

DSHS Grand Rounds



Presenter:
Donald Dudley, MD, UT Health Science Center at San Antonio

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David Lakey, MD
DSHS Commissioner
is pleased to introduce today's
DSHS Grand Rounds speakers

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Healthy Texas Babies: Antenatal Glucocorticoid Therapy, Past, Present, and Future



Donald J. Dudley, M.D.
Division of Maternal-Fetal Medicine
Department of Obstetrics and
Gynecology
University of Texas Health Science
Center at San Antonio

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Learning Objectives

Participants will be able to:

1. Describe the past investigations that led to the discovery and early use of antenatal steroid therapy to prevent complications of preterm birth.
2. Analyze the indications, contraindications, and current recommendations regarding the use of antenatal steroid therapy to prevent the complications of preterm birth.
3. Recognize the gaps in knowledge regarding the use of antenatal steroid therapy and where future investigations should be focused to improve outcomes for preterm babies.

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Why Antenatal Steroid Therapy? The Past

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Liggins and Howie

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID
TREATMENT FOR PREVENTION OF THE RESPIRATORY
DISTRESS SYNDROME IN PREMATURE INFANTS

G. C. Liggins, M.B., Ph.D., F.R.C.O.G., and R. N. Howie, M.B., M.R.A.C.P.

From the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, New Zealand



PEDIATRICS, Vol. 50, No. 4, October 1972

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Results from Liggins and Howie

TABLE III
INFLUENCE OF THERAPY ON COURSE OF PREGNANCY
IN UNPLANNED PREMATURE LABOR

	<i>Betamethasone-Treated Group</i>		<i>Control Group</i>	
	No.	%	No.	%
Interval Between First Injection and Delivery:				
Under 24 hours	28	23.9	22	22.9
24 hours and under 7 days	44	37.6	43	44.8
7 and under 21 days	6	5.1	4	4.2
21 days and over	39	33.4	27	28.1
All mothers	117	100.0	96	100.0
Mean interval (days)		22.1		14.4
Median interval		3.7		2.8

TABLE IV
INFANT SURVIVAL IN UNPLANNED PRE-
MATURE LABOR (ALL INFANTS)

	<i>Betamethasone-Treated Group</i>		<i>Control Group</i>		<i>p*</i>
	No.	%	No.	%	
Fetal deaths, antepartum	3	2.4	...	0.0	NS†
Fetal deaths, intrapartum	1	0.8	3	3.0	
Early neonatal deaths	4	3.2	15	15.0	.01
Perinatal deaths	8	6.4	18	18.0	.02
Survived 7 days	118	93.6	82	82.0	
All babies	126	100.0	100	100.0	

* *p* values in this and subsequent Tables are derived using the chi-squared test with Yates's correction.
† NS = difference not significant ($p > 0.05$).

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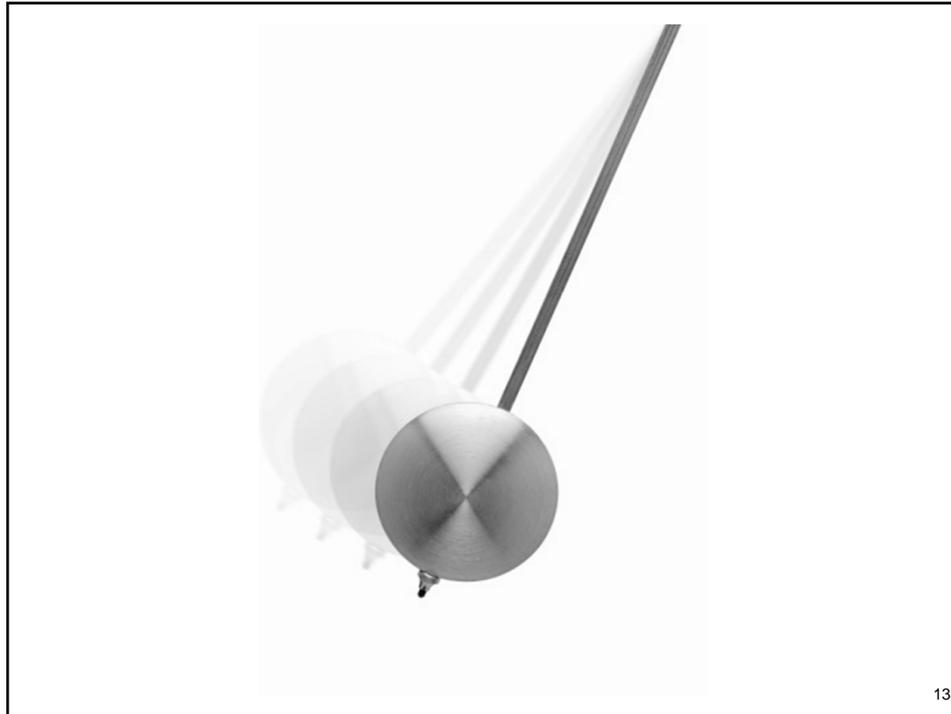
TABLE V
OCCURRENCE OF RDS IN LIVEBORN INFANTS RELATED TO ENTRY-DELIVERY INTERVAL
IN INFANTS DELIVERED AFTER UNPLANNED PREMATURE LABOR

<i>Entry-Delivery Interval</i>	<i>Betamethasone-Treated Group</i>			<i>Control Group</i>			<i>p</i>
	No.	RDS	% RDS	No.	RDS	% RDS	
Under 24 hours	29	7	24.1	22	7	31.8	NS
24 and under 48 hours	20	2	10.0	19	7	36.8	NS
2 and under 7 days	28	1	3.6	24	8	33.3	.03
7 days and over	45	1	2.2	32	3	9.4	NS
All live births	122	11	9.0	97	25	25.8	.003
All infants born alive over 24 hours after entry to trial	93	4	4.3	75	18	24.0	.002

TABLE VIII
INCIDENCE OF RDS ACCORDING TO GESTATIONAL AGE AT DELIVERY IN LIVEBORN INFANTS
OF UNPLANNED DELIVERIES AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

	<i>Betamethasone-Treated Group</i>			<i>Control Group</i>			<i>p</i>
	<i>No. of Infants</i>	<i>RDS No.</i>	<i>% RDS</i>	<i>No. of Infants</i>	<i>RDS No.</i>	<i>% RDS</i>	
Gestational Age at Delivery:							
26 and under 32 weeks	17	2	11.8	23	16	69.6	0.02
32 and under 37 weeks	43	2	4.7	29	2	6.9	NS
37 weeks and over	38	0	0.0	23	0	0.0	NS
All liveborn infants	98	4	4.3	75	18	24.0	0.002

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Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome*

COLLABORATIVE GROUP ON ANTENATAL STEROID THERAPY**
 Bethesda, Maryland (AM. J. OBSTET. GYNECOL. 141:276, 1981.)

Multicenter Prospective Randomized Trial of Dexamethasone in Women At Risk for Preterm Birth (overall N=661 women/720 infants)

Table III. Incidence of RDS "mothers" (mothers with at least one infant with RDS) by treatment and plurality of deliveries

Plurality of deliveries	Treatment		Total
	Placebo	Steroid	
Single	48/299 (16.1)	31/307 (10.1)	79/606 (13.0)
Twins	10/26 (38.5)	10/24 (41.7)	20/50 (40.0)
Triplets	1/3 (33.3)	1/2 (50.0)	2/5 (40.0)
All	59/328 (18.0)	42/333 (12.6)	101/661 (15.3)

P=0.05

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Table VII. Percentage of single infants with RDS by treatment and various subgroups

