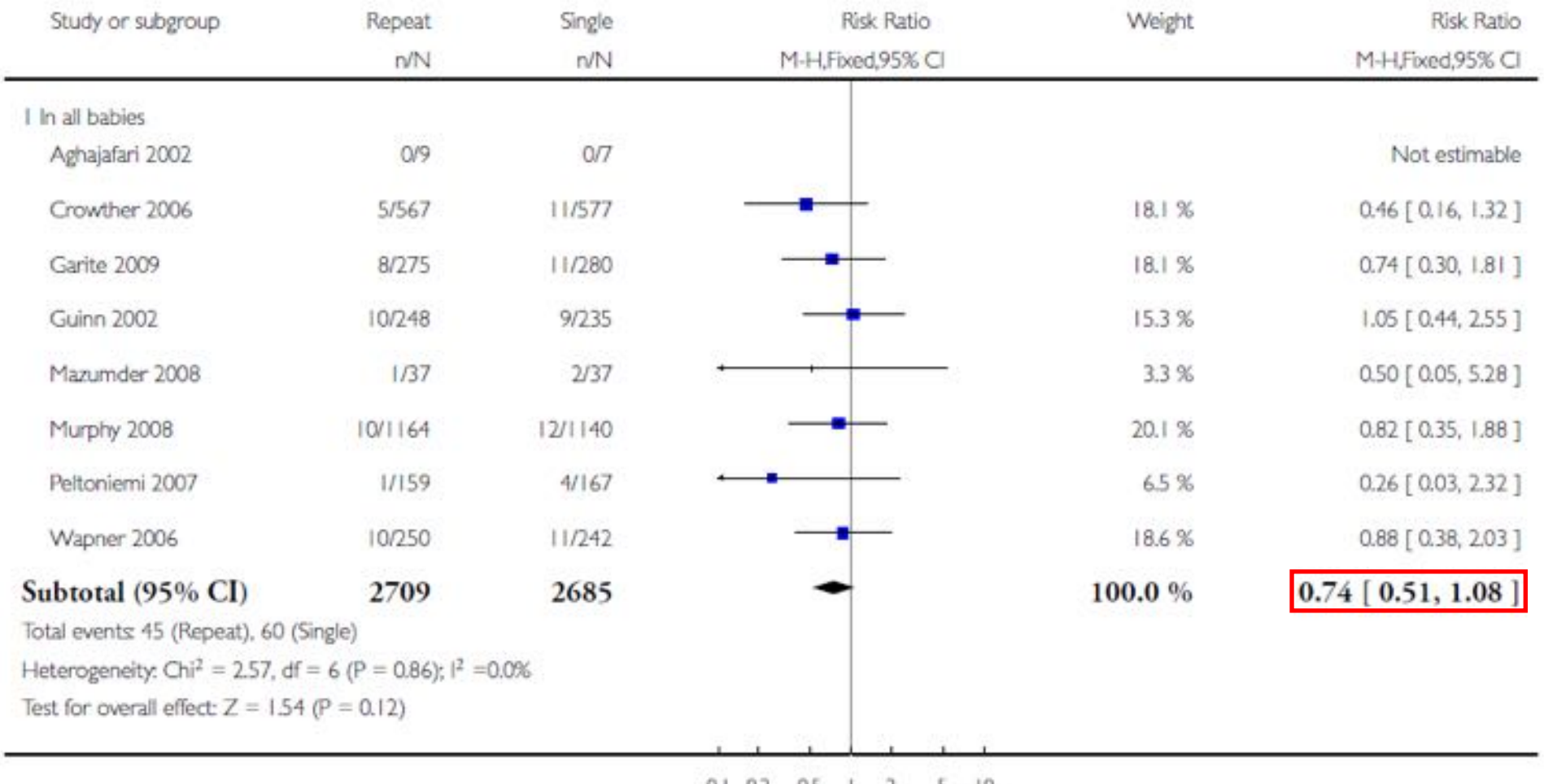
Outcome: 12 Intraventricular haemorrhage

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	34/567	39/577		28.1 %	0.89 [0.57, 1.38]
Garite 2009	19/272	25/274		18.1 %	0.77 [0.43, 1.36]
Guinn 2002	30/248	25/235		18.7 %	1.14 [0.69, 1.87]
Mazumder 2008	0/37	3/37		2.5 %	0.14 [0.01, 2.67]
Peltoniemi 2007	31/159	27/167		19.2 %	1.21 [0.76, 1.93]
Wapner 2006	15/250	18/242		13.3 %	0.81 [0.42, 1.56]
Subtotal (95% CI)	**1533**	**1532**		**100.0 %**	**0.94 [0.75, 1.18]**
Total events: 129 (Repeat), 137 (Single)					
Heterogeneity: $Chi^2 = 3.99$, $df = 5$ ($P = 0.55$); $I^2 = 0.0\%$					
Test for overall effect: $Z = 0.50$ ($P = 0.61$)					

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

Crowther CA, McKinlay CJD, Middleton P, Harding JE

Outcome: 38 Necrotising enterocolitis



Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

Crowther CA, McKinlay CJD, Middleton P, Harding JE

Outcome: 10 Neonatal death

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	0/9	0/7			Not estimable
Crowther 2006	26/567	28/577		53.0 %	0.94 [0.56, 1.59]
Garite 2009	4/275	6/281		11.3 %	0.68 [0.19, 2.39]
Guinn 2002	4/248	8/235		15.7 %	0.47 [0.14, 1.55]
Mazumder 2008	4/38	7/38		13.4 %	0.57 [0.18, 1.79]
McEvoy 2010	1/56	0/56		1.0 %	3.00 [0.12, 72.10]
Peltoniemi 2007	8/159	3/167		5.6 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**1352**	**1361**		**100.0 %**	**0.91 [0.62, 1.34]**
Total events: 47 (Repeat), 52 (Single)					
Heterogeneity: $Chi^2 = 5.40$, $df = 5$ ($P = 0.37$); $I^2 = 7\%$					
Test for overall effect: $Z = 0.46$ ($P = 0.65$)					

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PRÉMATURITÉ SPONTANÉE

Prévention des complications de la prématurité par l'administration anténatale de corticoïdes

Prevention of preterm birth complications by antenatal corticosteroid administration

Malgré son association à des bénéfices néonatals immédiats, principalement respiratoires, la répétition systématique toutes les semaines ou toutes les deux semaines des cures de corticoïdes anténatals n'est pas recommandée en raison d'altération de la croissance fœtale, de l'absence de bénéfice à long terme et même de possibles effets délétères neurologiques (grade A).

