Neonatal Encephalopathy The Sepsis Connection

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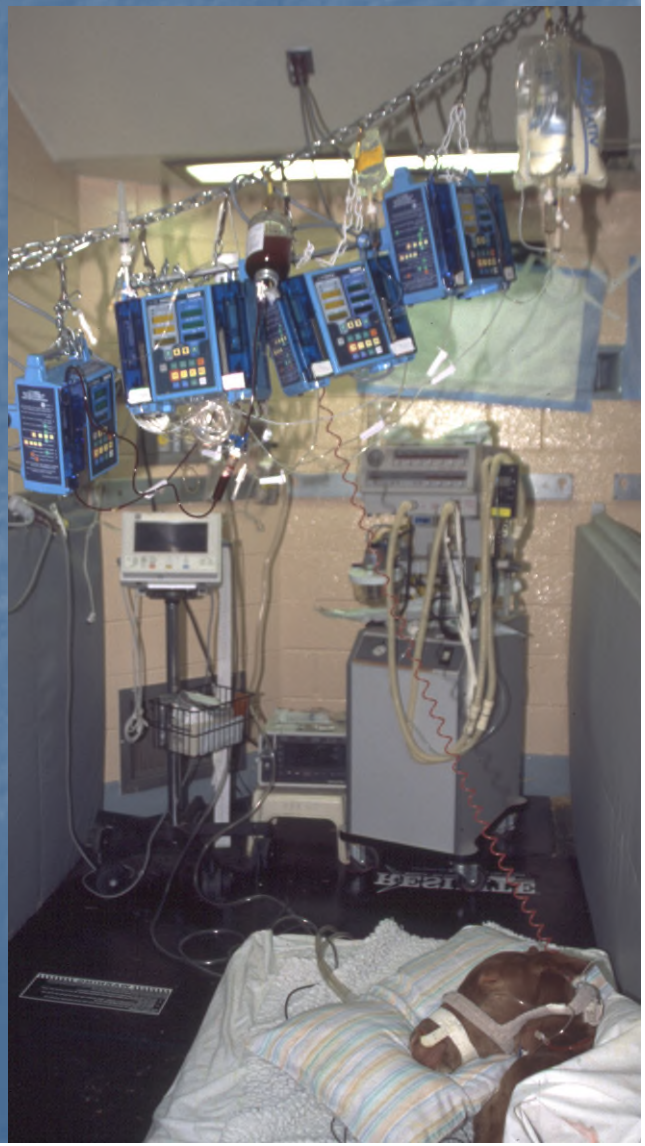
Neonatal Encephalopathy

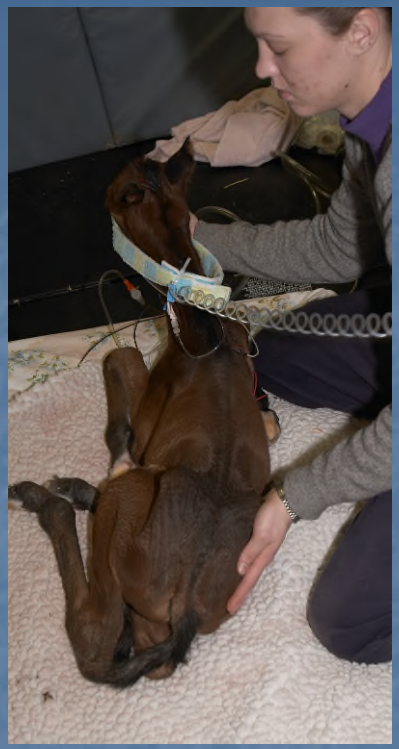
Etiology of Neonatal Diseases

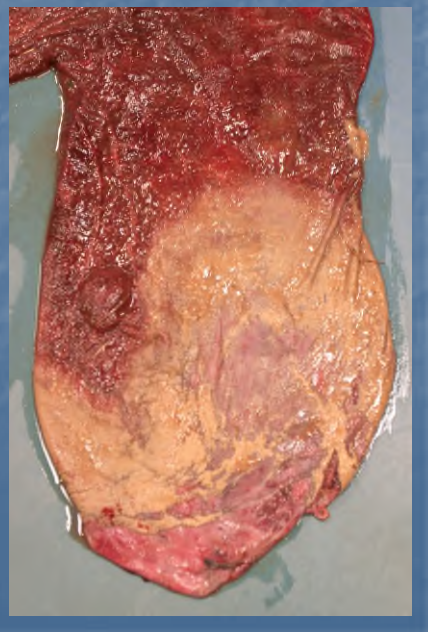
- Neonatal Encephalopathy
- Neonatal Nephropathy
- Neonatal Gastroenteropathy
- Prematurity
- IUGR
- Sepsis - FIRS



Role of Placentitis

- Risk factor for neonatal diseases
- Disrupt the fetal environment
  - Change placental metabolism
  - Change nutrient transfer
  - Inflammatory mediators
    - Cytokines
    - Other mediators
- Negative effects
- Positive effects





Hypothesis

- The occurrence of neonatal diseases including NE is influenced by fetal exposure to placentitis
- Treatment of placentitis will protect against the development of neonatal diseases

Methods

- Observational retrospective study
- Population
  - Hospitalized mare/foals 1997-2008
    - Foals referred for critical care
    - High Risk Pregnancy cases
  - Fetal membranes examined
  - Foal examined
  - Data source – clinician notes
    - Placental evaluation – PLS
    - Foal evaluation – JEP

Methods

- Presence of placentitis
  - Gross findings
  - Histologic findings
  - Retained fetal membranes
    - > 3 hours postpartum
- Prepartum therapy
- Occurrence of birth problems
  - Prolonged Stage II
  - Premature placental separation (PPS)
  - Need for birth resuscitation

Methods

- Occurrence of neonatal problems
  - Neonatal Encephalitis (NE)
  - Neonatal Nephropathy (NN)
  - Neonatal Gastroenteropathy (NG)
  - Clinical prematurity
  - Intrauterine growth restriction (IUGR)
  - Sepsis
  - Bacteremia

