The Late Preterm Birth Infant

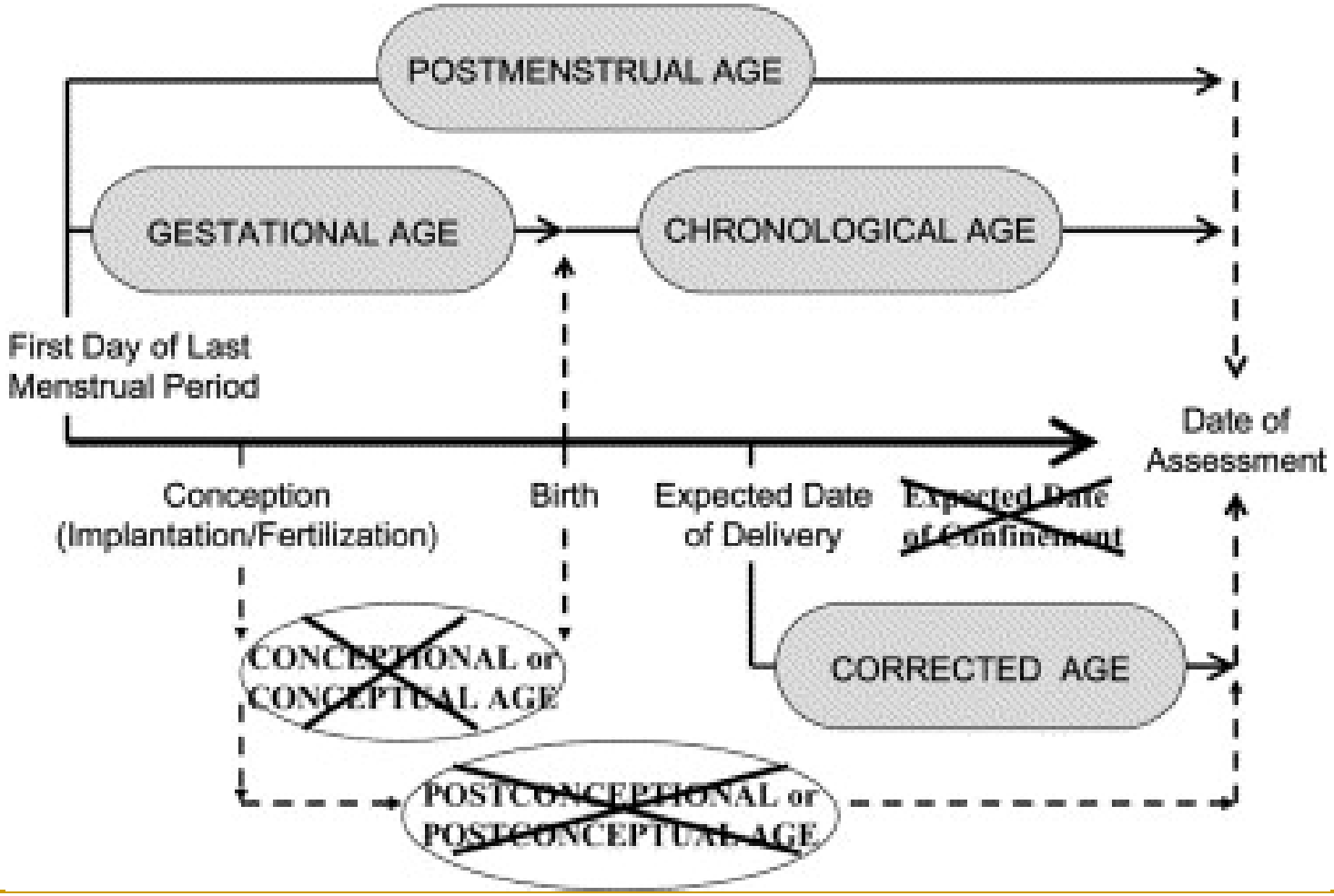
Thomas Hegyi, M.D.
Program Director, Division of Neonatology
Professor and Vice-Chairman, Department of Pediatrics
UMDNJ-Robert Wood Johnson Medical School
New Brunswick, NJ

Moderately Preterm Infants: "Underprivileged Newborns"

[32-36 weeks]

Amiel-Tison et al, 2002

Age Terminology During the Perinatal Period



Antepartum Gestational Age Assessment

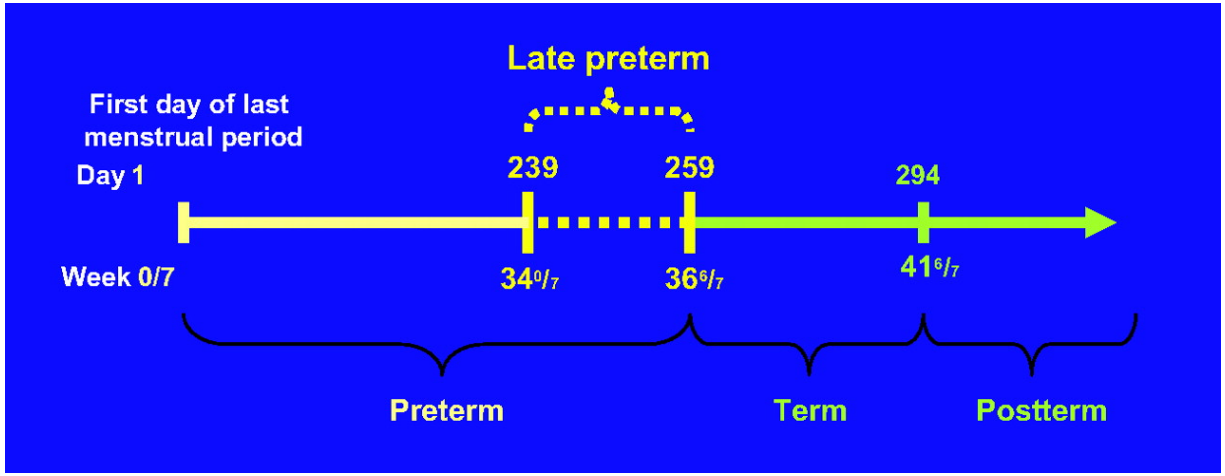
	Accuracy	Comment
Clinical		
Last menstrual period	± 2 wks	Depends on cycle length and recall
Uterine size-1st trimester	± 2 wks	Depends on operator skill
Fetal heart tones-auscultation	± 2 wks	~ 20 wks (fetoscopy) 12 wks (doppler scope)
Fundal height measurement	± 3 wks	Varies with maternal body habitus
Sonography		
Gestational sac diameter	± 5 days	Variable shape affects measurement Performed 4.5–5.5 wks
Embryonic crown–rump length	± 3 days	Performed 5–12 wks
Biparietal diameter	± 10 days	Performed 15–22 wks
Femur length, cerebellar transverse diameter	± 14 days	Performed > 22 wks

Postnatal Gestational Age Determination

Variability: ± 2 weeks if ≥ 28 weeks' gestation
± 3 weeks if < 28 weeks' gestation

Definition of Late Preterm Infant

- Defined as preterm birth between the end of the last day of the 34th week of gestation (34 0/7 or beginning of the 239th day since the first day of the mother's last normal menstrual period) through and including the 36 6/7th completed week of gestation (end of the 259th day since the first day of the mother's last normal menstrual period).

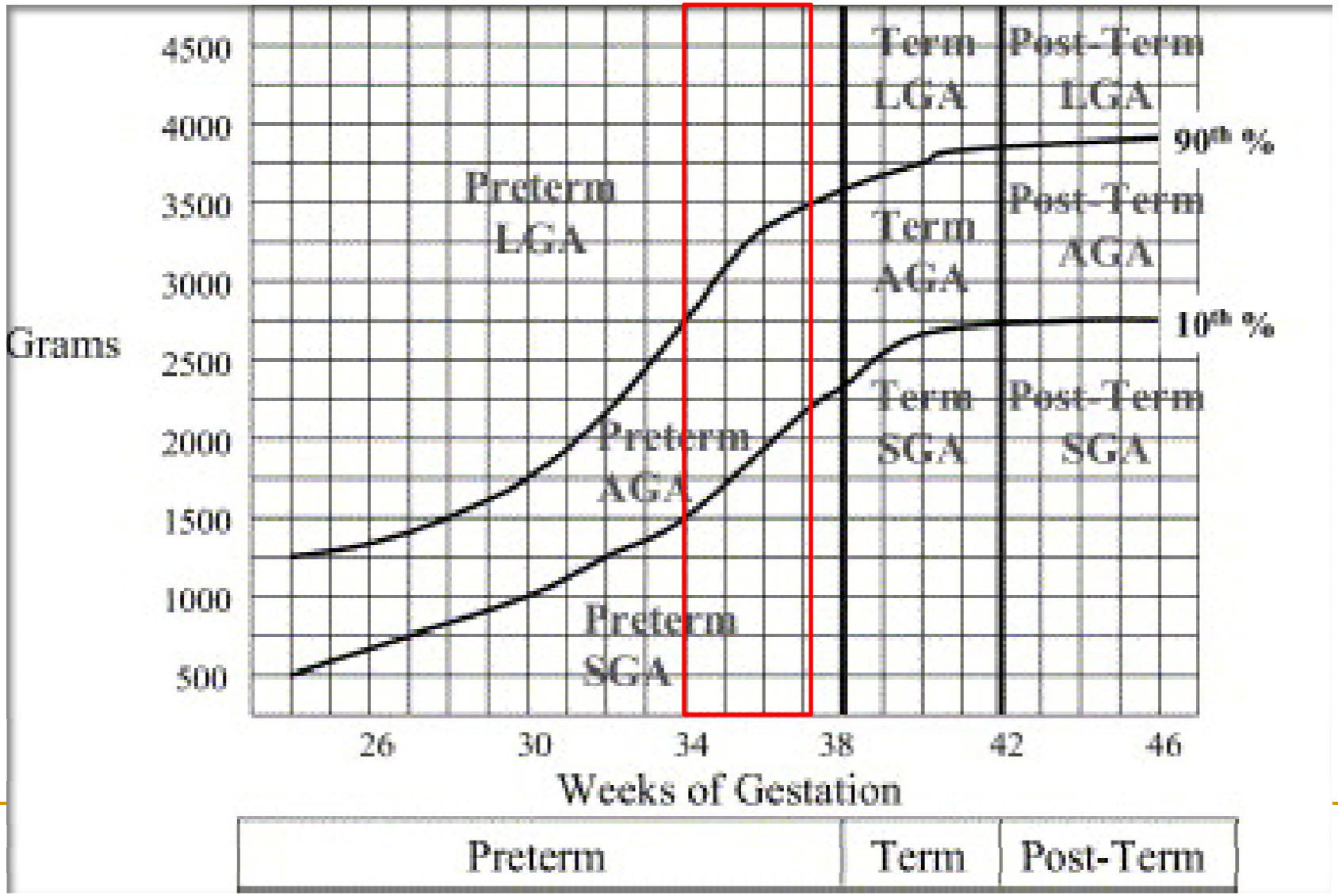


Engle, W. A. et al. Pediatrics 2007;120:1390-1401

Impact to Infant Health from Rising Late Preterm Birth

- Higher Neonatal and Infant mortality:
  - U.S. neonatal deaths/1000 live births (2002)
    - 34-36 weeks = 4.1
    - 37-41 weeks =0.9
  - U.S. infant deaths/1000 live births (2002)
    - 34-36 weeks = 7.7
    - 37-41 weeks = 2.5

University of Colorado Classification of Newborns by Birth Weight and Gestational Age



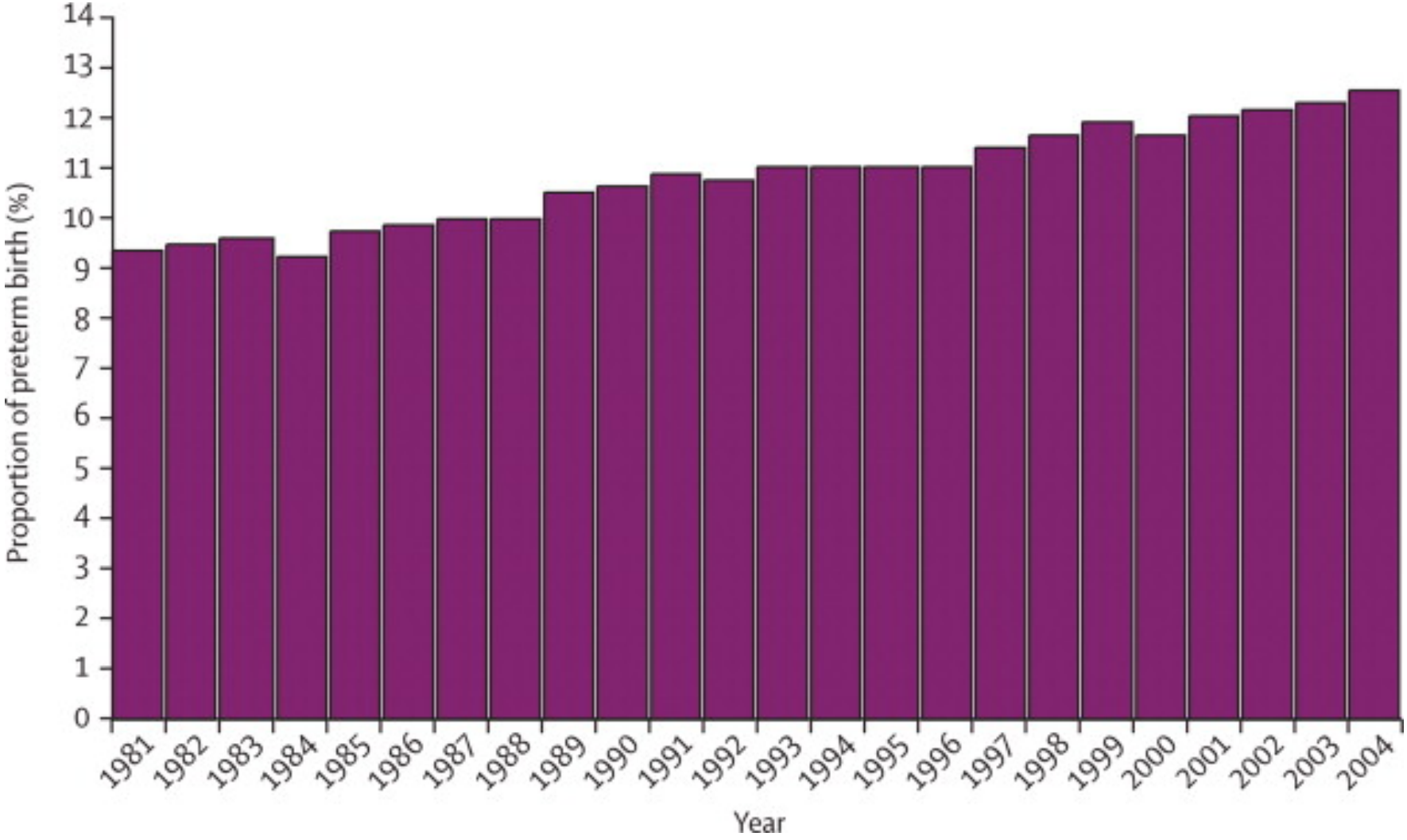
Background

- U.S. PTB has increased more than 30%
  - ~3/4 of all singleton preterm infants (34-36 weeks)
  - 7.5% of all U.S. births (2003)

- Factors associated with PTB increasing
  - Multiples
  - C-sections
  - Inductions

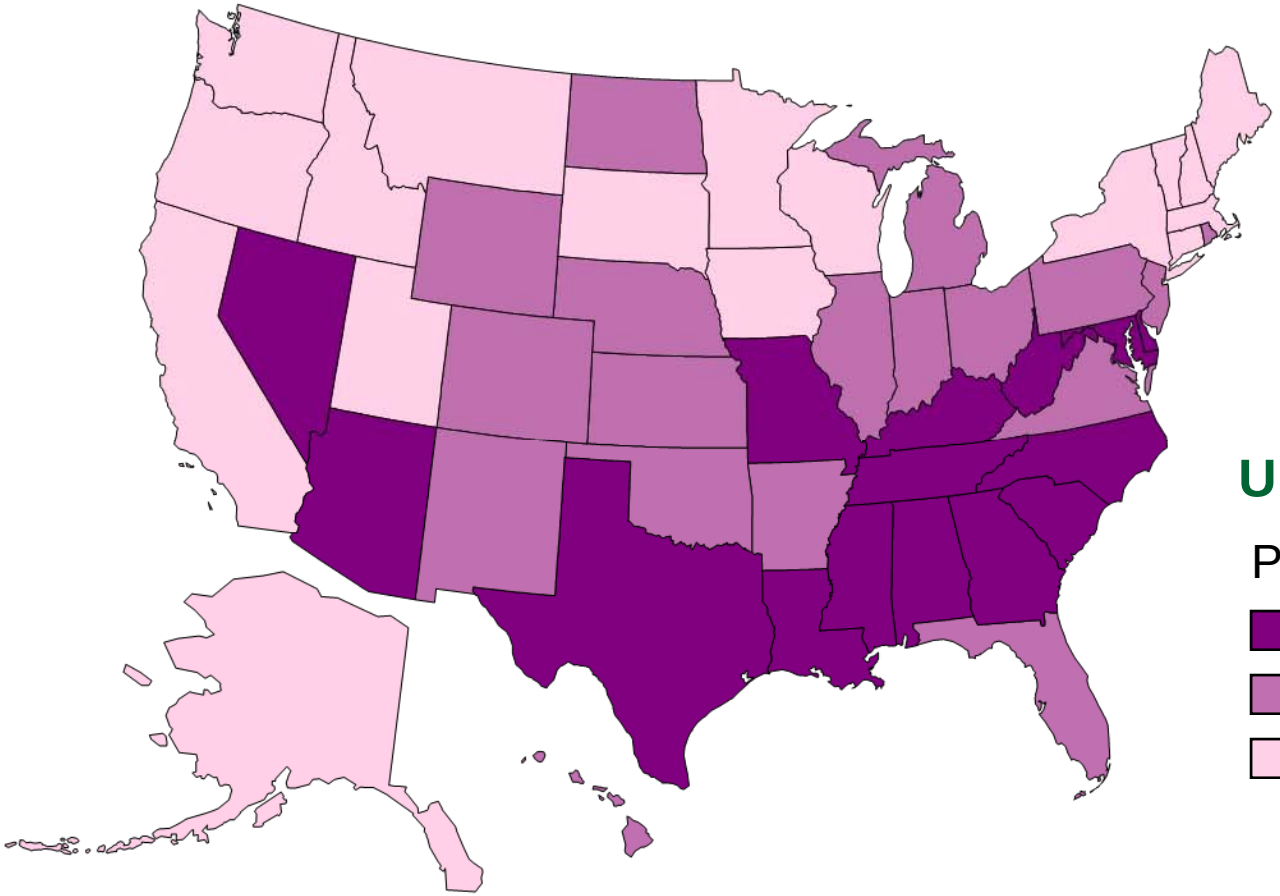
- Recent studies: 34-36 weeks increased risk for certain morbidities
  - Often go to the "normal nursery"

Percentage of all births classified as preterm in the USA, 1981–2004



Preterm Birth Rates by State

United States, 2003



U.S. Total = 12.3%

Percent of Live Births

- Over 13.0 (16)
- 11.6 to 13.0 (18)
- Under 11.6 (17)

Note: Value in ( ) = number of states (includes District of Columbia). Value ranges are based on equal counts.

Source: National Center for Health Statistics, 2003 final natality data. Prepared by March of Dimes Perinatal Data Center, 2005.

Economic Consequences of Preterm Birth

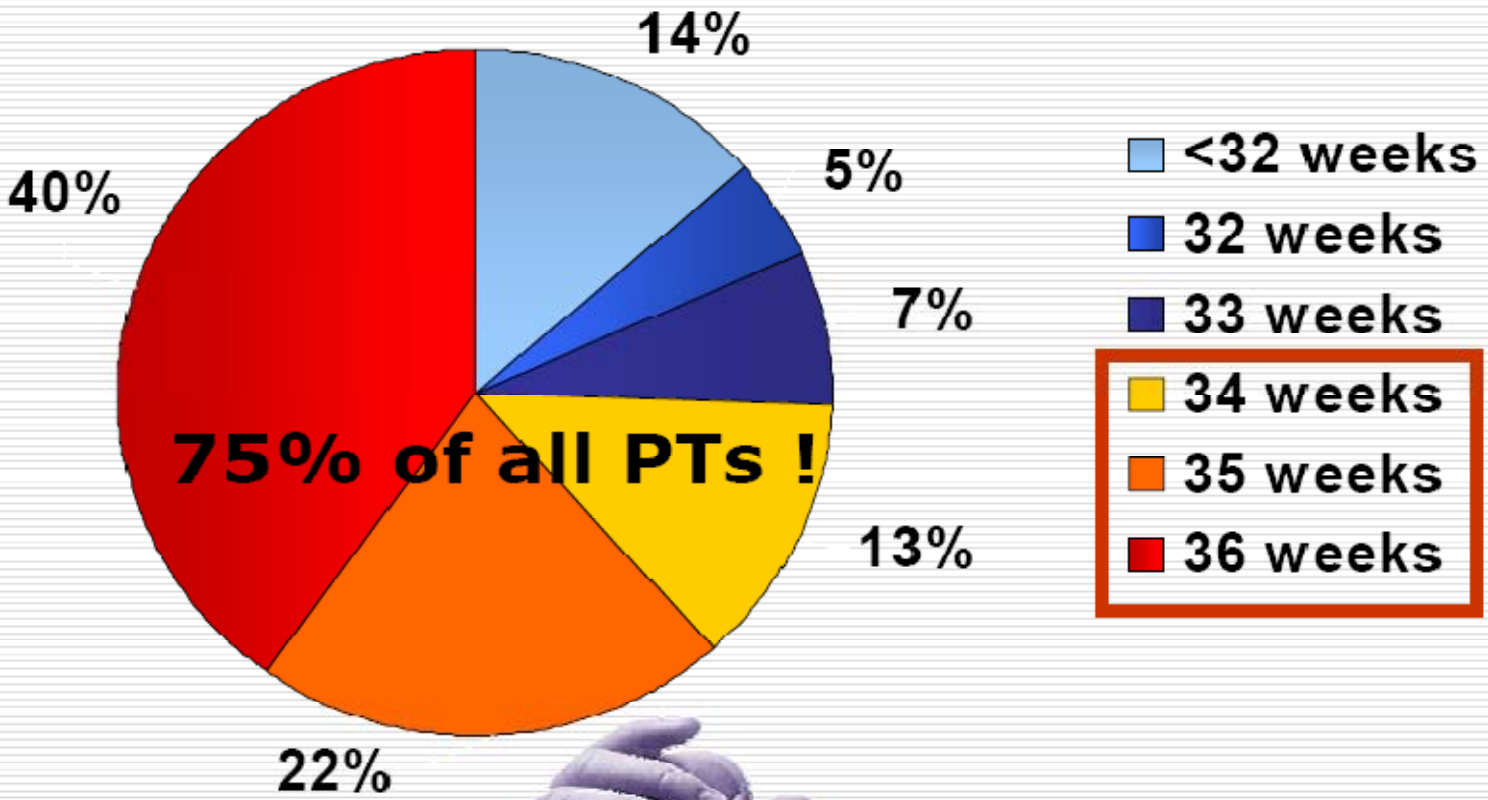
- **Hospital charges for premature infants[1] totaled $18.1 billion in 2003.**
- **Premature infants accounted for half of the hospital charges for all infants ($36.7 billion).**
- **The average charge for the most severe stays[2] was $77,000 compared to $1,700 for an uncomplicated newborn stay.**

[1]Includes any diagnosis of prematurity/low birthweight
[2]Defined as having a principal diagnosis of prematurity
Source: Agency for Healthcare Research and Quality, 2003 Nationwide Inpatient Sample.
Prepared by March of Dimes Perinatal Data Center, 2006.