Rescue course

OBSTETRICS

Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial

Thomas J. Garite, MD; James Kurtzman, MD; Kimberly Maurel, MSN; Reese Clark, MD; for the Obstetrix Collaborative Research Network

OBJECTIVE: Previous studies using repetitive courses of antenatal corticosteroids (ACS) have demonstrated marginal or no benefit and concern over potential risk. No prior prospective or randomized studies have evaluated the option of a single rescue course of ACS on neonatal outcome.

STUDY DESIGN: A multicenter randomized double-blind placebo-controlled trial was performed from May 2003 through February 2008 in 18 private (15) and university (3) medical centers. Patients with singletons or twins < 33 weeks who had completed a single course of ACS before 30 weeks and at least 14 days before inclusion, and were judged to have a recurring threat of preterm delivery in the coming week, were included. Patients were randomized to receive a single rescue course of betamethasone, 2 12-mg doses 24 hours apart, or placebo. Exclusion criteria included: premature rupture of membranes, advanced dilation (> 5 cm), chorioamnionitis, and other steroid use.

RESULTS: In all, 437 patients were randomized (223 rescue steroid group and 214 placebo group). A total of 55% of patients in each group delivered at < 34 weeks. There was a significant reduction in the primary outcome of composite neonatal morbidity < 34 weeks in the rescue steroid group vs placebo (43.9% vs 63.6%; odds ratio, 0.45; 95% confidence interval, 0.27-0.75; $P = .002$) and significantly decreased respiratory distress syndrome, ventilator support, and surfactant use. Perinatal mortality and other morbidities were similar in each group. Including all neonates in the analysis (regardless of gestational age at delivery) still demonstrated a significant reduction in composite morbidity in the rescue course group (32.1% vs 42.6%, odds ratio, 0.65; 95% confidence interval, 0.44-0.97; $P = .0034$) and improvement in respiratory morbidities.

CONCLUSION: Administration of a single rescue course of ACS before 33 weeks improves neonatal outcome without apparent increased short-term risk.

Key words: antenatal corticosteroids, neonatal respiratory morbidity, prematurity

Cite this article as: Garite TJ, Kurtzman J, Maurel K, et al. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol 2009;200:248.e1-248.e9.

TABLE 4

Neonatal morbidity–all newborns

Neonatal morbidity	ACS n/N (%)	Placebo n/N (%)	OR[a] (95% CI)	*P* value[a]
Composite morbidity	88/276 (32.1)	120/282 (42.6)	0.65 (0.44-0.97)	.034
RDS	83/275 (30.2)	116/281 (41.3)	0.64 (0.43-0.95)	.026
BPD	27/273 (9.9)	20/278 (7.2)	1.50 (0.76-2.94)	.239
Surfactant	70/273 (25.6)	99/280 (35.4)	0.65 (0.43-0.98)	.038
Ventilator	70/267 (26.2)	95/273 (34.8)	0.70 (0.46-1.06)	.088
ROP	21/260 (8.1)	19/267 (7.1)	1.15 (0.56-2.34)	.704
ROP grade 3 or 4	3/260 (1.2)	2/267 (0.8)	2.51 (0.25-24.83)	.432
IVH	19/272 (7.0)	25/274 (9.1)	0.76 (0.38-1.49)	.422
IVH grade 3 or 4	6/272 (2.2)	4/274 (1.5)	1.65 (0.43-6.31)	.462
NEC	8/275 (2.9)	11/280 (3.9)	0.72 (0.27-1.91)	.503
Sepsis	7/275 (2.6)	12/288 (4.3)	0.55 (0.19-1.60)	.275
Perinatal death	5/276 (1.8)	7/282 (2.5)	0.60 (0.17-2.18)	.440
Pneumothorax	4/275 (1.5)	4/281 (1.4)	1.03 (0.26-4.13)	.967
PVL	3/269 (1.1)	4/272 (1.5)	0.76 (0.17-3.40)	.718
Pneumonia	3/274 (1.1)	5/281 (1.8)	0.66 (0.14-3.04)	.589
IUGR (< 10th percentile)	29/275 (10.6)	28/278 (10.1)	1.07 (0.61-1.86)	.822

ACS, antenatal corticosteroids; *CI*, confidence interval; *IUGR*, intrauterine growth restriction; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *OR*, odds ratio; *RDS*, respiratory distress syndrome.

[a] OR, 95% CI, and *P* value are determined using a repeated measures model where each twin is considered a repeated measure.

Garite. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol 2009.