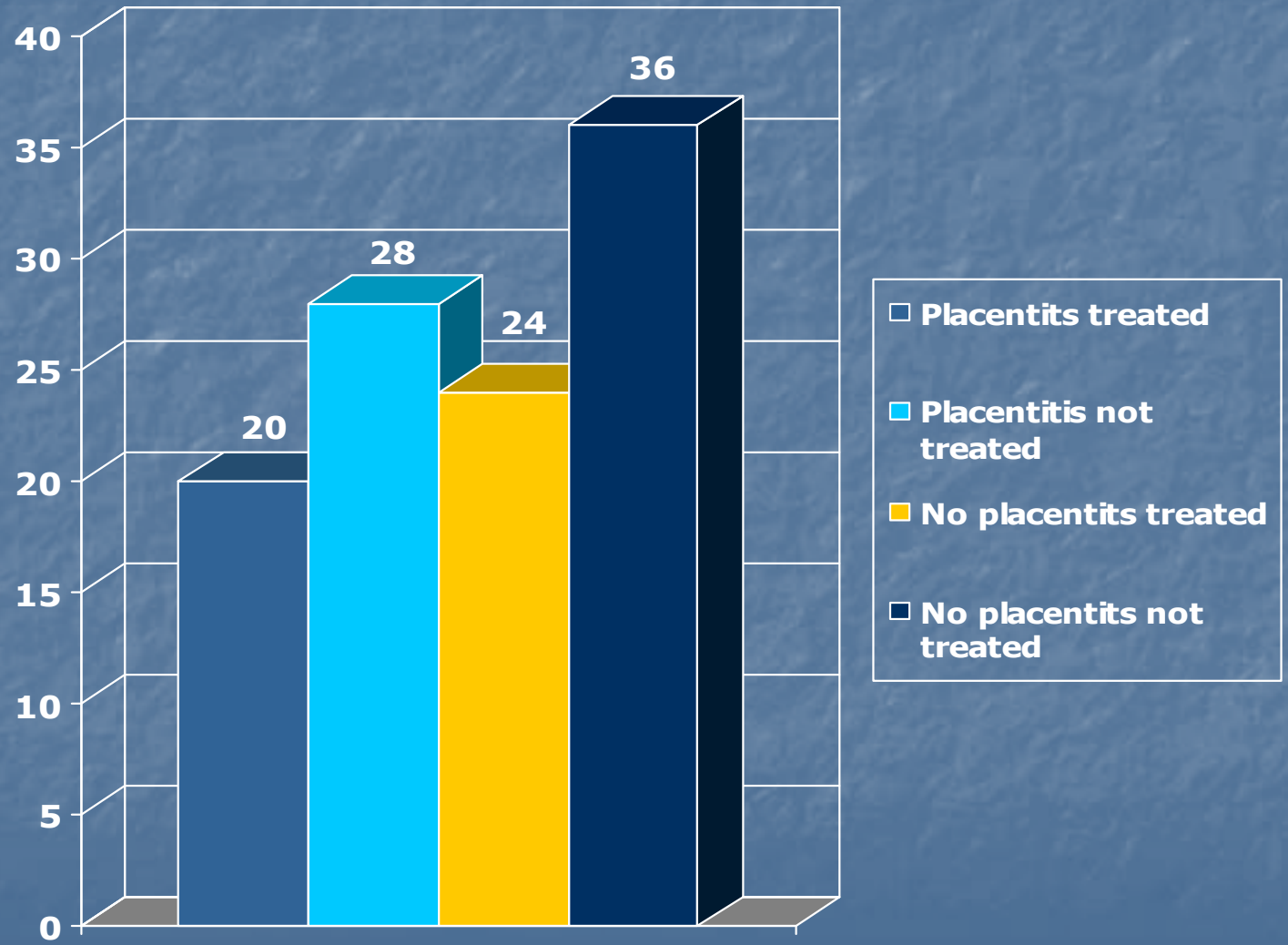
Statistical Analysis

- Logistic regression
  - Odds of occurrence of neonatal disease states
    - Based on presence or absence of placentitis
  - Interaction of treatment and outcome
- Kruskal-Wallis analys
- Fishers Exact test
- Significance level
  - $p \leq 0.05$
  - Trend p 0.05-0.10
  - Odds ratio confidence interval 95%

Results

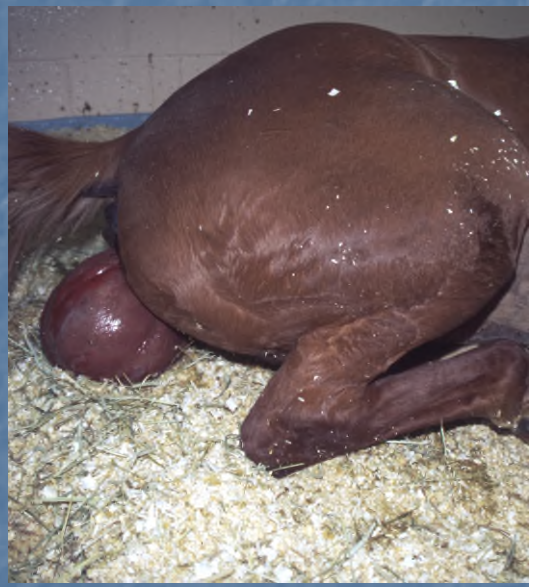
- 108 cases (full data set 220)
- Placentitis - 44% (48/108)
  - Gross - 56% (27 cases)
  - Histologic 60% (29 cases)
  - Retention 33% (16 cases)
- Prepartum treatment 41% (44/108)
  - Placentitis cases treated 42% (20/48)

