FETAL LUNG IMMATURITY:
NOVEL APPROACH

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The widespread introduction of surfactant therapy in the newborn and the use of antenatal corticosteroids (GC) has dramatically changed the incidence and the severity of NRDS and the typology of the preterm infants that are at risk of chronic lung disease (Jobe et al. Ann Rev Physiol 2000;62:825-46). However, neither surfactant nor antenatal corticosteroids are devoid of side effects and do not represent a panacea.

Multiple courses of antenatal corticosteroids are associated with a delay in long-term psychomotor development in children with birth weights < 1,500 grams.

Therefore these findings suggest caution with the routine use of multiple courses of antenatal corticosteroids.

(AJOG 182 – Part 27:S24)

Surfactant administration is considered as:

1) Prophylactic if given systematically during the first 15 min of life

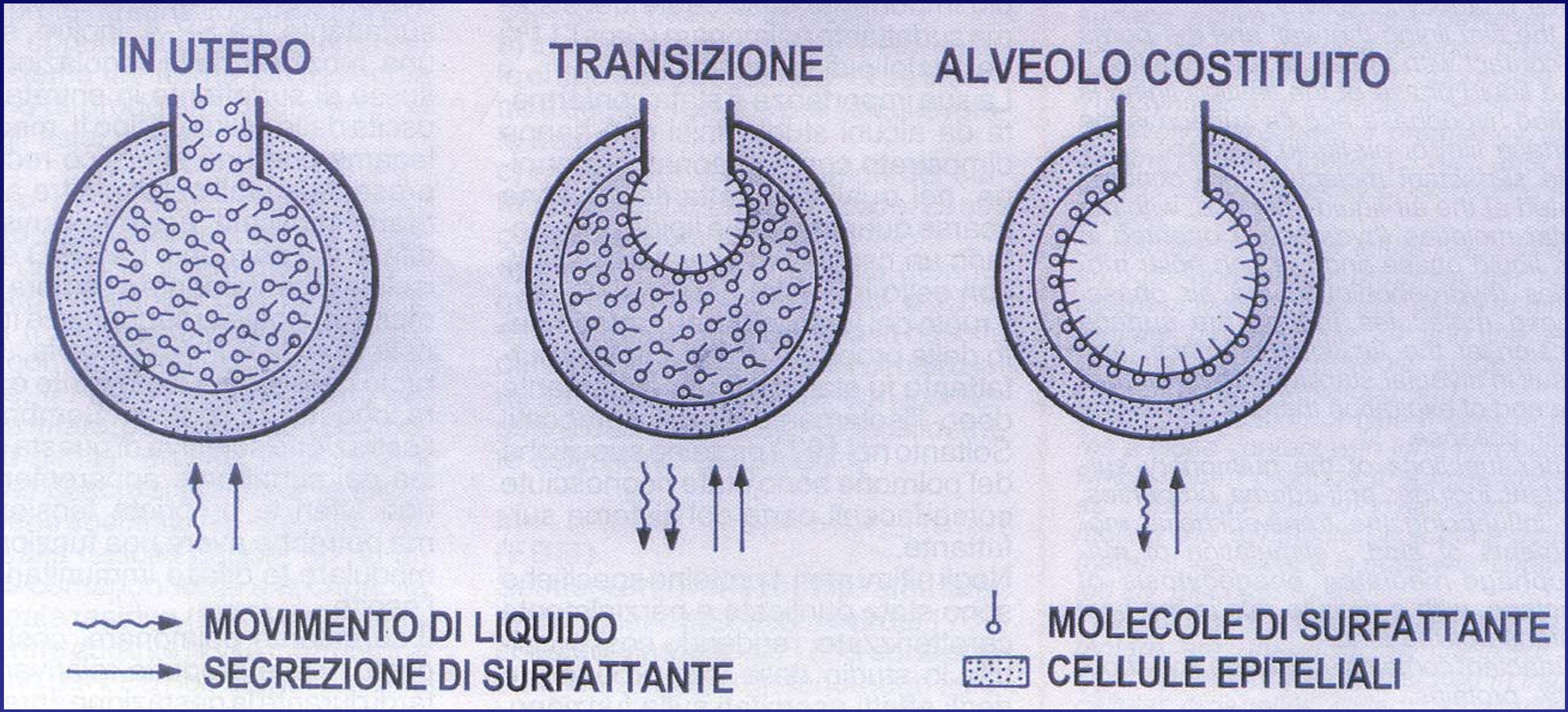
2) Early, if given between 15 min and 2 hours of life

3) Rescue, if given after 2 hours of life after diagnosis of NRDS has been made.

Prenat Neonat Med Sept. 2001 - Report of EURAIL (EV Cosmi et al. (Ed))

In 1981 we have indicated that the most rational approach would be the prevention rather than treatment of RDS and that the most natural way would be to instill SS in fetal pulmonary liquid (FPL) compartment, i.e., at birth before the first breath or in utero by direct injection into amniotic fluid (AF) close to the fetal nostrils and mouth so that it will undergo uniform distribution within the FPL.

(Cosmi EV Ed.
Obstetric Anesthesia and Perinatology. Appleton-Century-Crofts. NY 1981)

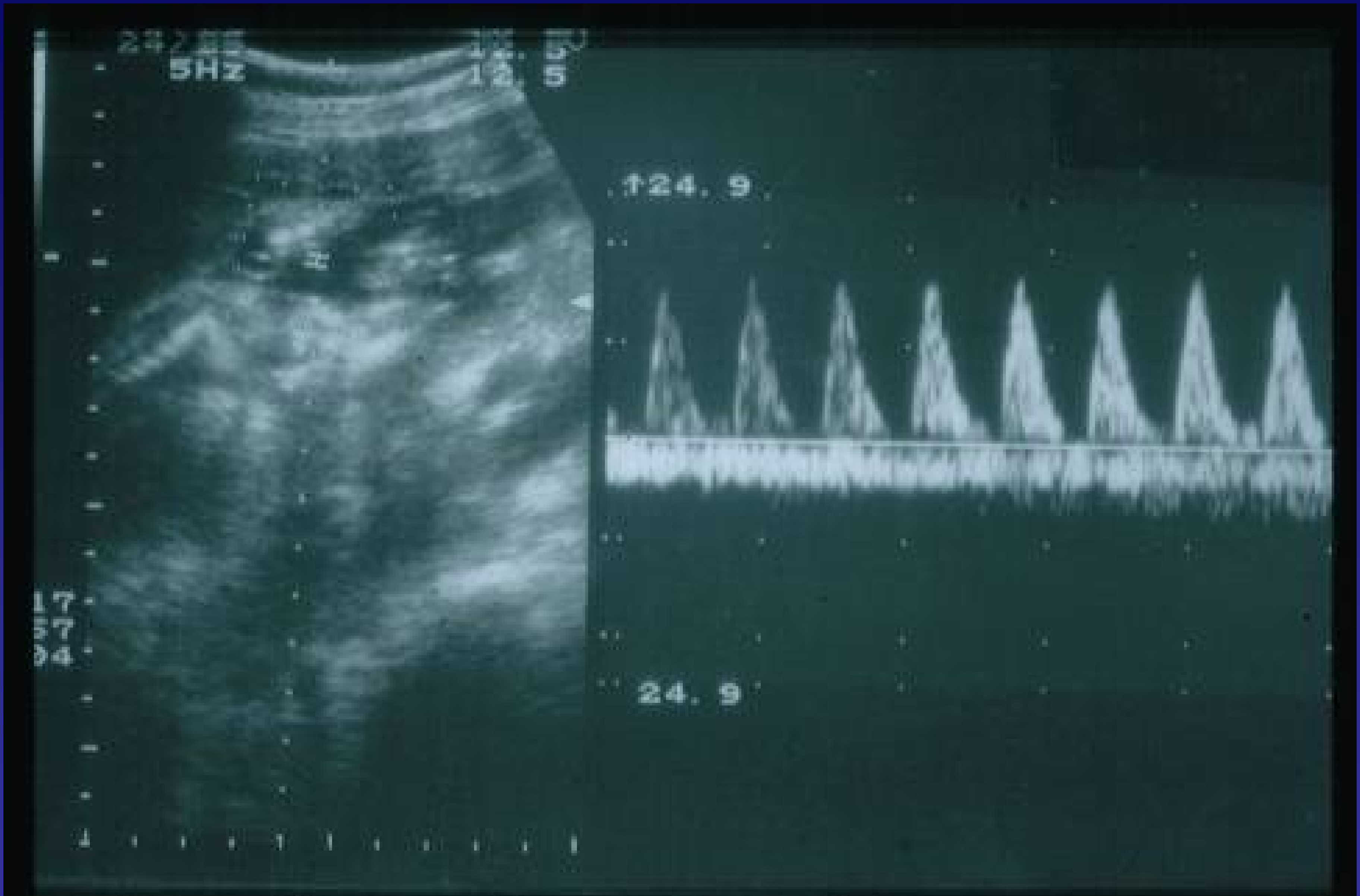


Left: alveoli filled with liquid containing surfactant. A shift of fetal pulmonary liquid (FPL) and secretion of surfactant inside the alveoli is observed. Center: after the onset of respiration, FPL rapidly leaves the alveoli and secretion of surfactant increases. Right: immediately after birth the lining layer is formed and a normal balance of the liquid occurs. Surfactant secretion continues.

OBJECTIVE

To determine whether intramniotic (IA) supplementary surfactant (SS) given to fetuses in severe distress, with documented lung immaturity and requiring emergency delivery by CS could result in successful adaptation to air-breathing at birth.