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PRÉMATURITÉ SPONTANÉE

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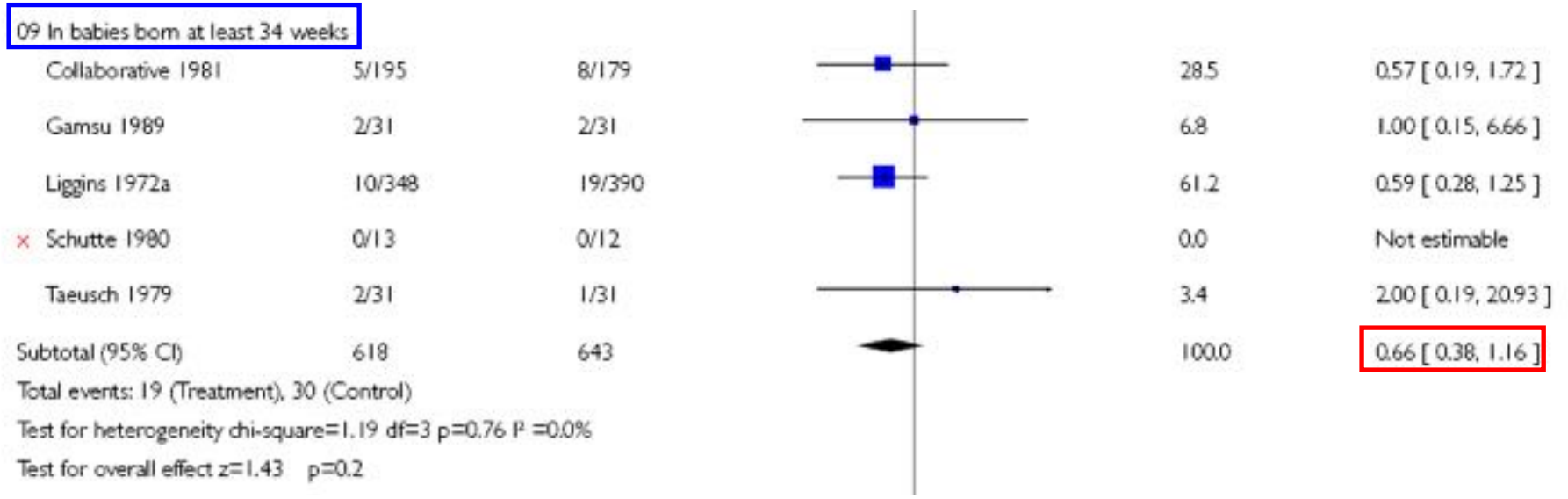
Au total, les données relatives aux bénéfices associés à une cure de sauvetage sont contradictoires. Si bénéfices il y a, ils ne concernent que la période néonatale et sont uniquement respiratoires (NP2). Compte tenu, d'une part, des possibles effets délétères associés à cette stratégie lorsque la naissance a lieu dans les 24 heures suivant la première injection (NP2), et d'autre part, des craintes soulevées par la répétition des cures quant au développement neurologique de l'enfant (NP2), la cure de sauvetage ne peut pas être recommandée (accord professionnel).

Risque d’accouchement prématuré ≥ 34 SA

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)



3,0% versus 4,6%, NNT=63

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, A.T.N. Tita, U.M. Reddy, G.R. Saade, D.J. Rouse, D.S. McKenna, E.A.S. Clark, J.M. Thorp, Jr., E.K. Chien, A.M. Peaceman, R.S. Gibbs, G.K. Swamy, M.E. Norton, B.M. Casey, S.N. Caritis, J.E. Tolosa, Y. Sorokin, J.P. VanDorsten, and L. Jain, for the NICHD Maternal–Fetal Medicine Units Network*

Février 2016

Table 1. **Characteristics of the Participants at Baseline.***

Characteristic	Betamethasone (N = 1429)	Placebo (N = 1402)
Indication for trial entry — no. (%)		
Preterm labor with intact membranes	400 (28.0)	392 (28.0)
Ruptured membranes	316 (22.1)	304 (21.7)
Expected delivery for gestational hypertension or preeclampsia	370 (25.9)	385 (27.5)
Expected delivery for fetal growth restriction	46 (3.2)	48 (3.4)
Expected delivery for oligohydramnios	50 (3.5)	42 (3.0)
Expected delivery for other indication	247 (17.3)	231 (16.5)
Gestational age at trial entry — no. (%)		
≤34 wk 6 days	369 (25.8)	399 (28.5)
35 wk 0 days to 35 wk 6 days	571 (40.0)	532 (37.9)
≥36 wk 0 days	489 (34.2)	471 (33.6)
Mean (±SD) maternal age — yr	28.6±6.3	27.8±6.1
Race or ethnic group — no. (%)†		
Black	376 (26.3)	381 (27.2)
White	828 (57.9)	800 (57.1)
Asian	57 (4.0)	39 (2.8)
Other, unknown, or more than one race	168 (11.8)	182 (13.0)
Hispanic	405 (28.3)	448 (32.0)
Nulliparous — no. (%)	457 (32.0)	448 (32.0)
Smoking during current pregnancy — no. (%)	204 (14.3)	186 (13.3)
Preeclampsia or gestational hypertension — no. (%)	433 (30.3)	440 (31.4)
Gestational diabetes — no. (%)	153 (10.7)	153 (10.9)
Major congenital anomaly in infant — no. (%)‡	11 (0.8)	21 (1.5)

Col ≥ 3cm
Déclenchées

84% < 37 SA

Table 2. Neonatal Respiratory Outcomes.*

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value	NNT
	no. (%)				
Primary outcome†	165 (11.6)	202 (14.4)	0.80 (0.66–0.97)	0.02	35
CPAP or high-flow nasal cannula for ≥2 continuous hr	145 (10.2)	184 (13.1)	0.77 (0.63–0.95)	0.01	34
Fraction of inspired oxygen of ≥0.30 for ≥4 continuous hr	48 (3.4)	61 (4.4)	0.77 (0.53–1.12)	0.17	
Mechanical ventilation	34 (2.4)	43 (3.1)	0.78 (0.50–1.21)	0.26	
ECMO	0	0	NA	NA	
Stillbirth or neonatal death ≤72 hr after birth	0	0	NA	NA	
Severe respiratory complication‡	115 (8.1)	169 (12.1)	0.67 (0.53–0.84)	<0.001	25
CPAP or high-flow nasal cannula for ≥12 continuous hr	93 (6.5)	147 (10.5)	0.62 (0.48–0.80)	<0.001	25
Fraction of inspired oxygen of ≥0.30 for ≥24 continuous hr	20 (1.4)	34 (2.4)	0.58 (0.33–1.00)	0.05	
Need for resuscitation at birth§	206 (14.5)	260 (18.7)	0.78 (0.66–0.92)	0.003	24
Respiratory distress syndrome	79 (5.5)	89 (6.4)	0.87 (0.65–1.17)	0.36	
Transient tachypnea of the newborn	95 (6.7)	138 (9.9)	0.68 (0.53–0.87)	0.002	
Apnea	33 (2.3)	37 (2.6)	0.88 (0.55–1.39)	0.57	
Bronchopulmonary dysplasia	2 (0.1)	9 (0.6)	0.22 (0.02–0.92)¶	0.04	
Pneumonia	6 (0.4)	13 (0.9)	0.45 (0.17–1.19)	0.10	
Surfactant use	26 (1.8)	43 (3.1)	0.59 (0.37–0.96)	0.03	80
Composite of respiratory distress syndrome, transient tachypnea of the newborn, or apnea	198 (13.9)	249 (17.8)	0.78 (0.66–0.93)	0.004	26
Pulmonary air leak	5 (0.4)	6 (0.4)	0.82 (0.25–2.68)	0.74	