Placentitis and Treatment



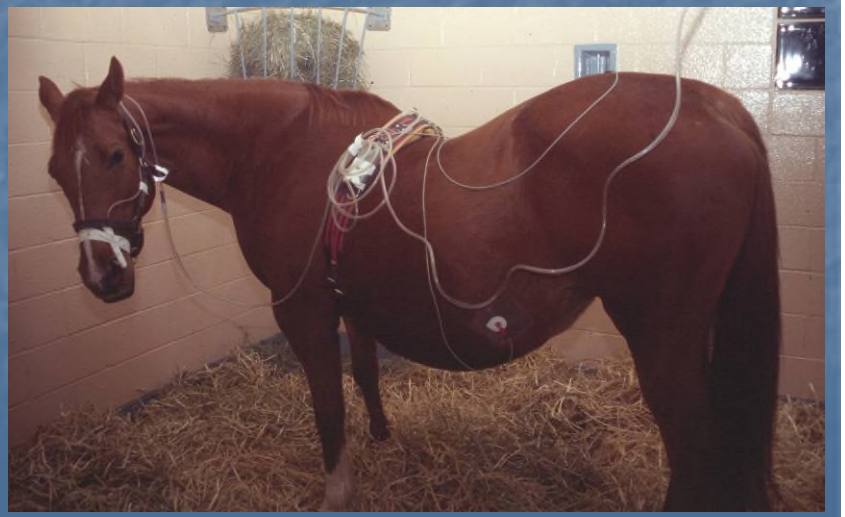
Possible Confounders

- Diagnosis of "Placentitis"
  - No definitive diagnosis during gestation
  - Placentitis could resolve during gestation
- Severe placentitis not included
- Birth problems
  - Prolonged stage II labor (5/71)
    - > 30 minutes
  - Premature placental separation (27/97)
  - Need for birth resuscitation (20/108)



Clinical Diagnosis

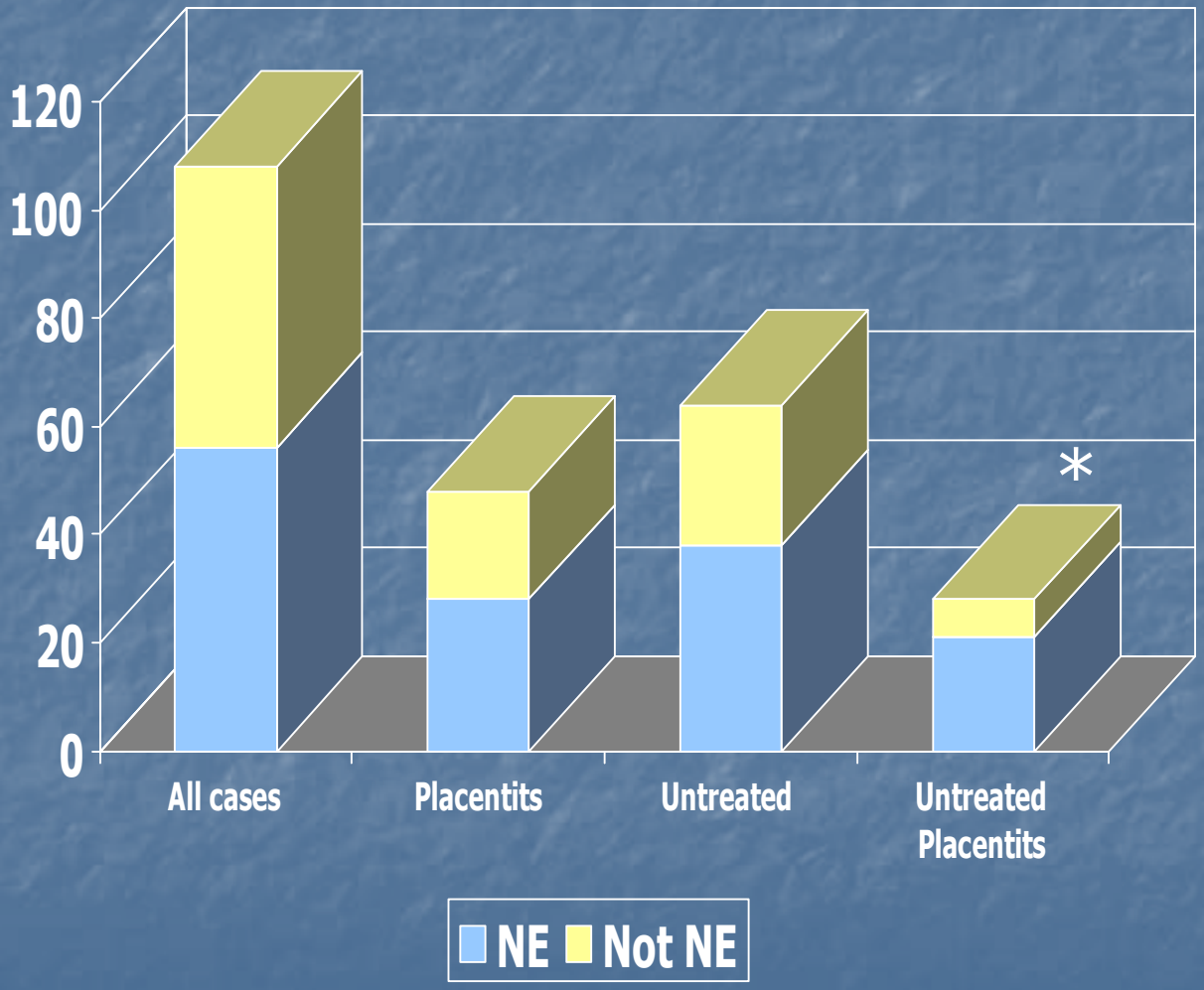
- NE 52% - 56/108
- NN 40% - 43/108
- NG 37% - 40/108
- Clinical prematurity 4.6% - 5/108
- IUGR 9% - 10/108
- Sepsis 56% - 61/108
- Bacteremia 18% - 19/108
- Normal 27% - 29/108
  - None of these problems
  - Other neonatal problems
    - Musculoskeletal problems
    - Neonatal isoerythrolysis.