Epidemiology of Preterm Birth

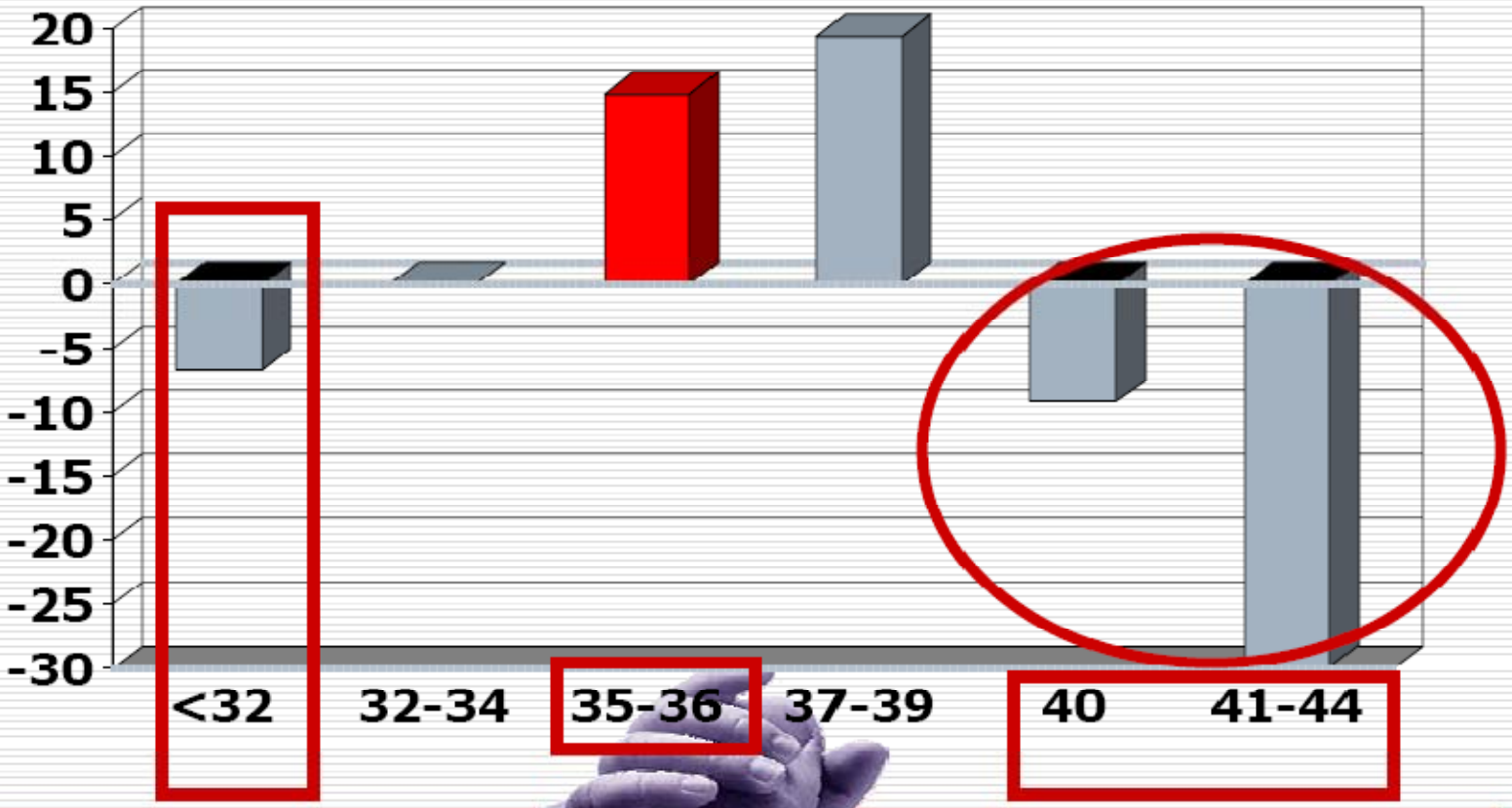
- Obstetric precursors leading to preterm birth
  - Delivery for maternal or fetal indications
    - Labor is either induced or the infant is delivered by prelabor caesarean section
  - Spontaneous preterm labor with intact membranes
  - Preterm premature rupture of the membranes irrespective of whether delivery is vaginal or by caesarean section
- Racial/ethnic differences
  - Spontaneous preterm birth is most commonly caused by preterm labor in white women, but by PPROM in black women.
- Gestational age
  - 5% of preterm births occur at less than 28 weeks' (extreme prematurity)
  - 15% at 28–31 weeks' (severe prematurity)
  - 20% at 32–33 weeks' (moderate prematurity),

US Near Term Singleton Births



Source: NCHS, final natality data
Prepared by March of Dimes Perinatal Data Center, April 2006.

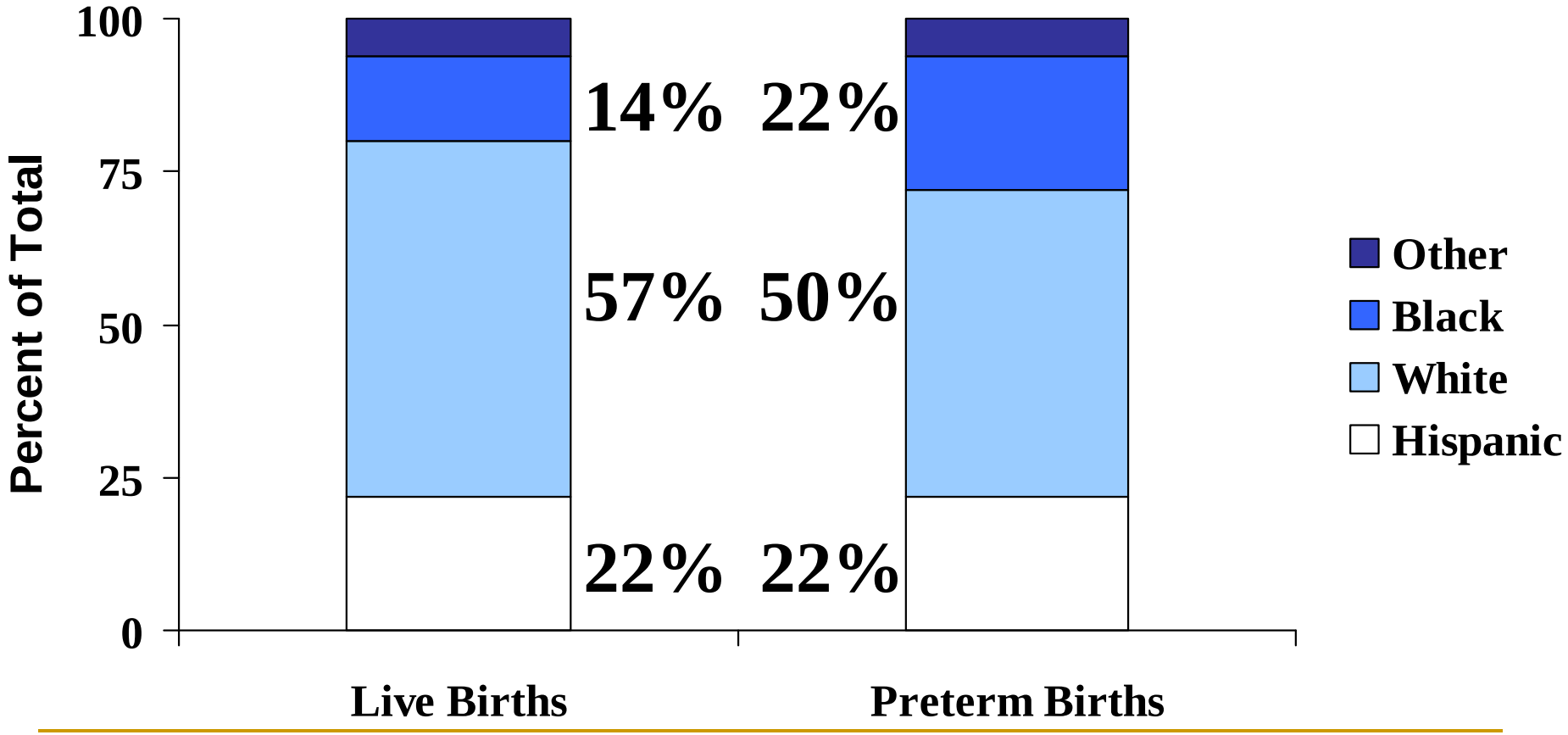
US Near Term live births are on the rise: % Change 1992-2002



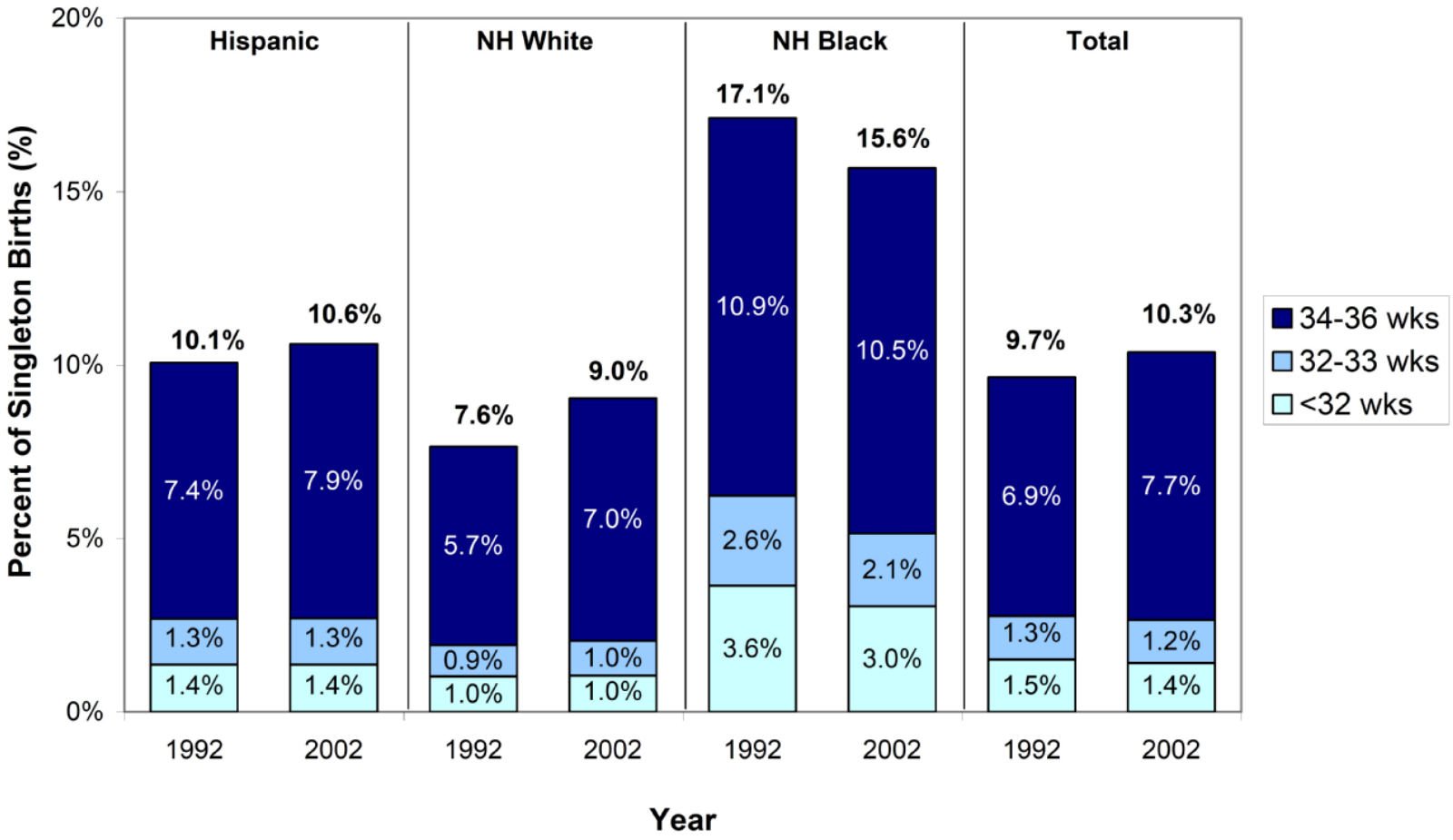
United States Live Births

MOD: Davidoff 2005

Race/ Ethnicity Comparison:
Singleton Live Births and Preterm Births, U.S., 2002

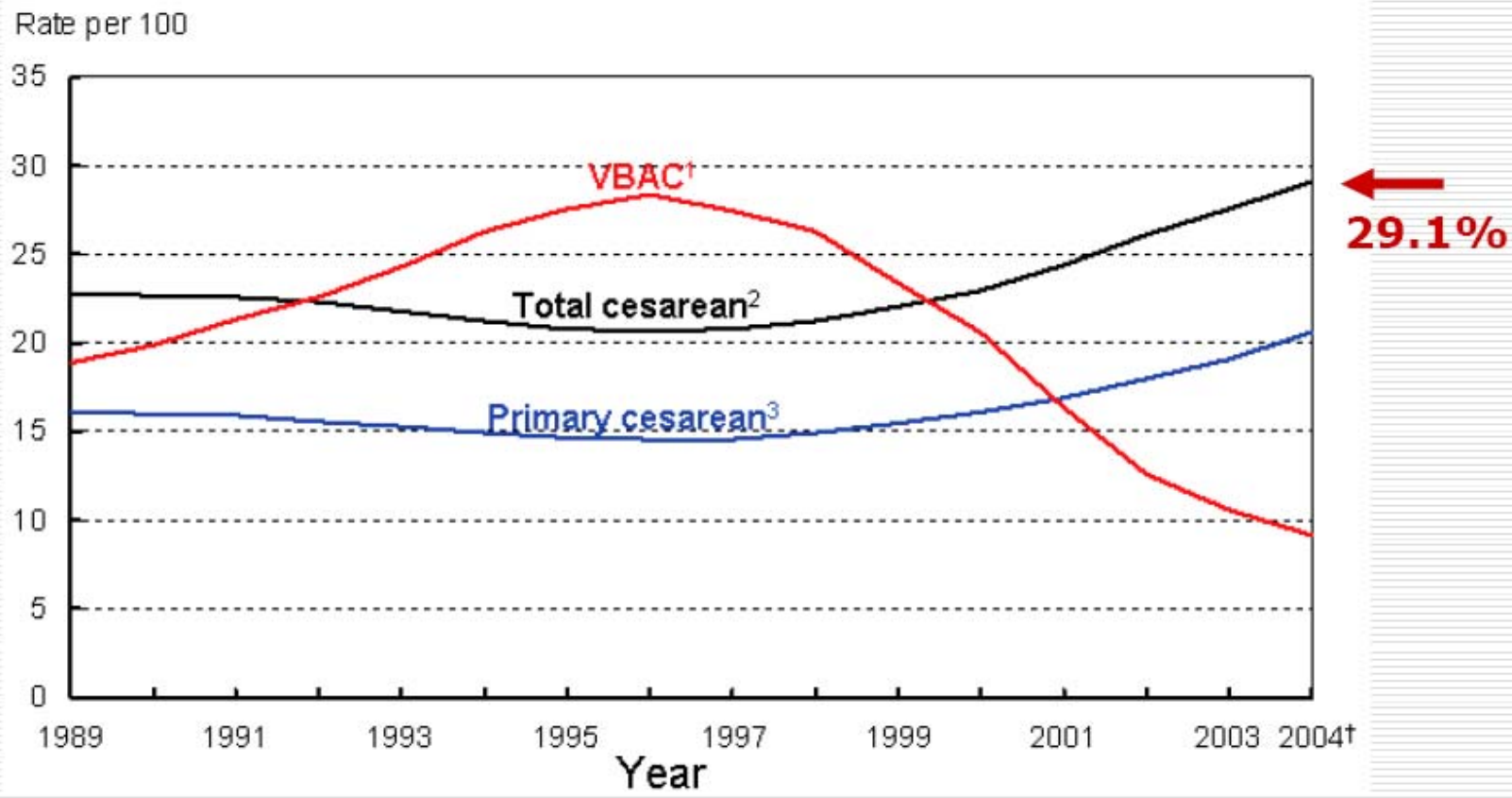


Singleton Preterm Birth Rates by Race/Ethnicity, 1992 and 2002

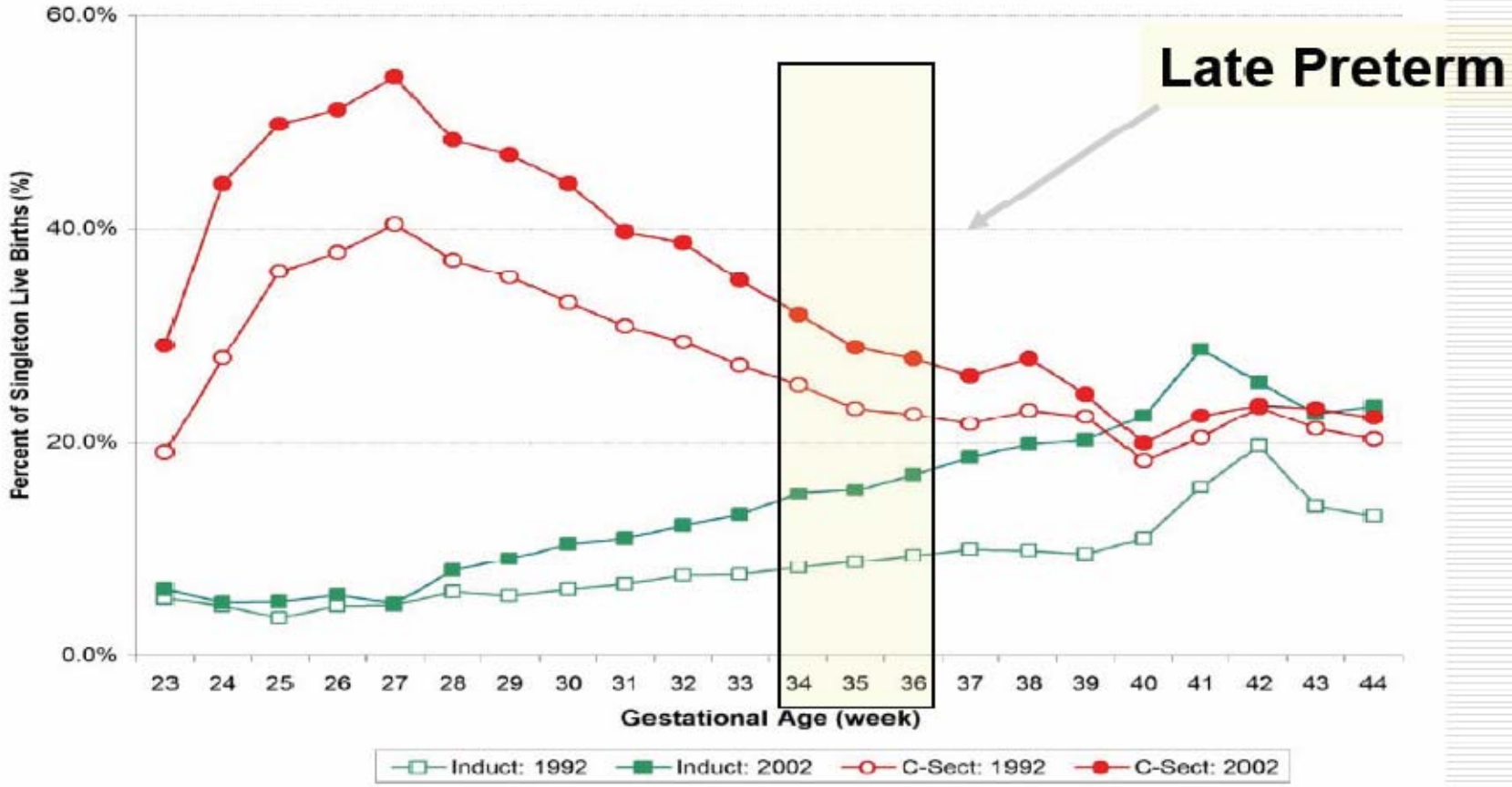


Source: National Center for Health Statistics
Prepared by the March of Dimes Perinatal Data Center, November 2005.

Cesarean deliveries are on the rise in the US & elsewhere!