Table 3. **Other Secondary Neonatal Outcomes.***

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value	NNT	NNH
Neonatal death — no. (%)	2 (0.1)	0	NA	0.50		
Mean (±SD) birth weight — g	2637±480	2654±484		0.32		
Birth weight in <10th percentile — no. (%)	255 (17.9)	220 (15.7)	1.14 (0.96–1.34)	0.13		
Gestational age at delivery — no. (%)				0.10		
≤34 wk 6 days	193 (13.5)	213 (15.2)				
35 wk 0 days to 35 wk 6 days	394 (27.6)	386 (27.6)				
36 wk 0 days to 36 wk 6 days	609 (42.7)	568 (40.6)				
37 wk 0 days to 38 wk 6 days	202 (14.2)	185 (13.2)				
≥39 wk 0 days	29 (2.0)	48 (3.4)				
Necrotizing enterocolitis — no. (%)	0	1 (0.1)				
Proven neonatal sepsis — no. (%)	9 (0.6)	11 (0.8)	0.80 (0.33–1.93)	0.62		
Grade 3–4 intraventricular hemorrhage — no. (%)	2 (0.1)	0				
Composite of respiratory distress syndrome, intraventricular hemorrhage, or necrotizing enterocolitis — no. (%)	81 (5.7)	90 (6.4)	0.88 (0.66–1.18)	0.40	133	
Hypoglycemia — no. (%)†	343 (24.0)	210 (15.0)	1.60 (1.37–1.87)	<0.001		11
Median time until first feeding (IQR) — hr	5.5 (1.4–24.7)	9.9 (1.7–29.1)		0.004		
Feeding difficulty — no. (%)	211 (14.8)	223 (15.9)	0.93 (0.78–1.10)	0.40		
Hyperbilirubinemia — no. (%)	167 (11.7)	140 (10.0)	1.17 (0.95–1.40)	0.15		
Hypothermia — no. (%)	132 (9.3)	112 (8.0)	1.16 (0.91–1.47)	0.24		
Admission to intermediate care nursery or NICU — no. (%)						
Any duration	596 (41.8)	629 (44.9)	0.93 (0.85–1.01)	0.09		
Duration ≥3 days	470 (32.9)	518 (37.0)	0.89 (0.80–0.98)	0.03		
Median length of hospital stay (IQR) — days	7 (4–12)	8 (4–13)		0.20		

Table S6: Tests for Interaction for Severe Respiratory Complications

	Betamethasone N (%)	Placebo N (%)	RR (95% CI)	Interaction P
Sex				0.25
Female	28 (4.1)	37 (5.8)	0.71 (0.44-1.14)	
Male	51 (6.9)	52 (6.9)	1.01 (0.69-1.46)	
Race				0.84
African American	11 (2.9)	12 (3.2)	0.93 (0.42-2.08)	
Other race	68 (6.5)	77 (7.6)	0.86 (0.62-1.17)	
Ethnicity				0.19
Hispanic/Latina	23 (5.7)	21 (4.7)	1.21 (0.68-2.16)	
Not Hispanic/Latina	56 (5.5)	67 (7.1)	0.78 (0.55-1.10)	
Planned Delivery Type				0.05
Attempt at vaginal delivery	55 (4.6)	52 (4.4)	1.06 (0.73-1.53)	
Planned cesarean	24 (10.3)	37 (17.6)	0.58 (0.36-0.94)	
Indication for Trial Entry				0.38
Preterm labor	13 (3.3)	10 (2.6)	1.28 (0.57-2.89)	
Ruptured membranes	16 (5.1)	14 (4.6)	1.10 (0.55-2.21)	
Obstetrical or medical indication	50 (7.0)	65 (9.2)	0.76 (0.53-1.08)	
Gestational age at randomization				0.22
< 36 weeks 0 days	60 (6.5)	75 (8.1)	0.80 (0.58-1.10)	
≥ 36 weeks 0 days	19 (3.8)	14 (2.9)	1.28 (0.65-2.52)	