Placentitis, Treatment and Disease

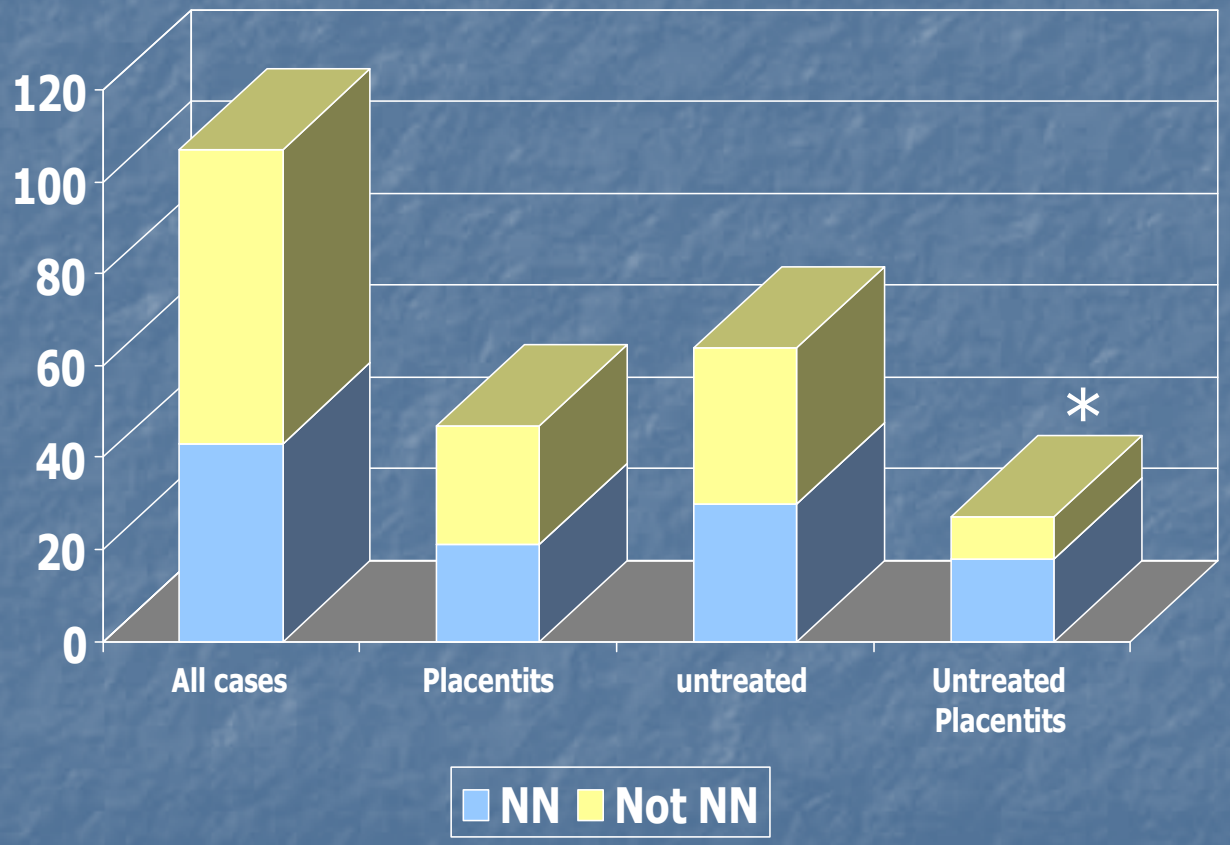
- No association of NE, NN or NG
  - With placentitis
  - With prepartum treatment
    - Regardless of the occurrence of placentitis
- Untreated placentitis
  - NE – p = 0.028, OR 3.4, 95% CI 1.1-9.8
  - NN – p = 0.011, OR 4, 95% CI 1.4-11.5
  - NG – p = 0.031, OR 3.1, 95% CI 1.1-8.6
  - Sepsis – p = 0.087, OR 2.8, 95% CI 0.86-9.1
  - Bacteremia – p = 0.018, OR 4.8, 95% CI 1.3-17.9

