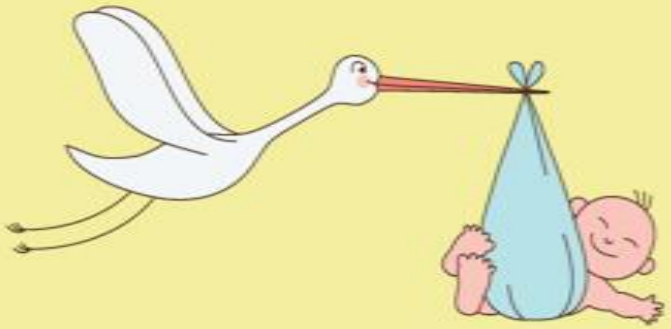
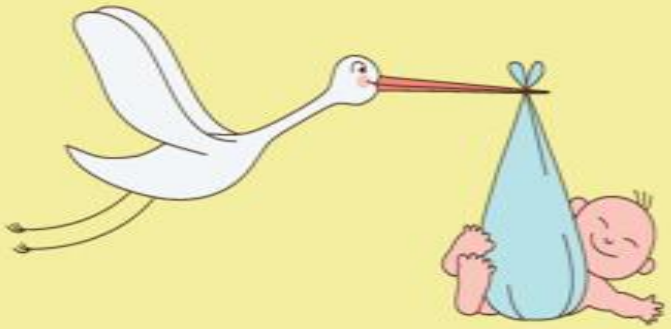


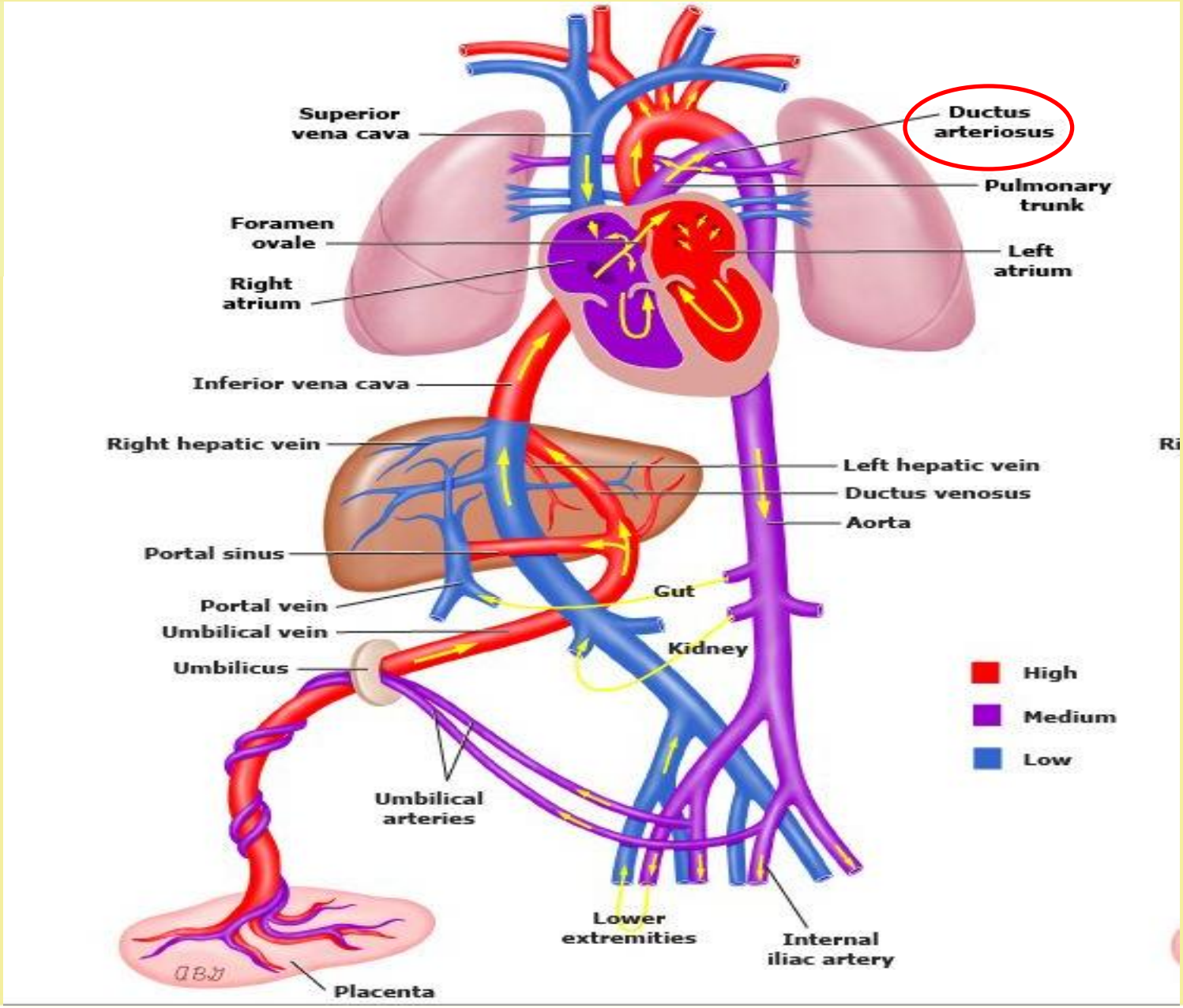
Update on mangement of patent ductus arteriosus in preterm infants

Dr. Trinh Thi Thu Ha



Outline

1. Overview of PDA
2. Timing of screening PDA?
3. When to treat PDA?


Superior vena cava
Ductus arteriosus
Pulmonary trunk
Foramen ovale
Left atrium
Right atrium
Inferior vena cava
Right hepatic vein
Left hepatic vein
Ductus venosus
Aorta
Portal sinus
Gut
Portal vein
Umbilical vein
Kidney
Umbilicus
High
Medium
Low
Umbilical arteries
Lower extremities
Internal iliac artery
Placenta