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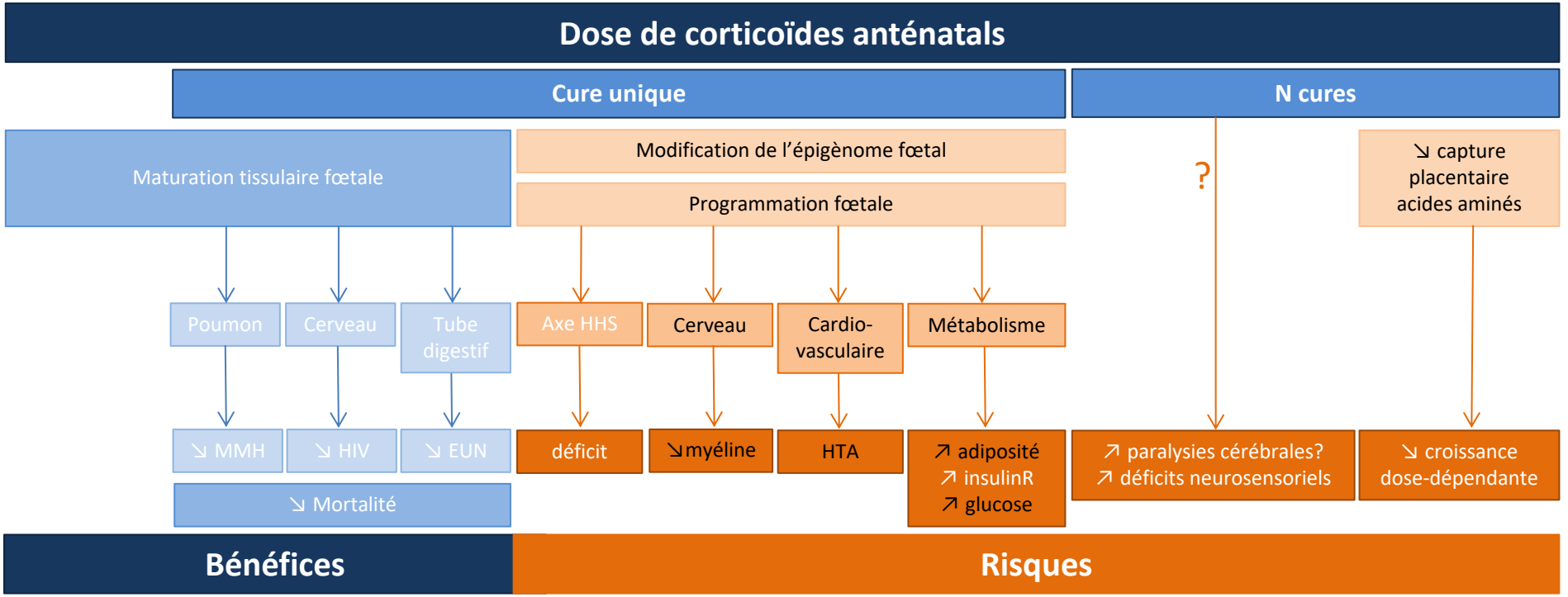
Prevention of preterm birth complications by antenatal corticosteroid administration

Pas de bénéfices neurologiques ou digestifs
Pas de réduction de la mortalité néonatale
Risques à long terme modérés

Après 34 SA, il n'existe pas d'arguments suffisants pour recommander l'administration systématique d'une cure de corticoïdes anténatals (grade B), mais celle-ci pourra toutefois être discutée dans les situations à haut risque de détresse respiratoire « sévère », en particulier en cas de césarienne programmée (grade C).

Comment réduire les risques associés à la corticothérapie anténatale?

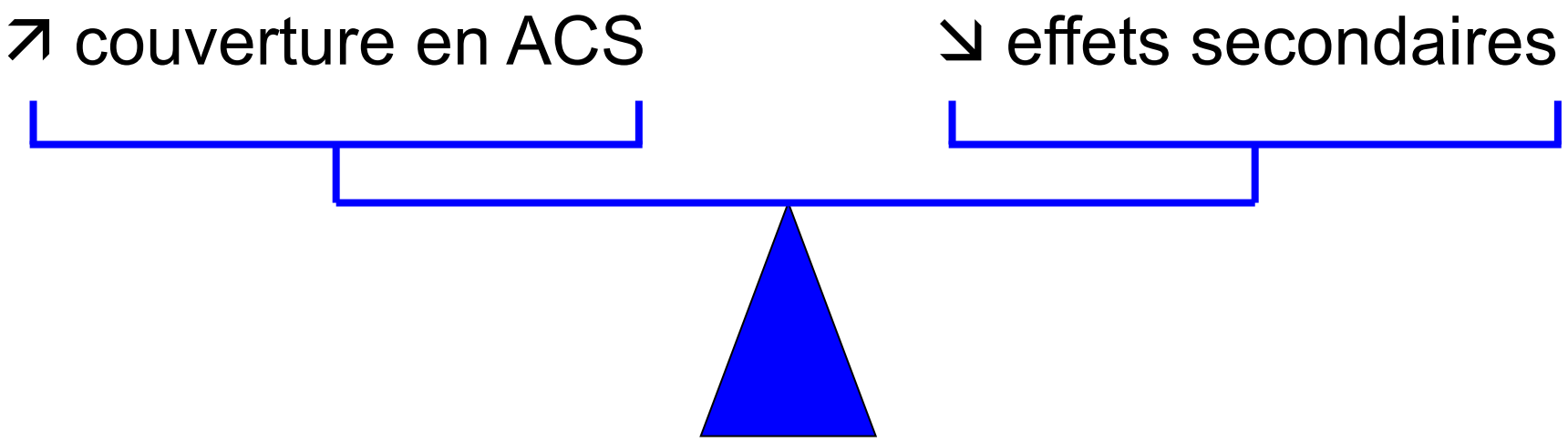
Bénéfices et risques de la corticothérapie anténatale



En blanc: preuves apportées par les études animales et les essais chez la femme, En noir: preuves apportées par les études animales uniquement
MMH: Maladie des membranes hyalines, HIV: hémorragie intra-ventriculaire, EUN: entérocolite ulcéro-nécrosante,
insulinR: insulino-résistance, HHS: hyphothalamo-hypophyso-surrénalien