Neonatal Encephalopathy



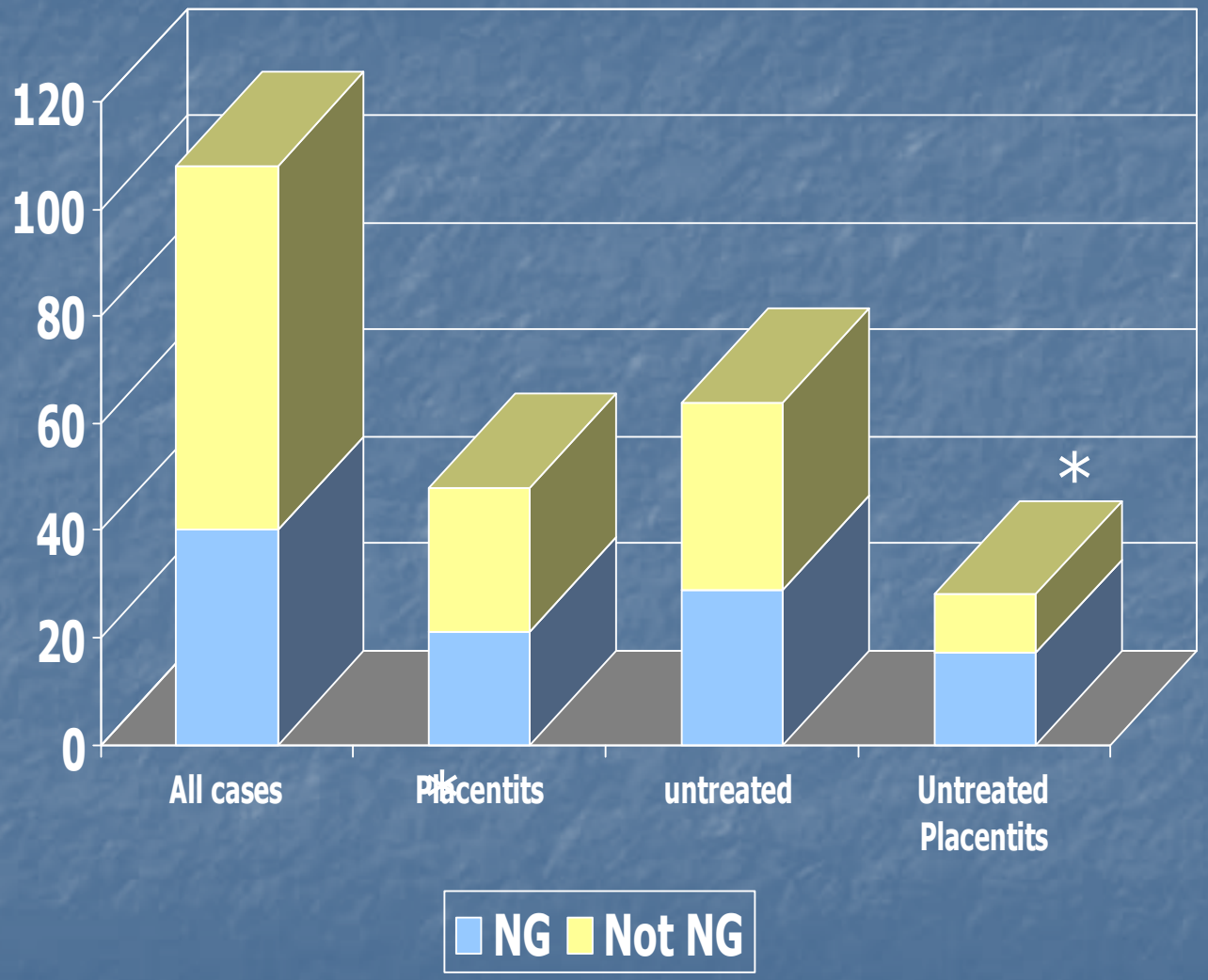
p = 0.028, OR 3.4, 95% CI 1.1-9.8

Neonatal Nephropathy



p = 0.011, OR 4, 95% CI 1.4-11.5

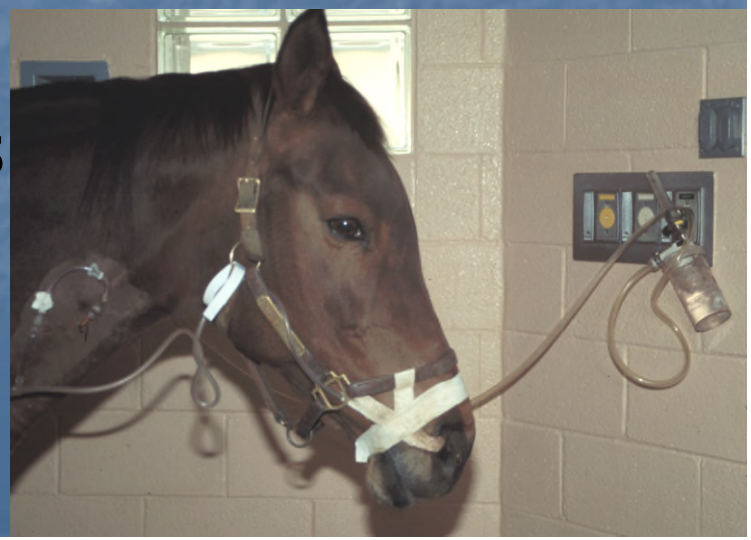
Neonatal Gastroenteropathy



p = 0.031, OR 3.1, 95% CI 1.1-8.6

Treatment of Placentitis

- Antimicrobials – 36 cases
  - TMS - 34 cases
  - Gentamycin/Penicillin – 3 cases
- NSAIDs – 30 cases
  - Flunixin melamine – 29 cases
  - Phenylbutazone – 1 case
- Progestins – 30 cases
  - Altrenogest
- Intranasal oxygen – 9 cases
- Vitamin E – 6 cases
- Pentoxifylline – 2 cases