Fetal conditions were severely compromised as documented by Doppler velocimetry and in some cases by cardiotocography. After informed consent, amniocentesis was performed under ultrasound (US) guidance close to the fetal nostrils and/or mouth of the fetus in order to collect AF for testing fetal lung maturity (FLM), and the needle was kept in place. FLM was assessed by a rapid test, the “shake test”, and later on by L/S and PG determination or lamellar bodies measurement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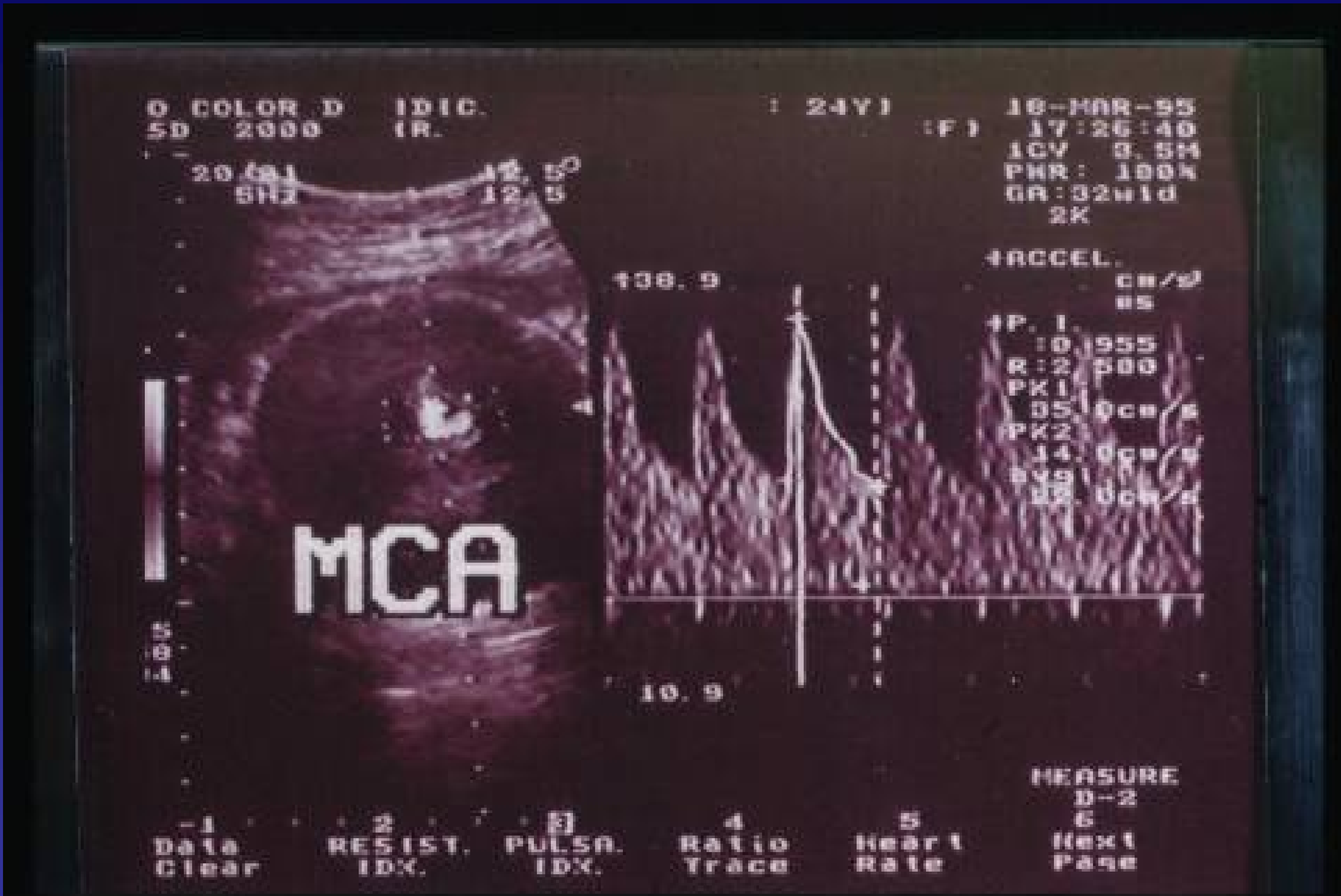
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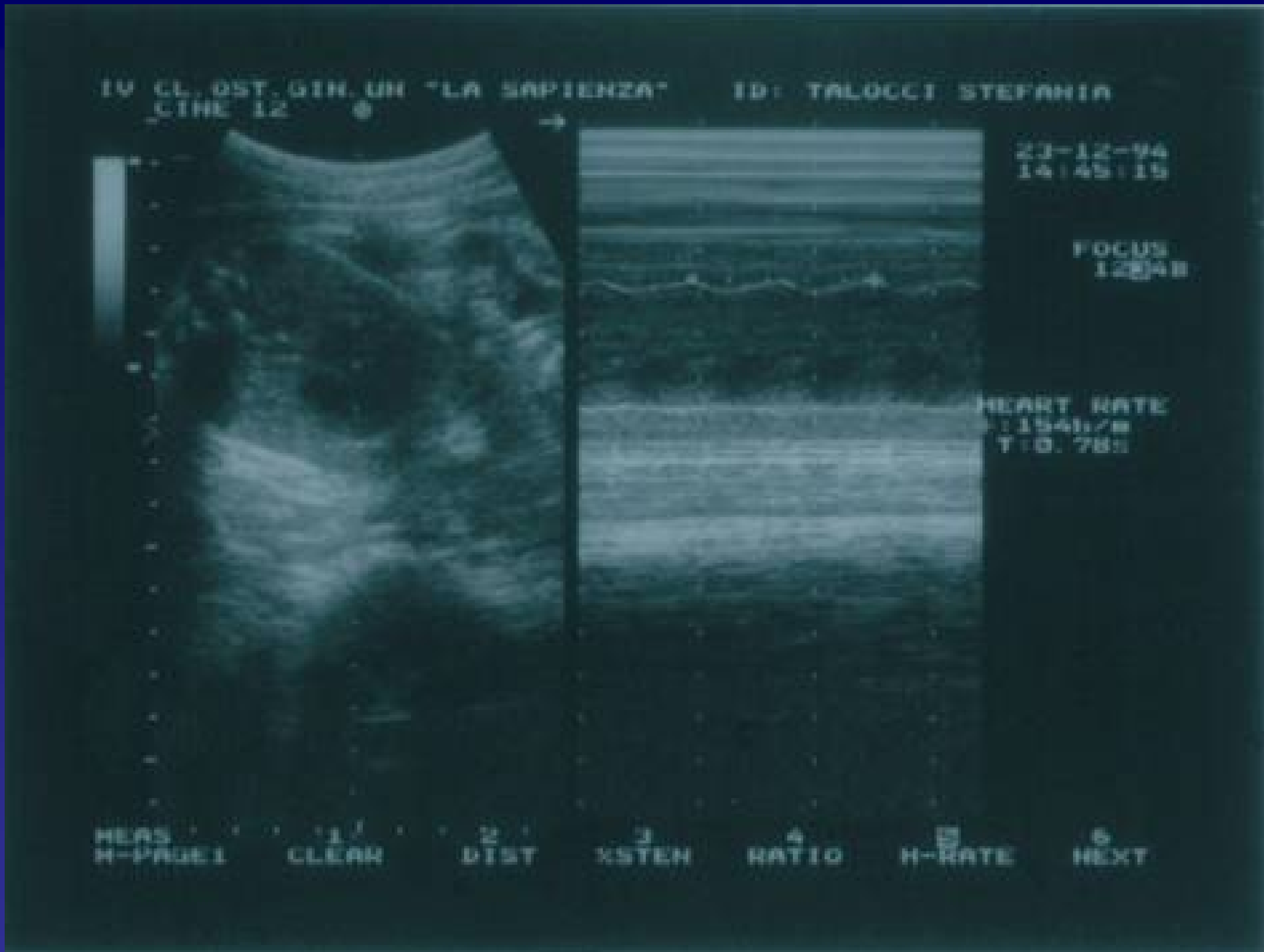
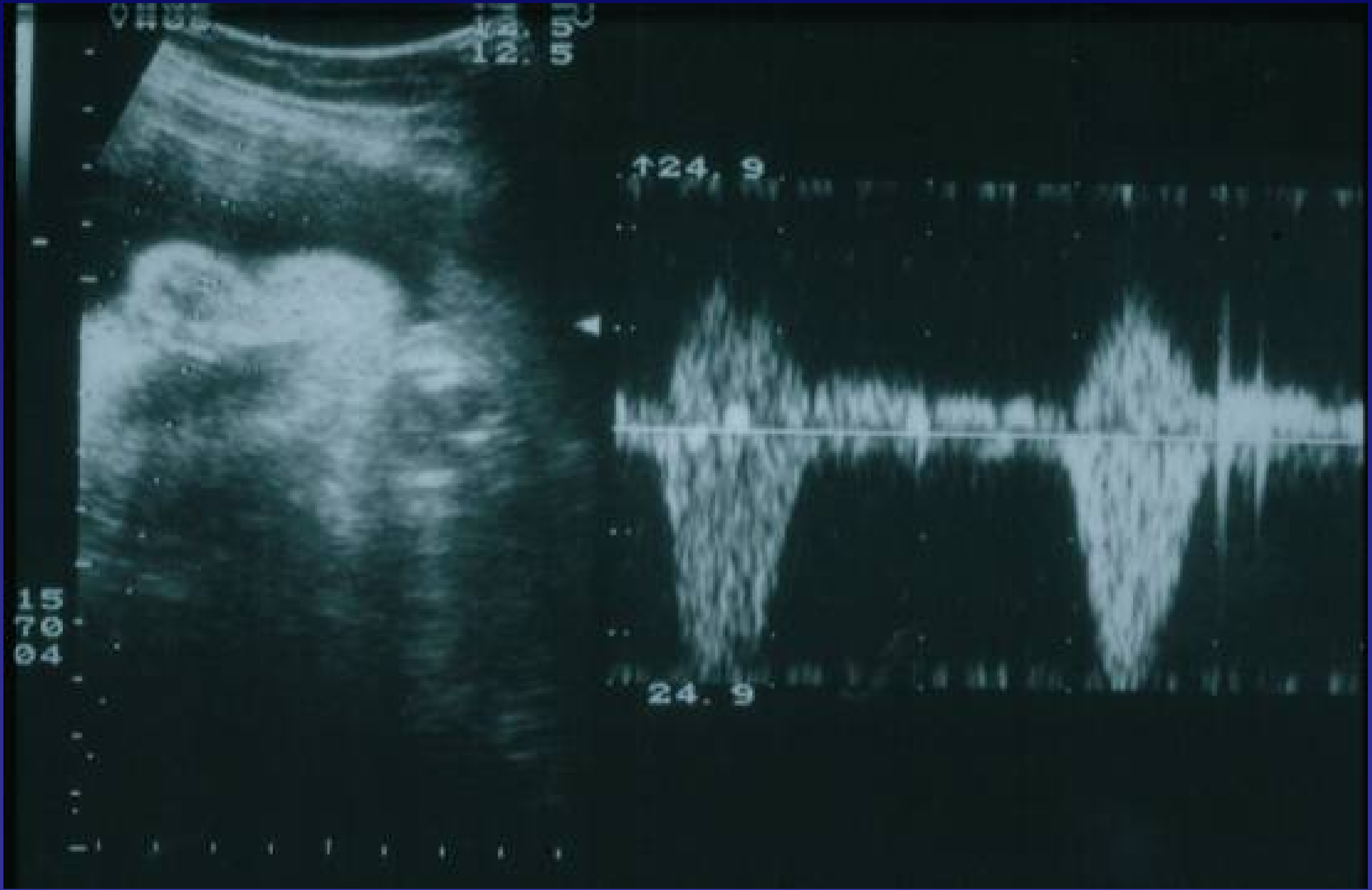