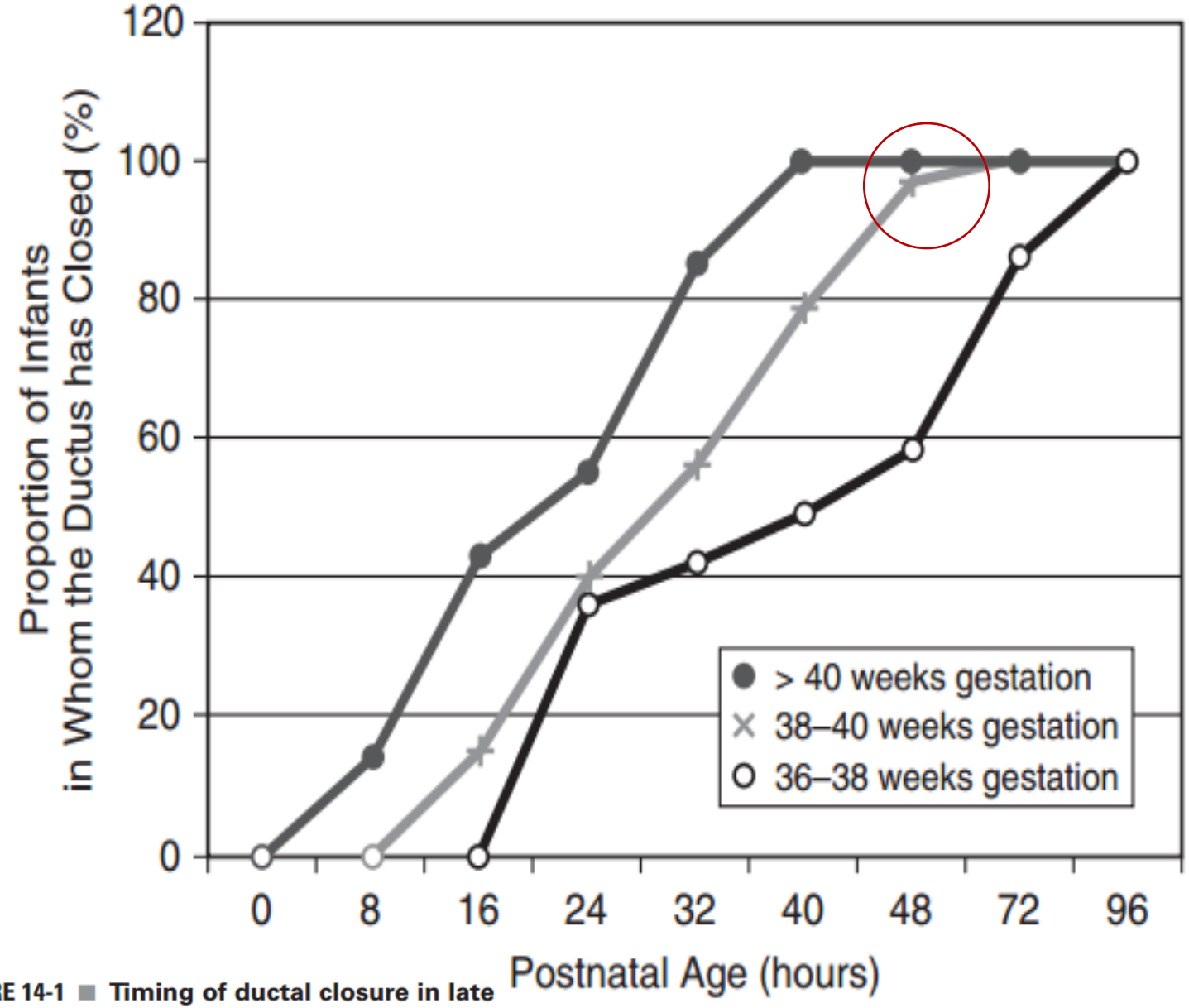


FIGURE 14-1 ■ Timing of ductal closure in late preterm and term infants. (From Gentile R, Stevenson G, Dooley T, et al: Pulsed Doppler echocardiographic determination of time of ductal closure in normal newborn infants, *J Pediatr* 98:443-448, 1981.)

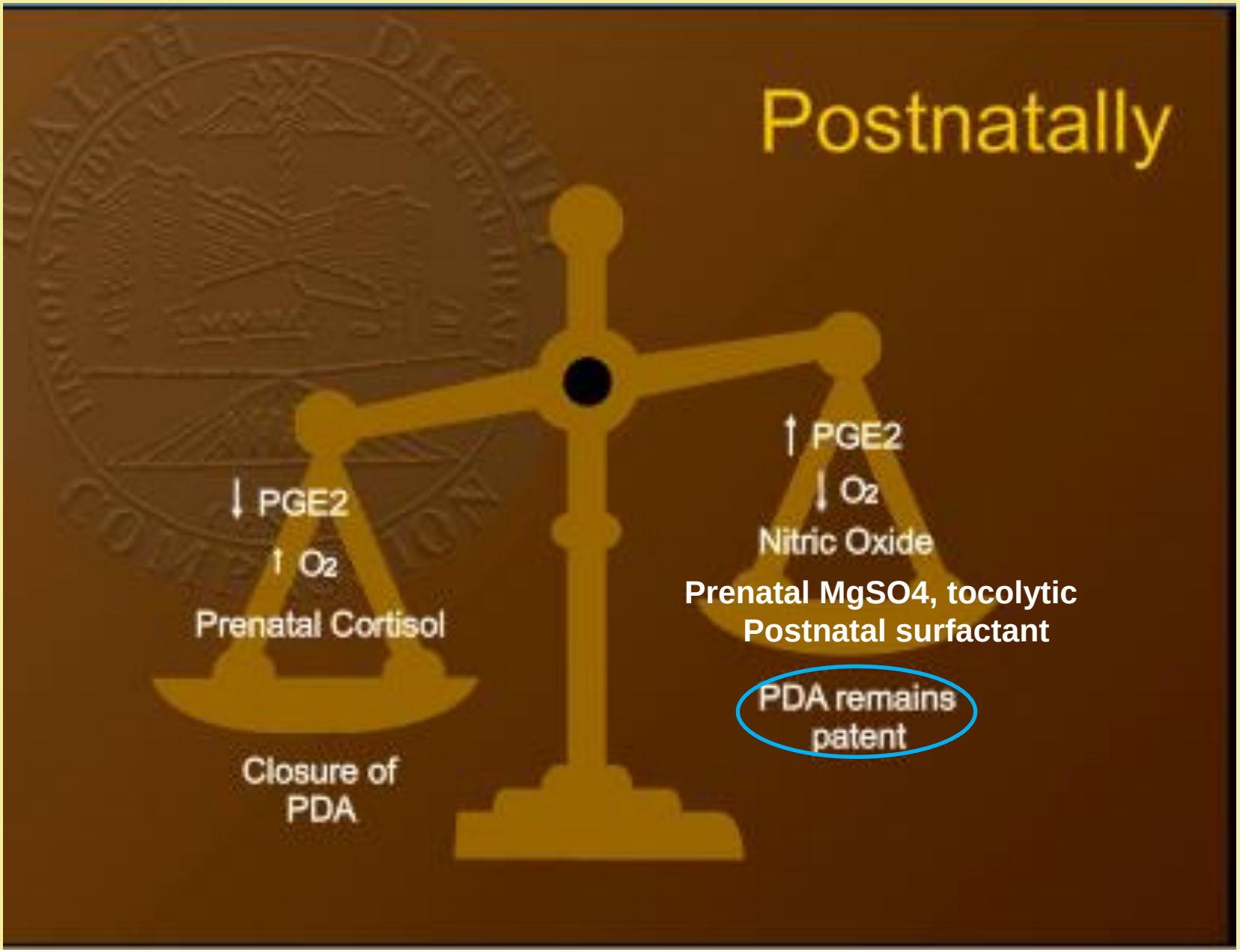
Timing of ductal closure

TABLE 14-1 Timing of Spontaneous Closure of the Ductus Arteriosus

Patient Group	Percentage of Infants with Closed Ductus		
	By Day 4	By Day 7	By Discharge
EGA >38 weeks	100	100	100
EGA 30-37 weeks	90	98	98
EGA 27-28 weeks	22	36	NA
EGA 25-26 weeks	20	32	NA
EGA 24 weeks	8	13	NA
BW 1000-1500 g	35	67	94
BW <1000 g	21	34	NA

BW, Birth weight; *EGA*, estimated gestational age.