Sub-groups	Treatment		P value
	Placebo	Steroid	
	16.0 (48/299)	10.1 (31/307)	
Availability of L/S ratio at entry			
L/S immature	17.3 (24/139)	8.7 (14/160)	0.03
L/S not assessed	15.0 (24/160)	11.6 (17/147)	0.39
Mode of delivery*†			
Vaginal	11.9 (24/202)	6.8 (14/205)	
Cesarean	23.7 (22/93)	14.7 (14/95)	
In labor	11.3 (6/53)	12.8 (6/47)	
Not in labor	40.5 (15/37)	15.9 (7/44)	
State of labor unknown	3	4	
Preeclampsia* (P = 0.02)‡			
No	14.1 (37/262)	7.9 (21/267)	0.021
Yes	27.3 (9/33)	21.2 (7/33)	0.57
PROM* (P = 0.03)‡			
No	18.1 (29/160)	8.8 (13/147)	0.016
Yes	12.6 (17/135)	9.8 (15/153)	0.45
Sex (P = 0.001)‡			
Male	14.1 (24/170)	14.9 (24/161)	0.96
Female	18.8 (24/128)	4.8 (7/146)	<0.001
Sex unknown			
Race (P = 0.02)‡			
White, not Hispanic	19.7 (28/142)	16.7 (23/138)	0.42
Black, not Hispanic	9.8 (13/132)	4.3 (6/138)	0.076
Others§	28.0 (7/25)	6.4 (2/31)	0.028

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Table VIII. Percentage of single infants with RDS by treatment in race/sex subgroups

Race/sex subgroups	Treatment		P value	Total
	Placebo	Steroid		
Female				
White, not Hispanic	24.2 (16/66)	9.4 (6/64)	0.02	16.9 (22/130)
Black, not Hispanic	9.6 (5/52)	1.5 (1/67)	0.04	5.9 (6/119)
Others*	30.0 (3/10)	0 (0/15)	0.05	12.0 (3/25)
Male				
White, not Hispanic	16.0 (12/75)	23.0 (17/74)	0.39	19.5 (29/149)
Black, not Hispanic	10.0 (8/80)	7.0 (5/71)	0.52	8.6 (13/151)
Others*	26.7 (4/15)	12.5 (2/16)	0.32	19.4 (6/31)

*Includes North American Indians and Hispanics.

Table IX. Percentage of single infants with RDS by treatment and subgroups of gestational age at delivery and duration in study

Gestational age at delivery (Dubowitz)	Duration in study	Placebo	Steroid	P value	Total
<30 wk	<24 hr	33.3 (1/3)	66.6 (2/3)	0.41	50.0 (3/6)
	24-7 days	41.6 (5/12)	60.0 (3/5)	0.54	47.0 (8/17)
	>7 days	100.0 (1/1)	50.0 (1/2)	0.39	66.6 (2/3)
30-34 wk	<24 hr	31.8 (7/22)	30.8 (8/26)	0.75	31.2 (15/48)
	24-7 days	25.4 (16/63)	10.6 (7/66)	0.03	17.8 (23/129)
	>7 days	26.9 (7/26)	26.3 (5/19)	1.0	26.7 (12/45)
34+ wk	<24 hr	0 (0/25)	3.8 (1/26)	0.32	1.9 (1/51)
	24-7 days	6.2 (4/64)	5.0 (4/80)	0.74	5.5 (8/144)
	>7 days	5.2 (4/77)	0 (0/77)	0.05	2.6 (4/154)
Dubowitz determination not performed					9

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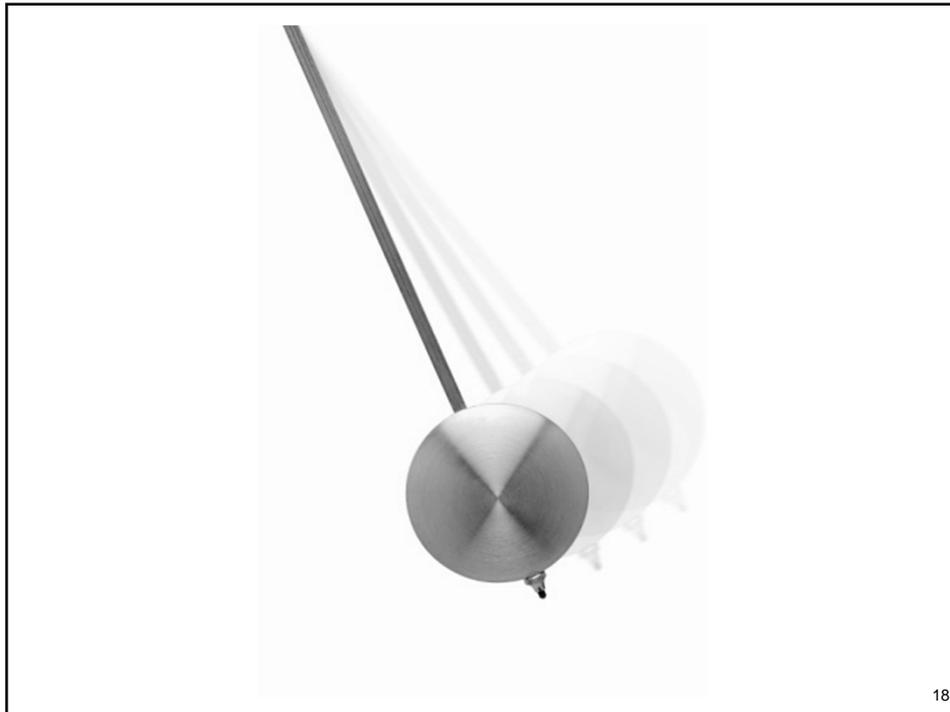
Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome*

COLLABORATIVE GROUP ON ANTENATAL STEROID THERAPY**
Bethesda, Maryland

the overall incidence of RDS. However, since the effect of treatment is dependent upon multiple deliveries, sex, race, and other characteristics of the infant and mother, its potential usefulness will be dictated by those limitations. These and the still unknown long-term effects of this therapy, in our opinion, indicate that antenatal steroid therapy should be used selectively and with caution.

Use Antenatal Steroids in African American Women with Singleton Girl Babies Between 30-34 Weeks Gestation

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NIH Consensus Statement

Volume 12, Number 2
February 28–March 2, 1994



Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes

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Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes

NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes

Evidence for Efficacy of Corticosteroids and Strength of Recommendation According to Delivery Interval, Gestational Age, Status of Membranes, and Neonatal Outcome

	Quality of Evidence for Benefit, Grade	Strength of Recommendation
Interval from treatment to delivery		
<24 h	I	B
24 h to 7 d	I	A
>7 d	I	C
Gestational age		
Delivery at 24-28 wk	I	A
Delivery at 29-34 wk	I	A
Delivery at >34 wk	I	C
Preterm premature rupture of membranes	I	B
Neonatal outcomes		
Mortality	I	A
Respiratory distress syndrome	I	A
Intraventricular hemorrhage	I	A

Conclusions.—Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs. The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health.

(*JAMA*. 1995;273:413-418)

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Prophylactic Corticosteroids for Preterm Birth

- Crowley P, Cochrane Database 2000;2:CD000065
- Steroid Therapy for Fetal Lung Maturation:
 - Reduces Mortality, RDS, & IVH
 - Across Gestational Ages, Not Limited by Gender or Race
 - Greatest after 24 Hours, <24 Hours May Improve Outcome

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Single Versus Repeat Courses of Antenatal Steroids to Improve Neonatal Outcomes: Risks and Benefits

Clarissa Bonanno, MD,* Karin Fuchs, MD,* and Ronald J. Wapner, MD†

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Obstetrical and Gynecological Survey