Il existe des effets secondaires liés à la dose

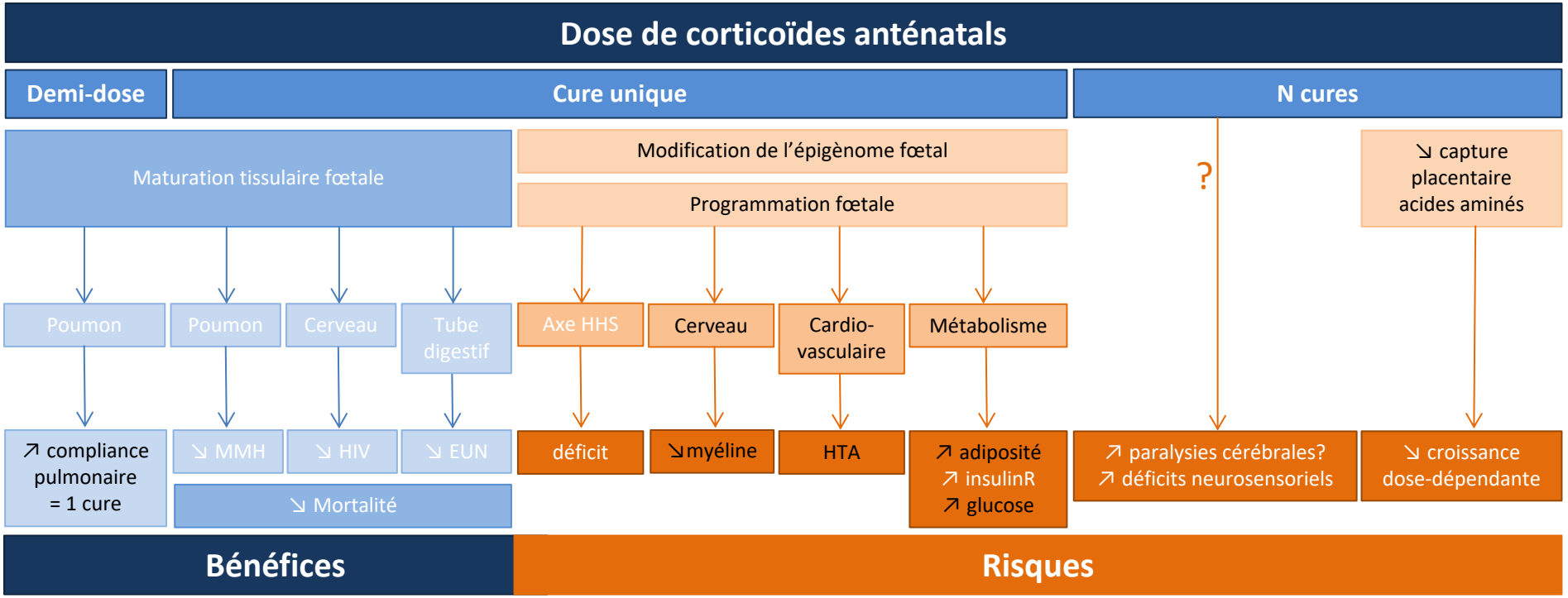
Dilemme pour l'obstétricien



- Mieux identifier le risque d'accouchement prématuré
  - Prématurité induite: possible voire facile
  - Prématurité spontanée: difficile

- Diminuer la dose des ACS

Bénéfices et risques de la corticothérapie anténatale



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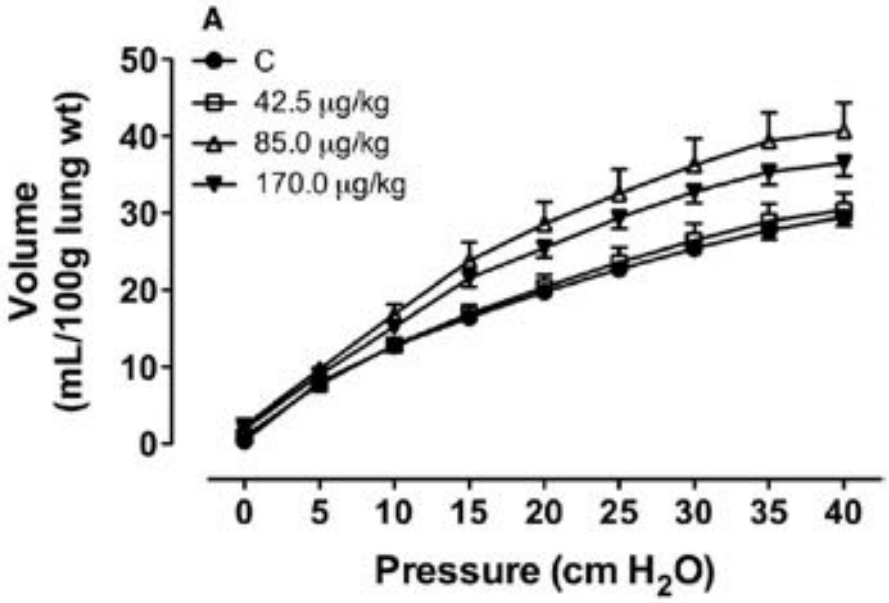
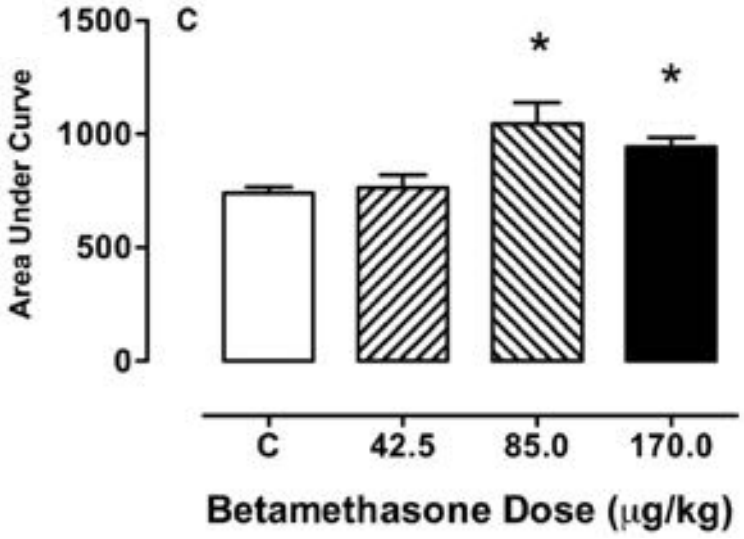
Dose-response effects of betamethasone on maturation of the fetal sheep lung

Matthias Loehle, MD, PhD; Matthias Schwab, MD, PhD; Susan Kadner, MS; Kristal M. Maner, PhD; Jeffrey S. Gilbert, PhD; J. Thomas Brenna, PhD; Stephen P. Ford, PhD; Peter W. Nathanielsz, MD, PhD; Mark J. Nijland, PhD