Adapted from Clyman RI, Couto J, Murphy GM: Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol *36:123-129, 2012.*


Postnatally
↓ PGE2
↑ O2
Prenatal Cortisol
Closure of PDA
↑ PGE2
↓ O2
Nitric Oxide
Prenatal MgSO4, tocolytic
Postnatal surfactant
PDA remains patent

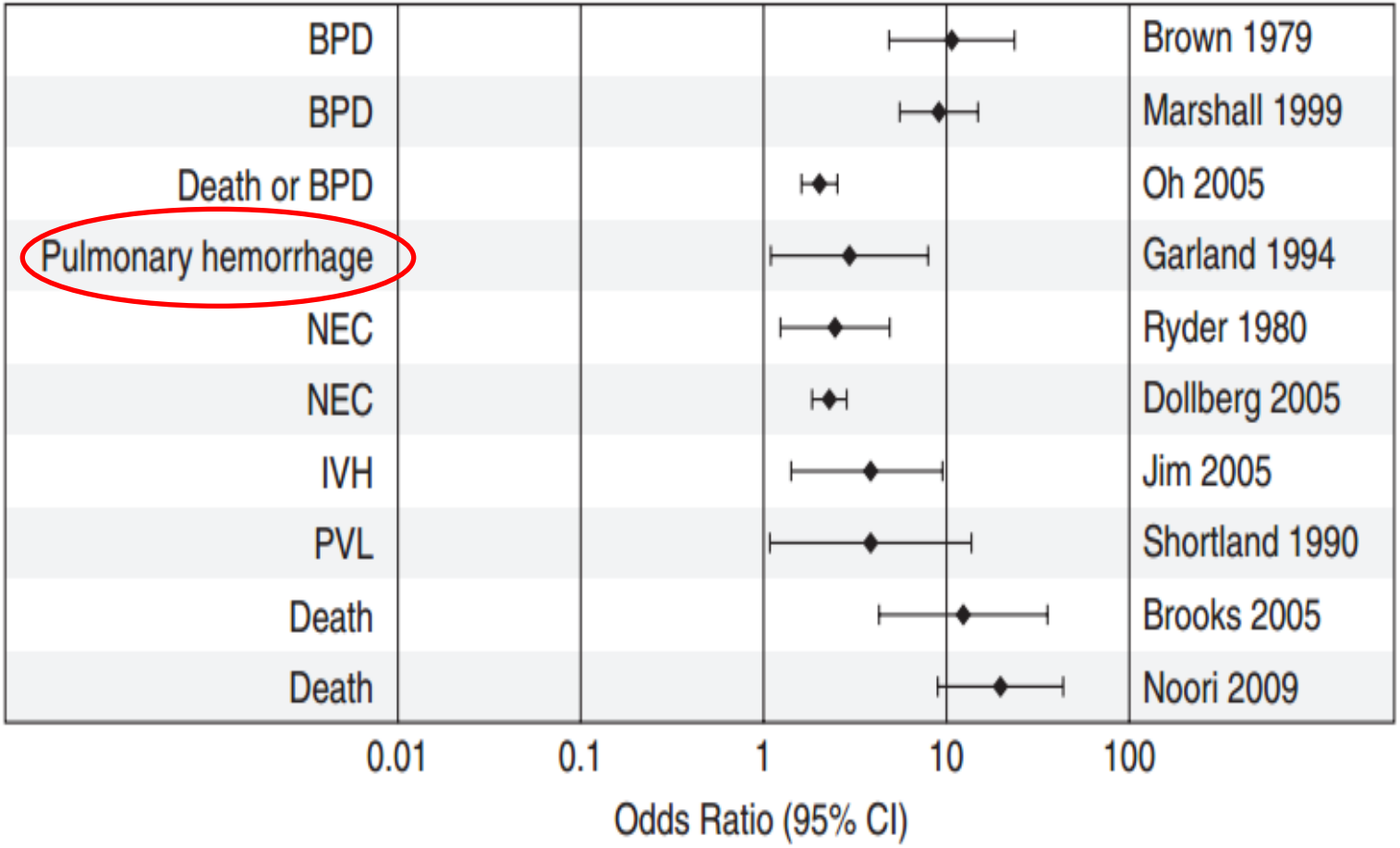
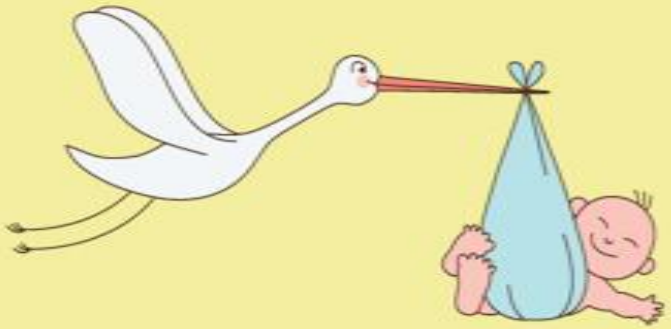
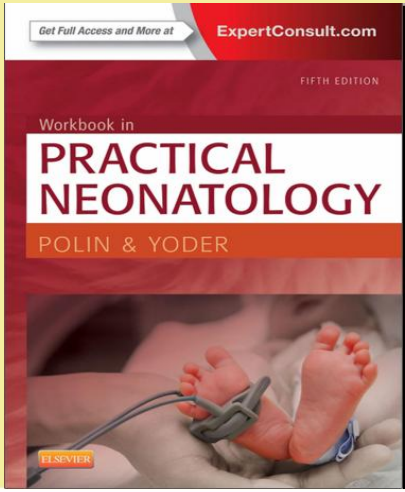


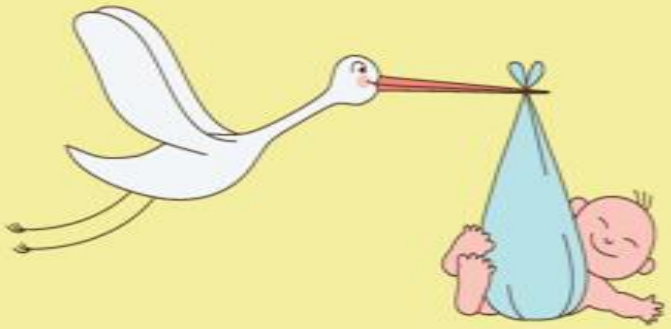
FIGURE 14-2 ■ Odds ratios for adverse outcomes associated with persistent patent ductus arteriosus. Black diamonds represent the point estimates for each odds ratio and the error bars represent the 95% confidence interval for those estimates. None of these confidence intervals include 1, so all outcomes are statistically more likely to occur in preterm infants with persistent PDA ($P < 0.05$). Values for each odds ratio point estimate are provided in the text. (Data from suggested readings: Brooks, 2005; Brown, 1979; Dollberg, 2005; Garland, 1994; Jim, 2005; Marshall, 1999; Noori, 2012; Oh, 2005; Ryder, 1980; and Shortland, 1990.)