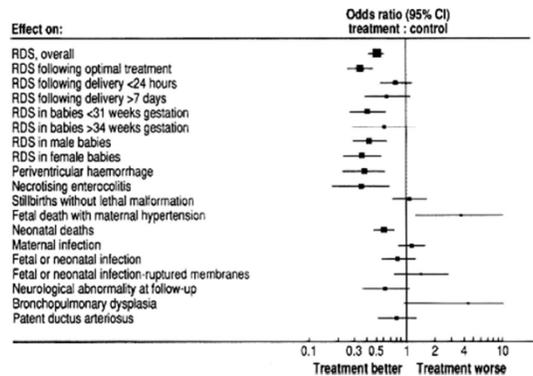


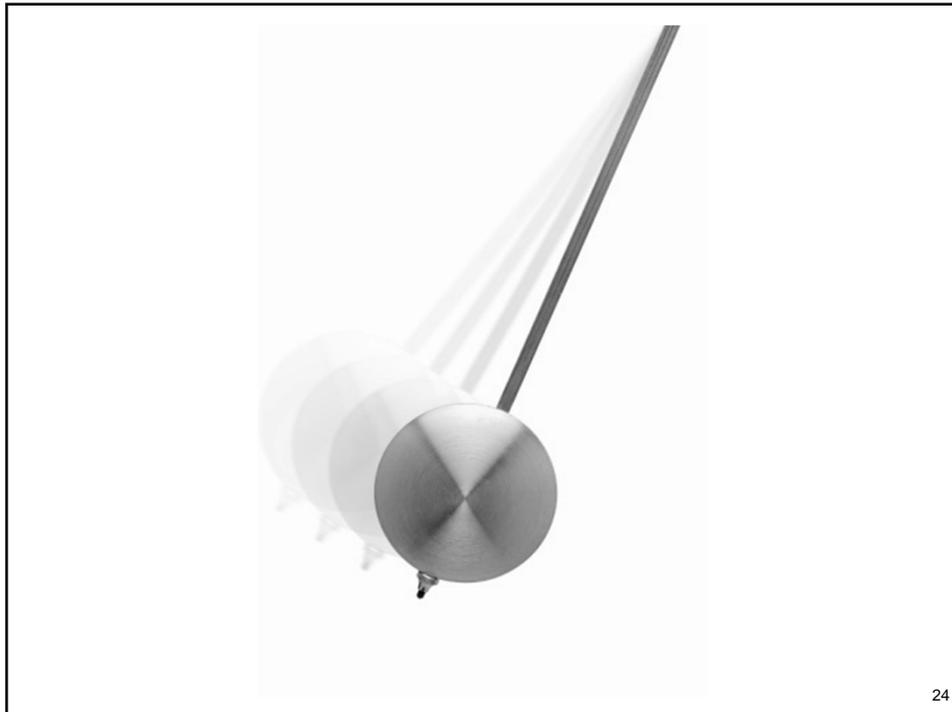
Fig. 1. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Reproduced from Crowley, PA. Am J Obstet Gynecol 1995;173:322-335.

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Prophylactic Corticosteroids for Preterm Birth

- Crowley P, Cochrane Database 2000;2:CD000065
 - β methasone or Dexamethasone
 - No Evidence to Support or Condemn the Use of Repeated Doses of Steroids who Remain Undelivered after One Week
 - More Data Needed: Preeclampsia, Twins, Diabetes
 - Updated in 2004: No Changes, Not Enough Data Regarding Weekly vs. Single Course of Steroids

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Multiple Courses of Steroids

- Brocklehurst, et al, BJOG 1999;106:977
 - Surveyed 279 OB Units in the UK
 - 75% Response Rate
 - 98% Used Repeated Courses
 - Over 80% Use Repeated Courses in the Setting of PTL or PPRM

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Repeated Antenatal Corticosteroids: Size at Birth and Subsequent Development

- French et al, AJOG 1999;180:114
 - Observational Study of 477 Singletons Born at <33 Weeks GA
 - Dose Response on BW: 3+, 122 grams Smaller
 - Dose Response on HC: 3+, 1.02 cm Smaller
 - No Benefit to Repeated Courses

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Multiple Courses of Antenatal Corticosteroids and Outcome of Premature Neonates

- Banks, et al, AJOG 1999;181:709
 - Secondary Analysis of TRH Trial, n=710
 - Three Groups: 1, 2, or ≥ 3 Courses
 - No Differences in Incidence of RDS, IVH
 - If ≥ 2 Courses, Lower BW (by 39 gm)
 - If ≥ 3 Courses, Increased Death Risk (OR 2.8)
 - If ≥ 3 Courses, Prolonged Adrenal Suppression

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Neonatal Sepsis and Death After Multiple Courses of Antenatal Betamethasone Therapy

- Vermillion, et al, AJOG 2000;183:810
 - “Nonconcurrent Prospective Analysis” of Single vs. Multiple Courses
 - N=267 Single Course, N=186 Multiple Course
 - Multiple Courses Significantly Associated with Neonatal Sepsis (OR=5), Chorioamnionitis (OR=9.96), Endometritis (OR=3.6), and Neonatal Death (OR=2.92)

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Problems with Studies of Single vs. Multiple Courses of Steroids

- Most are Retrospective
- Insufficient Power
- Inappropriate Grouping (is 3 courses the same as 6 courses?)
- Inappropriate Outcome Measures
- Inappropriate Study Groups

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Single vs. Weekly Courses of Antenatal Corticosteroids for Women at Risk of Preterm Delivery

- Guinn, et al, JAMA 2001;286:1581
- Randomized, Prospective, Controlled Trial (n=246 single course vs n=256 multiple course)
- Preterm Birth Risk based on:
 - Preterm Labor n=270
 - PPROM n=120
 - Maternal Illness n=79
 - Fetal Jeopardy n=33
 - Multiple Gestation n=73

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Single vs. Weekly Courses of Antenatal Corticosteroids for Women at Risk of Preterm Delivery

- Weekly Courses: 2 in 88, 3 in 55, 4 in 34, 5 in 20, and ≥ 6 in 48
- Results:
 - No Differences in GA at Delivery
 - No Differences in BW
 - No Differences in Head Circumference
 - No Differences in Composite Outcomes (22.5% vs. 28%)

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NIH Consensus Development Conference on Antenatal Corticosteroids: Repeat Courses

- O & G, 2001;98:144
 - Single Course of Antenatal Steroids is Unequivocally Beneficial
 - Not Enough Data to Comment on Repeated Courses
 - Repeat Courses, including Rescue Therapy, Should be Reserved for Patients Enrolled in Clinical Trials

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Single versus weekly courses of antenatal corticosteroids: Evaluation of safety and efficacy

American Journal of Obstetrics and Gynecology (2006) 195, 633–42

Ronald J. Wapner, MD,^{a,*} Yoram Sorokin, MD,^b Elizabeth A. Thom, PhD,^c
Francee Johnson, RN, BSN,^d Donald J. Dudley, MD,^e Catherine Y. Spong, MD,^f

- Wapner, et al: MFMU Network
- Randomized 495 Women: 252 Repeated Courses, 243 Placebo
- All Women at Risk for Spontaneous Preterm Birth (Previa, Abruptio)
- Primary Outcome: Composite of RDS, IVH, PVL, Chronic Lung Disease, Death
- Secondary Outcome: BW, HC

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MFMU Network Study on Repeated vs. Single Course

- 64% Received ≥ 4 Courses
- No Difference: Time to Delivery (47 Days), PPRM, PTD, GDM, Chorioamnionitis, Endometritis
- No Difference in Primary Outcome: 8% Repeat vs. 9% Single
- Repeat: Less Need for Vent Support, Surfactant Use

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Table III Neonatal outcomes for all patients

Neonatal outcome	Repeat (n = 250)	Placebo (n = 242)	Relative risk (95% CI)	P value
Composite—Severe RDS, IVH III-IV, PVL, CLD, perinatal death (No. [%])	20 (8.0)	22 (9.1)	0.88 (0.49-1.57)	.67
Perinatal death (No. [%])	3 (1.2)	6 (2.5)	0.48 (0.12-1.91)	.33
IVH III-IV/PVL* (No. [%])	0 (0)	2 (0.87)	0.00 (0.00-1.93)	.50
Severe RDS (No. [%])	6 (2.4)	10 (4.1)	0.58 (0.21-1.57)	.28
CLD (No. [%])	14 (5.6)	15 (6.2)	0.90 (0.45-1.83)	.78