RR

T.S. 16 years **LMP 31.5** **EGA 28.5**

AMINOPHYLLINE 1.4 mg /kg/hr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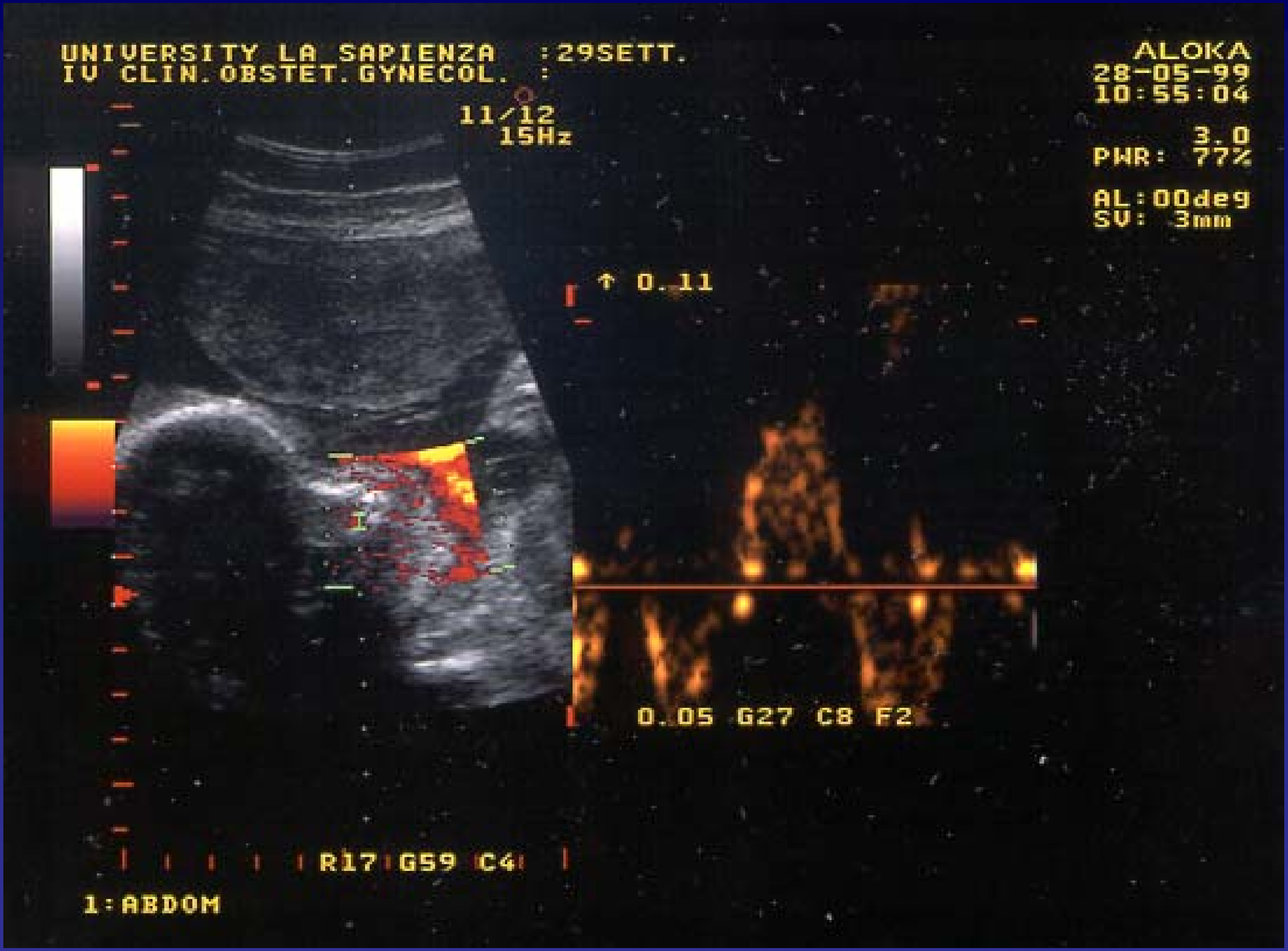
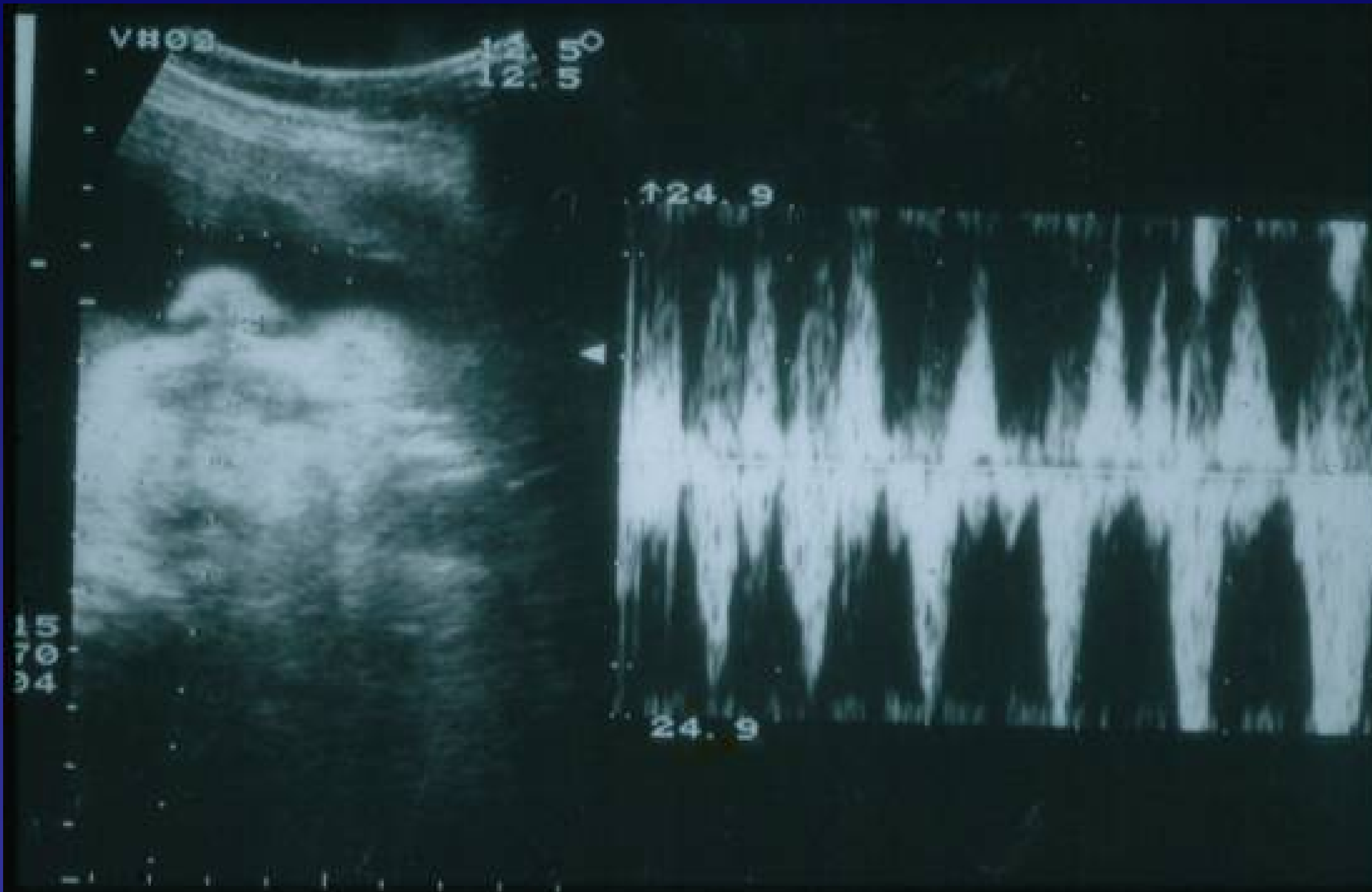