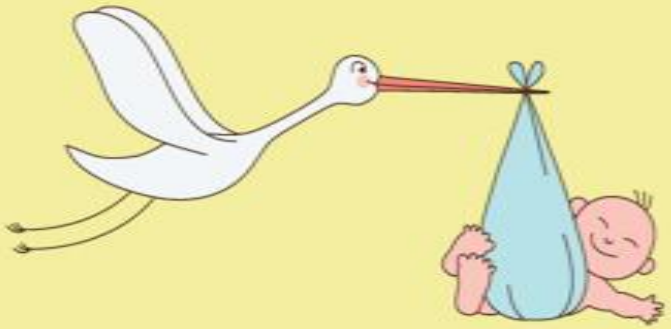
→ Early, severe pulmonary hemorrhage is associated with ductal patency at *12 to 18 hours of age*, but later pulmonary hemorrhage (after the first week) is not related to persistent ductal patency

(Workbook in Practical Neonatology 5th Edition 2015)



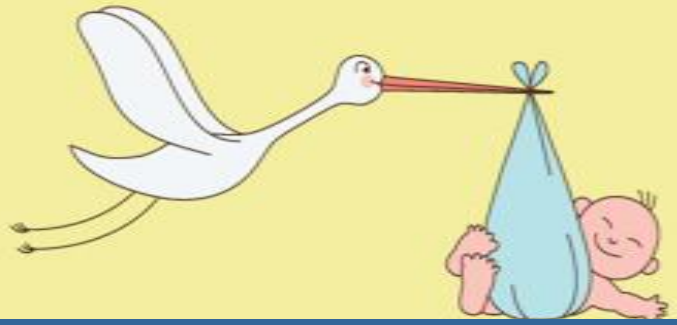


- Diagnosis: In most cases, the clinically silent PDA during the first few days goes undetected unless an echocardiogram is performed



- Signs of bounding pulses, active precordium, and systolic murmur were of reasonable specificity but *very low sensitivity in the first 3 to 4 days* of birth for diagnosis of an echocardiographically defined significant PDA
- Relying on clinical signs alone led to a mean diagnostic *delay of 2 days*

(A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus.Skelton R[1], Evans N, Smythe J. JPaediatr Child Health. 1994 Oct;30(5):406-11)



Timing of screening PDA?

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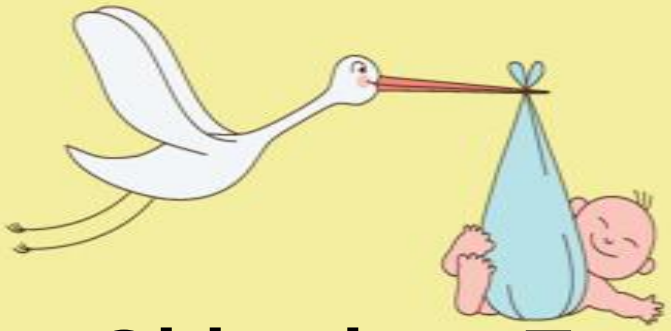
Format: Abstract

Send to

JAMA. 2015 Jun 23-30;313(24):2441-8. doi: 10.1001/jama.2015.6734.

Association Between Early Screening for Patent Ductus Arteriosus and In-Hospital Mortality Among Extremely Preterm Infants.

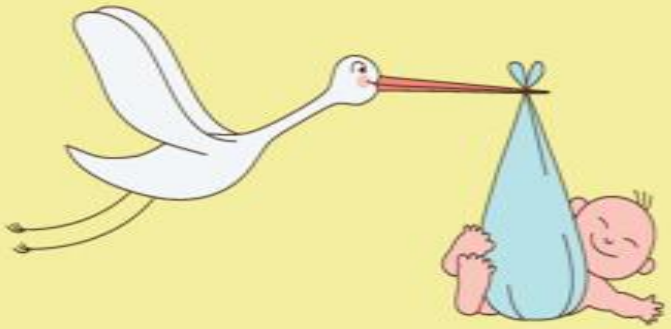
Rozé JC[1], Cambonie G[2], Marchand-Martin L[3], Gournay V[4], Durrmeyer X[3], Durox M[3], Storme L[5], Porcher R[6], Ancel PY[7]; Hemodynamic EPIPAGE 2 Study Group.



- **Objective:** To evaluate the association between early screening echocardiography for PDA and in-hospital mortality
- **Exposures:** Early screening echocardiography before day 3 of life.
- **Design, Setting, and Participants:**

✓ National prospective population-based cohort

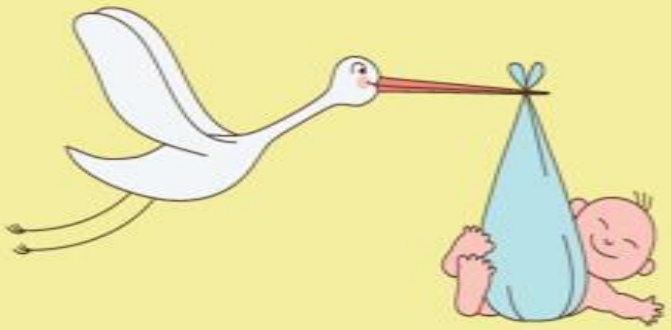
✓ All preterms <=29 weeks hospitalized in 68 NICU in France from April through December 2011.



- **Main Outcomes and Measures**:

✓ Death between day 3 and discharge.

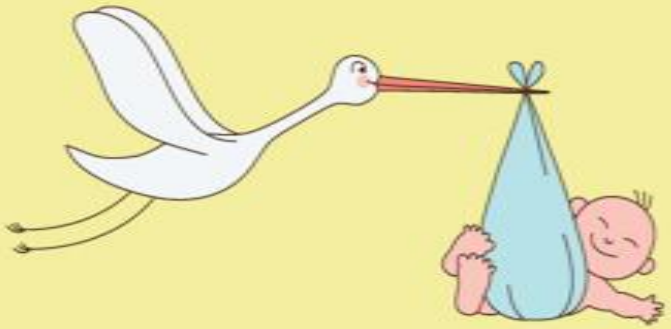
✓ Neonatal morbidities (pulmonary hemorrhage, severe bronchopulmonary dysplasia, severe cerebral lesions, and necrotizing enterocolitis).



Result

1210 preterm infants

- *Treat for PDA more frequently* (55.1% vs 43.1%; [OR], 1.62 [95% CI, 1.31 to 2.00]
- *Lower in-hospital mortality* (55.1% vs 43.1%; OR, 0.73 [95% CI, 0.54 to 0.98])
- *Lower risk of pulmonary hemorrhage* (5.6% vs 8.9%; OR, 0.60 [95% CI, 0.38 to 0.95]
- No different in severe BPD, severe cerebral lesions, and NEC

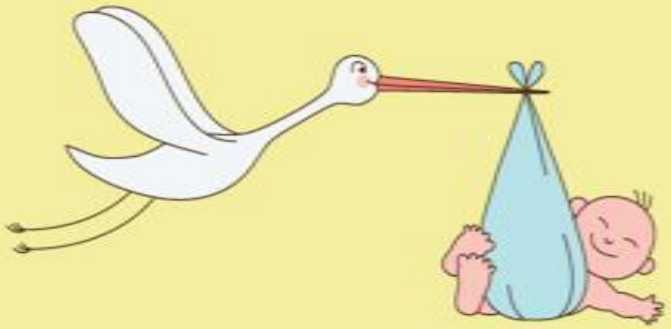


Treatment

- *Options for dealing with PDA in preterm infants:*

(1) Prophylactic pharmacologictreatment (COX inhibitors),
(2) Pre-symptomatic pharmacologic treatment of PDA,
(3) Symptomatic pharmacologic treatment of PDA

- Conservative management,
- Pharmacological closure of the PDA
- Surgical ligation.
- Percutaneous transcatheter occlusion



Prophylactic Pharmacotherapy ?