	1-3 study courses		P value	4+ study courses		P value
	Repeat (N = 105)	Placebo (N = 117)		Repeat (N = 191)	Placebo (N = 177)	
Birth weight (gm)	1820.7 ± 810.4	1879.5 ± 851.1	.57	2399.6 ± 650.6	2560.6 ± 617.0	.01
Head circumference (cm)	29.0 ± 3.4	29.0 ± 3.8	.74	31.6 ± 2.4	32.1 ± 2.1	.11
Length (cm)	42.2 ± 5.4	42.1 ± 5.9	.97	45.4 ± 3.6	46.5 ± 3.4	.006
Length MOMs	1.00 ± 0.06	0.99 ± 0.05	.13	0.97 ± 0.05	0.99 ± 0.06	.004
Ponderal Index (kg/m ³)	22.8 ± 3.6	23.6 ± 2.7	.06	25.3 ± 3.4	25.1 ± 3.8	.51
Arm circumference (cm)	8.1 ± 1.9	8.0 ± 1.9	.77	9.2 ± 1.8	9.5 ± 1.6	.14
Birth weight < 10 th percentile - no. (%)	9 (10.3)	10 (10.8)	.93	50 (30.9)	27 (18.1)	.009
Birth weight < 5 th percentile - no. (%)	4 (4.6)	8 (8.6)	.28	28 (17.3)	13 (8.7)	.03

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MFMU Network Study on Repeated vs. Single Course

- Subset Analysis: < 32 Weeks (n=60 vs. n=52)
- Near Significant Decrease in Primary Outcome: 23% vs. 39%
- Much Less Pulmonary Complications
- Lower Incidence of Infectious Morbidity

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Long-Term Outcomes after Repeat Doses of Antenatal Corticosteroids

N Engl J Med 2007;357:1190-8.

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.,

- Women Given Antenatal Steroids at 23-31 Weeks and Remained Pregnant for One Week were then Randomized to Weekly Doses until 34 Weeks or Delivery (Steroids vs Placebo)
- N= 248 ACS Infants vs. 238 Control Infants

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Table 1. Demographic and Birth Characteristics of Mothers and Infants.*

Characteristic	Repeat Corticosteroids (N=206 Pregnancies and 248 Infants)	Placebo (N=195 Pregnancies and 238 Infants)	P Value
No. of treatment courses — median (range)	4 (1–11)	4 (1–9)	0.35
Gestational age at birth — wk	34.9±3.9	35.1±3.7	0.74
Birth weight — g	2204±778	2321±768	0.08
Birth weight <10th percentile — %†	24.4	16.4	0.048
Twin pregnancy — %‡	21.4	22.6	0.77
Race or ethnic group — %§			0.99
Black	38.8	39.5	
White	34.0	33.9	
Hispanic or other	27.2	26.7	
Maternal education — yr	11.9±2.5	12.1±2.6	0.23
Intraventricular hemorrhage — %†	5.7	6.9	0.64
Respiratory distress syndrome — %†	9.8	13.3	0.26
Severe respiratory distress syndrome — %†	2.9	3.1	0.93
Chorioamnionitis — %	3.4	2.1	0.41

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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.,

	Steroid	Placebo		
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

Increased Risk for CP with ≥ 4 Courses

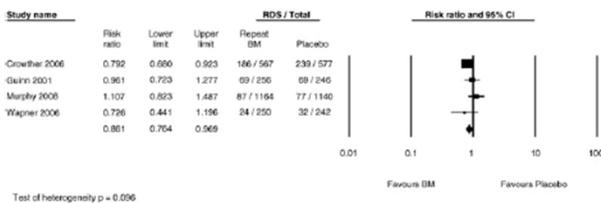
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Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis

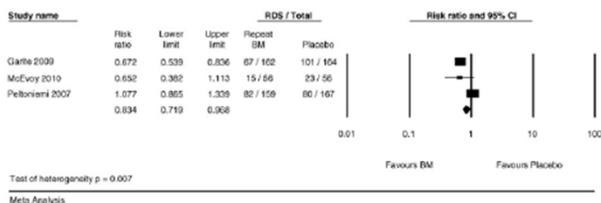
OUTI M. PELTONIEMI¹, M. ANNELI KARI² & MIKKO HALLMAN¹

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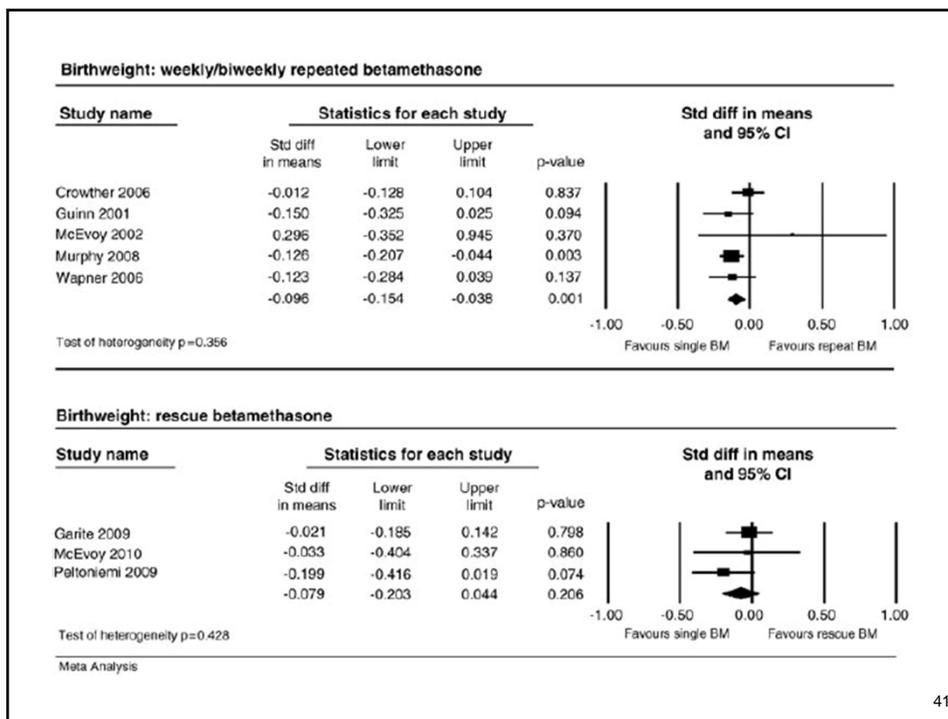
Weekly or biweekly repeated betamethasone: respiratory distress syndrome



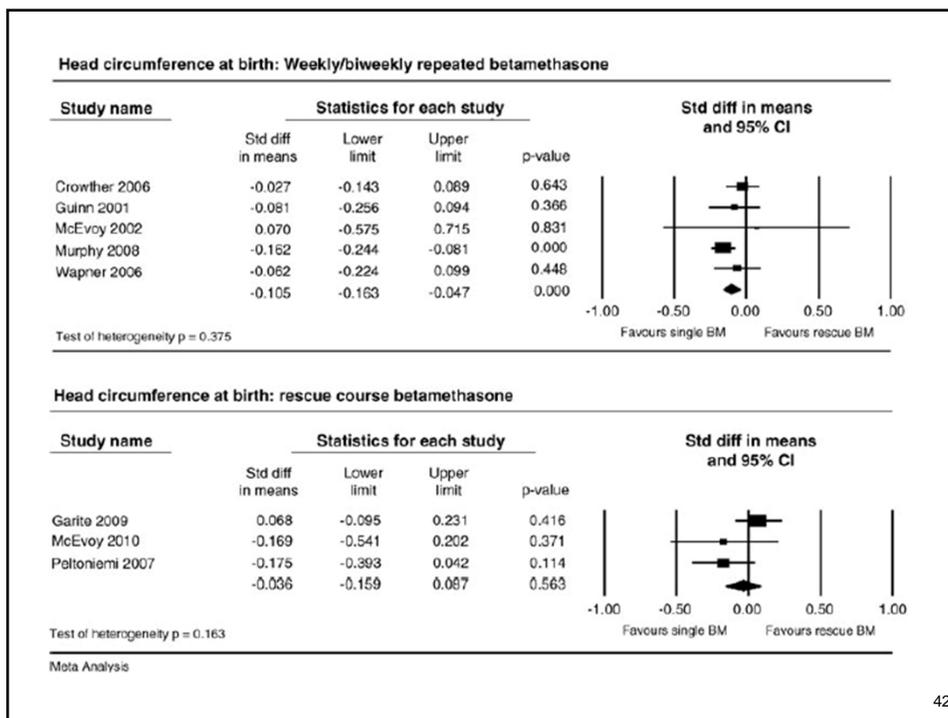
Rescue betamethasone: respiratory distress syndrome