NASAL FLUID FLOW DURING FBMs

POWER DOPPLER



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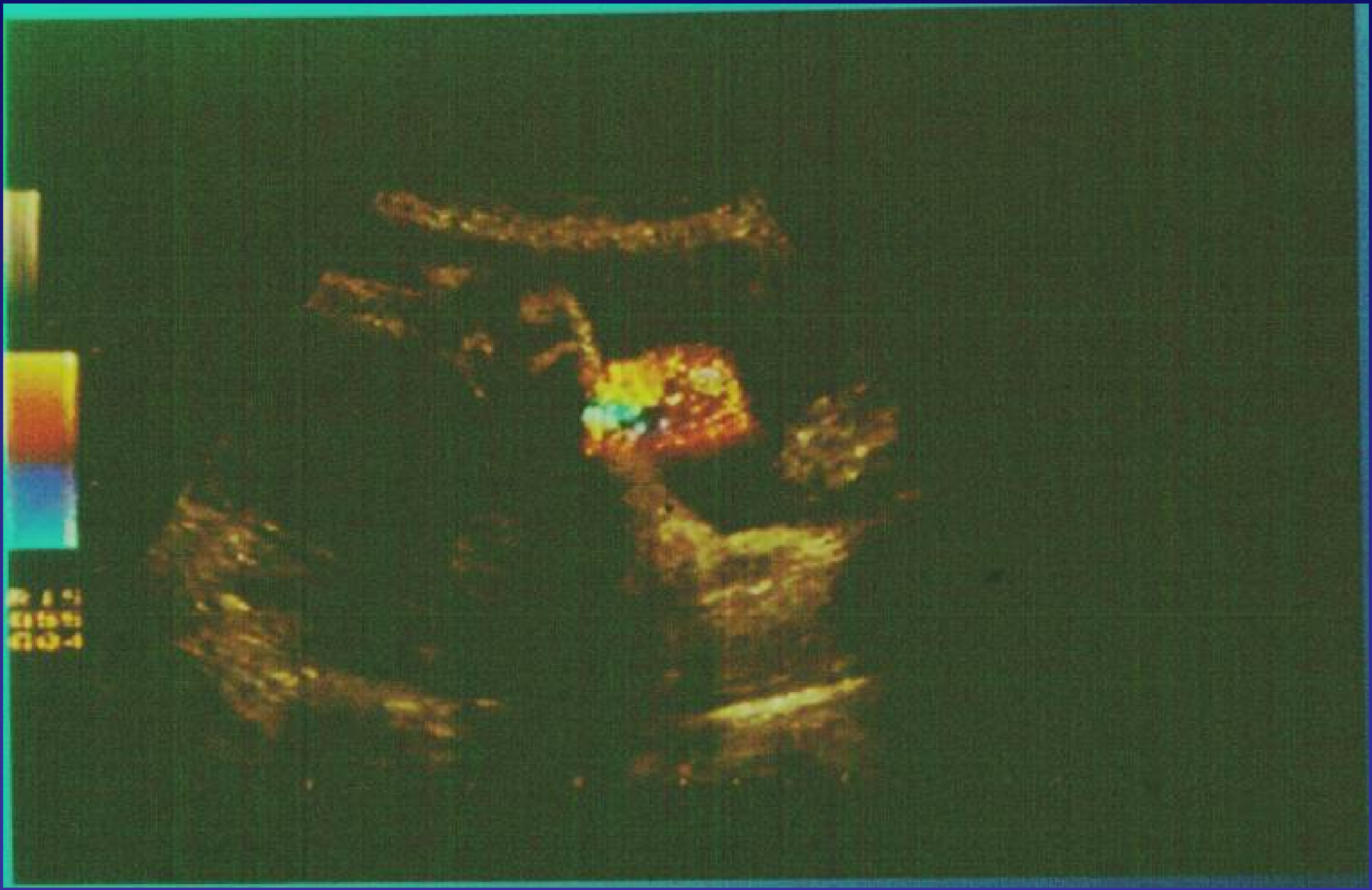
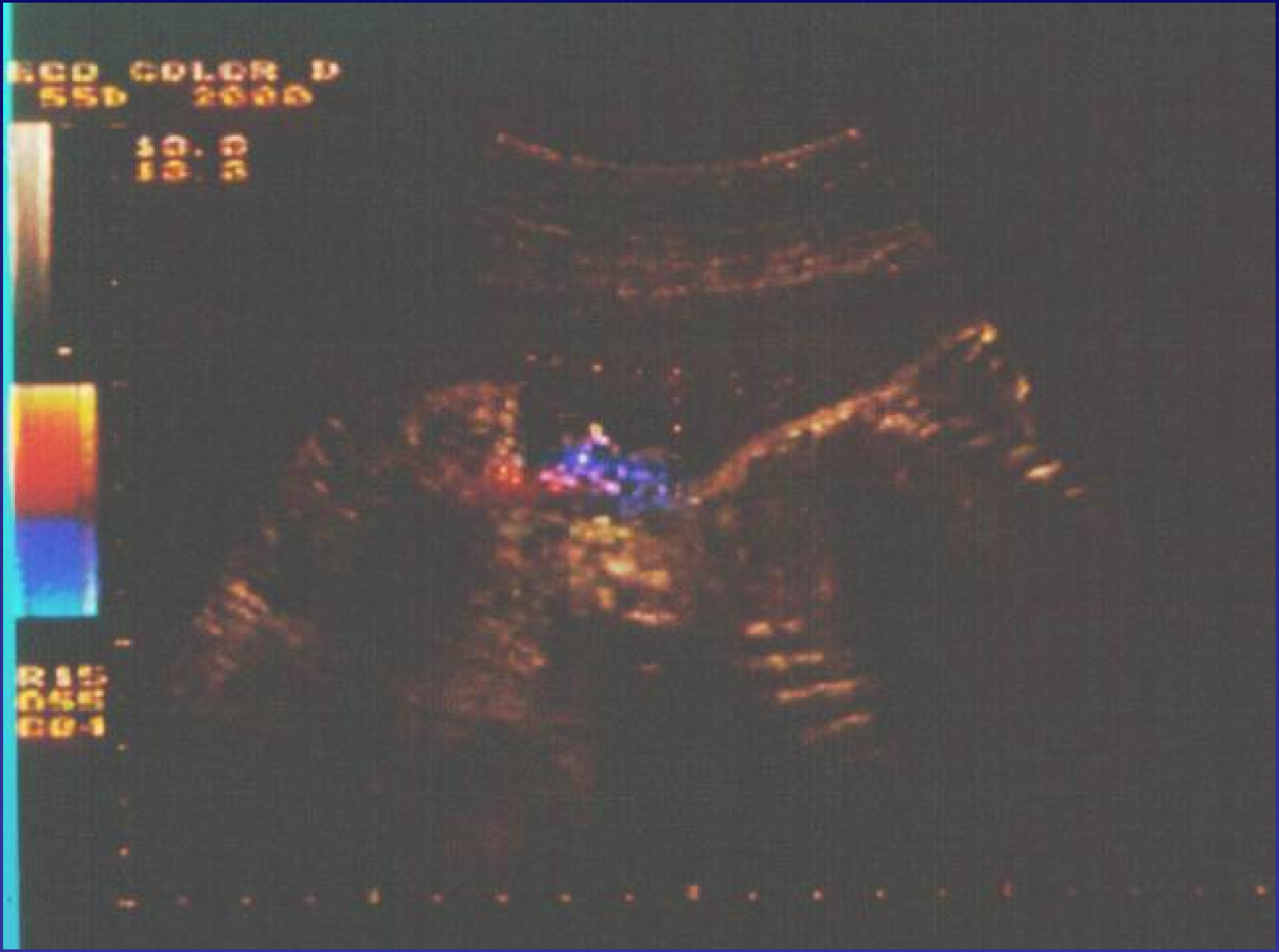
METHODS

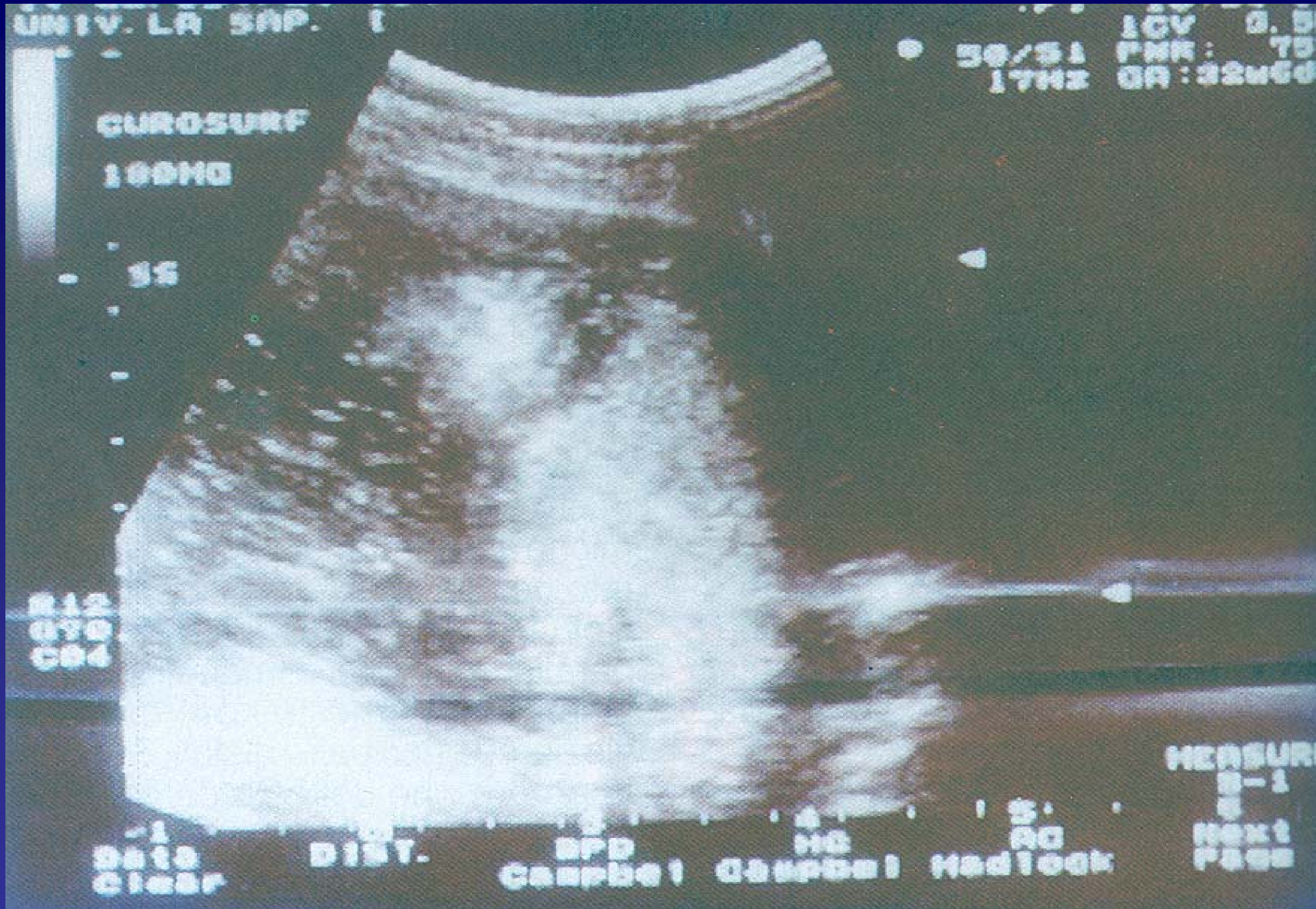
In cases with FL immaturity surfactant (80-120 mg) was then instilled through the amniocentesis needle directed toward the fetal nostrils. Entry of the surfactant in the AF compartment was seen by US as a sonolucent material that moved down the trachea and upper airways during fetal FBMs, which had increased in depth and frequency during A infusion; some of SS was swallowed by fetus.