Treatment of Placentitis

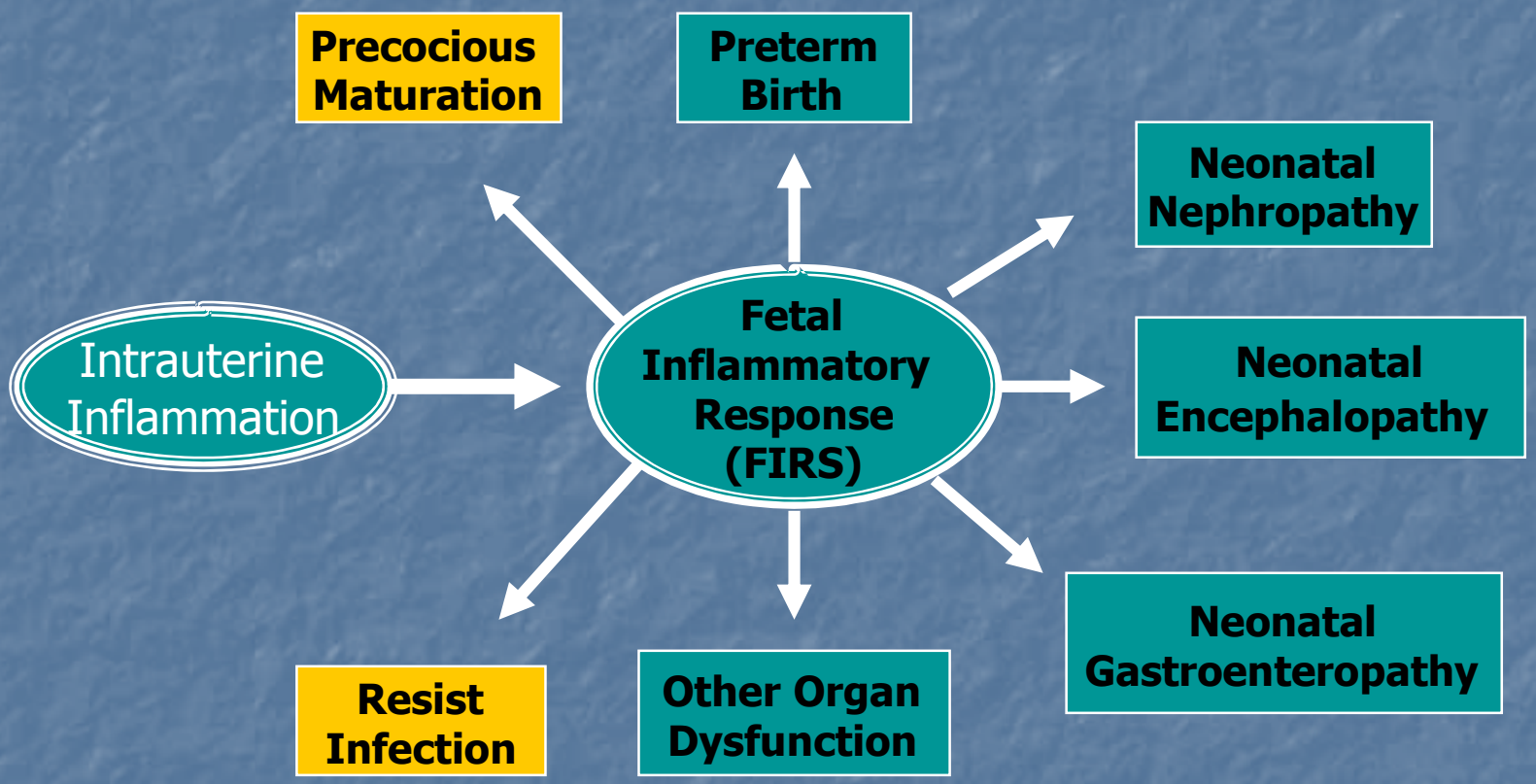
- Treatment of the mare with placentitis
  - Highly protective
  - NE - p=0.024, OR 0.15, 95% CI 0.03-0.77
  - NN - p=0.001, OR 0.04, 95% CI 0.005-0.27
  - NG - p=0.027, OR 0.13, 95% CI 0.02-0.79
- Treatment of the mare with placentitis
  - Increased the odds of a normal foal
  - p=0.032, OR 7.9, CI 1.2-52.6

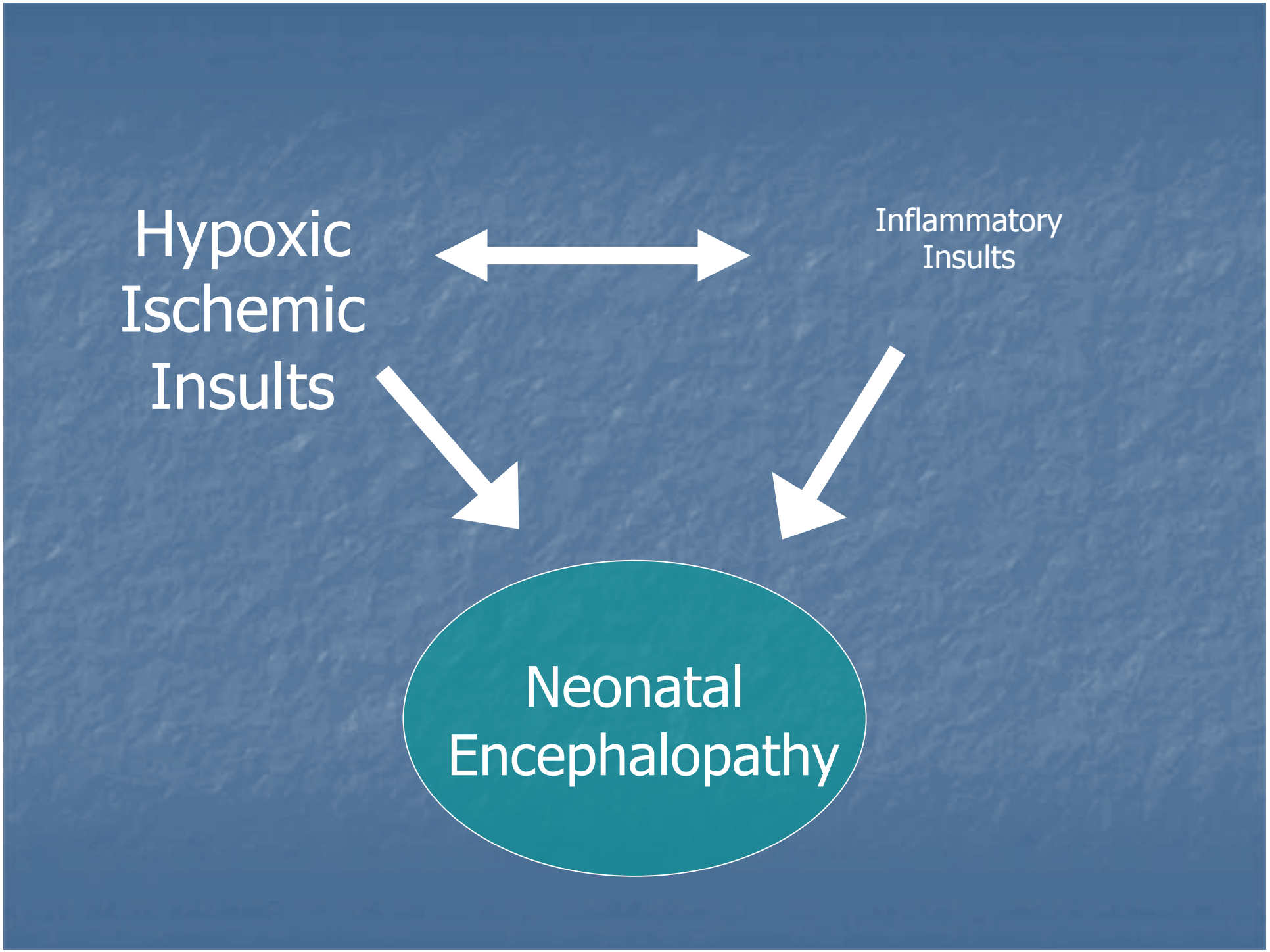
Conclusions

- Strong association of untreated placentitis
  - NE, NN and NG
  - Is placentitis the etiology?
- Prepartum treat of the mare for placentitis
  - Strongly protective
  - Antimicrobials, NSAIDs and progestins