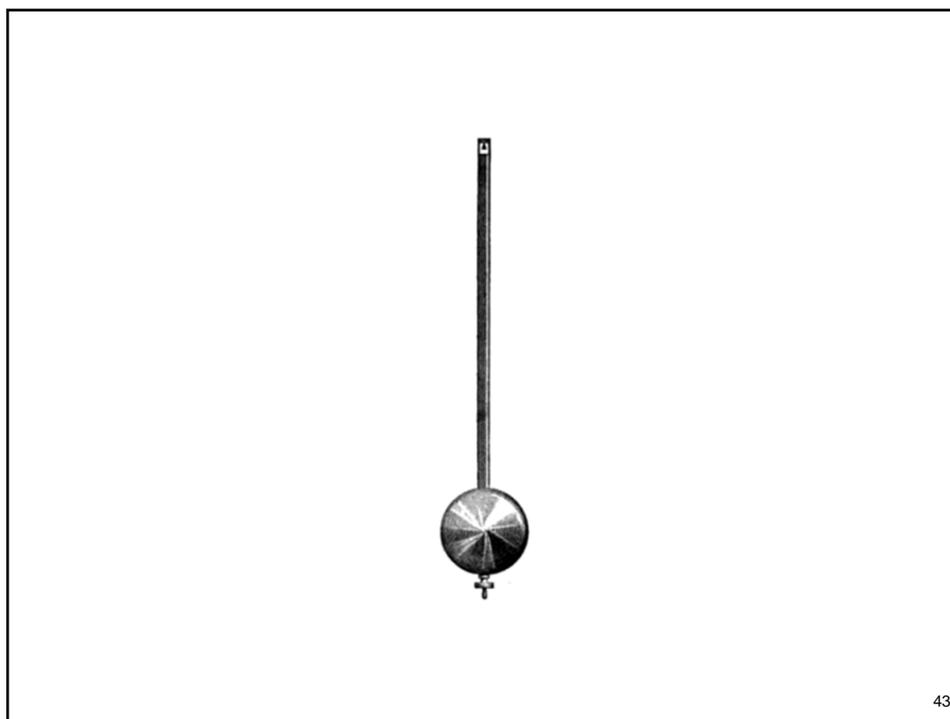
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Antenatal Steroid Therapy:

Where are We Now?
The Present

Effects of Antenatal Steroids

- Induction of fetal type II alveolar cells to make surfactant proteins A, B, C, D
- Increases activity of antioxidant enzymes that may protect neonatal lungs from oxidant damage
- Facilitates clearance of lung fluid from alveolar spaces
- Increases alveolar volume, lung compliance, reduces protein leak, enhances response to exogenous surfactant

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Current Recommendations

- Antenatal Glucocorticoids Should be Administered to Women from 24 to 34 Weeks Gestation who are At Risk for Preterm Birth Prior to 34 Weeks
- β -methasone 12 mg IM 24 hours Apart (Two Doses)
- Dexamethasone 6 mg q 12 hours IM for 4 Doses

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Indications for Antenatal Steroid Therapy

- Preterm Labor/Preterm Premature Rupture of the Membranes
- Hypertensive Diseases of Pregnancy
- Blood Group Isoimmunization
- Placental Abnormalities (Previa/Accreta)
- Other Conditions: Twins, Intrauterine Growth Restriction

But Remember Barney and His One Bullet....

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Weekly vs. Single Courses: “Rescue” Dosing?

- Peaceman, et al, The interval between a single course of antenatal steroids and delivery and its association to neonatal outcomes. AJOG 2005;193:1165
- N=197, half delivered within 7 days, half delivered after 7 days
- <7 Days: Lower RDS (62% vs. 81%)
- No Difference: Surfactant Rx, Ventilation, NEC, IVH, O2 Dependence, Mortality
- Refutes Concept of Decreasing Efficacy, Question the Need for Rescue Dosing

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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 Am J Obstet Gynecol 2009;200:248.e1-248.e9.

- Randomized Trial: 223 in the Rescue Group, 214 in the Placebo group
- 14 days after Initial Course
- Composite Neonatal Outcome
- 55% in Each Group Delivered < 34 Weeks
- 24-25 Days from Randomization to Delivery

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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

TABLE 3

Neonatal morbidity and mortality-delivery < 34 weeks

Neonatal morbidity	ACS n/N (%)	Placebo n/N (%)	OR* (95% CI)	P value ^a
Composite morbidity	71/163 (43.9)	105/165 (63.6)	0.45 (0.27-0.75)	.002
RDS	67/162 (41.4)	101/164 (61.6)	0.45 (0.27-0.75)	.002
BPD	27/160 (16.9)	20/163 (12.3)	1.53 (0.77-3.07)	.228
Surfactant	61/162 (37.7)	91/164 (55.5)	0.49 (0.30-0.80)	.004
Ventilator	59/157 (37.6)	83/157 (52.9)	0.56 (0.33-0.92)	.023

TABLE 4

Neonatal morbidity—all newborns

Neonatal morbidity	ACS n/N (%)	Placebo n/N (%)	OR* (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

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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

TABLE 5
Neonatal composite morbidity by days from first dose to delivery

	ACS n/N (%)	Placebo n/N (%)	P value ^a
0 or 1 d	13/25 (52.0)	15/20 (75.0)	.067
2-7 d	24/61 (39.3)	37/53 (69.8)	.035
8-14 d	15/37 (40.5)	24/47 (51.5)	.328
15-21 d	9/22 (40.9)	21/32 (65.6)	.173
22-28 d	13/31 (41.9)	12/39(30.8)	.550
> 28 d	14/100 (14.0)	11/91 (12.1)	.588

Rescue Courses Improved Outcome if Delivery Occurs 2-7 Days After Administration

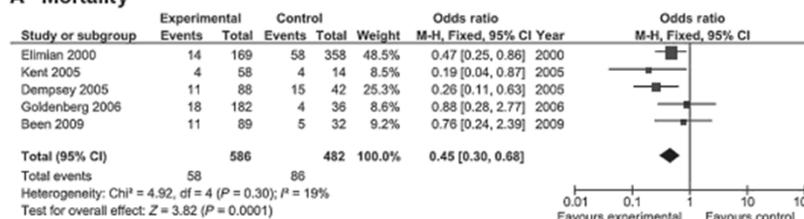
51

Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis

JV Been,^{a,b} PL Degraeuwe,^a BW Kramer,^{a,c} LJ Zimmermann^a BJOG 2011;118:113-122.

A Relative Contraindication to Antenatal Steroids Has Been Maternal Intrauterine Infection

A Mortality

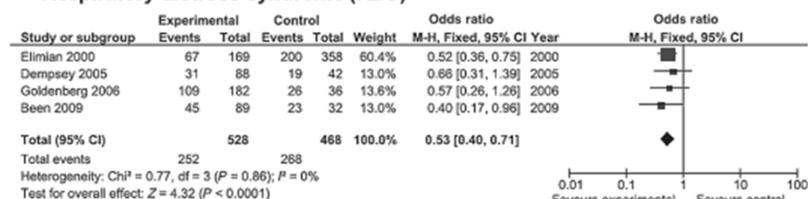


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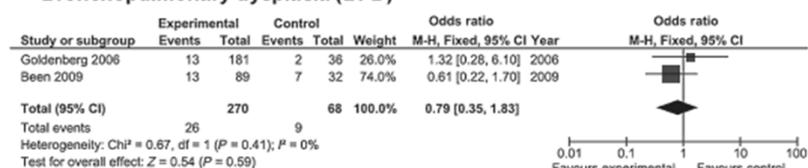
Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis

JV Been,^{a,b} PL Degraeuwe,^a BW Kramer,^{a,c} LJ Zimmermann^a

B Respiratory distress syndrome (RDS)



C Bronchopulmonary dysplasia (BPD)