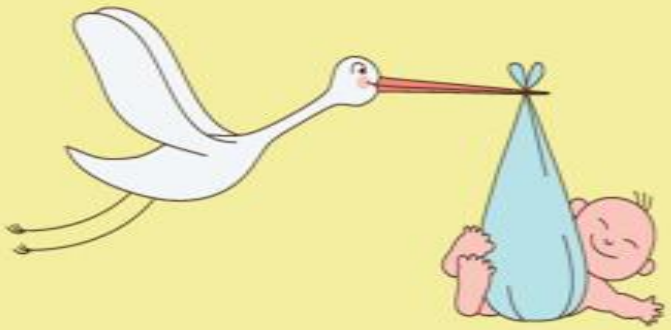
Administering COX inhibitors (indomethacin or ibuprofen) within the first 24h of life irrespective of the diagnosis of PDA

Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants

Indomethacin is the best studied with 2872 babies randomised in 19 trials

Authors' conclusions:

Prophylactic indomethacin has short-term benefits for preterm infants including a reduction in the incidence of symptomatic PDA, PDA surgical ligation, and severe intraventricular haemorrhage. However, there is no evidence of effect on mortality or neurodevelopment.



Indomethacin Prophylaxis

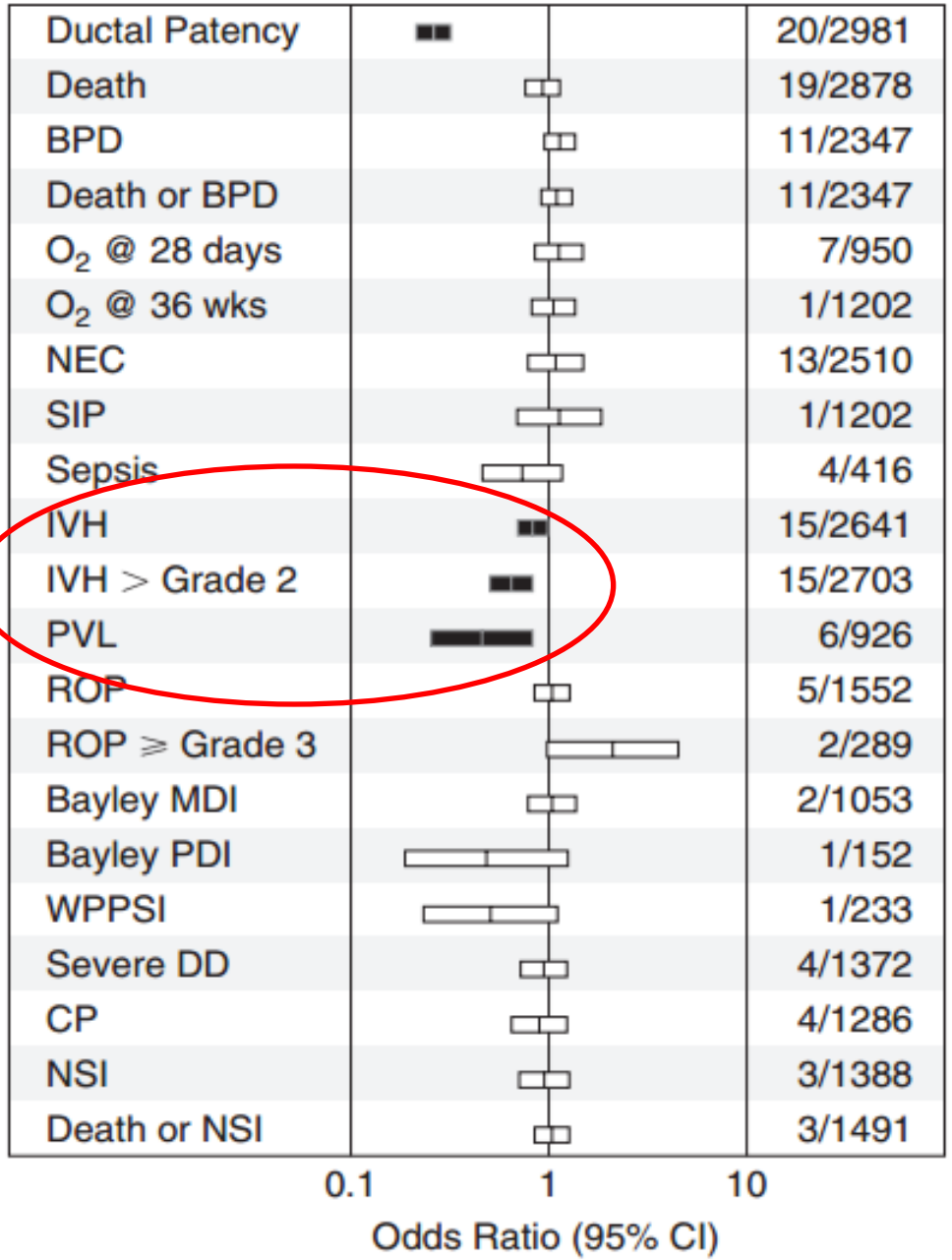
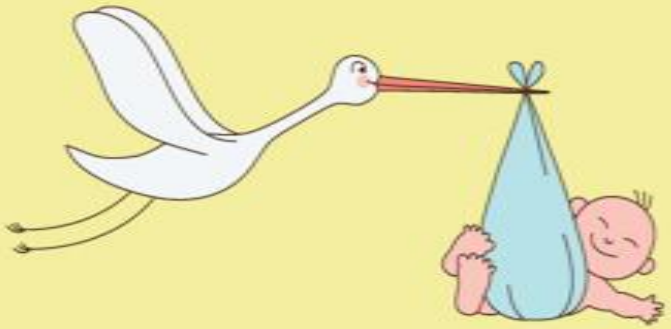


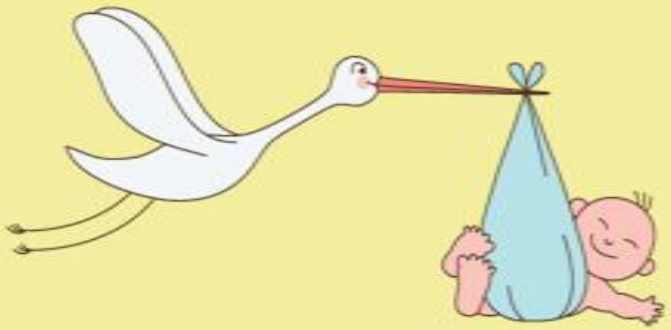
FIGURE 14-4 ■ Pooled odds ratios for outcomes observed in randomized controlled trials of indomethacin prophylaxis. Bars represent the 95% confidence intervals for each outcome; the line at the midpoint of each bar denotes the odds ratio (OR) point estimate. OR significantly different from 1 are indicated by black bars (two-tailed $P < 0.05$). The number of trials (N) and total included subjects (n) for each outcome are shown on the right (N/n). *BPD*, Bronchopulmonary dysplasia; *CLD*, chronic lung disease; *NEC*, necrotizing enterocolitis; *SIP*, spontaneous intestinal perforation; *IVH*, intraventricular hemorrhage; *PVL*, periventricular leukomalacia; *ROP*, retinopathy of prematurity; *MDI*, Mental Development Index; *PDI*, Psychomotor Development Index; *CP*, cerebral palsy. (Adapted from Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol* 30:241-252, 2010.)