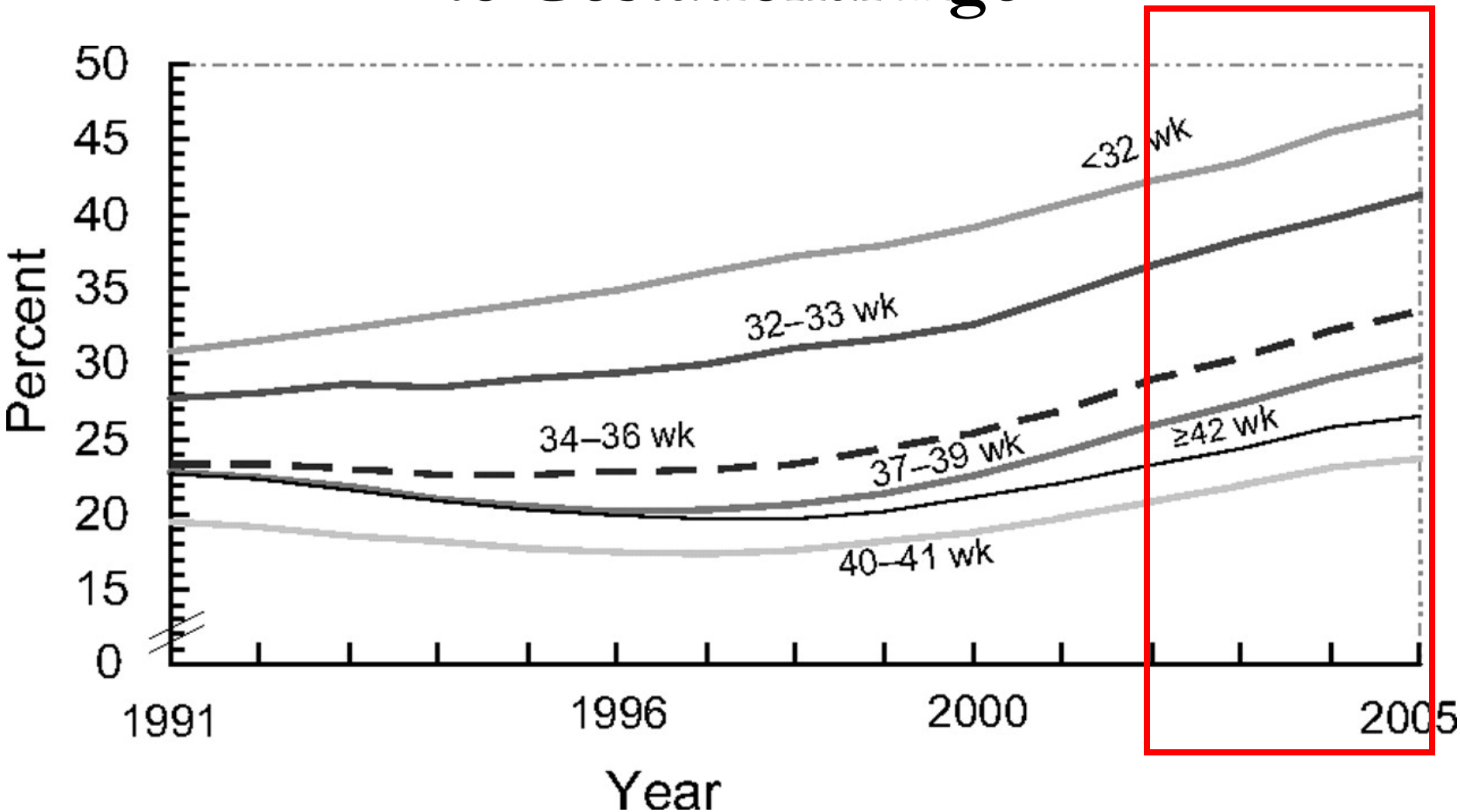


CS and Labor Induction Rates United States, 1992 and 2002



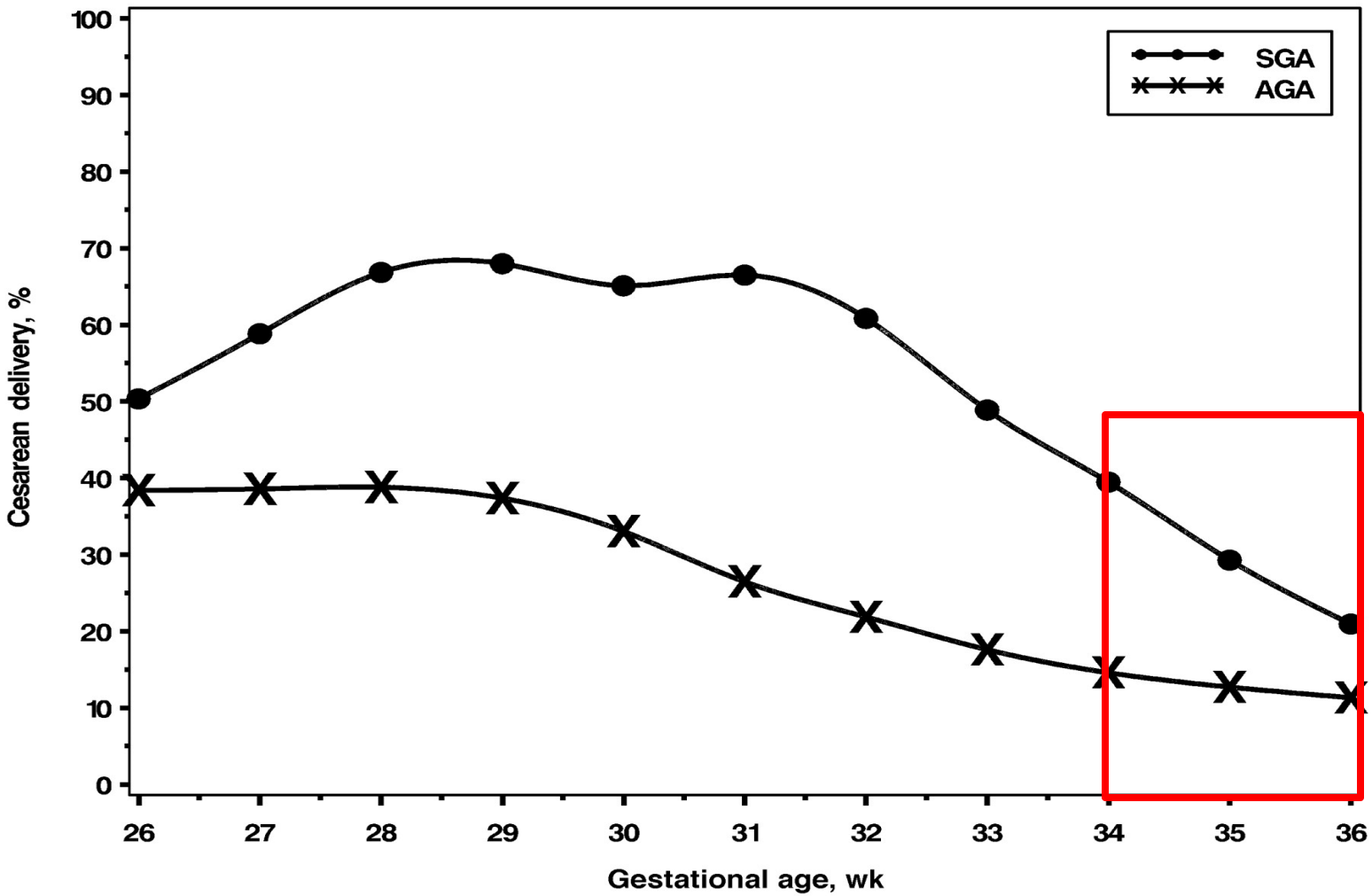
Source: NCHS, final natality data
Prepared by March of Dimes Perinatal Data Center, April 2006.

Caesarean-delivery Rates According to Gestational Age



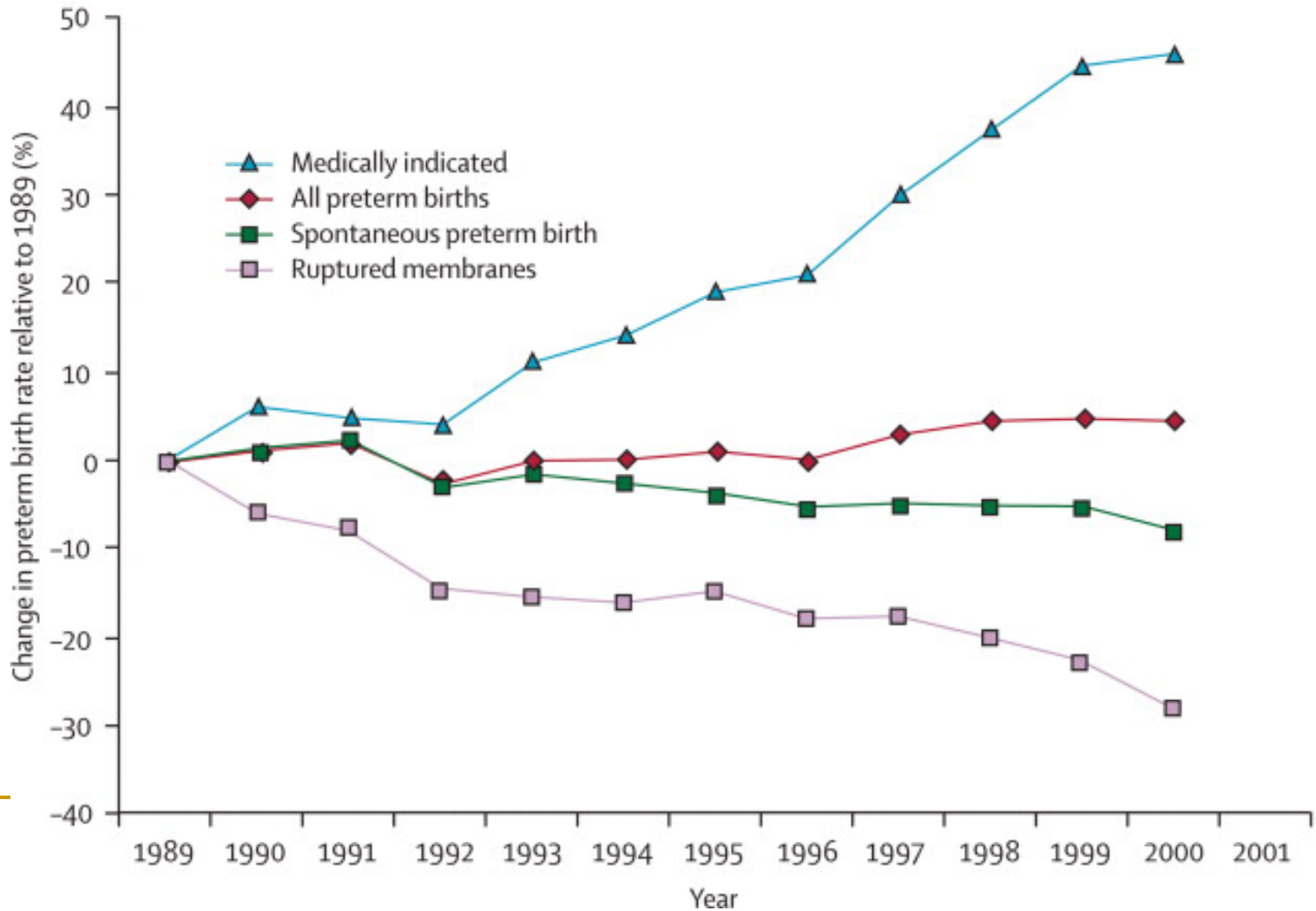
Martin, J. A. et al. Pediatrics 2008;121:788-801

Caesarean Section for Preterm Neonates According to Weight Percentile Group

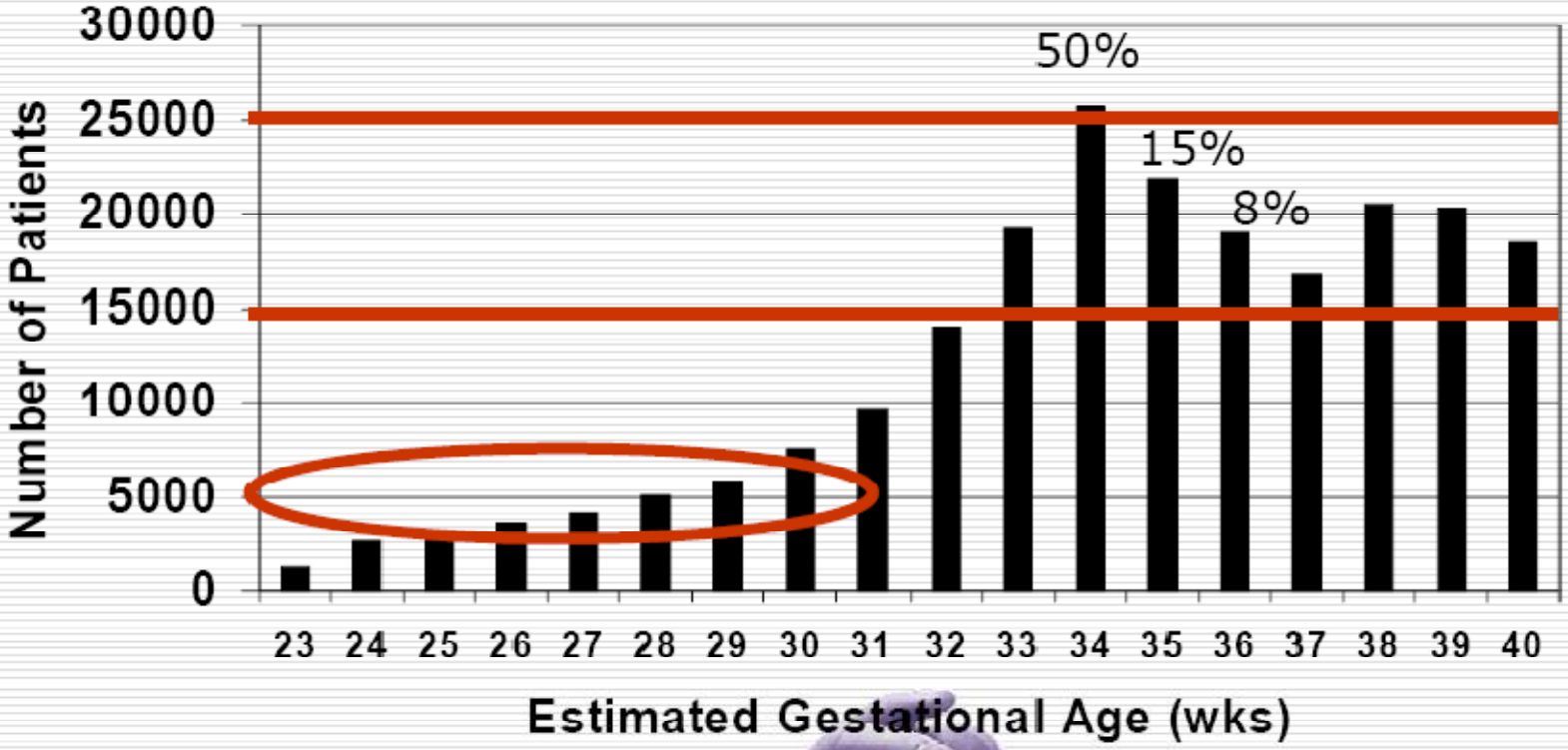


Lee, H. C. et al. Pediatrics 2006;118:e1836-e1844

Change in rates relative to 1989 of Singleton Preterm Births



NICU Admissions Among Term & Near Term Infants



Clark R et.al 2005

Morbidities of the Near-term Infant

At one tertiary medical center -

34 week babies represented:

- 1.6% of deliveries
- 7% of NICU admissions
- 19% of NICU bed-days

Gladstone, *Am J Perinatol* 2004

Morbidities Associated with Late Preterm Birth

- Increased immediate problems:
  - Respiratory distress
  - Jaundice
  - Feeding difficulties
  - Hypoglycemia
  - Temperature instability
  - Sepsis
- Increased NICU use (and re-admissions)
- Increased cost
- Long term outcome - *??* - NO DATA!

Morbidities in Late Preterm Infants According to Gestational Age

Gestational age (weeks)	34 - 34.6 (A) n=123	35 - 35.6 (B) n=122	36 - 36.6 (C) n=221	p
Respiratory distress	32 (26%)	20 (16.4%)	11 (5%)	0.04*
Hyperbilirubinemia	83 (67.5%)	57 (46.7%)	64 (29%)	<0.001*
Feeding difficulties	55 (44.7%)	19 (15.6%)	10 (4.5%)	<0.001*
Hypoglycemia	25 (20.3%)	14 (11.5%)	29 (13.1%)	<0.05
Average hospital stay (in hours)	262	147	98	A v/s B*, A v/s C*

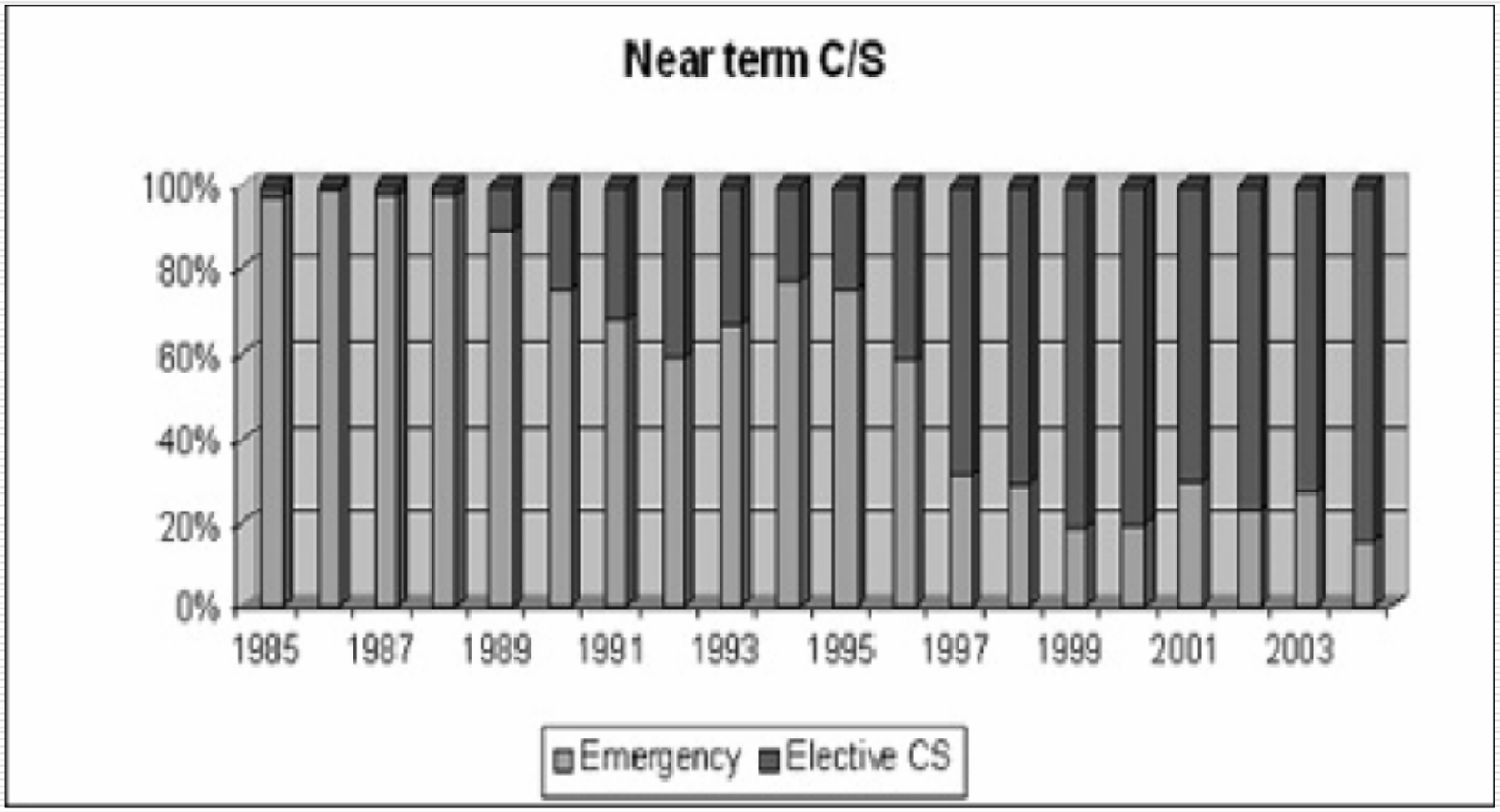
* Statistically significant

Jain, PAS 2008

Respiratory Issues

- TTN – lack of clearance of fetal lung fluid
  - Absence of labor, absence of catecholamine surge associated with labor.
- RDS – surfactant deficiency
  - Mature surfactant system but delayed release from lamellar bodies
- Persistent pulmonary hypertension
- Pneumonia
- Many respiratory diseases in the late-preterm infant are poorly defined

Do ECS deliveries contribute to HRF in Near-Term Births?