COROSURF Injection



Snow balls





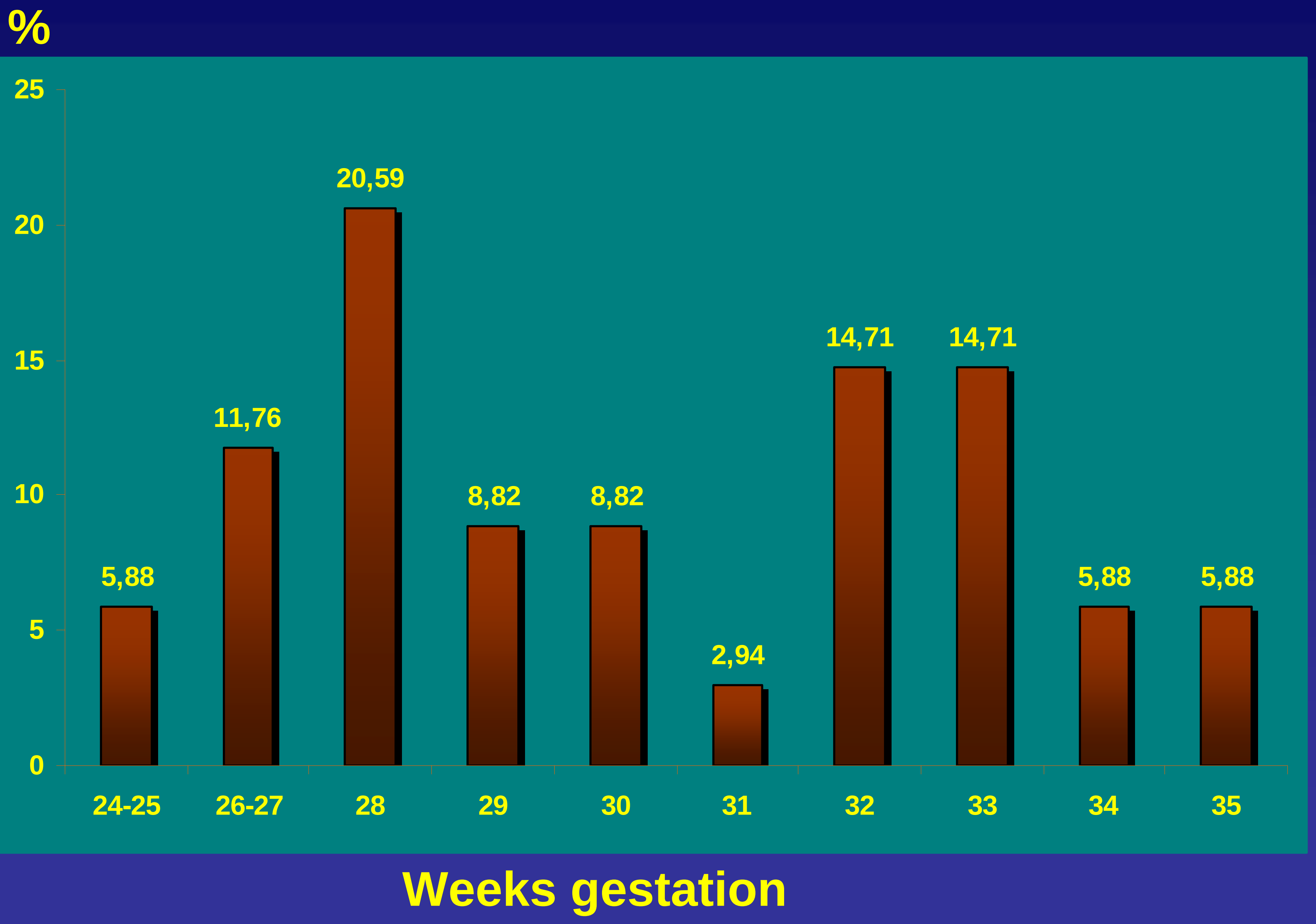
EXOGENUS SURFACTANT INJECTION (180 mg)

Curosurf through fetal trachea

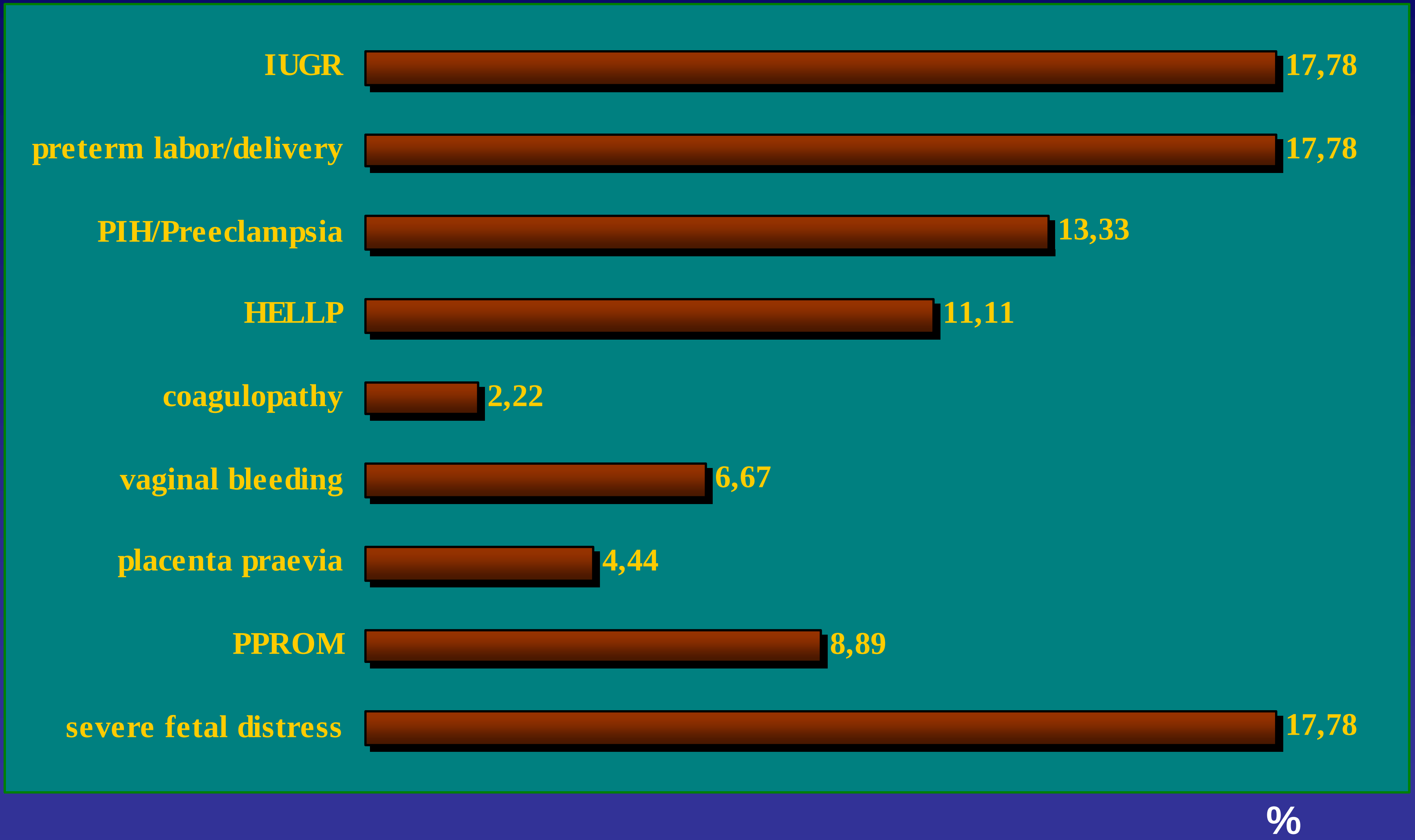
METHODS

CS was performed under epidural anesthesia 60 to 150 minutes after the administration of surfactant. Before the incision of amniotic membranes a sample of AF was collected with a 10 ml syringe.