Conclusions

- Treatment of mares with placentitis significantly increased the odds of having a foal without any of the neonatal problems studied
- Mares with suspect placentitis should be treated prepartum to prevent development of common neonatal diseases

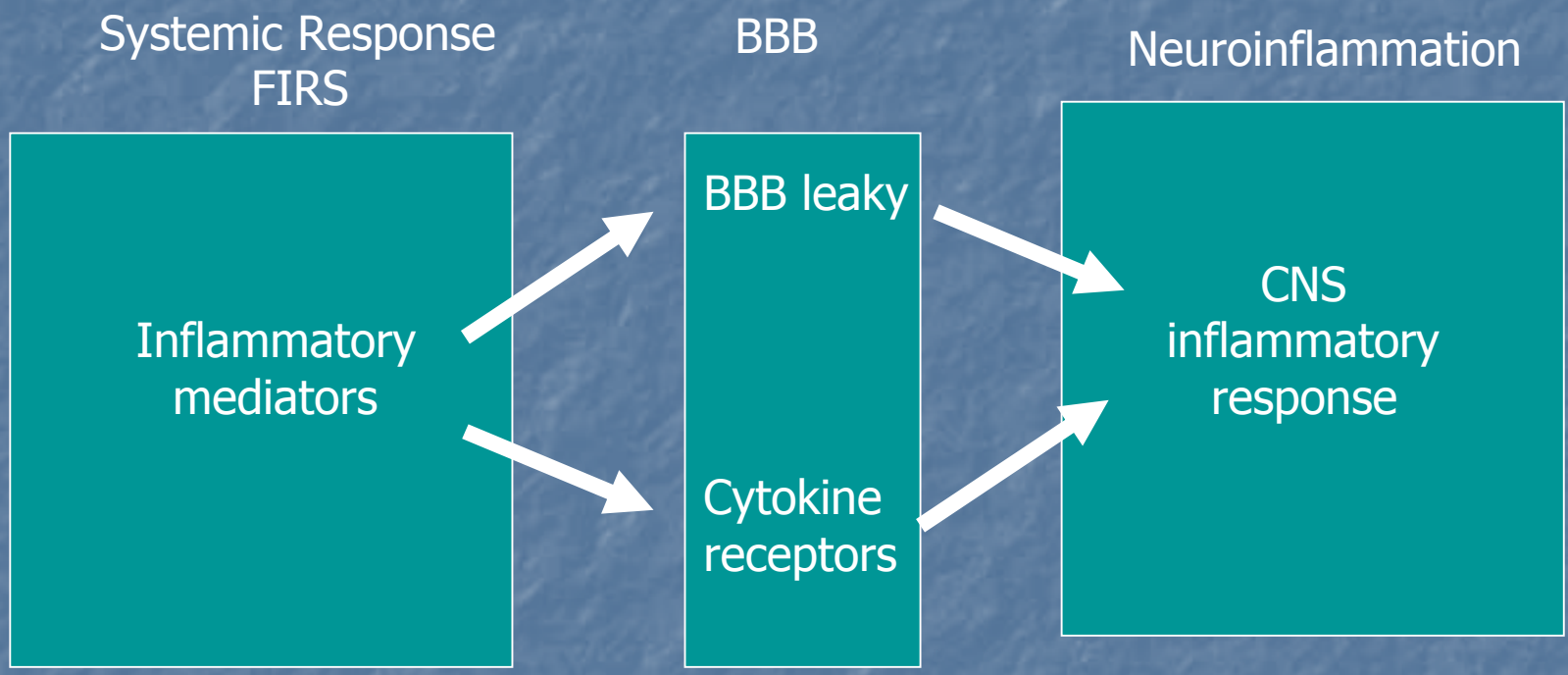

Precocious Maturation
Preterm Birth
Neonatal Nephropathy
Intrauterine Inflammation
Fetal Inflammatory Response (FIRS)
Neonatal Encephalopathy
Neonatal Gastroenteropathy
Resist Infection
Other Organ Dysfunction


Hypoxic
Ischemic
Insults
Inflammatory
Insults
Neonatal
Encephalopathy

Septic Encephalopathy

- Fetal
  - Neuroinflammation
  - FIRS (fetal inflammatory response syndrome)
    - Fetal placentitis
- Maternal
  - Maternal placentitis
  - SIRS
  - Focal maternal infections