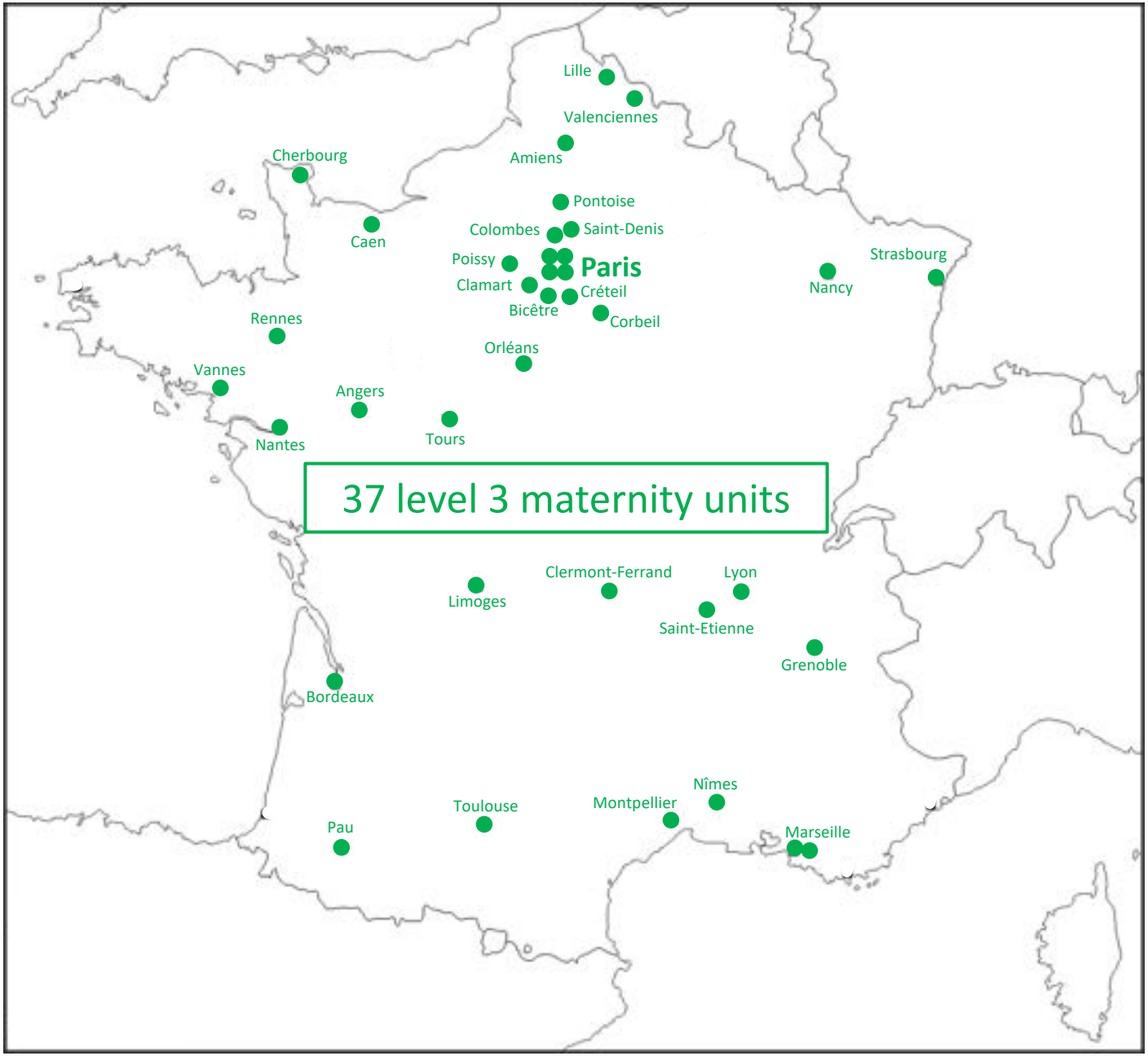
Trials comparing the commonly used corticosteroids are most urgently needed, as are trials of **dosages** and other variations in treatment regimens.

Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2013;8:CD006764.

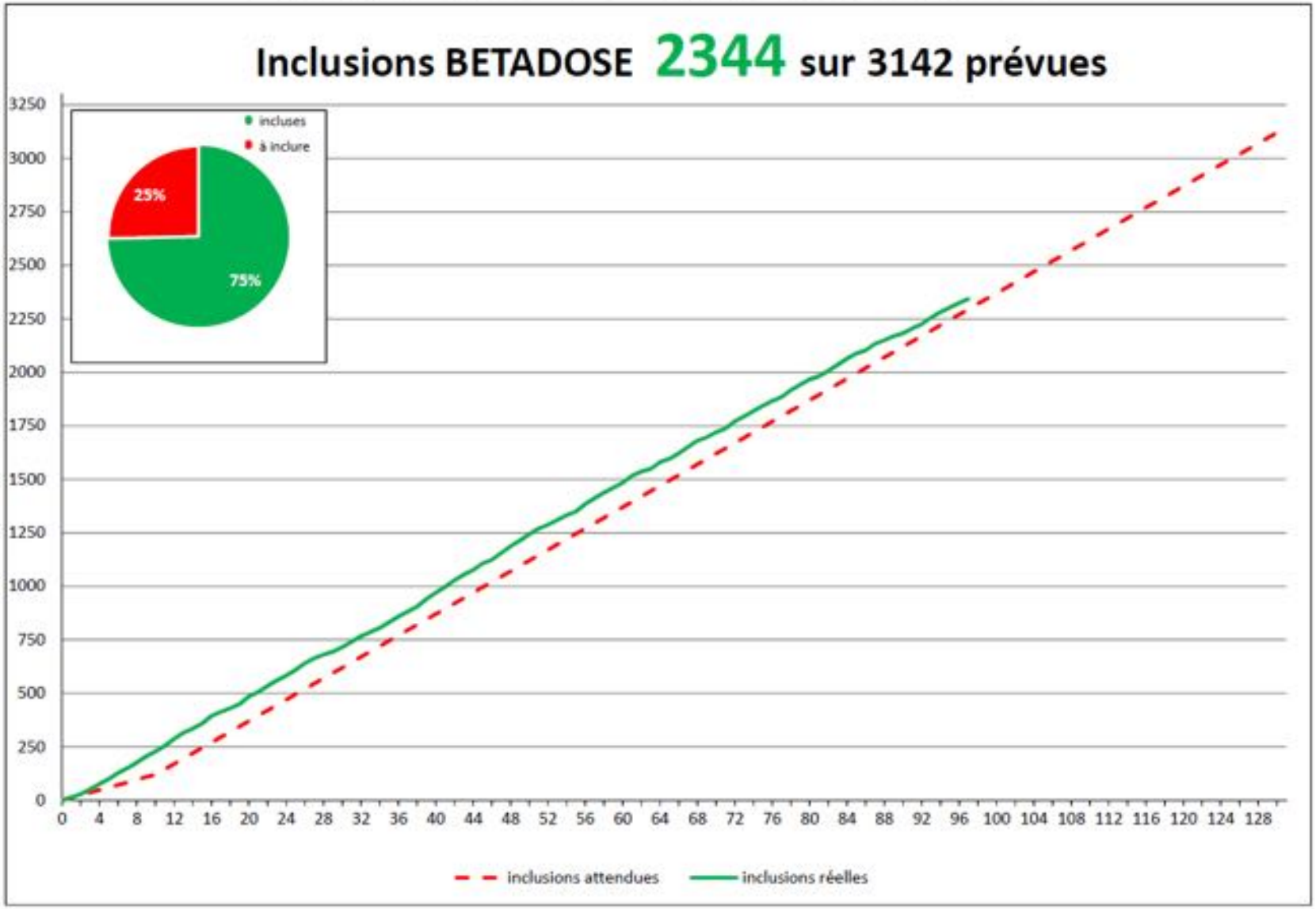
A randomised, multicenter, double blind, placebo-controlled, non-inferiority trial (BETADOSE)