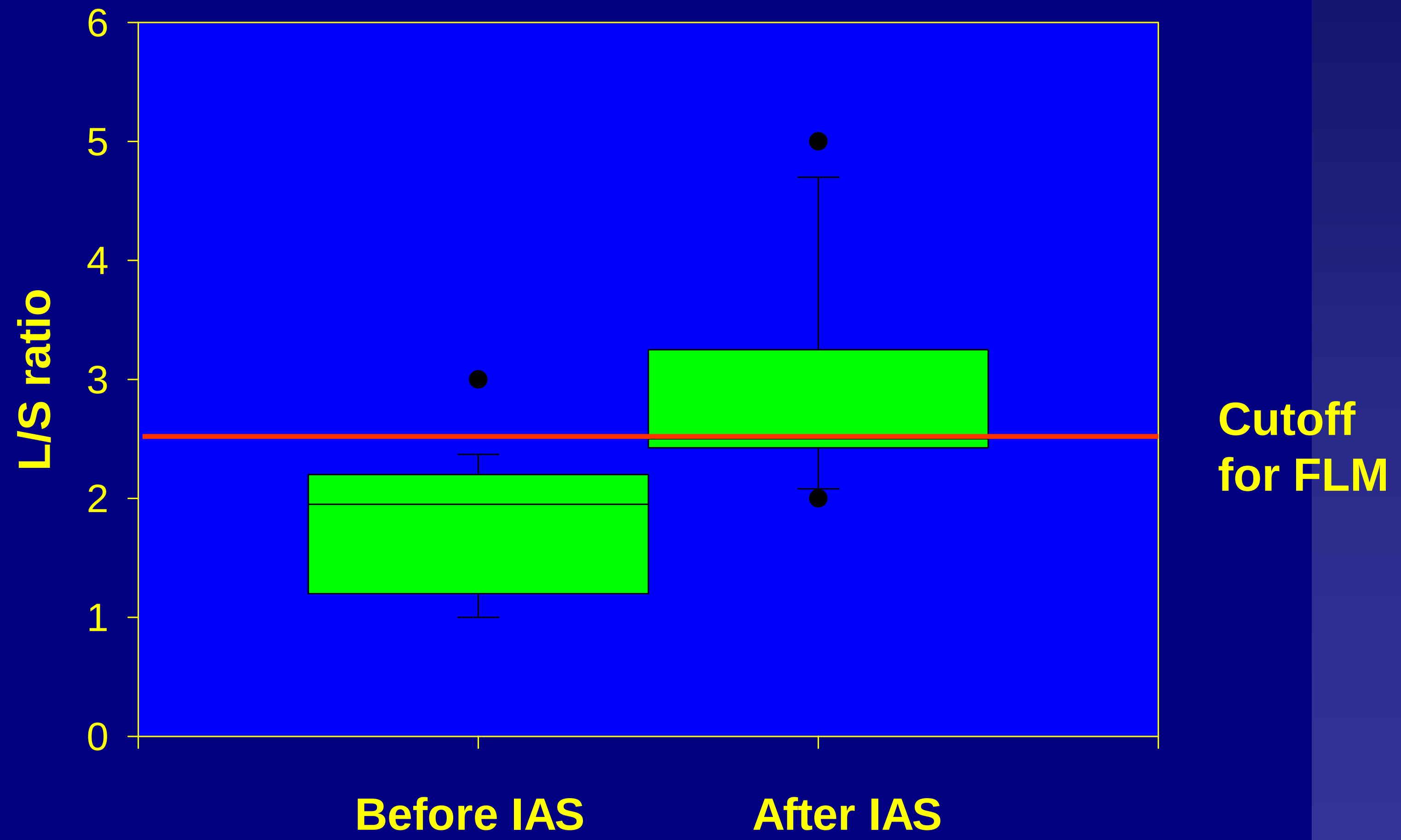
Distribution of pregnant women by gestational age



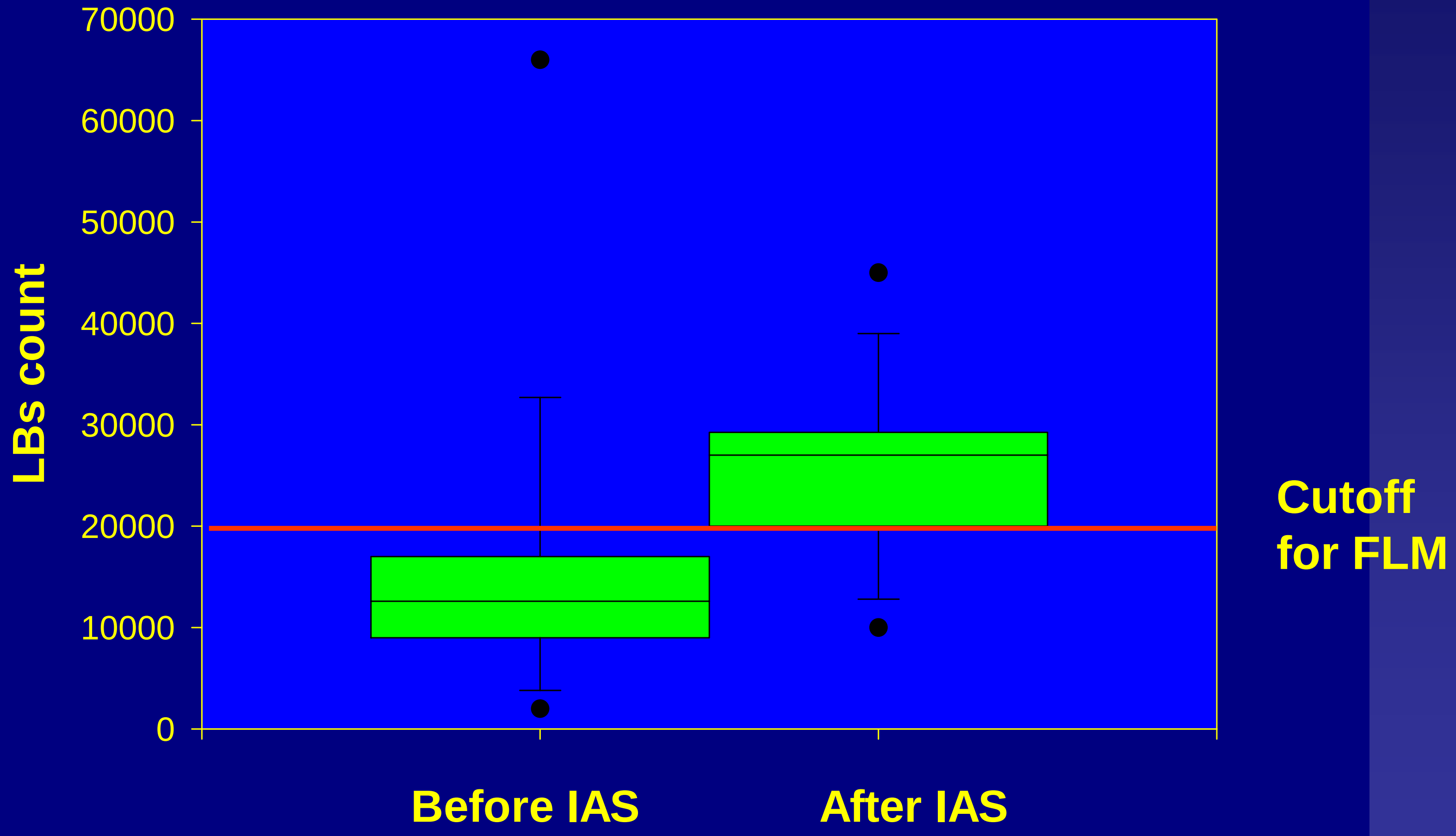
Rate of complications in the study group