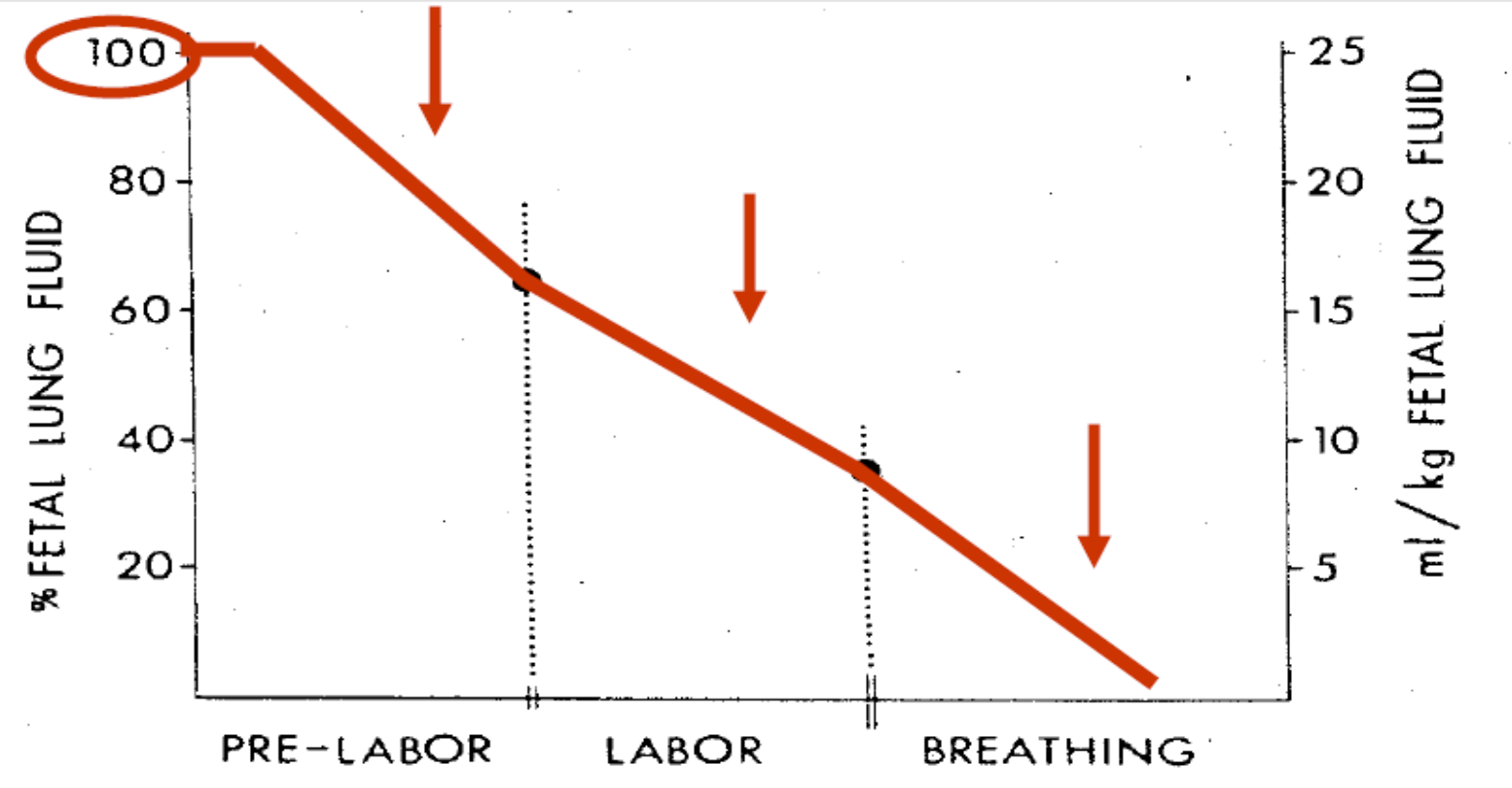
Neonatal Morbidity in ECS

- Nearly 50% of all near term infants are delivered by CS
- Up to 30% infants develop respiratory distress
- Problems with FLF clearance
- Higher rates in fetuses never exposed to labor

Neonatal Transition in the Near Term Infant

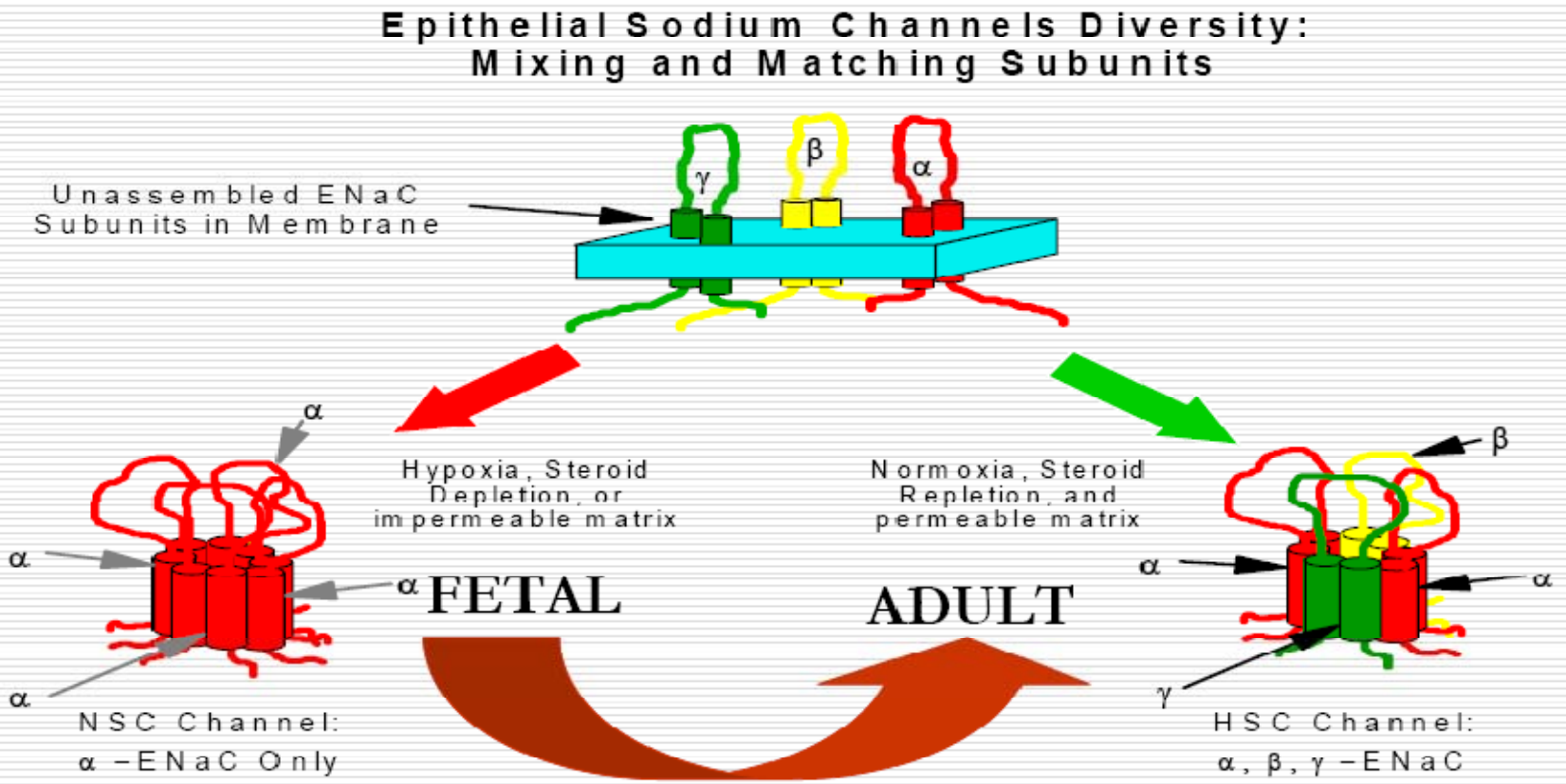
- Ability to clear FLF peaks at term gestation
- Surfactant maturity is not an all or none phenomenon
- Changes in pulmonary vasculature
- Developmentally regulated proteins (ENaC)

Fetal Lung Fluid Dynamics



Bland RD, 79.

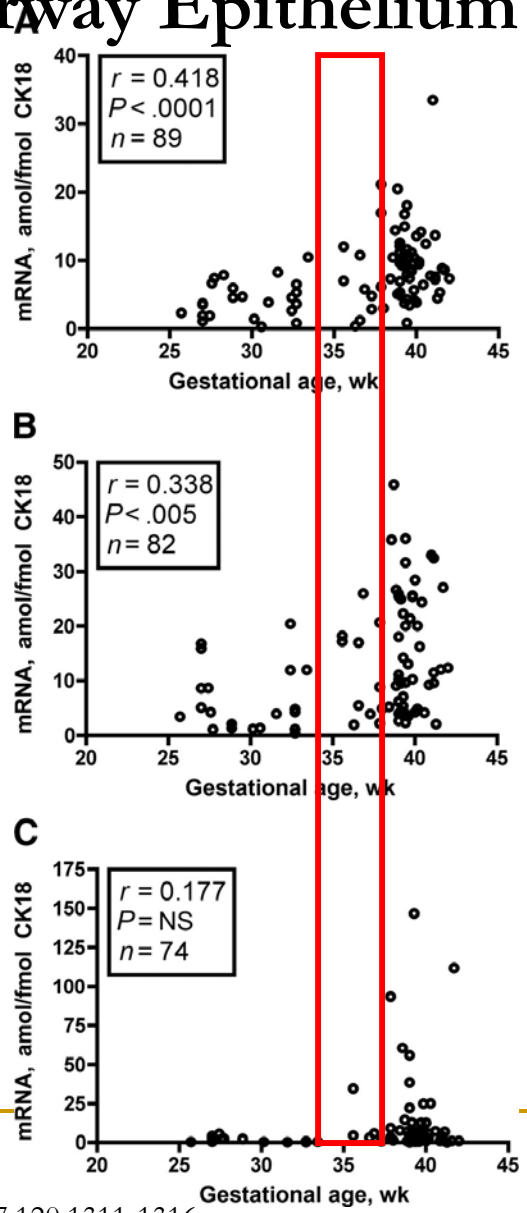
Fetal Lung Fluid Clearance



Term Gestation & Labor

Jain et al. 06

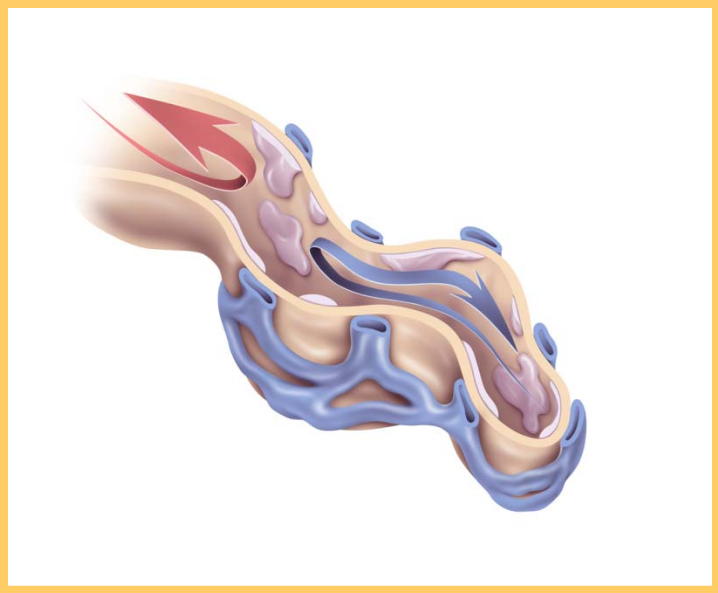
ENaC Subunit Expression and GA in Airway Epithelium 1 to 5 hours After Birth

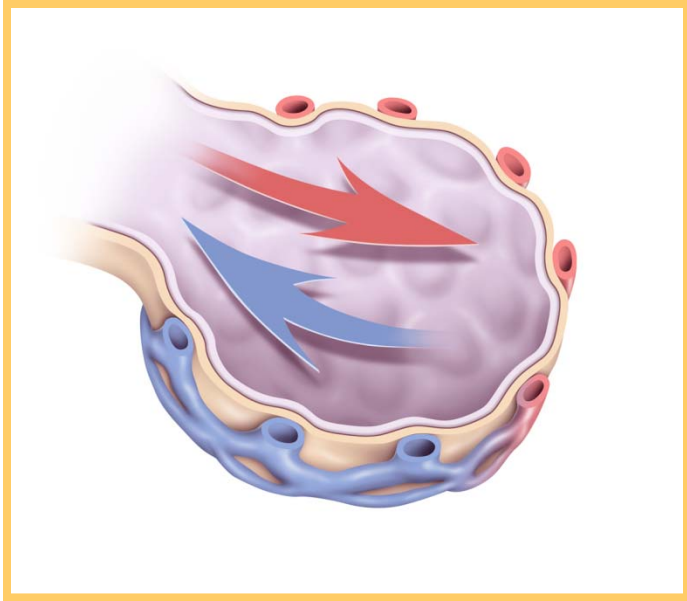


Correlation between ENaC subunit expression and gestational age in airway epithelium in newborn infants 1 to 5 hours after birth. A, α-ENaC; B, β-ENaC; C, γENaC. CK18 indicates cytokeratin 18;

Helve, O. et al. Pediatrics 2007;120:1311-1316

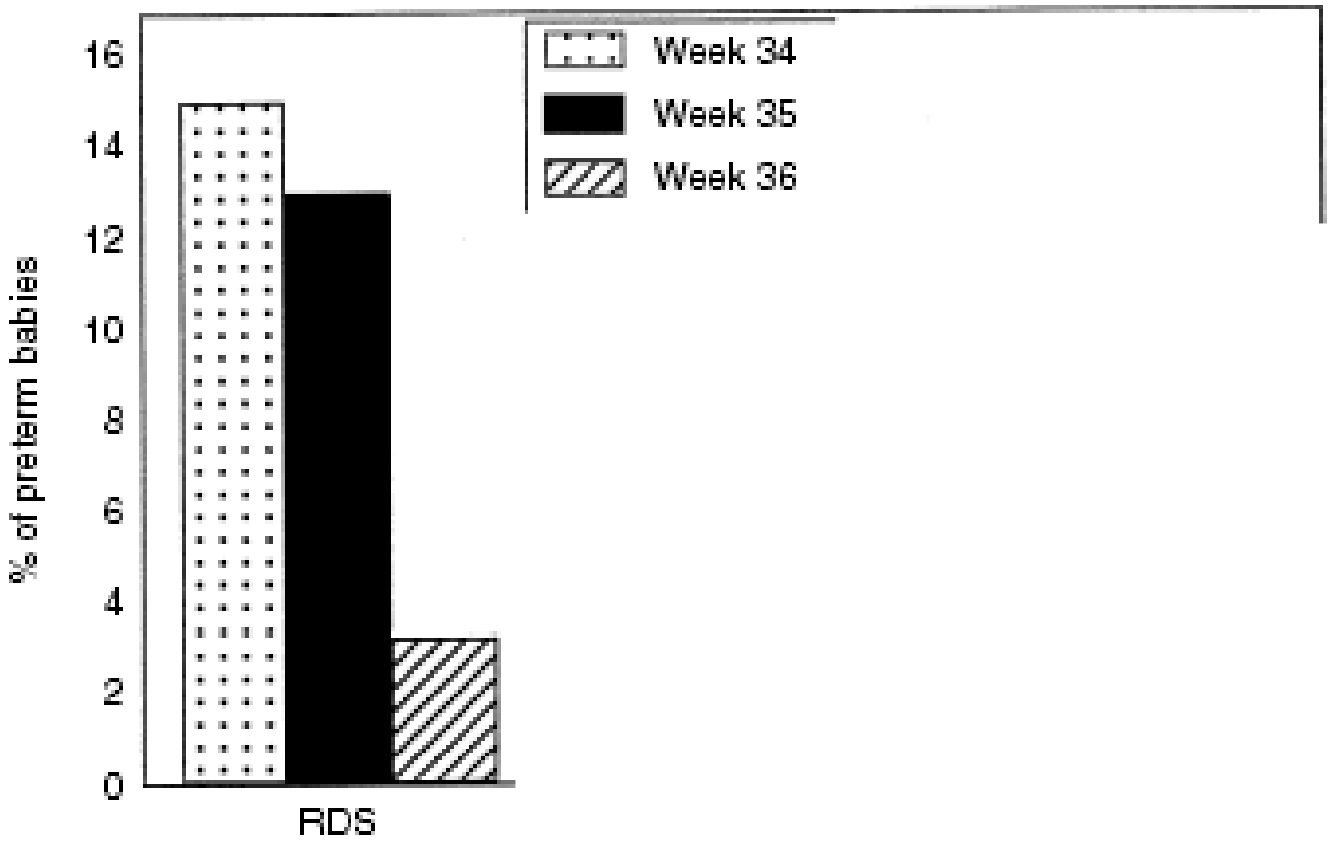
Respiratory Distress Syndrome





- **Insufficient surfactant**
  - Collapsed alveoli
  - Inadequate oxygen exchange
- **Sufficient surfactant**
  - Expanded alveoli
  - Adequate oxygen exchange

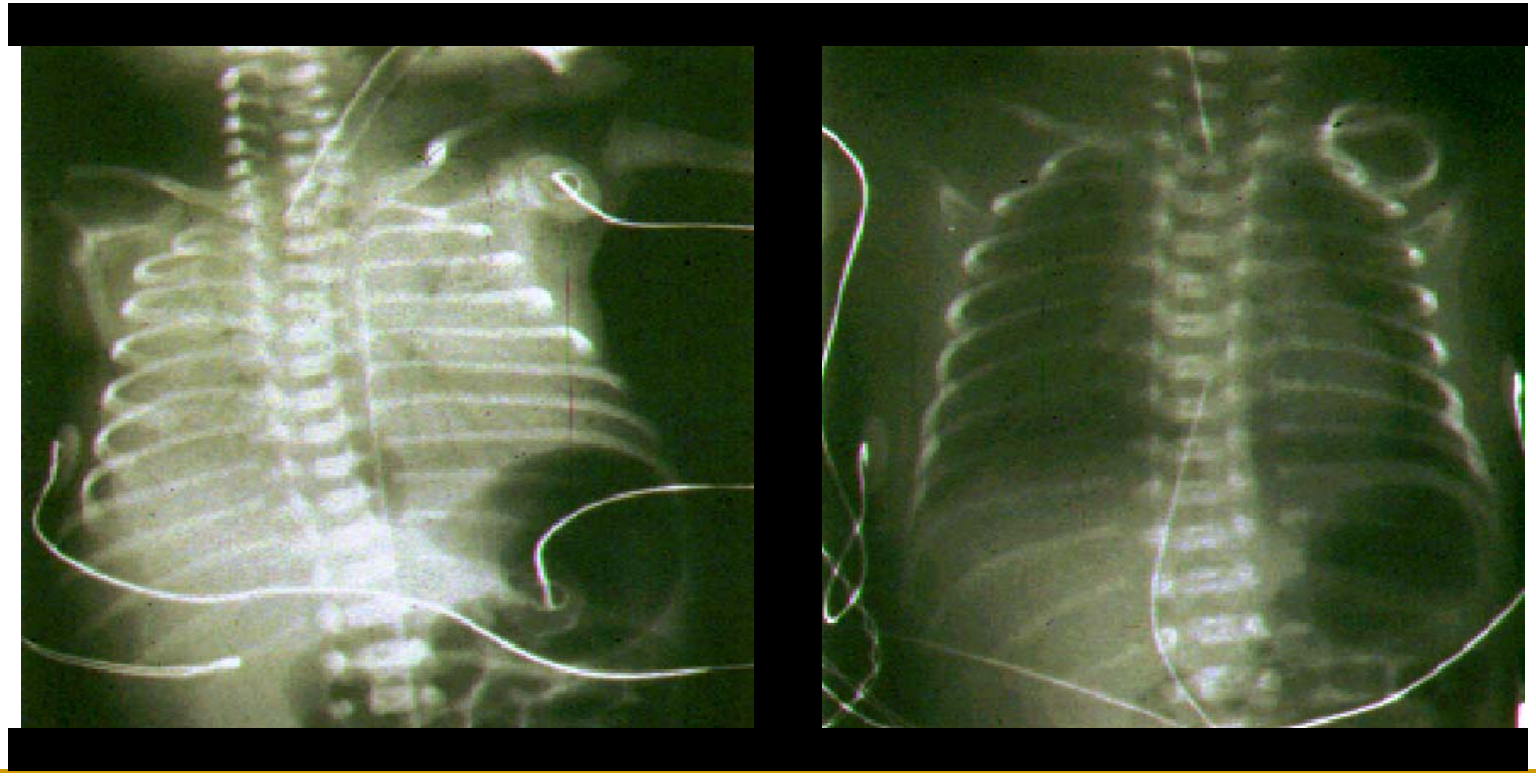
Frequency of RDS, Sepsis and Apnea in Late Preterm Infants



Arnon, et al. *Paediatr Perinat Epidemiol*, 2001

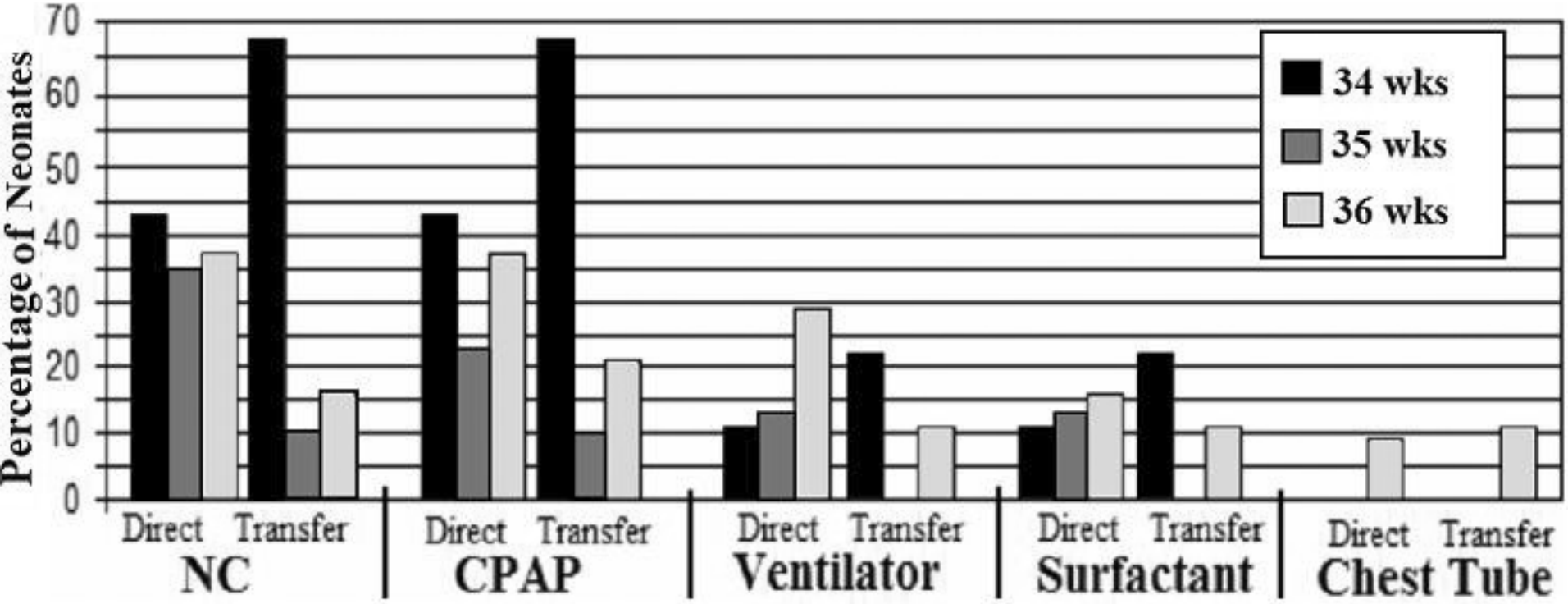
Surfactant Therapy for RDS

- Markedly reduced the mortality rate of premature infants
- Standard care for management of premature infants