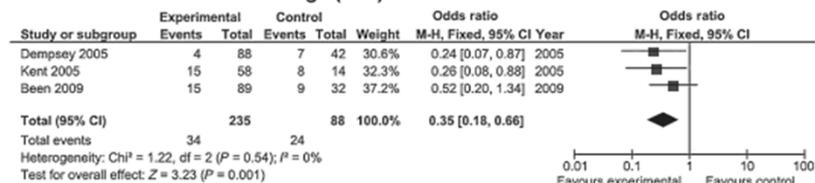


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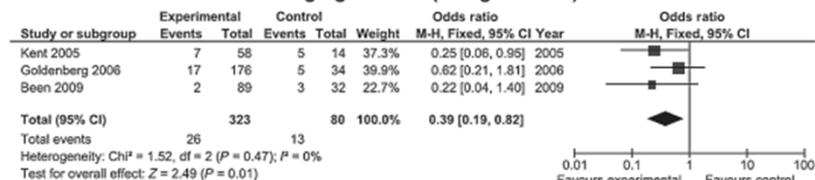
Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis

JV Been,^{a,b} PL Degraeuwe,^a BW Kramer,^{a,c} LJ Zimmermann^a

D Intraventricular haemorrhage (IVH)



E Intraventricular haemorrhage grade 3-4 (IVH grade 3-4)

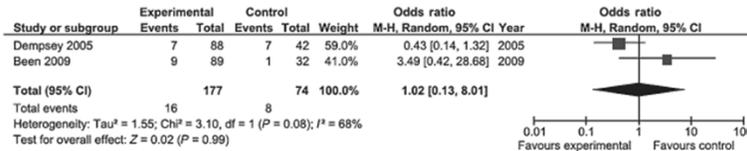


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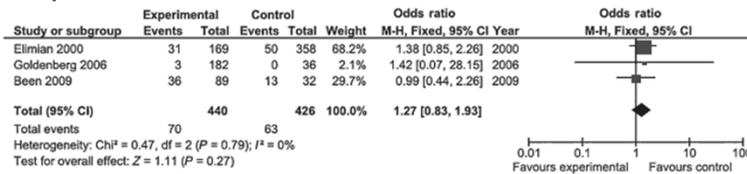
Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis

JV Been,^{a,b} PL Degraeuwe,^a BW Kramer,^{a,c} LJ Zimmermann^a

I Early onset sepsis



J Sepsis



Intrauterine Infection is Not a Contraindication For Antenatal Steroid Therapy

The Future
 Where Do We Go From Here?

Questions That Remain

- Which is the Best Steroid?
 - β -Methasone Acetate
 - β -Methasone Sodium Phosphate
 - Dexamethasone Phosphate
- What is the Correct Dose?
 - Powerful Drugs, Less Dose may be Just as Efficacious
- What is the Correct Schedule? Is Rescue Dosing Justified?
What about Incomplete Courses?
- What is the Best Route?
- What about in Pregnant Women between 34-37 Weeks?
What About Less than 24 Weeks?
- Long Term Outcome Data in the Children?

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Which is Better: β -Methasone or
Dexamethasone?

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Antenatal Glucocorticoid Treatment and Cystic Periventricular Leukomalacia in Very Premature Infants

- Baud, et al, NEJM 1999;341:1190
 - Retrospective Cohort Study of 3 Groups:
 - β -Methasone n=361
 - Dexamethasone n=165
 - No Steroid n=357
 - Cystic PVL Found in 4.4% if β -Methasone, 11% if Dexamethasone, and 8.4% if No Steroid
 - Dexamethasone does not Protect vs. PVL

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Two-year Infant Neurodevelopmental Outcome After Single or Multiple Antenatal Courses of Corticosteroids to Prevent Complications of Prematurity

- Spinillo, et al. AJOG 2004;191:217.
- Sample Size:
 - β -Methasone: N=138 (37 Multiple)
 - Dexamethasone: N=63 (33 Multiple)
- Increased Risk for PVL with Increased # Courses (26% 1, 44% >2)
- Increased Risk for Neuro Abnormalities with Increased # Courses (18% 1, 35% > 2)
- Increased Risk for PVL (OR 3.21) and Neuro Abnormalities (OR 3.63) with Dexamethasone

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β -Methasone is Better than Dexamethasone

- Less Risk for PVL & Neurodevelopmental Abnormalities
- Animal Studies: Better Development
- Only β -Methasone Reduces Risk of Neonatal Mortality

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STUDY PROTOCOL

Open Access

Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol

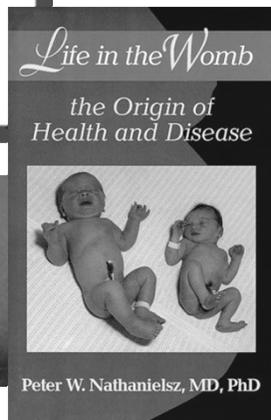
Caroline A Crowther^{1,2*}, Jane E Harding², Philippa F Middleton¹, Chad C Andersen³, Pat Ashwood¹, Jeffrey S Robinson¹, for the A*STEROID Study Group

Crowther *et al.* *BMC Pregnancy and Childbirth* 2013, **13**:104

This study aims to determine whether giving dexamethasone to women at risk of preterm birth at less than 34 weeks' gestation increases the chance of their children surviving free of neurosensory disability at two years' corrected age, compared with betamethasone.

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The Barker Hypothesis



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Long term effects of antenatal betamethasone on lung function: 30 year follow up of a randomised controlled trial

S R Dalziel, H H Rea, N K Walker, V Parag, C Mantell, A Rodgers, J E Harding



Thorax 2006;61:678-683. doi: 10.1136/thx.2005.051763

Table 5 Lung function in betamethasone and placebo exposed participants at age 30

	Betamethasone (n = 181)	Placebo (n = 202)	Difference between groups	p value
Mean FVC	105.9 (12.0)	106.6 (12.6)	-0.7 (-3.2 to 1.8)	0.59
Mean FEV ₁	98.9 (13.4)	98.5 (13.6)	0.3 (-2.4 to 3.1)	0.80
Mean FEV ₁ /FVC	0.80 (0.08)	0.79 (0.08)	0.01 (-0.01 to 0.02)	0.48
Mean PEF	101.3 (14.3)	99.1 (15.4)	2.2 (-0.8 to 5.2)	0.15
Mean F50	80.1 (23.2)	77.1 (22.3)	3.0 (-1.5 to 7.6)	0.19
Mean F25	64.0 (20.5)	63.6 (21.6)	0.4 (-3.8 to 4.7)	0.84
Mean FEF _{25-75%}	74.9 (21.6)	72.7 (21.3)	2.2 (-2.1 to 6.5)	0.31
FEV ₁ /FVC <70%	18 (10)	23 (11)	0.87 (0.49 to 1.57)	0.65

No Obvious Adverse Effects on Pulmonary Function at Age 30

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Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial

Stuart R Dalziel, Vanessa K Lim, Anthony Lambert, Dianne McCarthy, Varsha Parag, Anthony Rodgers, Jane E Harding

BMJ, doi:10.1136/bmj.38576.494363.E0 (published 5 September 2005)

Table 3 Psychological functioning and health related quality of life outcomes in groups exposed to betamethasone and placebo

Outcome	Measurement	Measured outcome		Difference (95% CI)	P value
		Betamethasone (n=87)	Placebo (n=105)		
Cognitive functioning					
Full IQ	Mean (SD)	102.6 (12.5)	103.7 (13.5)	-1.0 (-4.8 to 2.7)	0.58
Verbal IQ	Mean (SD)	97.6 (11.9)	98.3 (12.8)	-0.8 (-4.3 to 2.8)	0.67
Performance IQ	Mean (SD)	107.2 (13.8)	108.3 (14.7)	-1.1 (-5.2 to 3.0)	0.59
Psychiatric morbidity					
BDI-II total score	Median (IQR)	5 (2-12)	5 (1-10)	1 (-1 to 2)	0.44
Probable depression	No (%)	16 (18)	17 (16)	1.1 (0.61 to 2.1)†	0.69
State-trait anxiety inventory: total	Log mean	34.1	34.5	1 (0.9 to 1.1)*	0.74
Probable anxiety	No (%)	17 (20)	27 (26)	0.76 (0.44 to 1.3)†	0.31

No Obvious Long Term Effects on Psychological Functioning or Cognitive Ability at Age 30

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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

Blood pressure						
Systolic, mm Hg	119	221	118	234	1 (-2 to 3)	0.66
Diastolic, mm Hg	74	221	74	234	0 (-2 to 1)	0.87
Lipids (fasting sample)						
Total cholesterol, mmol/L	4.9	218	5.0	227	-0.1 (-0.3 to 0.1)	0.23
HDL cholesterol, mmol/L	1.4	218	1.4	227	0 (-0.1 to 0)	0.57
LDL cholesterol, mmol/L	3.0	218	3.1	227	-0.1 (-0.2 to 0.1)	0.28
Cholesterol ratio (total/HDL)	3.8	218	3.9	227	-0.1 (-0.2 to 0.2)	0.52
Geometric mean triglyceride, mmol/L	1.1	218	1.0	227	0.93 (0.73 to 1.17)†	0.63

No Obvious Adverse Effects on BP or Lipids at Age 30, But These Results Do Not Really Answer the Real Question.....