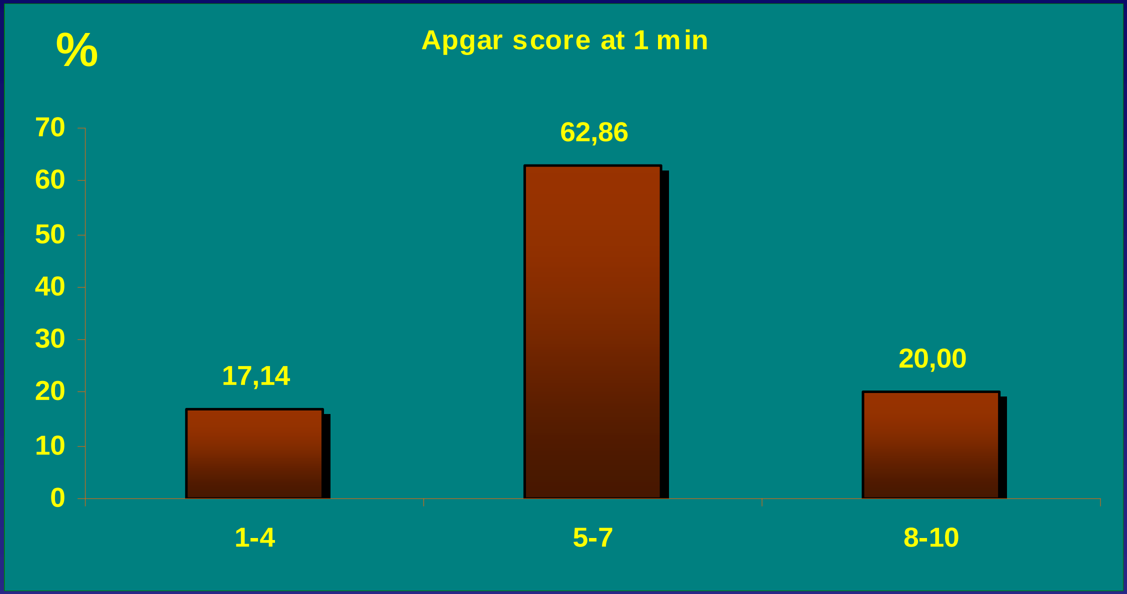
L/S ratio before and after IAS



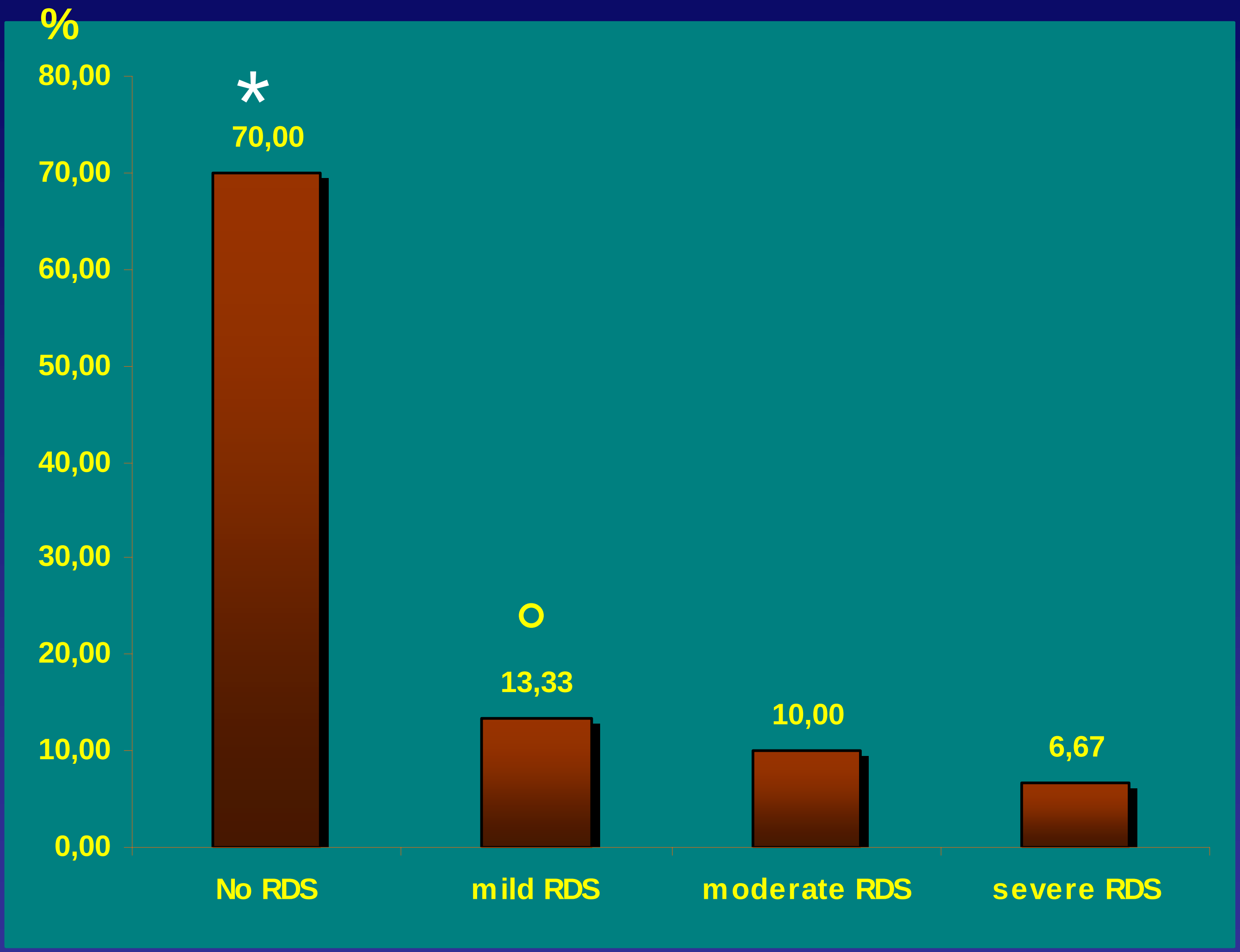
LBs count before and after IAS



Apgar score at 1 and 5 minutes



Incidence of NRDS following IAS



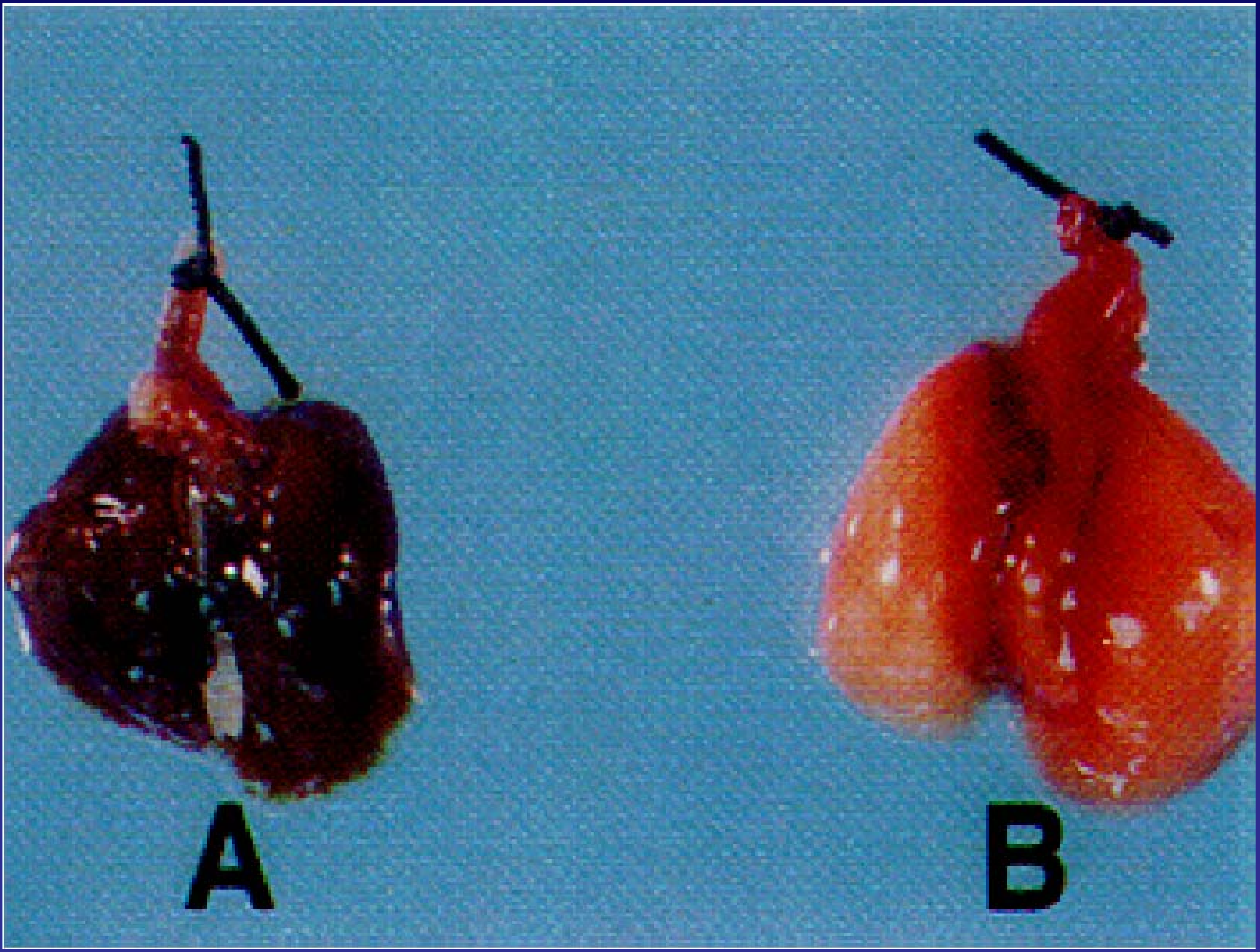
*In 2 cases IAS was administered 7 and 1 day before delivery, respectively