Presurfactant Postsurfactant

Respiratory Interventions by Gestational Age/Location Prior to NICU



Bailey, PAS 2008

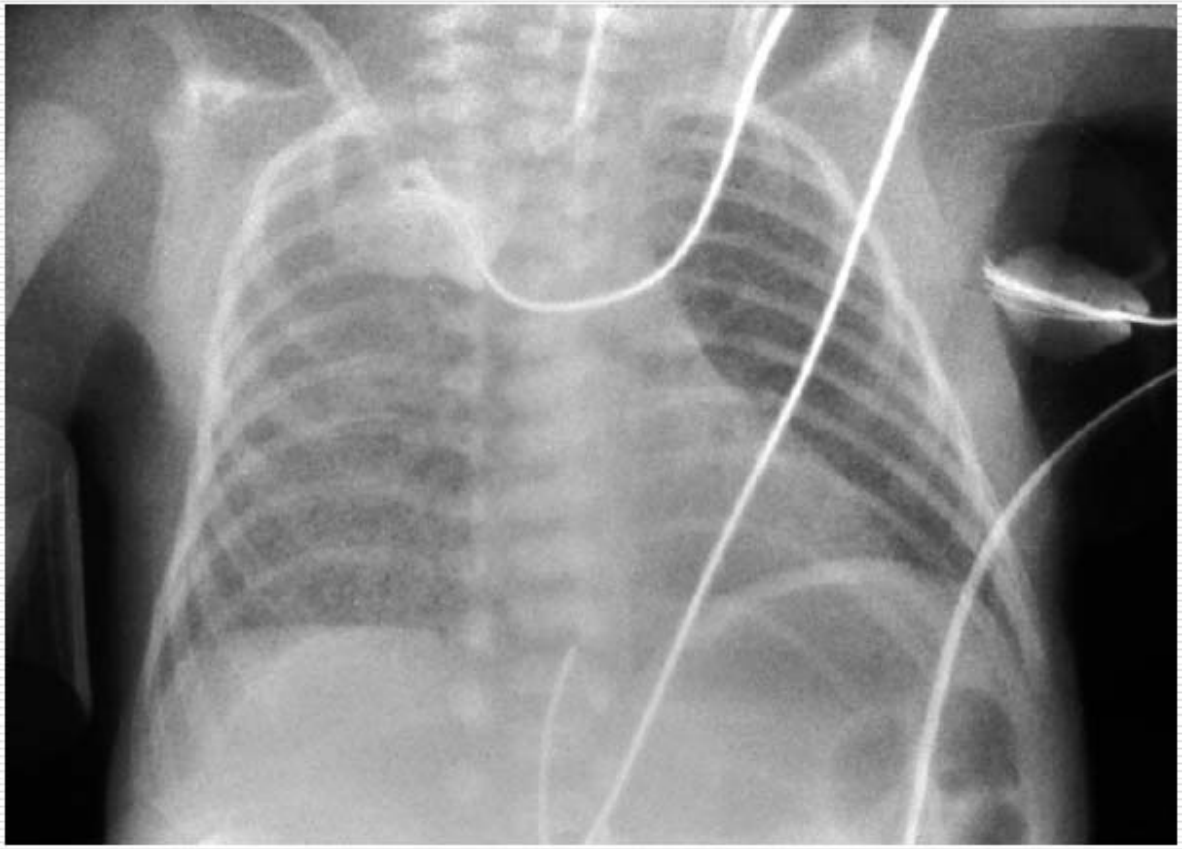
Near term Infant *Management*

- High oxygen oyxhoods are not benign
- Absorption atelectasis & Oxygen toxicity
- Pulmonary hypertension develops quickly and is self propagated

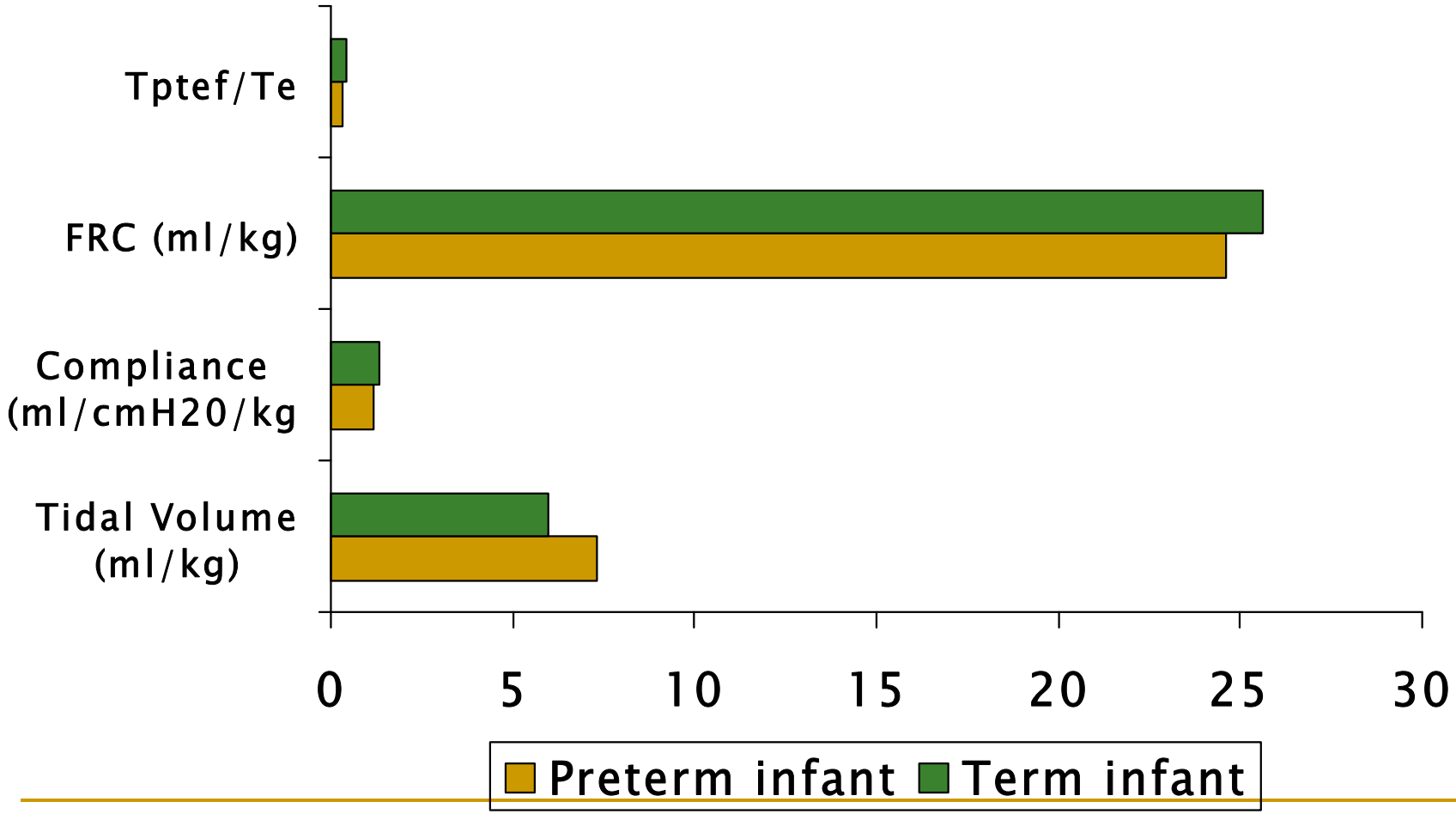
High Oxygen Atelectasis

- Alveolar collapse due to oxygen absorption and denitrogenation ("Nitrogen washout")
- 2X greater atelectasis in 100% VS 30% group *(Rothen, '95)*
- High FiO2 for 10 minutes before extubation increases post-operative atelectasis *(Benoit, '02)*
- Prevented by PEEP/CPAP *(Sirafini, '99)*

High Oxygen Atelectasis

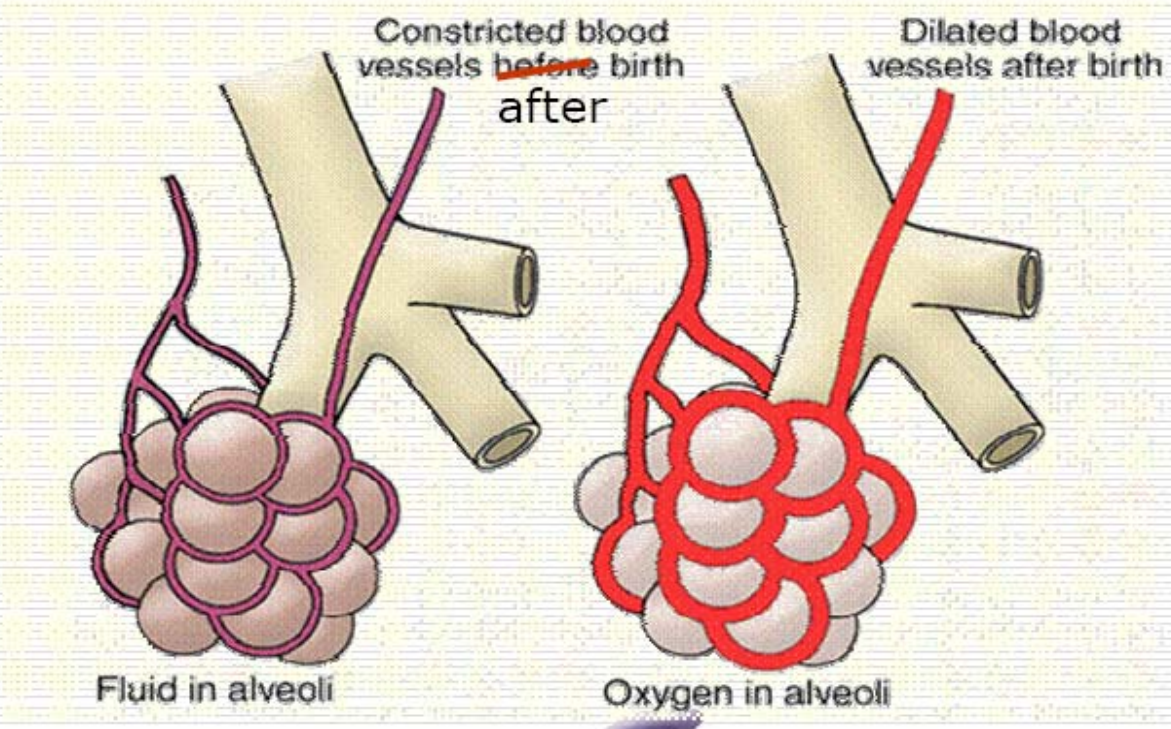


Lung Function in Healthy Late Preterm Infants

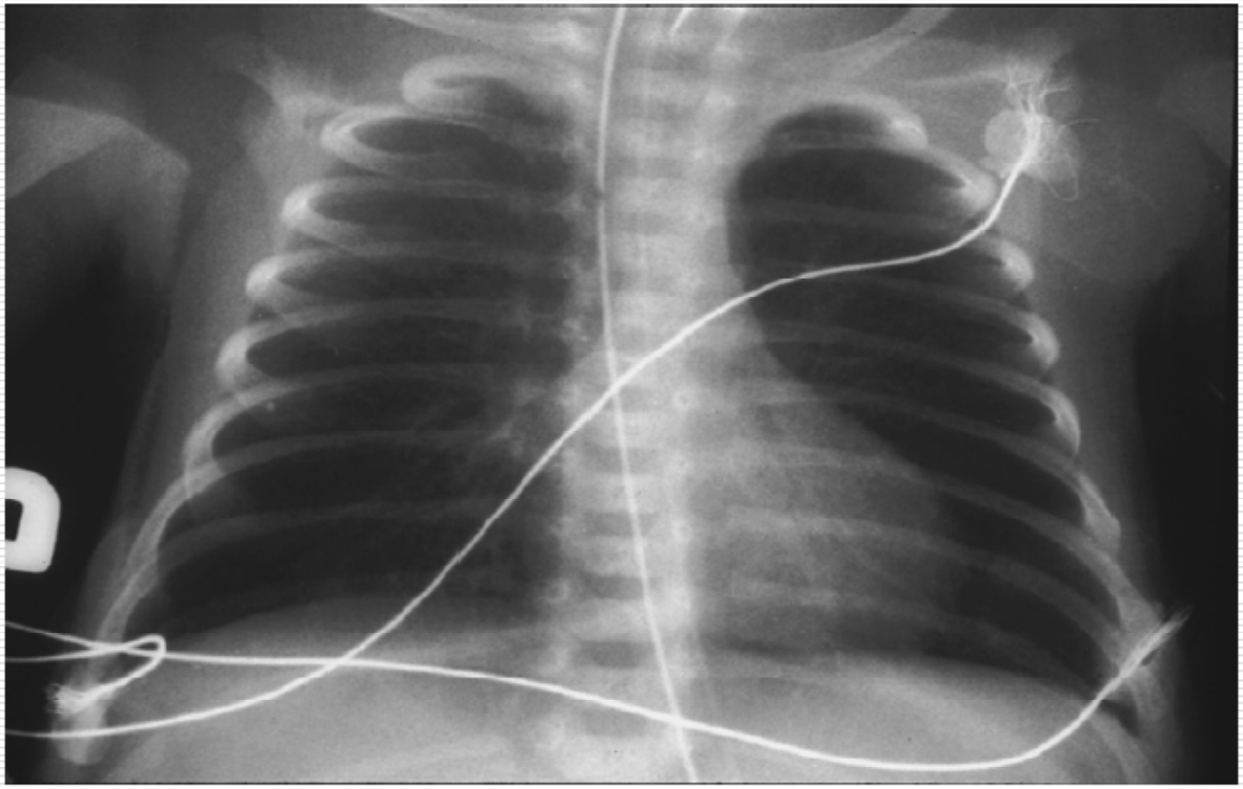


Venigalla, PAS 2008

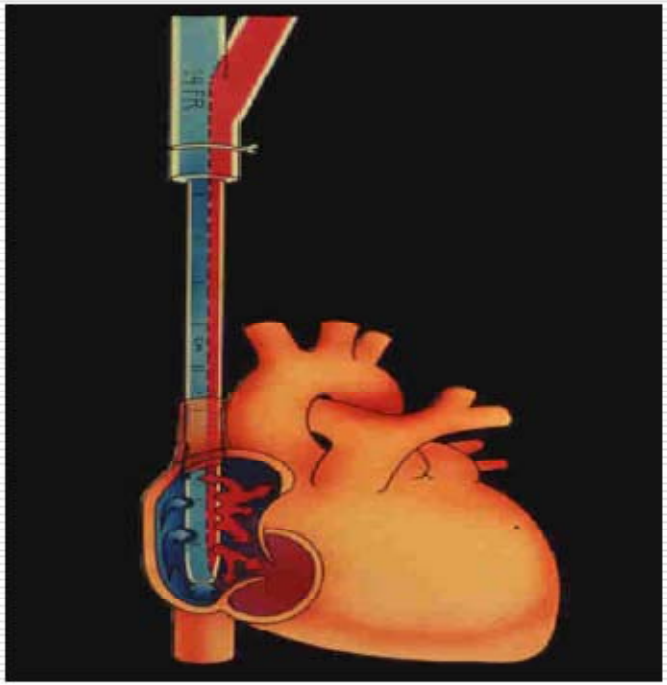
Pulmonary Hypertension is Common in Near Term Infants



HRF and PPHN in Near term Infants
A Case for Early iNO?



HRF in Near Term Infants: ECMO

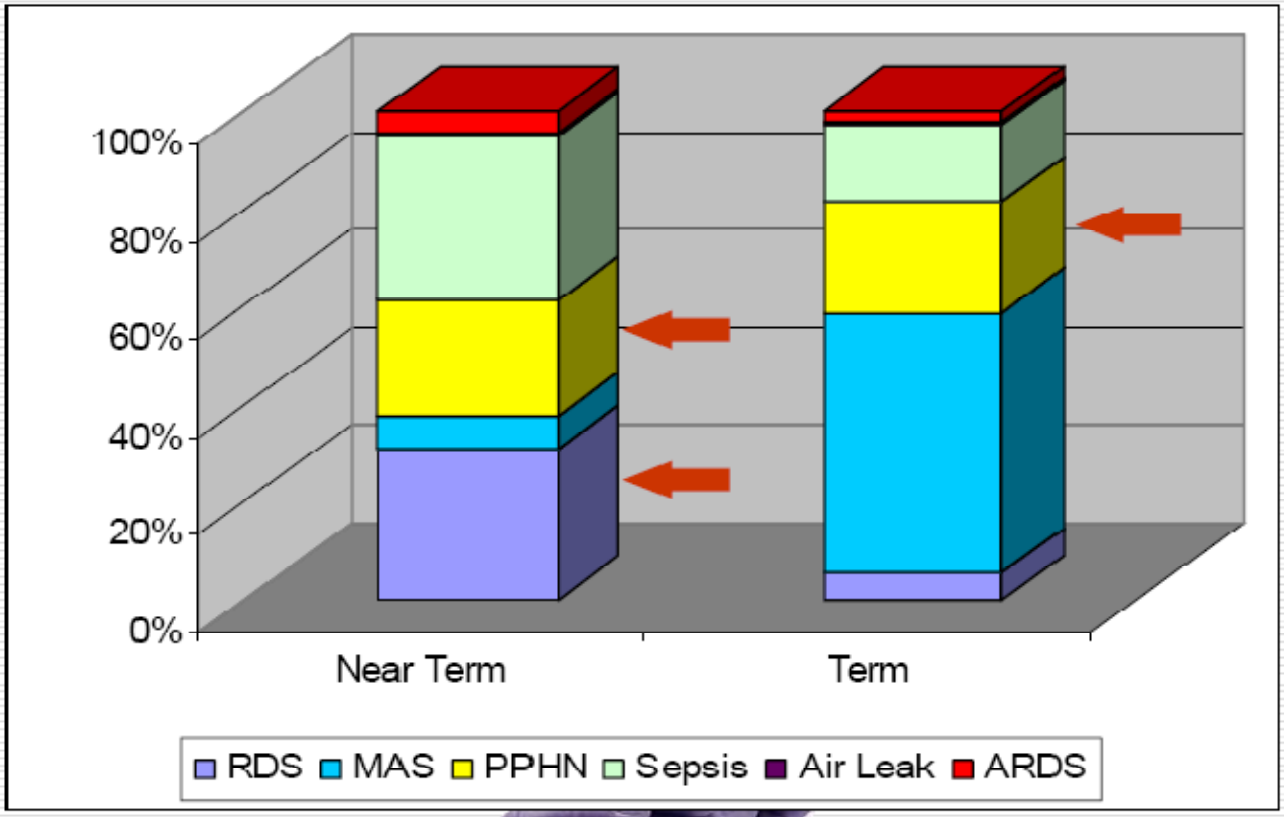


Near-Term ECMO Demographics

1989-2005	Near Term (N=2258)	Term (N=13,332)
Birth Weight (kg)	2.80 ± 0.51	3.42 ± 0.56
Gestation (wks)	35.3 ± 0.9	39.7 ± 1.5
Male	66%	57%
Median Apgar 1	6	5
Median Apgar 5	8	7