→ Some clinicians recommend indomethacin prophylaxis for extremely immature babies (23–25 weeks) to prevent IVH

→ At this time, less than 30% of neonatologists in the United -- States use indomethacin “prophylactically”, despite its short-term benefits

(Jhaveri N, Soll RF, Clyman RI. Feeding practices and patent ductus arteriosus ligation preferences-are they related? Am J Perinatol. 2009;27:667–674. [PubMed])



Ibuprofen Prophylaxis

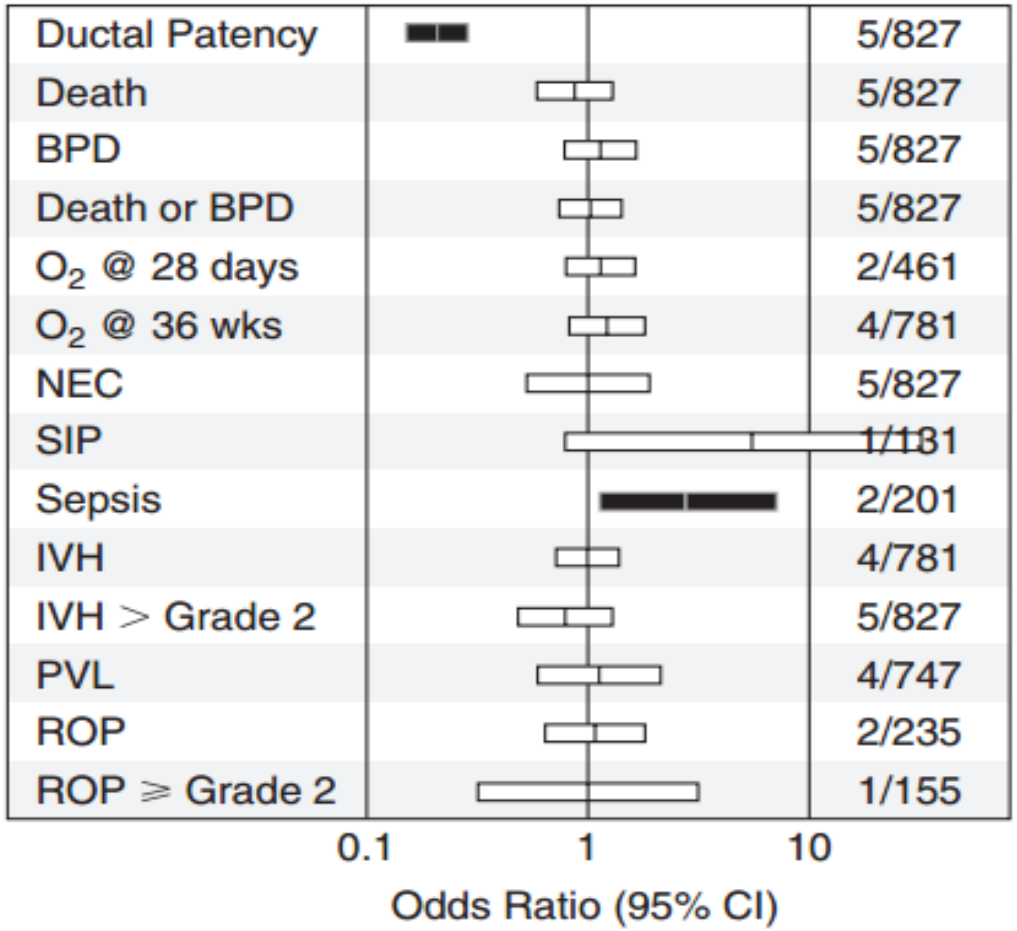
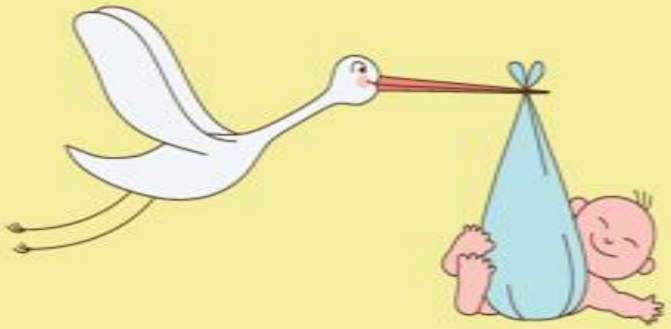
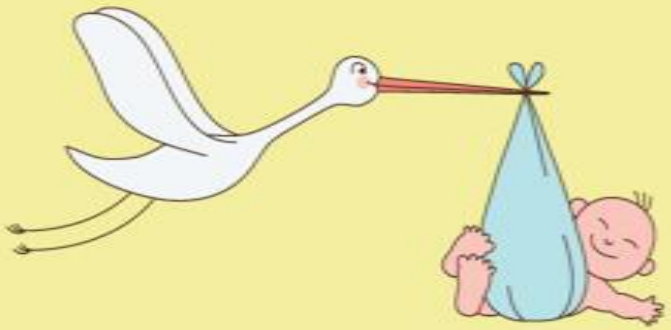


FIGURE 14-5 ■ Pooled odds ratios for outcomes observed in randomized controlled trials of ibuprofen prophylaxis. Symbols and abbreviations are as indicated for Figure 14-4. (Adapted from Benitz WE: Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol* 30:241-252, 2010.)



- No significant differences in mortality, IVH, or BPD
- No reduction in IVH, PAL in the treated group
- Increased risk of gastrointestinal bleeding

→ Prophylactic ibuprofen exposes many infants to renal and gastrointestinal side effects without any important short-term benefits and *is not recommended*



Pre-symptomatic Pharmacologic Treatment

- No effect on the rate of mortality, BPD, IVH, ROP, or length of ventilation, death, IVH, NEC,…
- More renal side effect

→ Presymptomatic indomethacin or ibuprofen therapy for PDA in preterm infants *is not recommended*.

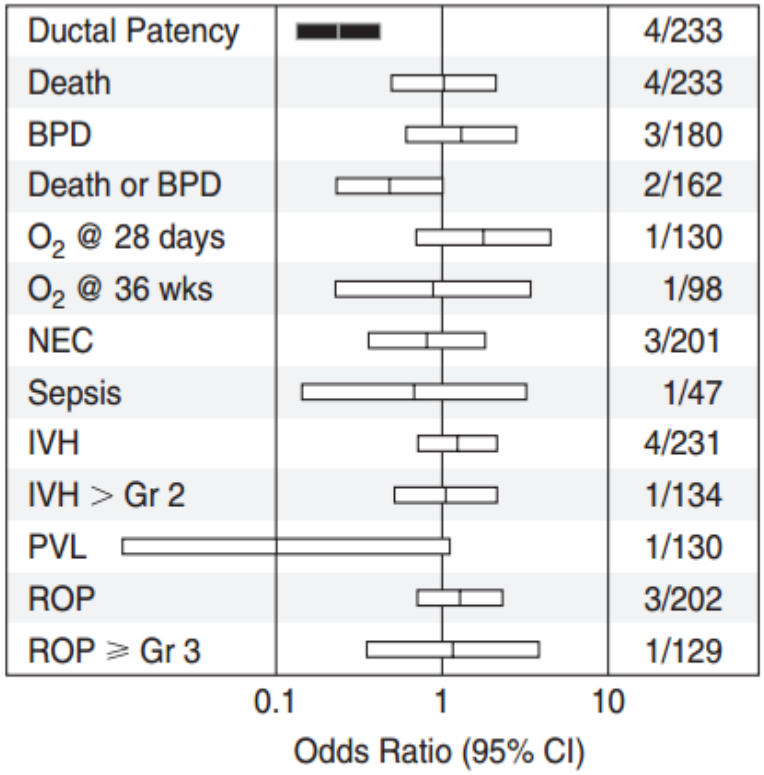
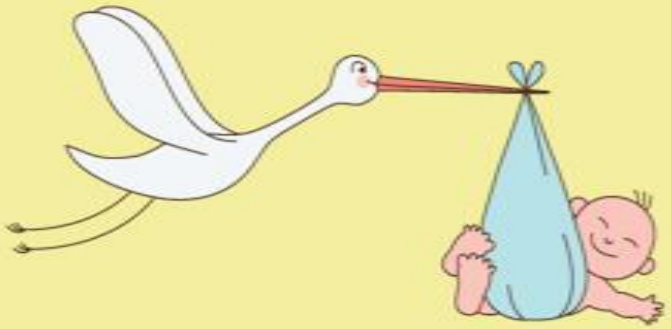