What Happens at Age 60?

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Maternal Fetal Medicine Units Network (MFMU)

ALPS

Antenatal Late Preterm: Randomized Placebo-Controlled Trial

Objective: To determine whether the administration of antenatal corticosteroids to patients between 34^o weeks to 36⁶ weeks gestation with an anticipated delivery in the late preterm period reduces the need for neonatal respiratory support

Project Status: Currently recruiting

Design Type: Double masked randomized clinical trial stratified by clinical center and gestational age (34/35 vs 36 weeks of gestation)

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MAIN ISSUE NOW: CORRECT USAGE

- How Come All Women Who Should Get Antenatal Steroid Therapy Do Not Receive It?
- What Can We Do to Address This?

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Approaching NIH Guideline Recommended Care for Maternal–Infant Health: Clinical Failures to Use Recommended Antenatal Corticosteroids

Elizabeth A. Howell · Joanne Stone ·

Lawrence C. Kleinman · Sarla Inamdar ·

Stephen Matseoane · Mark R. Chassin

Matern Child Health J (2010) 14:430–436

Table 2 Association of admission and delivery characteristics with failure to deliver recommended antenatal corticosteroids

Admission characteristics	Did not receive steroids n (%)	Received Steroids n (%)	P	Weekend admission		P
				Yes	No	
Patient sample	101 (19.6)	414 (80.4)		29 (26)	81 (74)	0.04
Gestational age			<.003*	Admitted with preterm labor		0.17
24–27 weeks	19 (14)	120 (86)		Yes	57 (22)	202 (78)
28–31 weeks	39 (18)	180 (82)		No	44 (17)	212 (83)
32–34 0/7 weeks	43 (27)	114 (73)		Admitted with PPROM		0.008
Cervical exam on admission (cm)			<.0001	Yes	11 (10)	94 (90)
Dilated 0–4 cm	38 (12)	279 (88)		No	90 (22)	320 (78)
Dilated 5–10 cm	27 (48)	29 (52)		Hospital of admission		0.0002
Missing data	36 (25)	106 (75)		Hospital #1	29 (37)	50 (63)
Night admission			0.74	Hospital #2	23 (18)	104 (82)
Yes	37 (19)	159 (81)		Hospital #3	49 (16)	260 (84)
No	64 (20)	255 (80)		Labor & delivery characteristics		
				Received tocolysis		<.0001
				Yes	28 (9)	293 (91)
				No	73 (38)	121 (62)

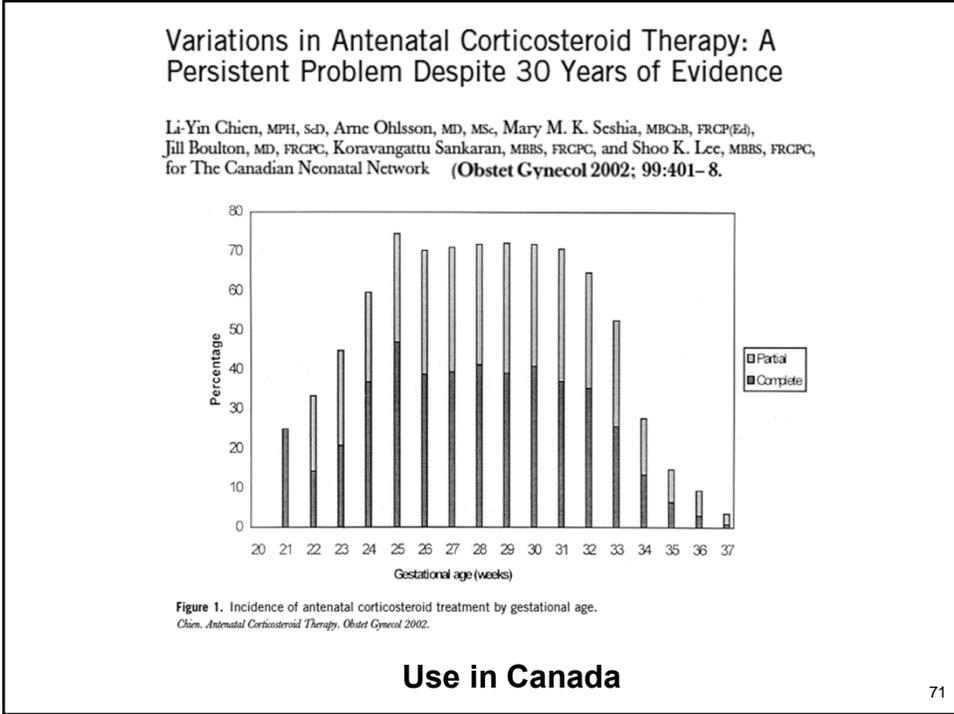
Several Hospitals in New York

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Approaching NIH Guideline Recommended Care for Maternal–Infant Health: Clinical Failures to Use Recommended Antenatal Corticosteroids

Characteristics	Failure to receive antenatal steroids		P
	Adjusted odds ratio	95% Confidence interval	
Black or Hispanic	0.63	(0.29–1.38)	NS
Race other	0.78	(0.30–2.06)	NS
Medicaid versus not	1.42	(0.75–2.69)	NS
Any prenatal care	0.29	(0.14–0.58)	.0005
Cervical exam 5–10 cm	8.22	(4.11–16.44)	<.0001
Cervical exam—missing	3.30	(1.83–5.97)	<.0001
Hospital #1	4.56	(2.18–9.54)	<.0001
Hospital #2	1.53	(0.73–3.19)	NS
Admitted with PPROM	0.42	(0.20–0.88)	0.02
Gestational age on delivery	1.14	(1.04–1.25)	0.004
Weekend admission	1.50	(0.85–2.66)	NS
Nighttime admission	1.01	(0.60–1.70)	NS

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Variations in Antenatal Corticosteroid Therapy: A Persistent Problem Despite 30 Years of Evidence

Li-Yin Chien, MPH, ScD, Arne Ohlsson, MD, MSc, Mary M. K. Seshia, MBChB, FRCP(Ed),
Jill Boulton, MD, FRCPC, Koravangattu Sankaran, MBBS, FRCPC, and Shoo K. Lee, MBBS, FRCPC,
for The Canadian Neonatal Network

Table 2. Factors Associated With Lack of Antenatal Corticosteroid Use Identified by Multivariable Logistic Regression Analysis for Infants 24–34 Weeks' Gestation and Infants 35–37 Weeks' Gestation

Variables	Infants 24–34 wk gestation (n = 7616)	Infants 35–37 wk gestation (n = 3702)
Gestational age category	24 wk: 1.58 (1.18, 2.11) 32 wk: 1.49 (1.28, 1.74) 33 wk: 2.57 (2.22, 2.96) 34 wk: 7.75 (6.74, 8.92)	36 wk: 1.65 (1.29, 2.11) 37 wk: 4.43 (3.09, 6.35)
Not small for gestational age	NS	2.12 (1.40, 3.22)
Vaginal delivery	NS	1.43 (1.14, 1.95)
Singleton pregnancy	1.35 (1.20, 1.52)	1.50 (1.14, 1.95)
No prenatal care	3.33 (2.32, 4.78)	NS
Outborn status	3.64 (3.18, 4.17)	1.90 (1.38, 2.63)

Still Seems to Be Confusion on When to Give Steroids

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Antenatal Steroid Administration for Premature Neonates in California

Henry C. Lee, MD, MS, Audrey Lyndon, RN, PhD, Yair J. Blumenfeld, MD, R. Adams Dudley, MD, MBA, and Jeffrey B. Gould, MD, MPH

Obstet Gynecol. 2011 March ; 117(3): 603–609.