Dudell & Jain 2006

Near-Term ECMOs: Primary Diagnosis



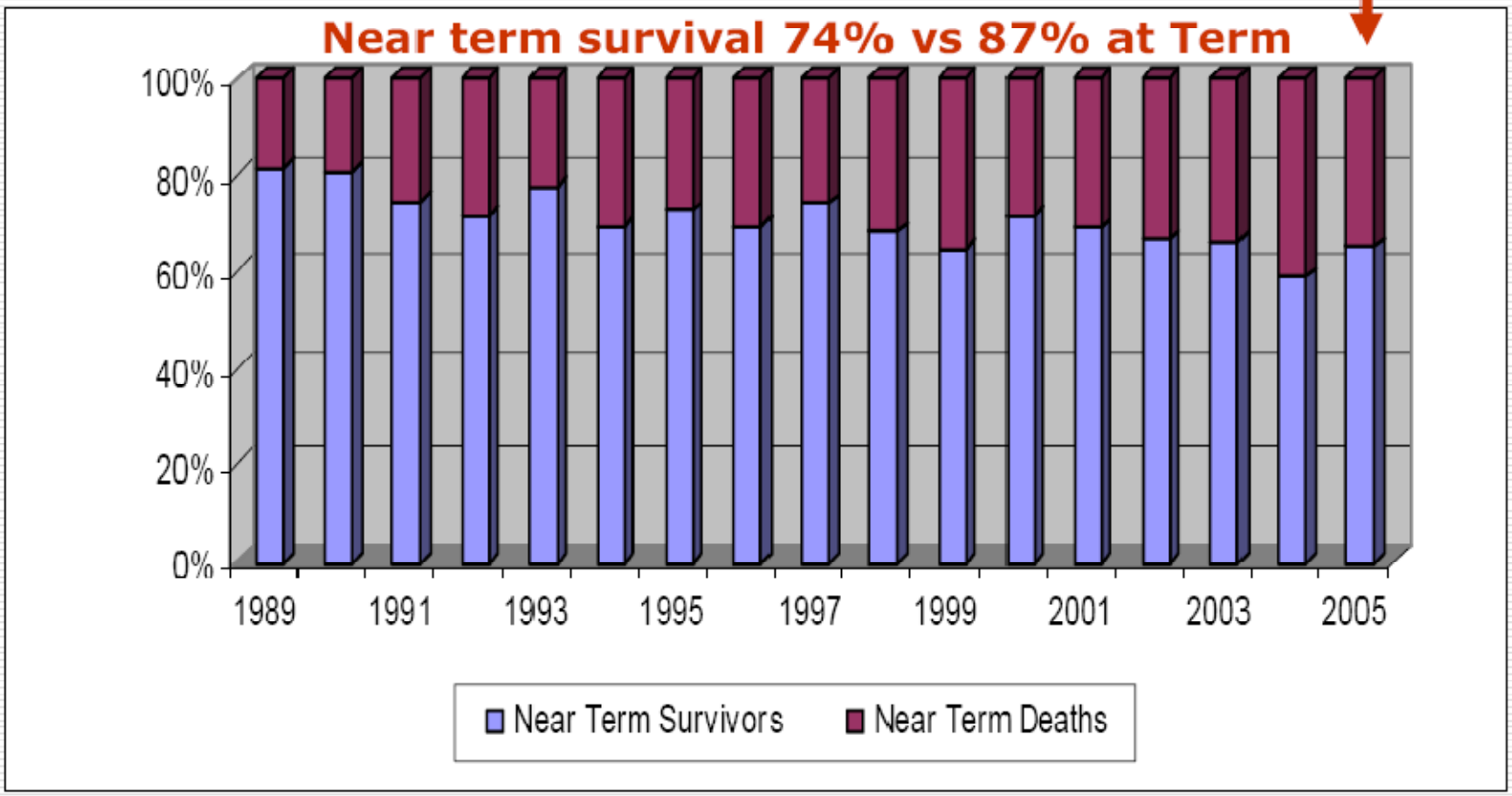
Near-Term ECMO Course

	Near Term (N=2258)	Term (N=13,332)	p
Age on ECMO(d)	2.7 ± 3.6	2.3 ± 2.9	<.0001
Hours on ECMO	146 ± 104	136 ± 86	<.0001
Discontinuation or Death on ECMO	28.2%	15.5%	<.0001

Complication Rates in Near Term ECMO

	Near Term	Term	RR	95% CI
Neurologic	12.4%	8.2%	1.51	1.40-1.63
IVH	4.4%	1.9%	2.33	2.02-2.69
Other	8.0%	6.3%	1.27	1.15-1.39
Hemofilt/ Dialysis	7.3%	5.6%	1.31	1.18-1.45

Survival Trends in the Near Term ECMO Patients



Hypothermia

- More body surface area / small body mass
- Thinner skin
- Less subcutaneous fat (insulation)
- Less brown fat
- Less flexed posture
- 10% at 35-36 weeks vs. 0% at term
- Assumption is that the late-preterm infant can be cared for in the same way as term
- Risk after birth and the first 24-48 hr of life

Hypoglycemia

- Less glycogen stores
- Delayed glycogenolysis & gluconeogenesis
- May have been delivered for fetal stress, maternal diabetes (to prevent fetal death)
- Greater glucose needs
- Respiratory distress
- Limited feeding
- Most now use a threshold of 50 mg/dL
- Incidence 18% at 35-36 weeks, 4% at term

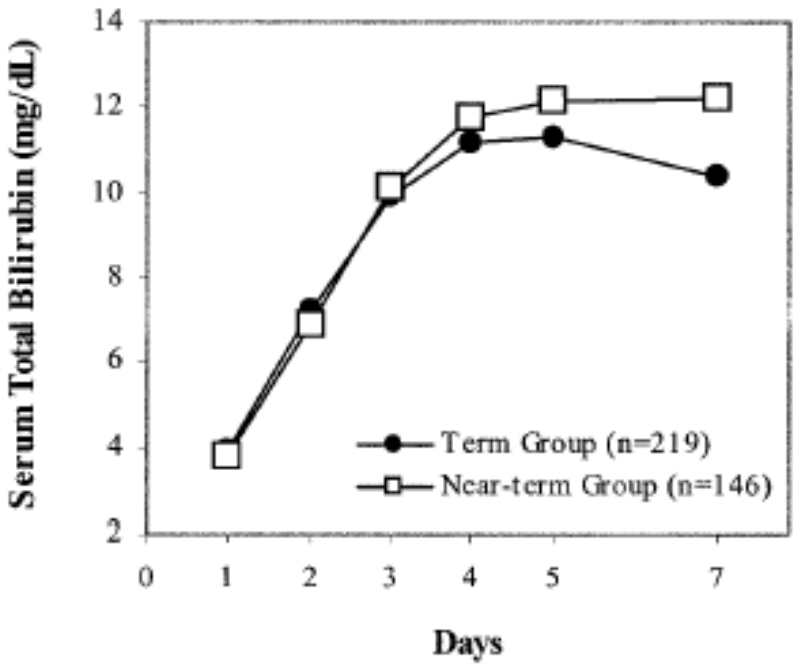
Gastrointestinal Issues

- Adapt quickly to enteral feedings
- Less mature peristalsis.
- Immature suck, suck swallow reflexes (maturity occurs at 36-38 weeks)
- Feeding behavior: fewer sucks, fewer sucks per burst, lower maximum pressure during sucking
- Delay in successful feeding, breast feeding
- Poor weight gain
- Dehydration
- Poor postnatal growth may affect long-term development
- Necrotizing enterocolitis rate is higher

Newborn Jaundice

- Nearly 60% of infants born in the United States will develop some level of jaundice (or hyperbilirubinemia) within the first two weeks of life.
- If untreated, the build-up of bilirubin in the blood can cause serious and irreversible damage or death (kernicterus)

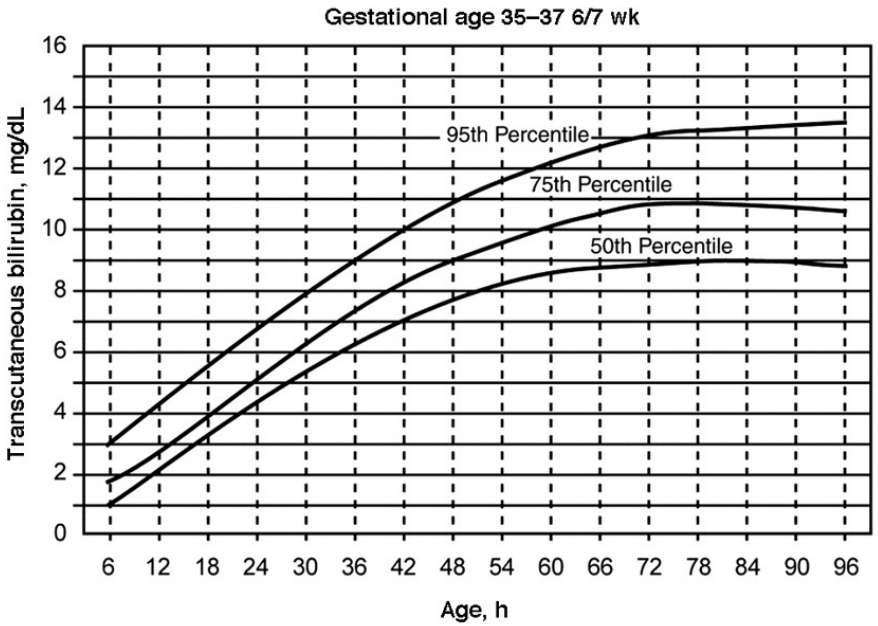
Near-term Infants: Hyperbilirubinemia

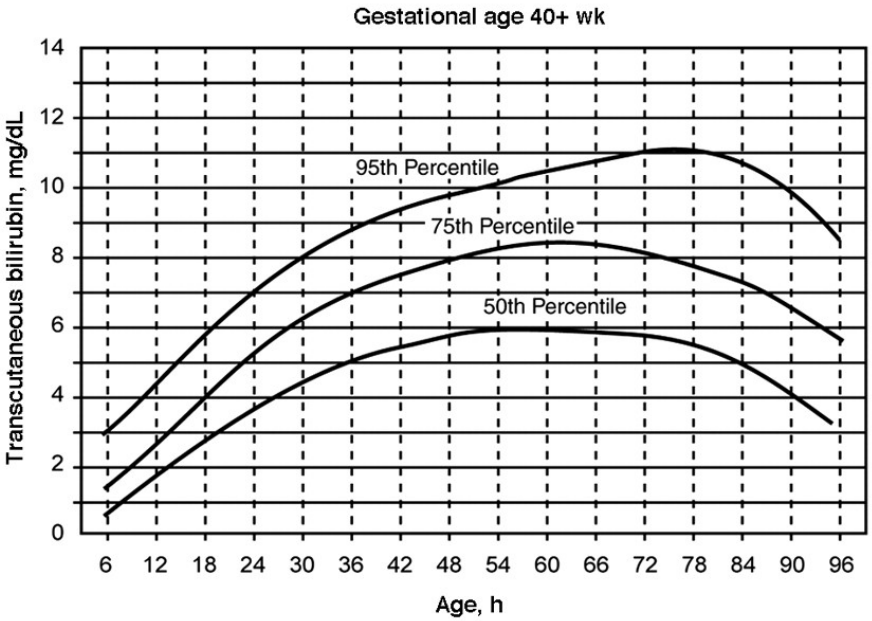


4/11 (36%) of infants in an HMO with serum bilirubin of 30+ were born at 35-36 weeks

Newman, Pediatrics 2003

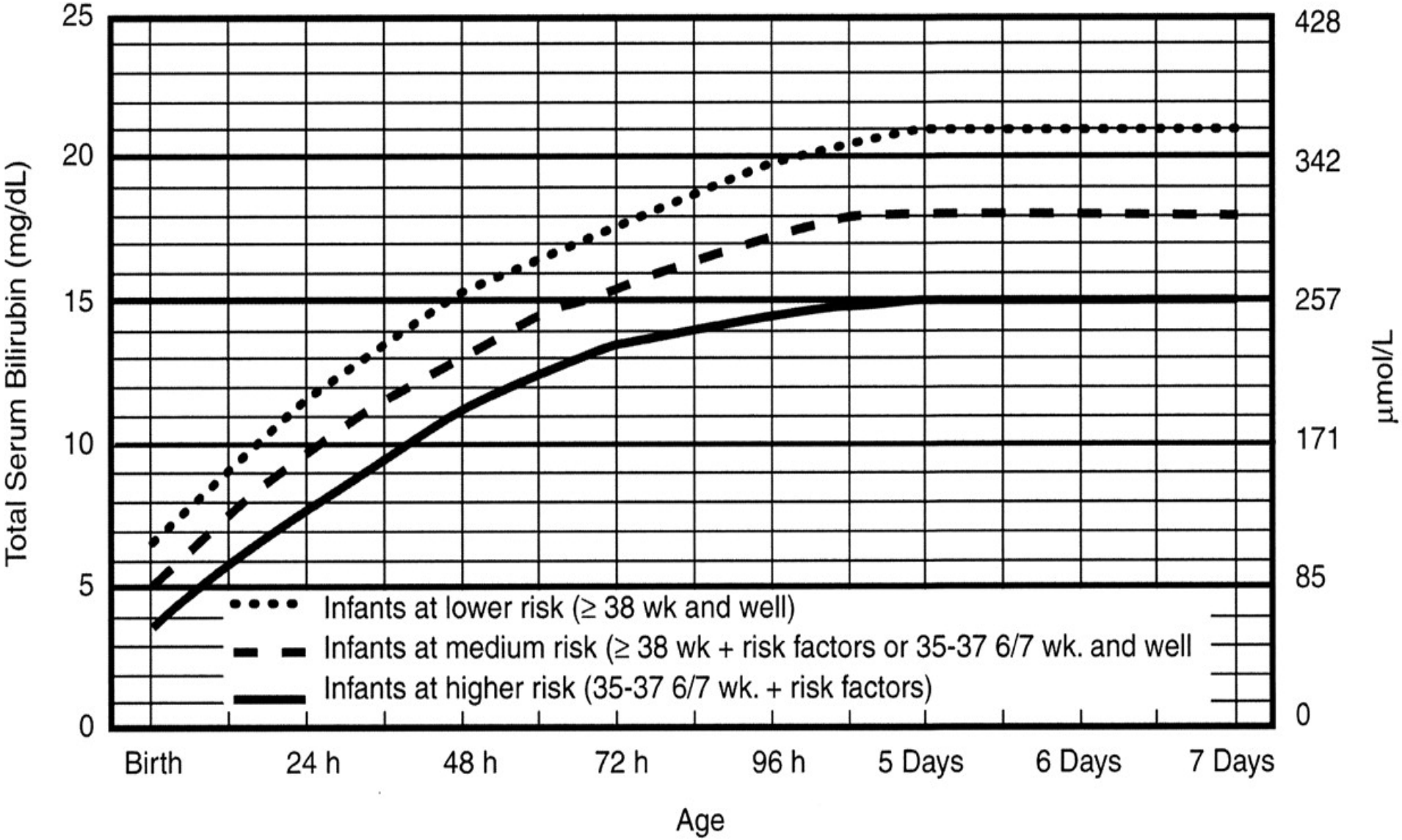
TcB Levels in the First 96 Hours in the Late Preterm Infant





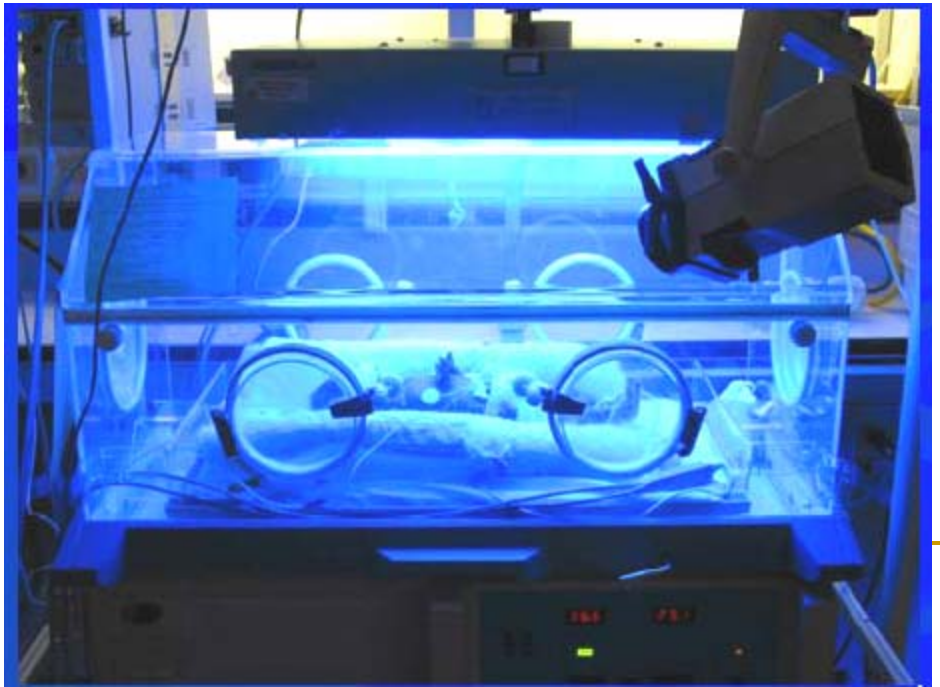
Maisels, M. J. et al. Pediatrics 2006;117:1169-1173

Guidelines for phototherapy in hospitalized infants



Kernicterus

- Kernicterus manifests through syndromes including: vision and hearing impairments, cerebral palsy, dental dysplasia and in some instances mental retardation.



Treatment with Phototherapy or exchange transfusions can prevent severe hyperbilirubinemia and kernicterus

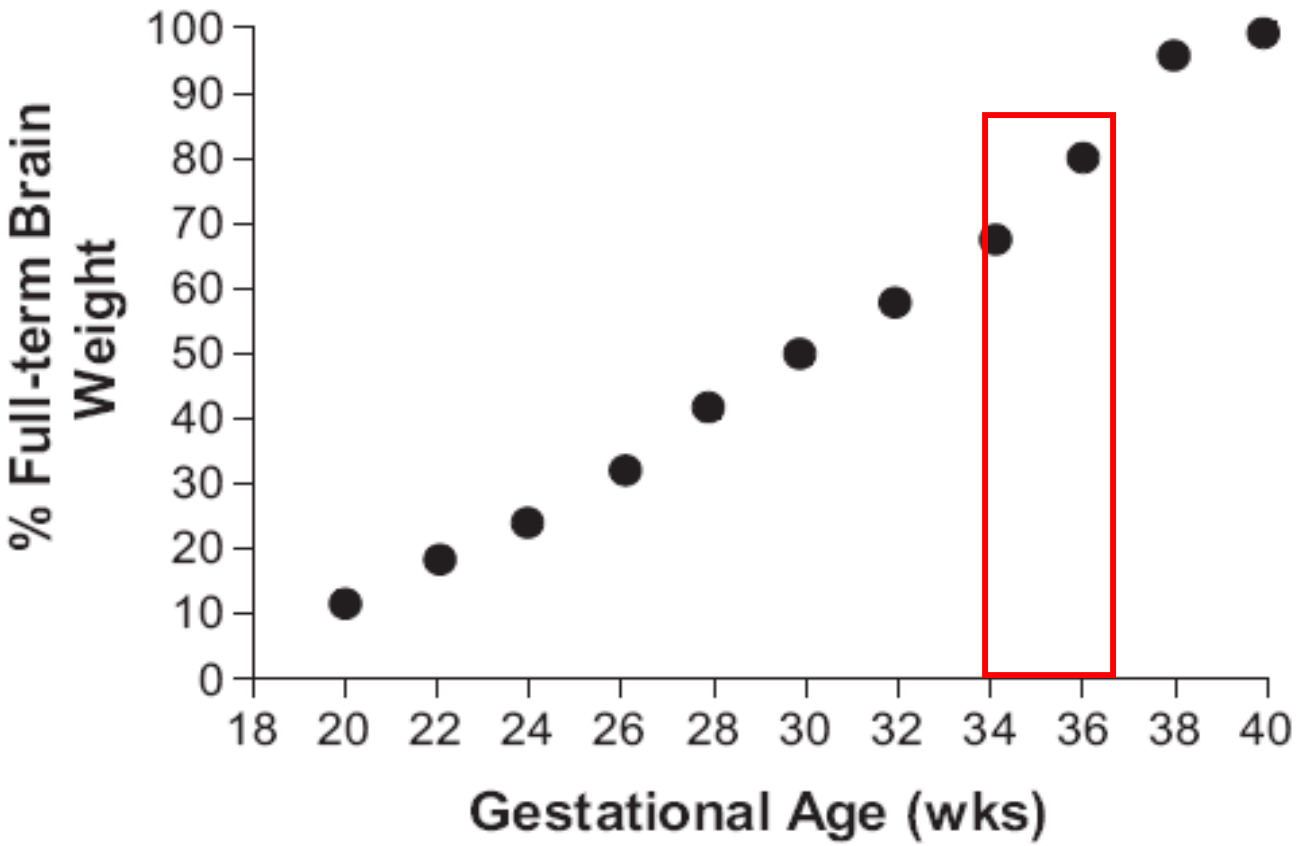
"Healthy" Term and Near-term Babies With Kernicterus Readmitted by Age 7 Days

	Readmission Age (days)					All Cases
Age (days)	2.5 to 3	4	5	6	7	2.5 to 7 days
# Total Babies	N = 8	N = 15	N = 17	N = 12	N = 9	N = 61
Median TSB value (mg/dl)	38.5	41	37	38.5	42	39 mg/dl
Range TSB values (mg/dl)	21.5 – 42.0	31.5 - 50.0	27.0 - 49.0	24.0 - 46.0	26.5 - 49.5	21.5 - 50.0
% 35 / 36 GA (weeks)	12.5%	33.3%	23.5%	33.3%	none	23% (14/61)
Contributory causes of hyperbilirubinemia†						
Idiopathic	2	7	6	2	4	19 (31.5%)
G6PD deficiency	3	5	4	5	2	19 (31.5%)
Increased hemolysis* (excl. sepsis and G6PD)	1	3	5	1	-	10 (14.7%)
Extensive Bruising and/or Cephalhematoma	-	1	2	2	1	6 (9.9%)
Systemic Infection (excl. G6PD deficiency)	-	-	1	2	1**	4 (6.6%)
Crigler Najjar syndromes	1	-	1	-		2 (3.2%)
Galactosemia	-	-	-	-	1	1 (1.6%)

The Late Preterm Human Brain and Risk for Periventricular Leukomalacia

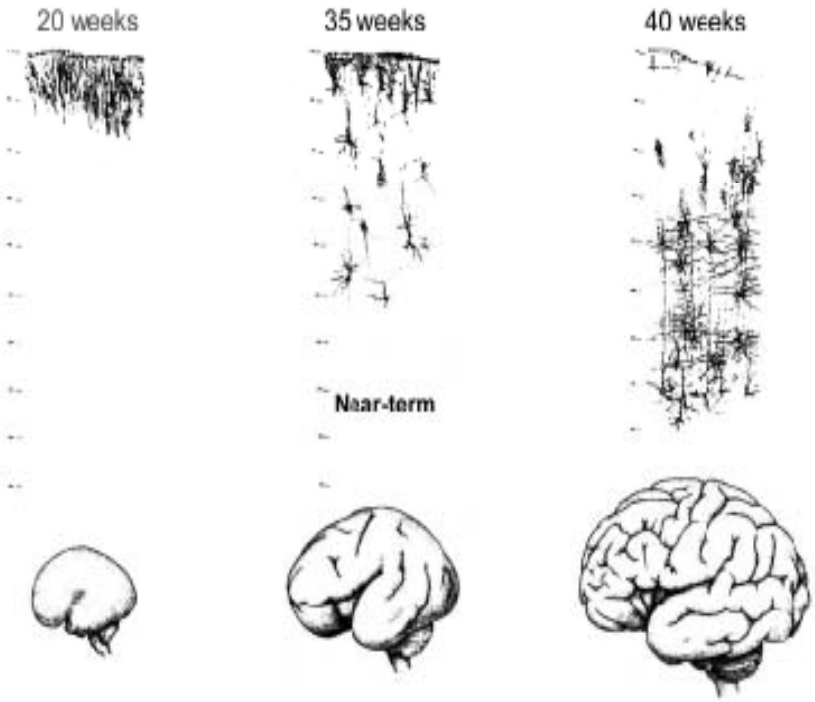
- In USA, ~55,000 infants born with BW<1500g and ~90% survive; ~10% develop CP and ~50% develop cognitive and behavioral deficits
- The common perception is that 'late preterm' infants, defined as 34 0/7 to 36 6/7 weeks, are spared substantial birth injury and are neurologically 'normal' or 'almost normal' in the neonatal period and beyond.