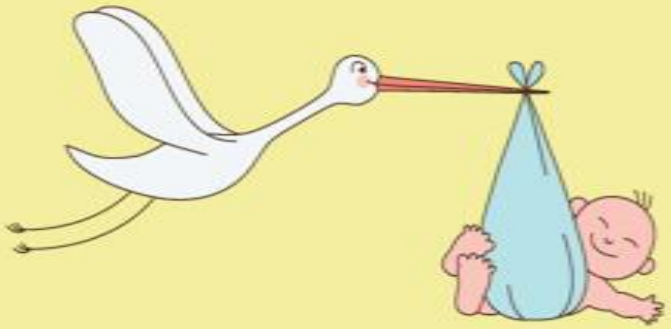
FIGURE 14-6 ■ Pooled odds ratios for outcomes observed in randomized controlled trials of ibuprofen or indomethacin treatment of asymptomatic preterm infants. Symbols and abbreviations are as indicated for Figure 14-4.



Conservative Management

- ✓ Fluid restriction
- ✓ Diuretics, *avoidance of loop diuretics*
- ✓ Maintaining a hematocrit of 35 to 40 percent
- ✓ Increased positive airway pressure
- ✓ Correction of alkalosis
- ✓ Avoidance of pulmonary vasodilators: oxygen or NO

- ➢ Asymptomatic infants with PDAs generally do not require medical management or surgical ligation. These infants should be monitored for evidence of CHF, failure or renal impairment, increasing oxygen requirement, or other complications



Pharmacological closure

- Indomethacine
- Ibuprofen
- Paracetamol (?)

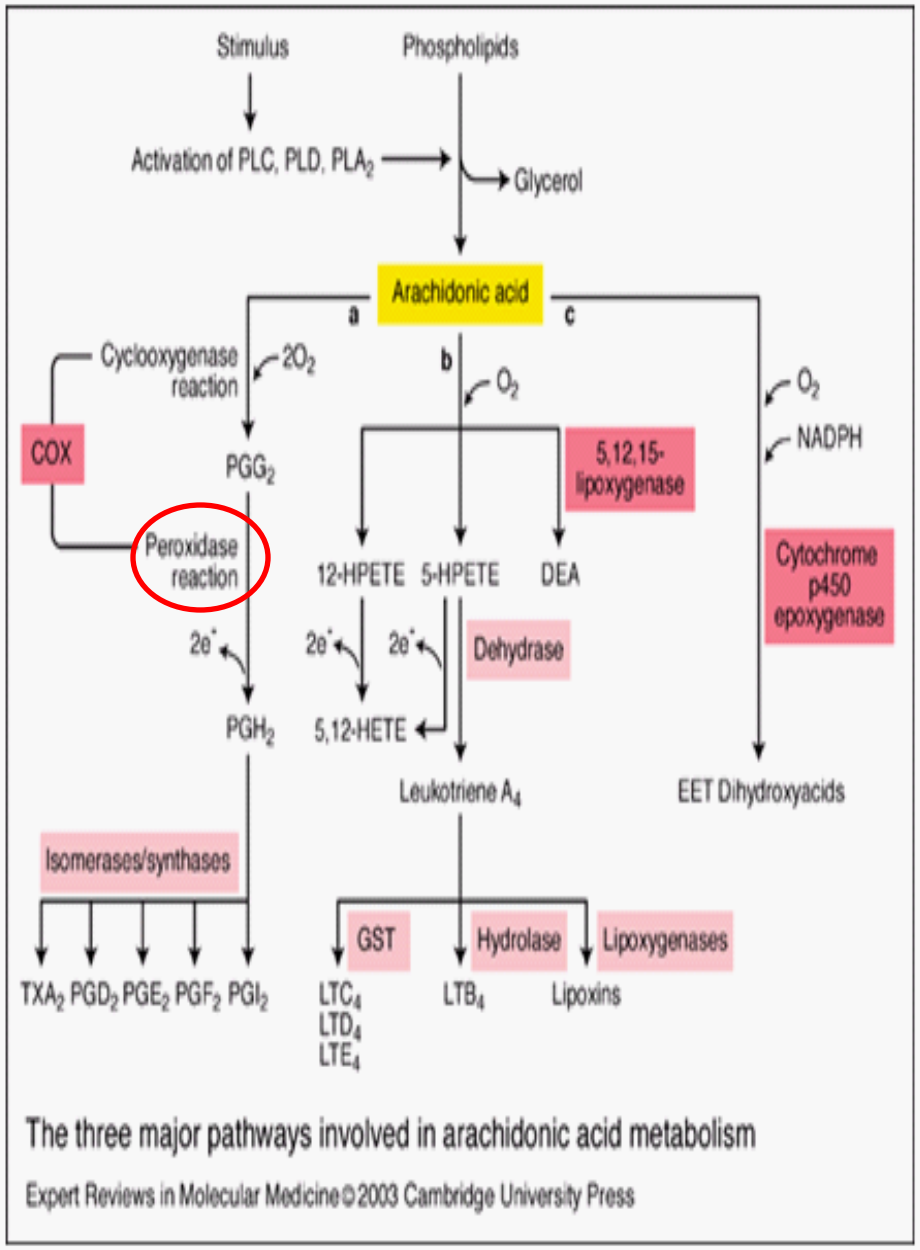
Cochrane Library

Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants

33 studies, 2190 infants, iv and oral administration

Authors' conclusions

Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of NEC and transient renal insufficiency. Oro-gastric administration of ibuprofen appears as effective as iv administration. To make further recommendations, studies are needed to assess the effectiveness of high-dose versus standard-dose ibuprofen, early versus expectant administration of ibuprofen, echocardiographically guided versus standard iv ibuprofen, and continuous infusion versus intermittent boluses of ibuprofen. Studies are lacking evaluating the effect of ibuprofen on longer-term outcomes in infants with PDA.



The three major pathways involved in arachidonic acid metabolism

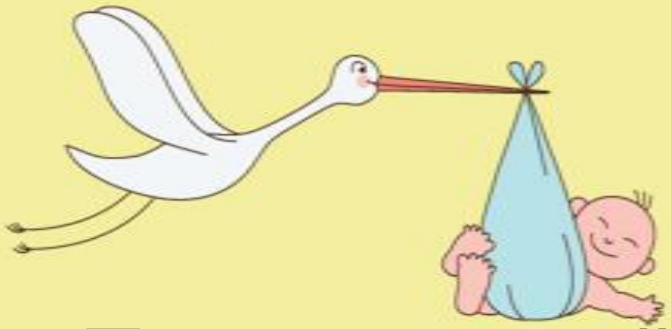
Paracetamol ?