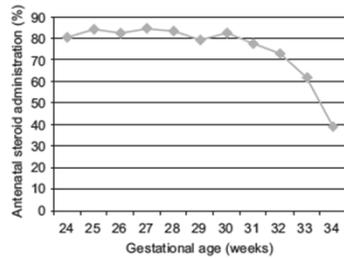


Fig. 1. Antenatal steroid administration by gestational age. Lee. *Antenatal Steroids for Premature Neonates. Obstet Gynecol* 2011.

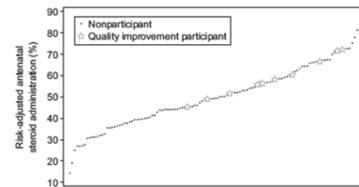


Fig. 2. Adjusted rates of antenatal steroid administration by hospital. Rates were risk-adjusted using a random-effects logistic regression model. Adjusted rates for the majority of hospitals were lower than actual crude rates. Lee. *Antenatal Steroids for Premature Neonates. Obstet Gynecol* 2011.

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Neonatal Survival 2

Evidence-based, cost-effective interventions: how many newborn babies can we save?

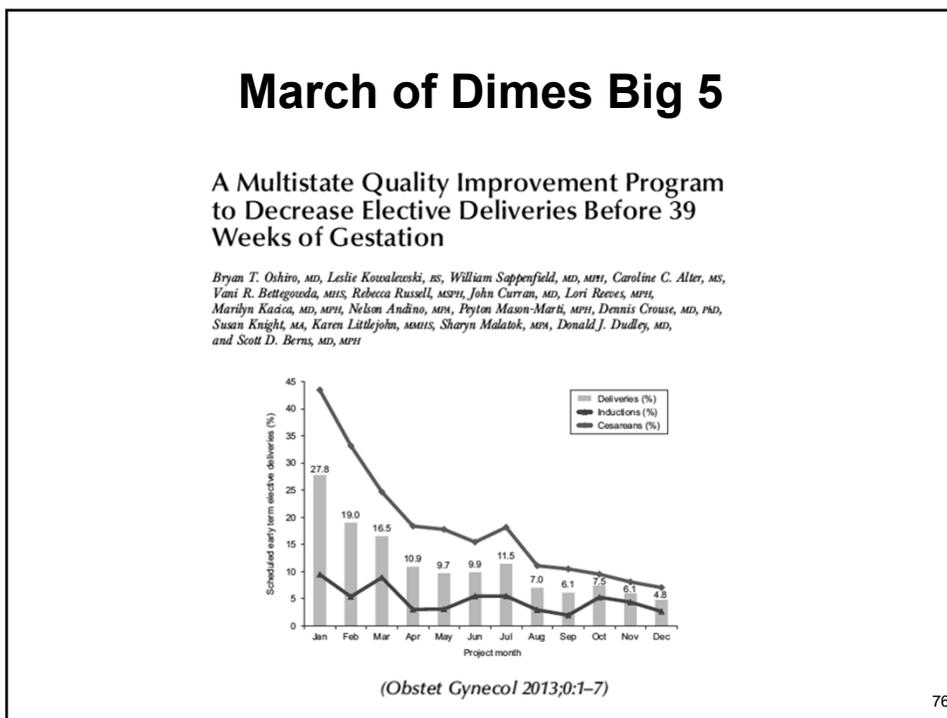
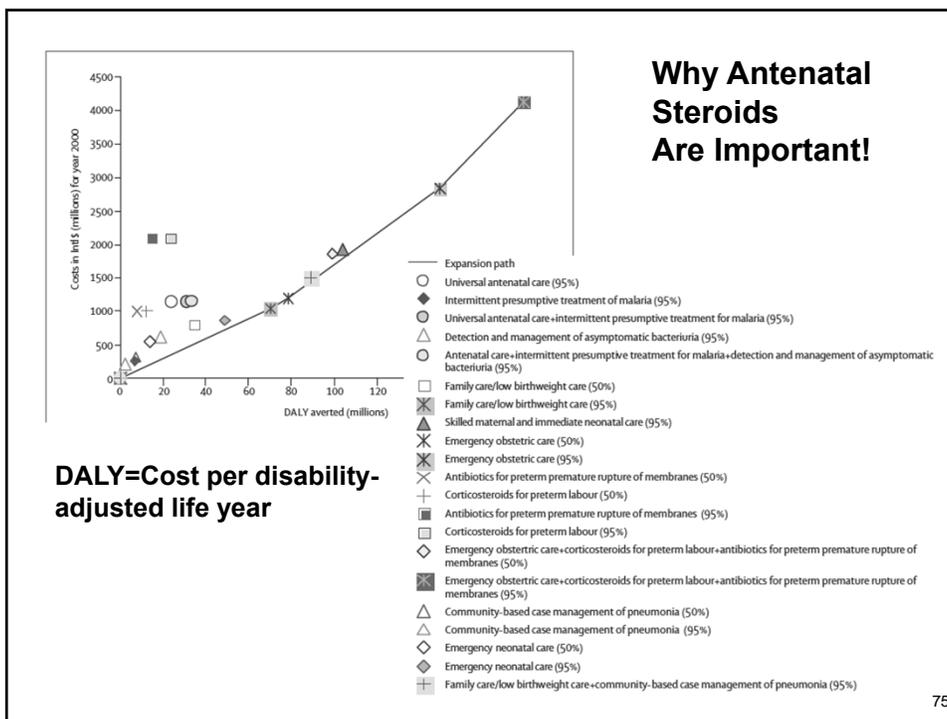
Lancet 2005; 365: 977–88

Gary I. Darmstadt, Zulfiqar A Bhutta, Simon Cousens, Taghreed Adam, Neff Walker, Luc de Bemis, for the *Lancet* Neonatal Survival Steering Team*

Intrapartum		
Antibiotics for preterm premature rupture of membranes	IV	Incidence of infections: 32% (13–47%)
Corticosteroids for preterm labour	IV	40% (25–52%)
Detection and management of breech (caesarian section)	IV	Perinatal/neonatal death: 71% (14–90%)
Labour surveillance (including partograph) for early diagnosis of complications	IV	Early neonatal deaths: 40%
Clean delivery practices	IV	58–78% Incidence of neonatal tetanus: 55–99%

Appropriate Use of Antenatal Steroids Can Decrease Neonatal Mortality in Low Resource Countries

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Summary

- One Course of Antenatal Steroids is Standard of Care for Women with Threatened Preterm Birth Whatever the Reason
- If You Don't Give Steroids in a Preterm Situation, You Need a Good Reason Why Not
 - Maternal Infection?
 - Imminent Delivery?
- If You Give More than One Course, You Need a Good Reason to Do So
 - Rescue Course is Probably OK in Specific Circumstances
- So the Next Question is....

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Questions and Answers



Evelyn Delgado, Assistant Commissioner
Division for Family and Community Health Services
Texas Department of State Health Services

Remote sites can send in questions by typing in the *GoToWebinar* chat box or email GrandRounds@dshs.state.tx.us.

For those in the auditorium, please come to the microphone to ask your question.

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Our Next Grand Rounds Presentation



Presenters:

Frank Patterson, Emergency Management Coordinator for City of Waco/McLennan County; Kelly Craine, Public Information Officer, Waco-McLennan County Public Health District; Dana Lafayette, LPC, LP-S, LCDC, Heart of Texas MHMR