Human Brain Growth



- The brain volume increases at a rate of ~15 mL (1.4%) per week between 29 and 41 weeks of gestation.
- At 28 weeks of gestation, the brain is ~13% of term brain volume; by about 34 weeks of gestation, the volume is ~65% of term brain
- More than one-third of brain size increase takes place during the final 6 to 8 weeks of gestation

Development of the Human Cerebral Cortex



The immaturity of the laminar position and dendritic arborization of neurons, as demonstrated by Golgi drawings, in the cerebral cortex in the late preterm infant at 35 gestational weeks is striking in comparison to neurons at midgestation (20 weeks) and at term (40 weeks).

Brain Structure

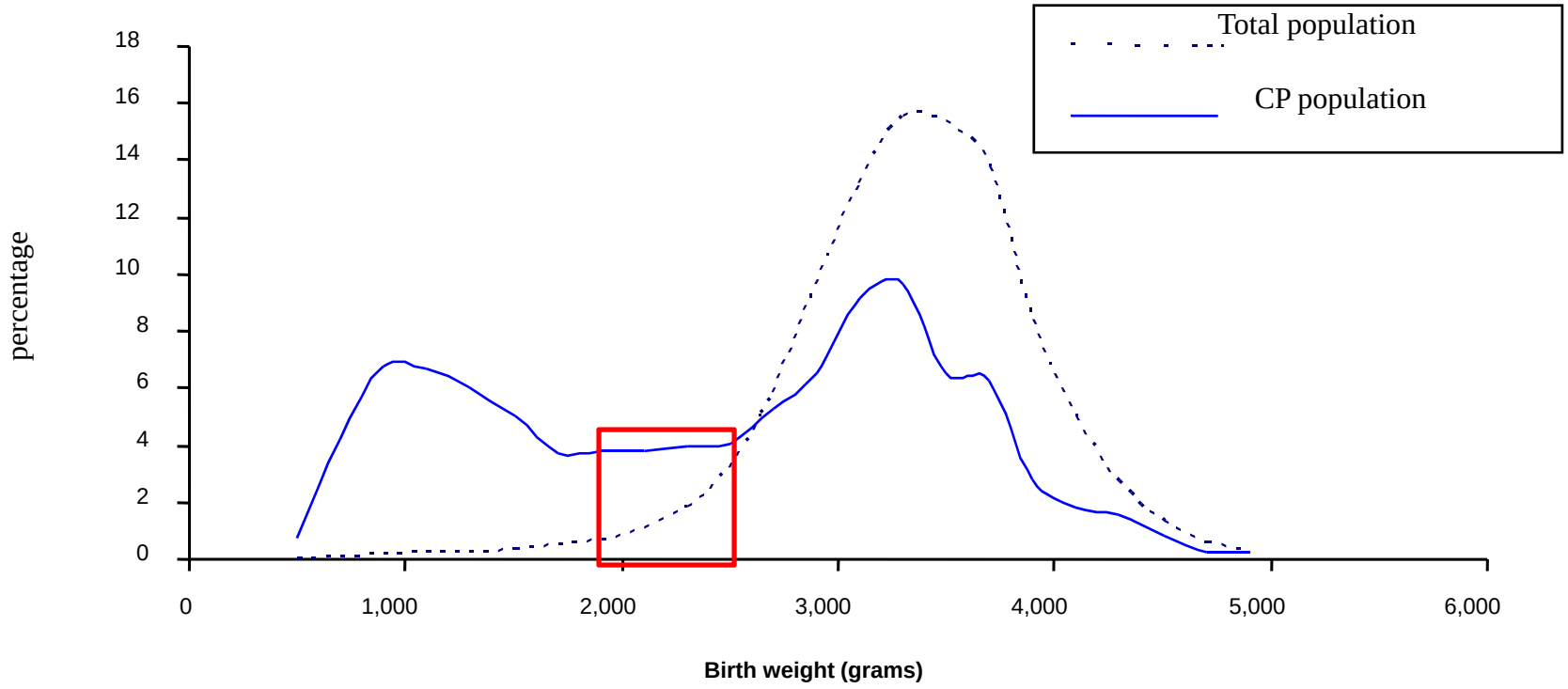
- A five-fold increase in white matter volume occurs between 35 and 41 weeks of gestation.
- Structural maturation during late preterm gestations include, increasing in neuronal connectivity, dendritic arborization and connectivity; increasing in synaptic junctions; and maturation neruochemical and enzymatic processes augmenting growth and maturation of the brain.

Relative Risks and Attributable Fractions for CP by Birth Weight/Gestational Age

Birth weight (grams) and Gestational age (weeks)	Terms commonly used to refer to this group	Relative risk for CP
1. <1501; any gestational age	very low birth weight	24.4
2. 1501-2500; ≤36 weeks	low birth weight and appropriate-for-gestational age; i.e., pre-term	6.2
3. 1501-2500; 37 weeks	low birth weight and small-for-gestational age; full term	1.8
4. 2500; ≤36 weeks	large-for-gestational age: pre-term	1.4
5. 2500; ≥37 weeks	normal and high birth weight; full term	1.0

Ellenberg J, Nelson K. *Am. J. Dis. Child.* 1979; 133:1044-1048

Birth Weight Distribution of Singleton Population with CP and of Total Singleton Population, Atlanta, 1981-1991



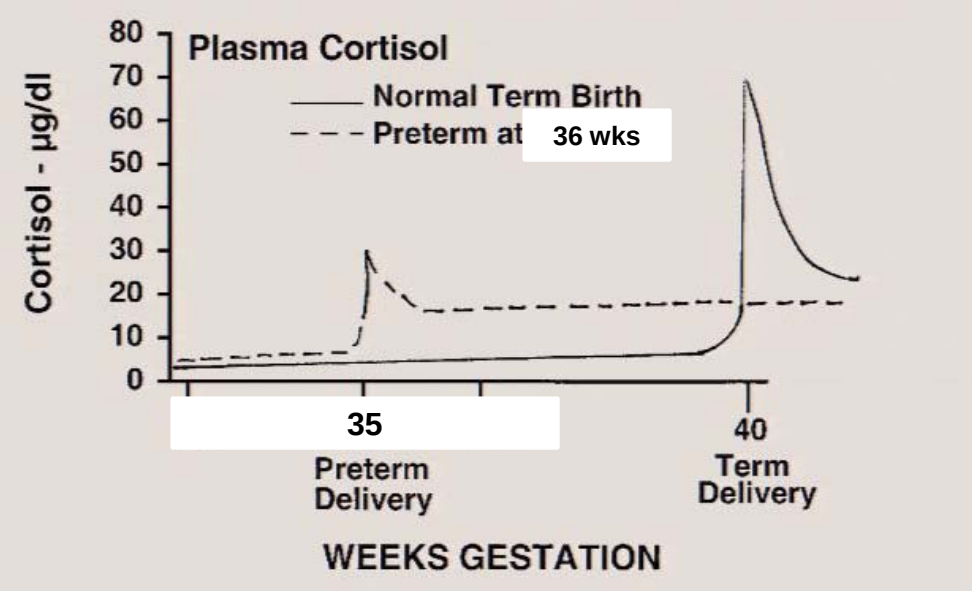
Source: 2005 Unpublished data from the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP).

Mechanisms of Brain Injury in Late the Preterm Infant

- Does prematurity alter normal 'fetal development'?
  - Injury model – cell loss, fibrosis (fetal insults, IVH, nutritional deficiencies)
  - Altered developmental program (prematurity alters timing and regulation of developmental processes)
- Do care strategies modulate development?
- Does accelerated maturation alter the subsequent developmental potential?

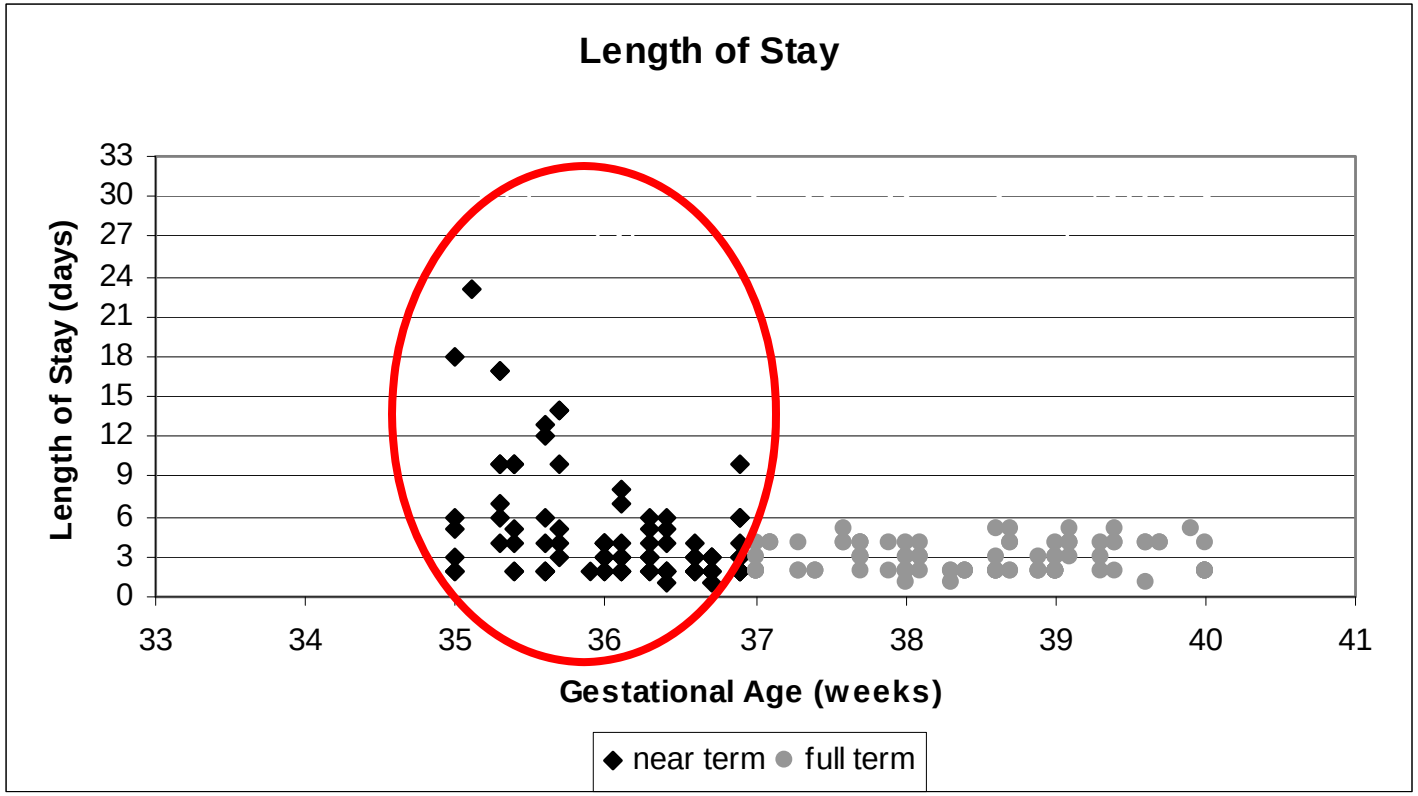
Common Events in the Care of the Preterm Infant that Might Adversely Affect the Adult

- Endocrine adaptations to preterm birth



- Fetal and/or postnatal growth failure
- Hyperalimentation solutions

Length of Hospital Stay: Full term vs. Near term

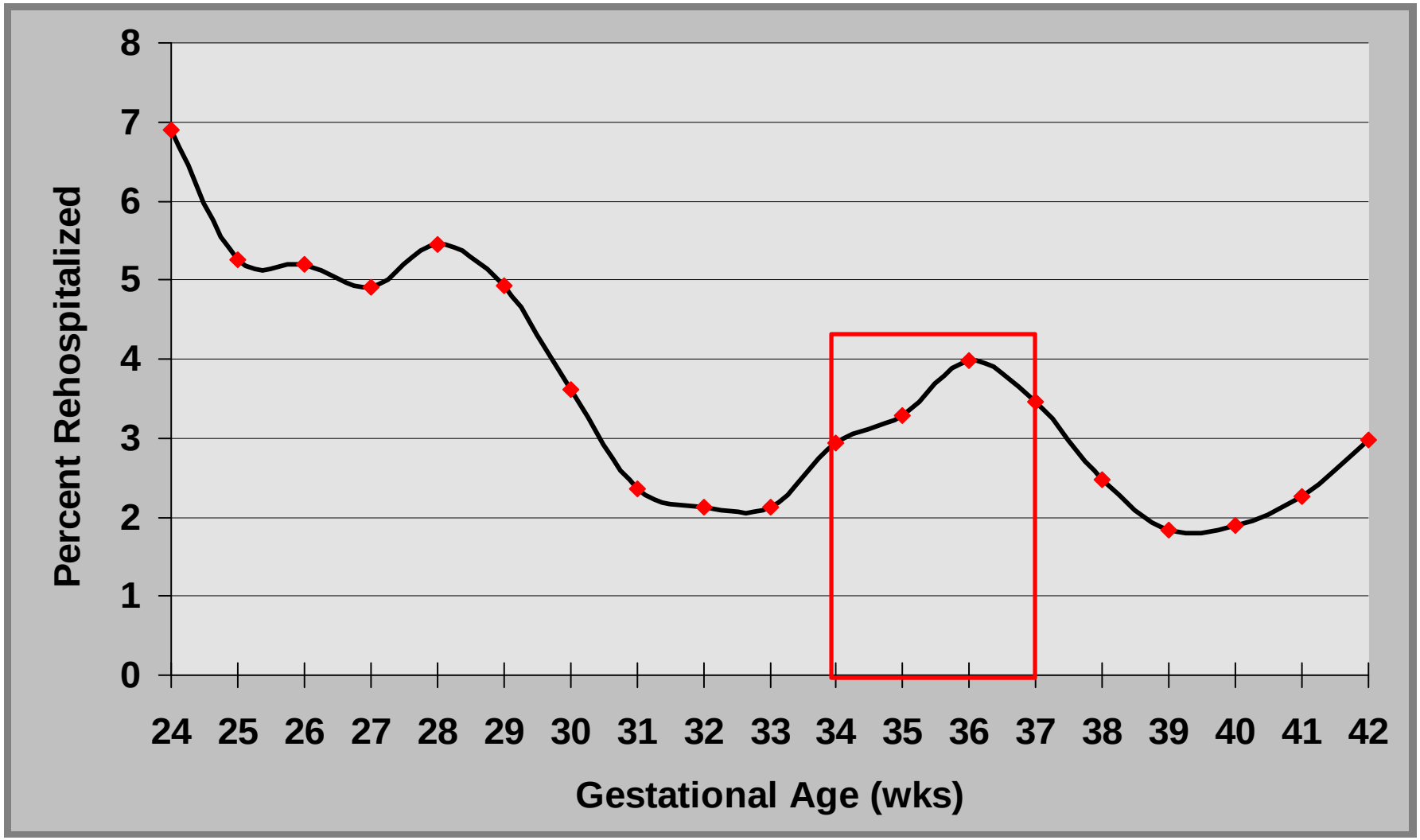


Wang, et al. *Pediatrics*, 2004

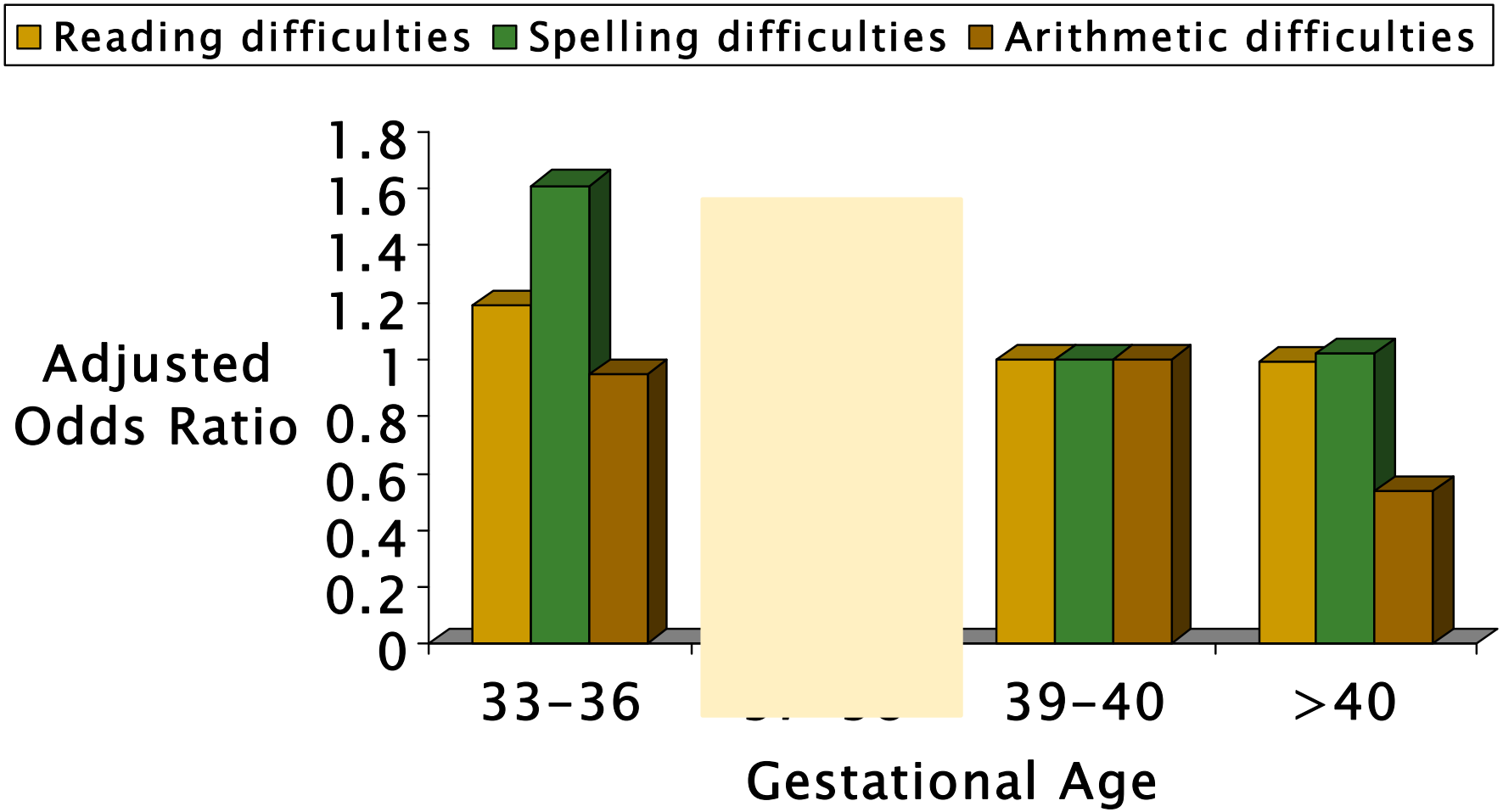
Near Term Births:
Excess Hospital Costs by Week of Gestation
Compared to Costs at 38 Weeks

Delivery group	Gestational age (wk)				
	34	35	36	37	38
All deliveries					
Number of cases	5788	9898	16,609	34,477	71,610
Difference in mean cost ($1000)	→ 6.01	→ 3.01	→ 1.44	0.55	0.00
Total excess cost ($1000)	→ 34,784	→ 29,797	→ 23,880	18,858	
Deliveries without induction or cesarean					
Number of cases	3892	6695	11,440	24,010	50,383
Difference in mean cost ($1000)	4.26	2.15	0.83	0.39	0.00
Total excess cost ($1000)	16,570	14,403	9534	9399	