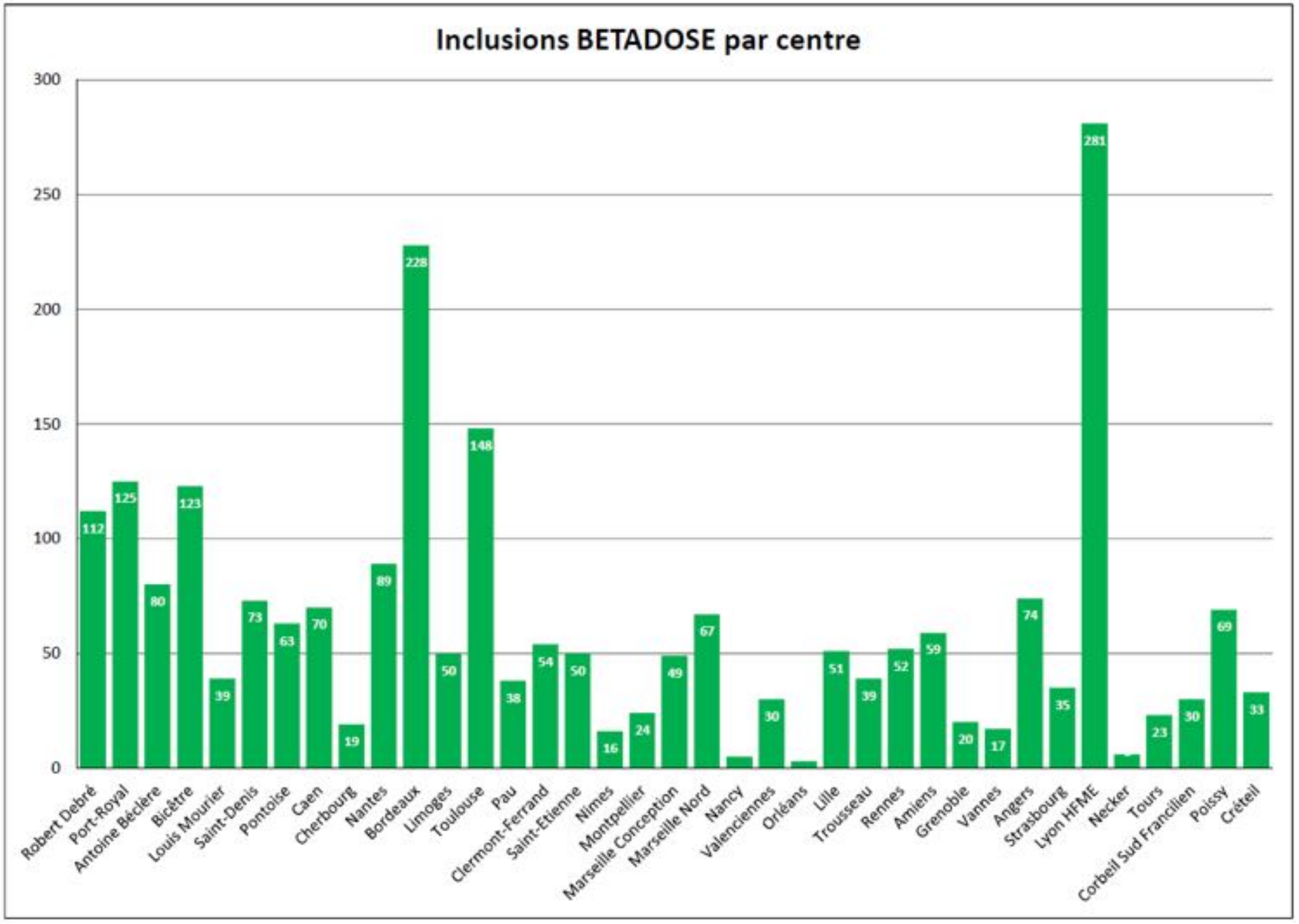
BETADOSE

The BETADOSE trial: participating centers



Essai BETADOSE 2018 semaine 97




Inclusions BETADOSE par centre
300
250
200
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89
228
50
148
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74
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281
8
23
30
69
33
Robert Debré
Port-Royal
Antoine Béclère
Bicêtre
Louis Mourier
Saint-Denis
Pontoise
Caen
Cherbourg
Nantes
Bordeaux
Limoges
Toulouse
Pau
Clermont-Ferrand
Saint-Etienne
Nimes
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Valenciennes
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Créteil