°In 1 cases IAS was administered 3 days before delivery

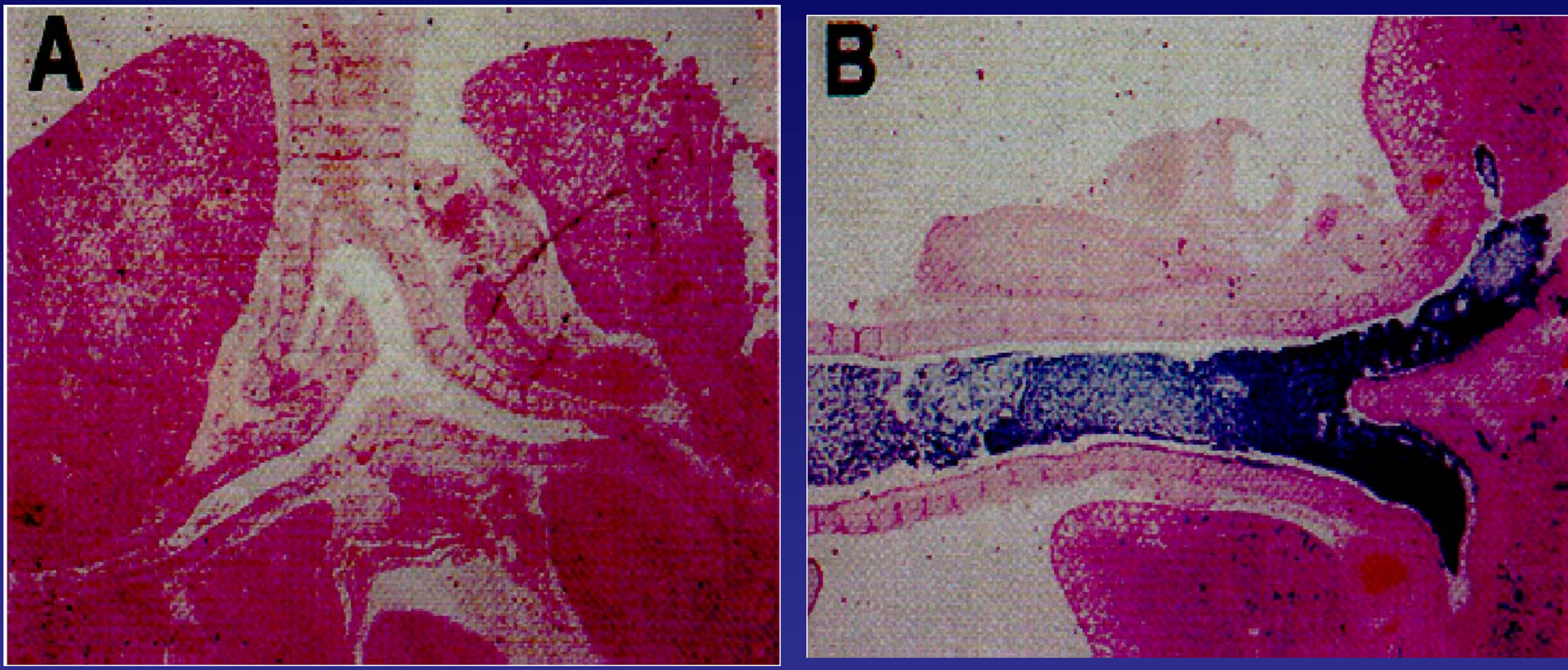
	Study group (No. 16) *	Control group (No. 30)	P value
Foam test			
--	1	10	
+	2	7	
++	4	9	
+++	9 (56.3%)	4 (13.3%)	< 0.01
Incidence of NRDS	1 (6.3%)	11 (23.3%)	< 0.01
CPAP ratio (%)	18.8 (3/16)	60 (18/30)	< 0.05
Hospital stay (days)	32.4 ± 7.6	42.0 ± 15.7	< 0.05
Outcome of neonates			
Survival	16	27	
Dead	0	3	< 0.05

**** A dose of Curosurf***

Zhang JP et al. Chin Med J 2004

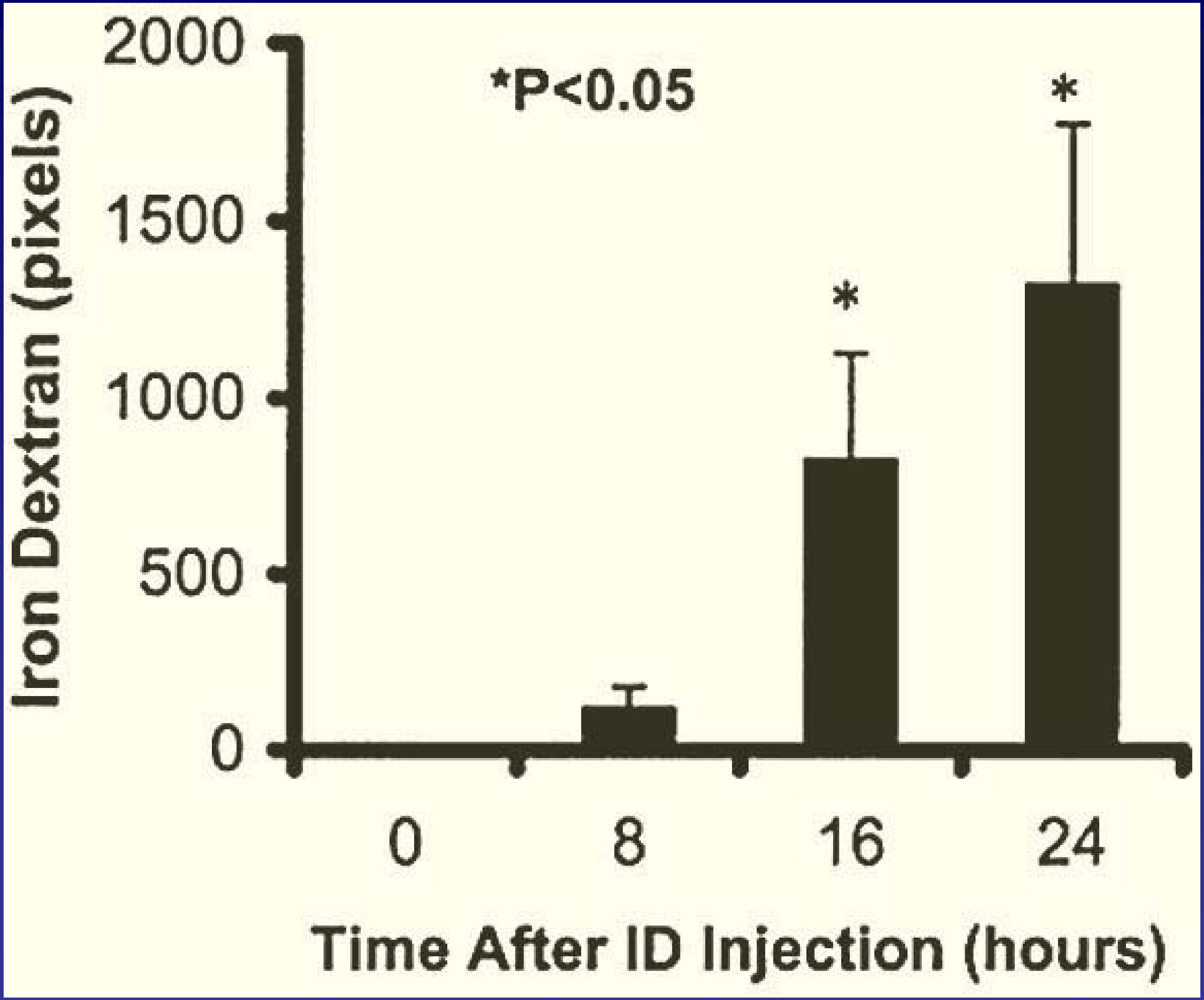


Gross lung examination of normal saline solution-treated (A) and pancuronium-treated (B) animals



Examination of trachea and mainstem bronchi displaying absence of iron (A) in pancuronium-treated animals and presence of iron (B) in normal saline solution-treated animals

Galan et al. Am J Obstet Gynecol 177:42-49; 1997



Galan et al. Am J Obstet Gynecol 2002; 187:S234

In a rabbit model aimed to investigate the metabolism of intra-amniotic surfactant, surfactant containing DPPC was injected into AF on days 23-27 of gestation. Within 44 hrs, DPPC was distributed to the gastrointestinal tract (45.9%), fetal membranes and placenta (8.2%), fetal lung (6.6%), and liver (1.9%).

DPPC uptake was higher in the upper than in the lower lung lobes.

Surfactant protein A, originating from intra-amniotic heterologous surfactant, was detected immunohistochemically in alveolar epithelium.

Hallman M et al. Am J Physiol 1997;273:L55-63.

Solana et al. (1998) have shown in rabbits that intra-amniotic administration of surfactant labeled with Tc99 is uniformly distributed into the lungs of treated fetuses.

Illia et al. (2004) have shown in guinea pigs that intra-amniotic administration of bovine surfactant labeled with Tc99, after stimulating FBMs with aminophylline 0.3 ml, is uniformly distributed into the lungs of treated fetuses, with a dose capture of between 1.0% and 5.3% of total dose.

Illia R et al. J Perinat Med 2004

FBMs may be important in the biochemical and endocrine function of the fetal lung. The flux of tracheal fluid within the lung created by breathing activity may aid in uniform distribution of surfactant in developing alveoli, and may even facilitate surfactant production and release.

Early administration of surfactant before the clinical signs of NRDS are established might allow more satisfactory distribution throughout the lung and thus, reduce the secondary pulmonary damage that occurs during assisted ventilation of poorly compliant lungs.

Our study is also in agreement with the results of clinical trials in the newborn infants exposed to “early” (prophylactic) treatment which has shown better results when compared to late (rescue) treatment.

Even after therapeutic intratracheal installation surfactant to the postnatal infant - first reported in the pioneering study of Fujiwara et al. (1980), significant clinical intervention is required. For example, multiple doses of SS maybe needed and the positions of the neonate must be changed regularly to facilitate an even distribution of SS into the lungs.

CRITERIA AND GUIDELINES FOR THE USE OF INTRA-AMNIOTIC SURFACTANT (I)

1. The fetus is at high-risk and subject to imminent delivery.
2. An amniocentesis is performed immediately prior to surfactant administration to confirm surfactant deficiency.
3. If confirmed, fetal breathing movements (if not already spontaneous) are induced by IV administration of aminophylline to the mother.
4. The goal is to facilitate transfer of surfactant from the oronasal injection site to trachea and peripheral lung units.

CRITERIA AND GUIDELINES FOR THE USE OF INTRA-AMNIOTIC SURFACTANT (II)

5. When breathing movements are underway, the position of the same needle near the fetal nose and mouth is verified and in this position the surfactant is injected.
6. Continuous ultrasonic and Doppler monitoring at every step permits proper placement of the needle using the one puncture site for both sampling and injection.
7. Careful selection and continuous monitoring of the fetus are paramount.

CONSOLIDATED AND POTENTIAL USES OF SUPPLEMENTARY SURFACTANT ADMINISTRATION

Neonatal respiratory distress syndrome (NRDS)

- **Meconium aspiration syndrome (MAS)**
- **Preterm premature rupture of the membranes (PPROM)**
- **Neonatal otitis media**
- **Neonatal pneumonia**
- **Pulmonary hypoplasia from CDH**
- **SIDS**
- **Cystic fibrosis (depending on type of gene mutation)**

Maternal Mendelson's syndrome, i.e., inhalation of acid gastric juice

Maternal infertility due to dysfunction of the Fallopian tubes