→ Paracetamol act at the peroxidase segment of the enzyme

→ Peroxidase activated at *10-fold-lower peroxide concentrations than is cyclooxygenase*

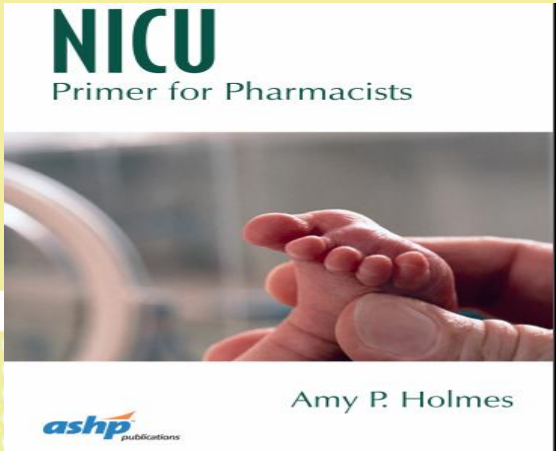
→ Firstline therapy, used when ibuprofen was contraindicated, and as rescue therapy, used when ibuprofen failed

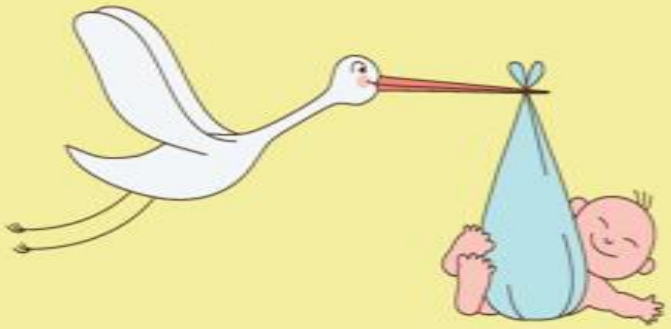
(PubMed Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis)



Feeding during treatment?

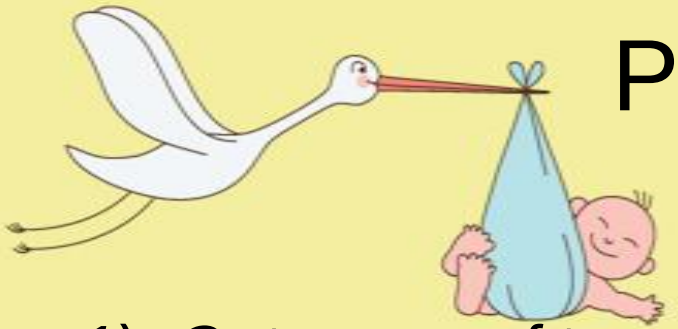
- Several studies have shown that enteral feeds during COX inhibitor therapy appear to be safe
- Some clinicians allow trophic feeds or continue the current feeding volume but do not advance the feeding regimen during treatment *(NICU Primer for Pharmacists)*





Surgical ligation

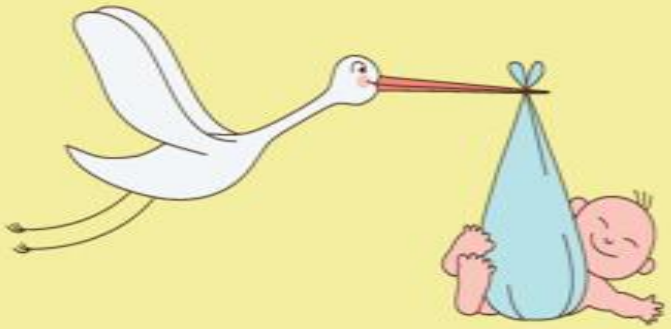
- ✓ If the patient remains symptomatic after one or two courses of cyclooxygenase (COX) inhibitor or if COX inhibitor treatment is contraindicated
- ✓ Risks of blood pressure fluctuations, respiratory compromise, infection, intraventricular hemorrhage (IVH),chylothorax, recurrent laryngeal nerve paralysis.



Percutaneous transcatheter occlusion

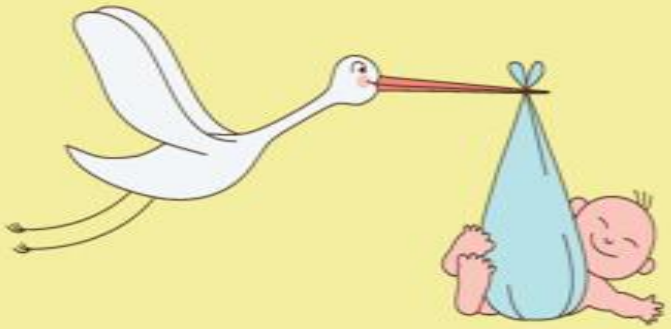
1) *Outcomes of transcatheter occlusion of patent ductus arteriosus in infants weighing ≤ 6 kg. JACC Cardiovasc Interv 2010; 3:1295.*
2) *Percutaneous Patent Ductus Arteriosus (PDA) Closure in Very Preterm Infants: Feasibility and Complications. J Am Heart Assoc 2016; 5*
3) *Transcatheter occlusion of patent ductus arteriosus in pre-term infants. JACC Cardiovasc Interv 2010; 3:550.*

→ *Need more randomized controlled trials for both efficacy and safety .*

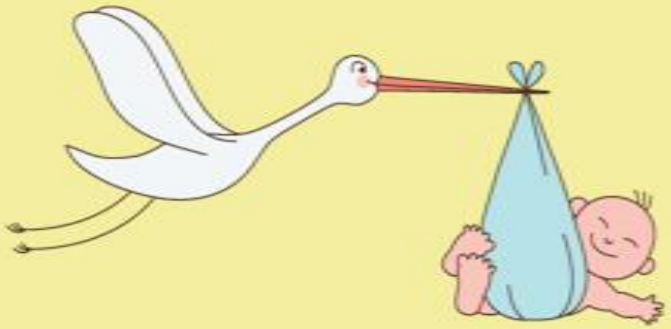


Conclusion

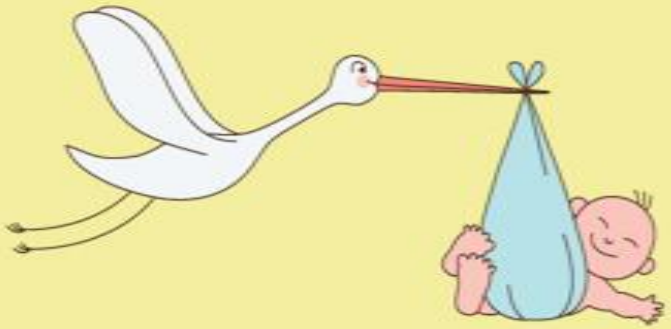
- No randomized controlled trials comparing long-term outcomes of the three different approaches →no data to determine the optimal management of PDA in preterm infants → Practice can vary from NICU to NICU
- Relying on clinical signs alone led to a mean diagnostic *delay of 2 days*



- Early screening echocardiography before day 3 of life
- Severe pulmonary hemorrhage is associated with ductal patency at *12 to 18 hours of age*, but later pulmonary hemorrhage (after the first week) is not related to persistent ductal patency



- *Infants 23-25 wk* (without antenatal steroid) at a higher risk of PDA-related morbidities and would benefit *from prophylactic low-dose* indomethacin *for prevention of IVH*
- Presymptomatic indomethacin or ibuprofen therapy for PDA in preterm infants *is not recommended*



- Ibuprofen is equally effective but has fewer adverse effects
- Paracetamol can be used when ibuprofen was contraindicated
- Continue the current feeding volume but do not advance the feeding regimen during treatment
- Avoidance of loop diuretics


Thank you