Rehospitalization in NICU Survivors



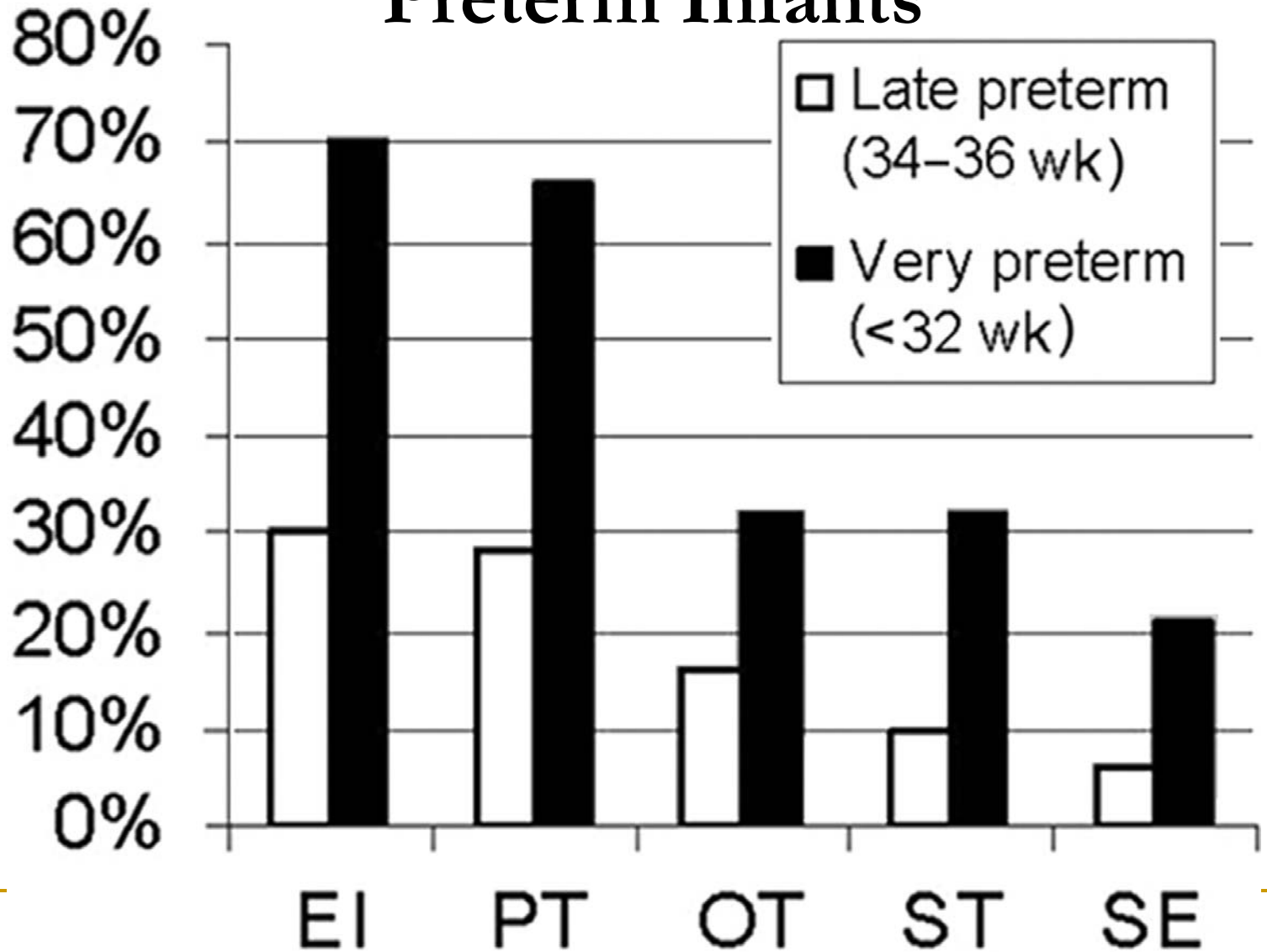
Reading, Spelling, and Arithmetic Difficulties in Late Preterm Infants



Adjusted for gender, breastfeeding, and parental educational level

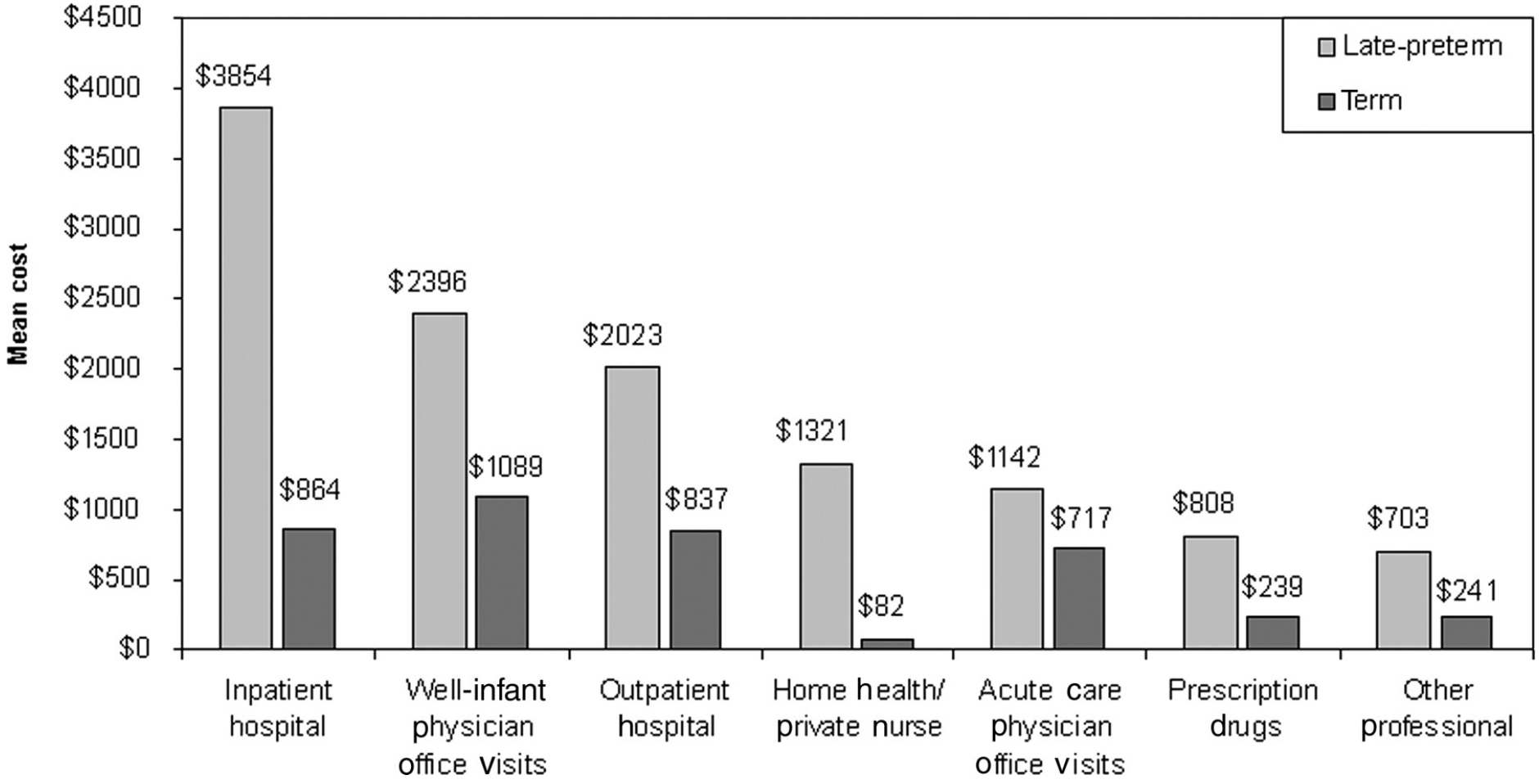
Kirkegaard, Pediatrics 2006;118:1600-6

Rate of Therapy Use in Late and Very Preterm Infants



Kalia, J. L. et al. Pediatrics 2009;123:804-809

First-year Medical Costs Among Late-preterm and Term Infants



McLaurin, K. K. et al. Pediatrics 2009;123:653-659

Near term Infant *Management*

- Community hospitals are important!
  - 3024 community hospitals in US deliver babies
  - 241 academic medical centers with deliveries*
- Less rigorous dating and timing of delivery
- Often cared for by pediatricians in term nurseries; more prone to clinical problems related to delayed transition
- Transitional care requires higher level of monitoring and support

Variations in Neonatal Characteristics and Perinatal Management in California and Massachusetts Hospitals for Infants 33-35 Weeks Gestation

	A	B	C	D	E	G	I	J	K	L
Mean Birth Weight– (± St. Dev.)	2119.4 (324.6)	2196.9 (366.8)	2160.9 (392.6)	2215.4 (421.8)	2063.7 (444.2)	2015.0 (374.3)	2148.9 (352.2)	2058.8 (398.2)	2190.5 (394.6)	1959.3 (378.5)
Mean SNAP-IIPE-II Scores (± St. Dev.)	4.0 (5.7)	4.1 (5.6)	4.0 (6.8)	5.6 (7.2)	3.4 (5.0)	4.4 (6.0)	2.0 (3.3)	3.0 (4.4)	4.9 (6.1)	5.6 (6.9)
% with SNAP-II-II ≥20	1.7	0	5.1	4.2	0	5.4	0	0	3.8	4.4
% Small for Gestational Age (<5th percentile)	6.7	1.6	7.9	2.7	10.0	10.7	6.5	11.1	5.7	13.3
% Antenatal Steroids	53.3	53.1	50.8	67.1	55	50.9	65.2	63.9	52.8	52.3
% C-Section Delivery–	38.3	70.3	57.1	50.7	50.0	58.9	37.0	50.0	56.6	55.6

McCormick, Sem Perinatol, 2006;30:44-7

Variations in Neonatal Management in California and Massachusetts Hospitals for Infants 33-35 Weeks Gestation

Neonatal Management Variables	A	B	C	D	E	G	I	J	K	L
% Any Respiratory Support-	30.0	35.9	46.0	43.8	52.5	33.9	15.2	33.3	52.8	28.9
% Mechanical Ventilation	28.3	29.7	33.3	24.7	30.0	30.4	8.7	30.6	43.4	15.6
% Hyperalimentation	10.0	4.7	25.4	13.7	17.5	66.1	6.5	5.6	7.5	15.6
Mean Weigh Gain (g)/Day (± St. Dev.)	8.8 (14.7)	2.1 (22.1)	13.2 (11.8)	0.8 (17.6)	3.2 (30.2)	12.1 (10.3)	4.0 (13.9)	3.6 (16.8)	−8.1 (19.0)	−4.2 (28.4)
% Discharged on >20 Cal. Formula	70.0	38.7	61.9	71.2	62.5	70.9	23.9	16.7	7.5	4.5
Mean PMAD (± St. Dev.)	36.4 (1.2)	36.2 (1.2)	36.6 (1.3)	35.8 (0.8)	35.9 (0.7)	36.7 (1.5)	36.0 (0.8)	35.9 (1.2)	35.5 (0.6)	35.6 (1.0)

McCormick, Sem Perinatol, 2006;30:44-7

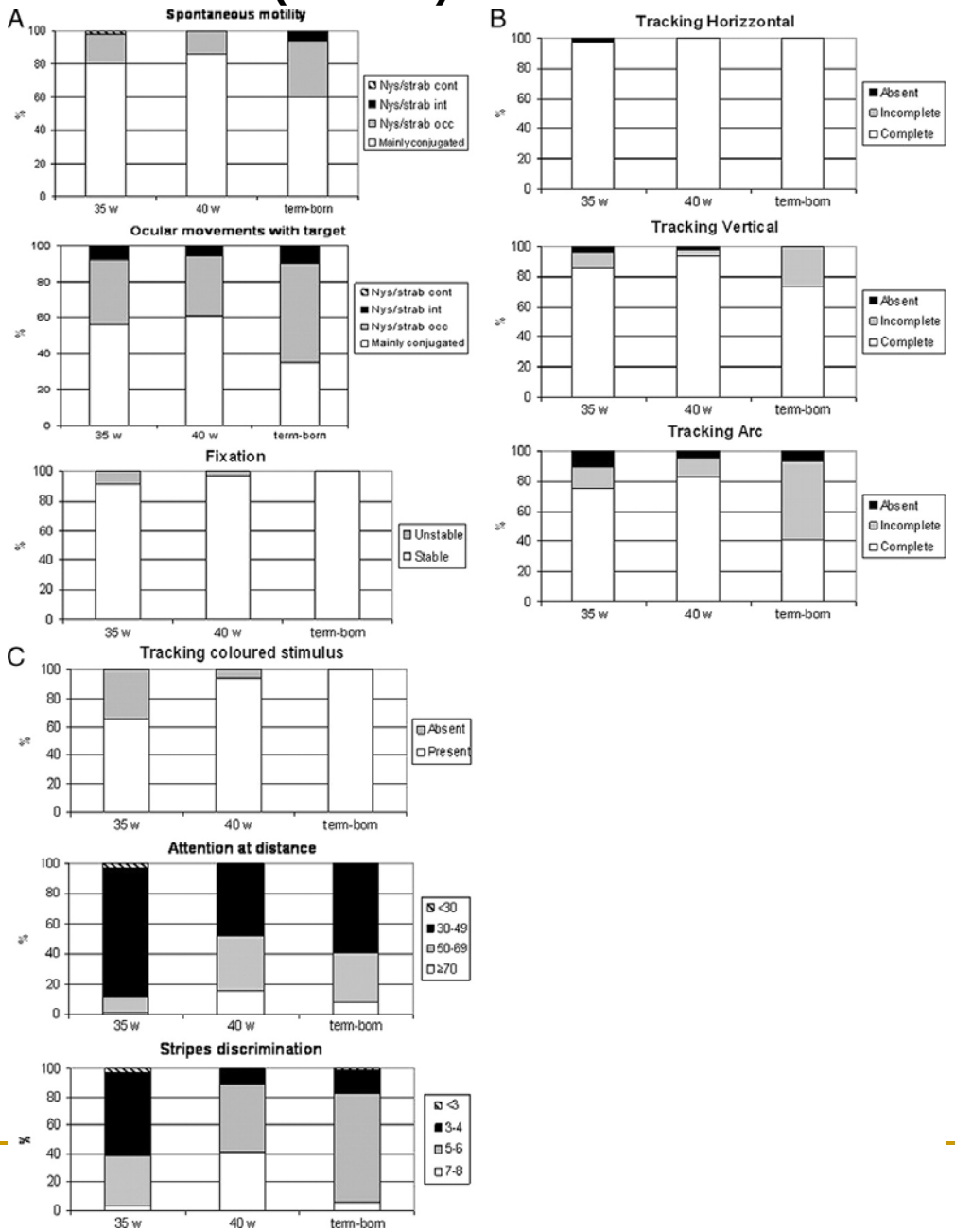
Variations in Care of the Late Preterm Infant

- Late preterm infants generally represent a low acuity population in NICUs.
- However, substantial differences across different institutions occur in the use of interventions like mechanical ventilation and hyperalimentation.
- These differences have implications not only for outcomes like growth but also length of stay, as well as costs of care.
- Evidence-based practice guidelines for the care of late preterm infants are needed to reduce unnecessary interventions and to improve outcomes.

Near term Infant *Summary*

- Near term infants: significant contributors to M & M
- Appear mature but more prone to clinical problems related to delayed transition
- Need for further studies in this vulnerable population

Visual Function in Preterm (35 wks) and Term Infants at 40 Hours of Age



Ricci, D. et al. Pediatrics 2008;122:e1193-e1198

Incidence of Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk 37 (N=834)	Wk 38 (N=3909)	Wk 39 (N=6512)	Wk 40 (N=1385)	Wk 41 (N=505)	Wk ≥42 (N=113)	P for Trend†
	number/total number (percent)						
Any adverse outcome or death	128/834 (15.3)	430/3909 (11.0)	524/6512 (8.0)	101/1385 (7.3)	57/505 (11.3)	22/113 (19.5)	<0.001
Adverse respiratory outcome							
Respiratory distress syndrome	31/833 (3.7)	75/3904 (1.9)	58/6510 (0.9)	13/1381 (0.9)	4/504 (0.8)	2/113 (1.8)	<0.001
Transient tachypnea of the newborn	40/833 (4.8)	153/3904 (3.9)	178/6508 (2.7)	34/1381 (2.5)	24/504 (4.8)	7/113 (6.2)	<0.001
Respiratory distress syndrome or transient tachypnea of the newborn	68/833 (8.2)	213/3904 (5.5)	221/6510 (3.4)	42/1381 (3.0)	26/504 (5.2)	9/113 (8.0)	<0.001
Admission to the NICU	107/833 (12.8)	316/3905 (8.1)	382/6510 (5.9)	66/1381 (4.8)	40/504 (7.9)	16/113 (14.2)	<0.001
Newborn sepsis‡	58/833 (7.0)	156/3904 (4.0)	163/6508 (2.5)	37/1381 (2.7)	19/504 (3.8)	12/113 (10.6)	<0.001
Proved case	3/833 (0.4)	3/3904 (0.1)	7/6508 (0.1)	2/1381 (0.1)	2/504 (0.4)	0/113	0.260
Treated hypoglycemia	20/833 (2.4)	35/3904 (0.9)	44/6508 (0.7)	11/1381 (0.8)	8/504 (1.6)	2/113 (1.8)	<0.001
CPR or ventilation in 1st 24 hr	16/833 (1.9)	35/3904 (0.9)	27/6509 (0.4)	5/1381 (0.4)	2/504 (0.4)	0/113	<0.001
Ventilation in 1st 24 hr	16/833 (1.9)	34/3904 (0.9)	27/6509 (0.4)	5/1381 (0.4)	2/504 (0.4)	0/113	<0.001
Hospitalization ≥5 days	76/831 (9.1)	221/3904 (5.7)	237/6503 (3.6)	56/1381 (4.1)	38/504 (7.5)	13/113 (11.5)	<0.001

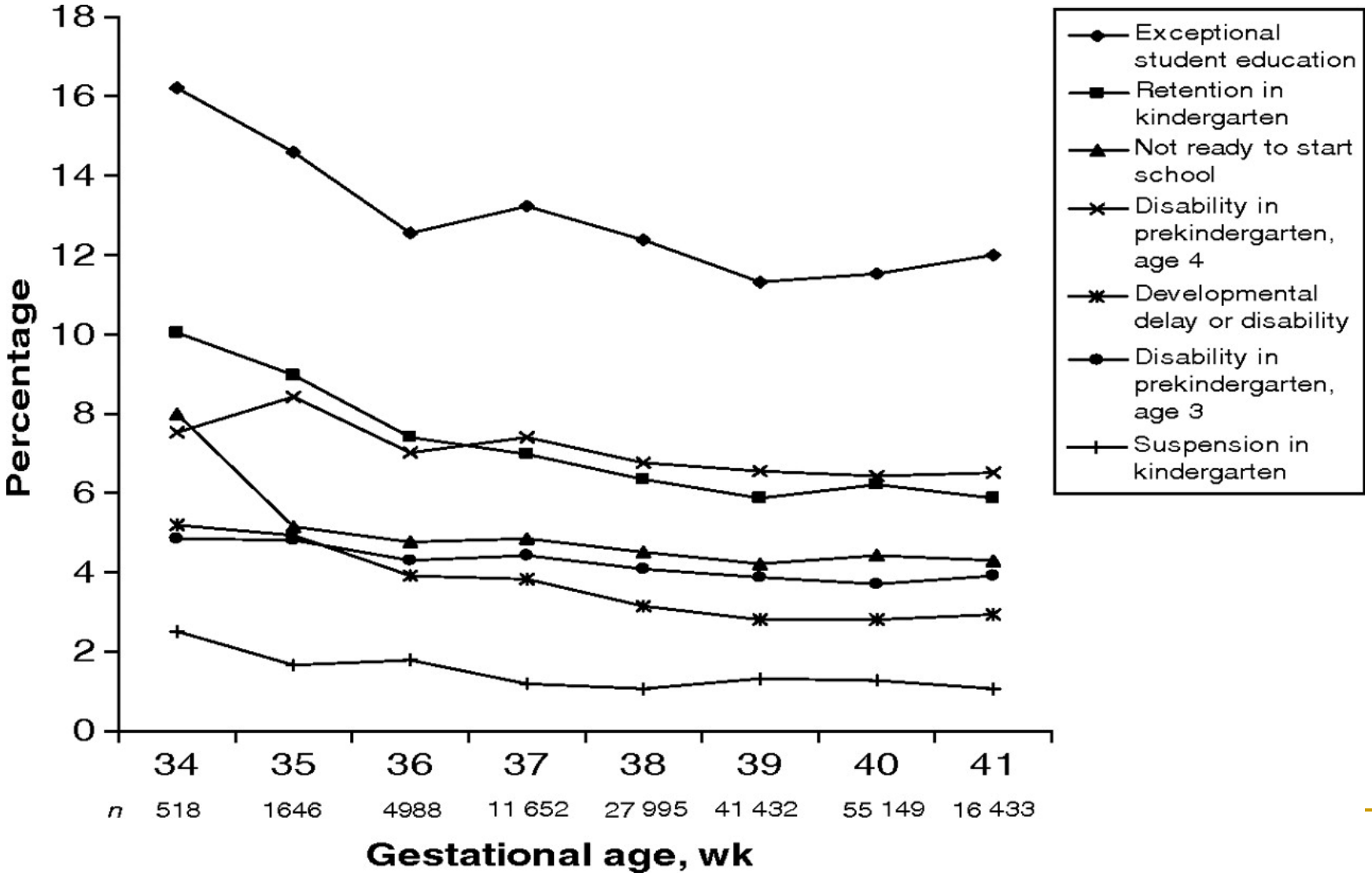
Tita ATN et al. N Engl J Med 2009;360:111-120

Odds Ratios for Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome†	Wk 37	Wk 38	Wk 39	Wk 40	Wk 41	Wk ≥42
			odds ratio (95% CI)			
Any adverse outcome or death	2.1 (1.7–2.5)	1.5 (1.3–1.7)	Reference	0.9 (0.7–1.1)	1.4 (1.0–1.8)	2.5 (1.5–4.0)
Adverse respiratory outcome						
Respiratory distress syndrome	4.2 (2.7–6.6)	2.1 (1.5–2.9)	Reference	1.1 (0.6–2.0)	1.0 (0.4–2.8)	2.3 (0.6–9.7)
Transient tachypnea of the newborn	1.8 (1.2–2.5)	1.5 (1.2–1.9)	Reference	0.9 (0.6–1.3)	1.7 (1.1–2.7)	2.2 (1.0–4.8)
Respiratory distress syndrome or transient tachypnea of the newborn	2.5 (1.9–3.3)	1.7 (1.4–2.1)	Reference	0.9 (0.6–1.2)	1.5 (1.0–2.4)	2.4 (1.2–4.9)
Admission to the NICU	2.3 (1.9–3.0)	1.5 (1.3–1.7)	Reference	0.8 (0.6–1.0)	1.3 (0.9–1.9)	2.5 (1.5–4.4)
Newborn sepsis‡	2.9 (2.1–4.0)	1.7 (1.4–2.2)	Reference	1.0 (0.7–1.5)	1.4 (0.8–2.2)	4.1 (2.2–7.6)
Treated hypoglycemia	3.3 (1.9–5.7)	1.3 (0.8–2.0)	Reference	1.2 (0.6–2.4)	2.6 (1.2–5.7)	2.8 (0.7–11.7)
Hospitalization ≥5 days	2.7 (2.0–3.5)	1.8 (1.5–2.2)	Reference	1.0 (0.8–1.4)	1.9 (1.3–2.7)	2.9 (1.6–5.3)

Tita ATN et al. N Engl J Med 2009;360:111-120

Children with Adverse Early School-age Outcome by Gestational Age



Morse, S. B. et al. Pediatrics 2009;123:e622-e629