Septic Encephalopathy



Preconditioning vs Sensitization

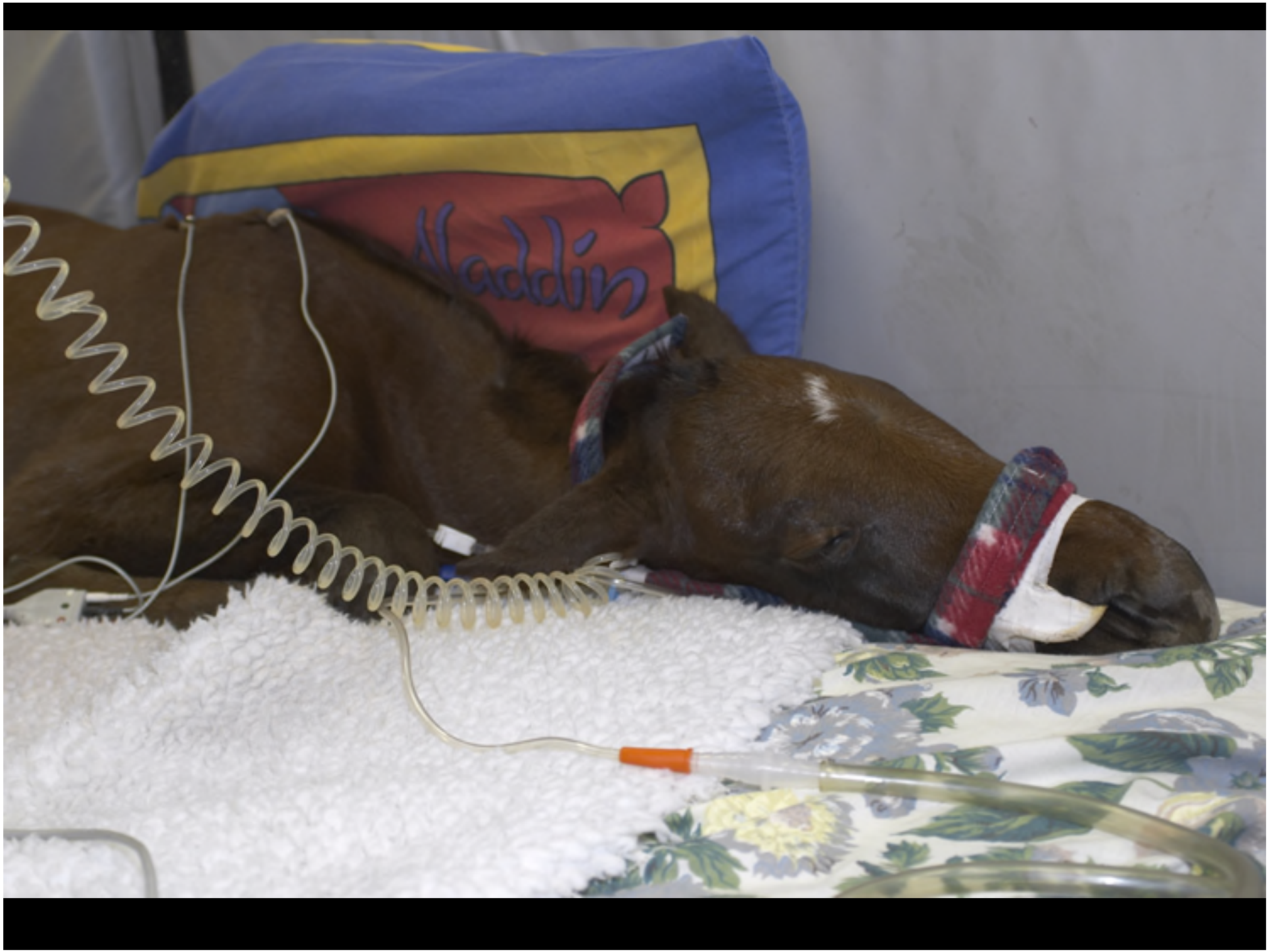
- Preconditioning
  - Exposure low levels of messengers
  - Protection
    - Repeat exposure to higher levels of mediators
    - Hypoxic ischemic insults
- Sensitization
  - Negative preconditioning
  - More susceptible
    - Repeat exposure of inflammatory messengers
    - Mild hypoxic ischemic insults

Neuroinflammation

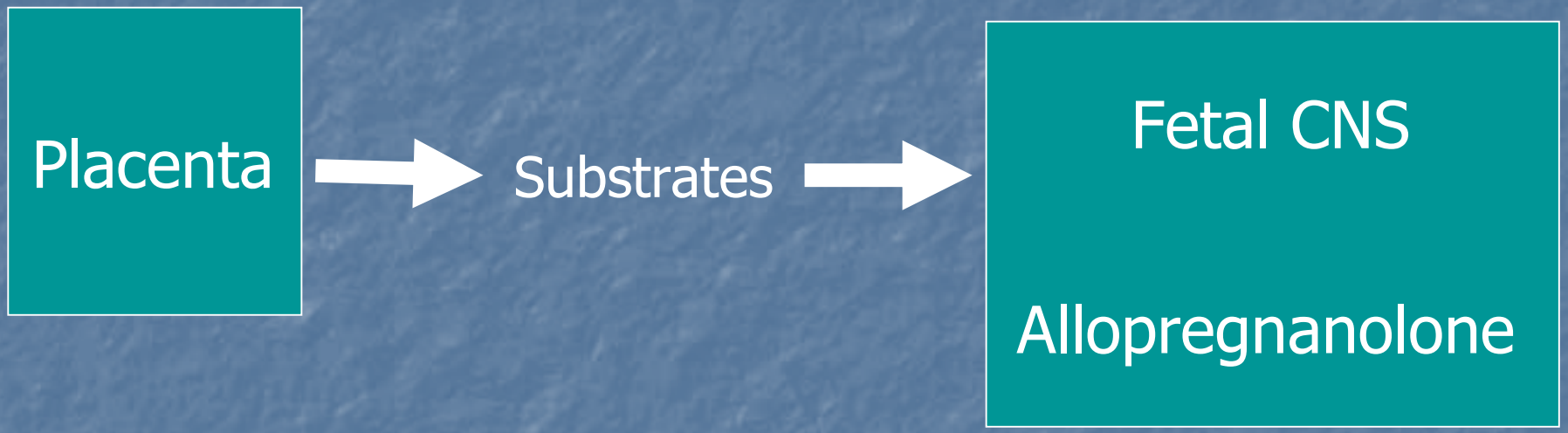
- Important in the pathogenesis of
  - Septic encephalopathy
  - Hypoxic ischemic encephalopathy
- Microglia cells are key
  - Up-regulation of proinflammatory cytokines
  - Up-regulation of trophic factors
- Can result in
  - Morphological alterations
  - Biochemical alterations
  - Functional alterations

Neuroinflammation

- Response depends on mix
  - Proinflammatory
  - Anti-inflammatory
  - Specific mediators
- Mild disease – often no morphologic changes
  - Motor
  - Perceptual, visual
  - Behavioral
  - Cognition
  - Excitatory responses
- Excitotoxicity


Aladdin

Neurosteroids



- Protect the brain during fetal life
- Responsible for the somnolence
- At birth
  - Removal of the placental
  - Levels drop rapidly
  - Fetus to “awake up”

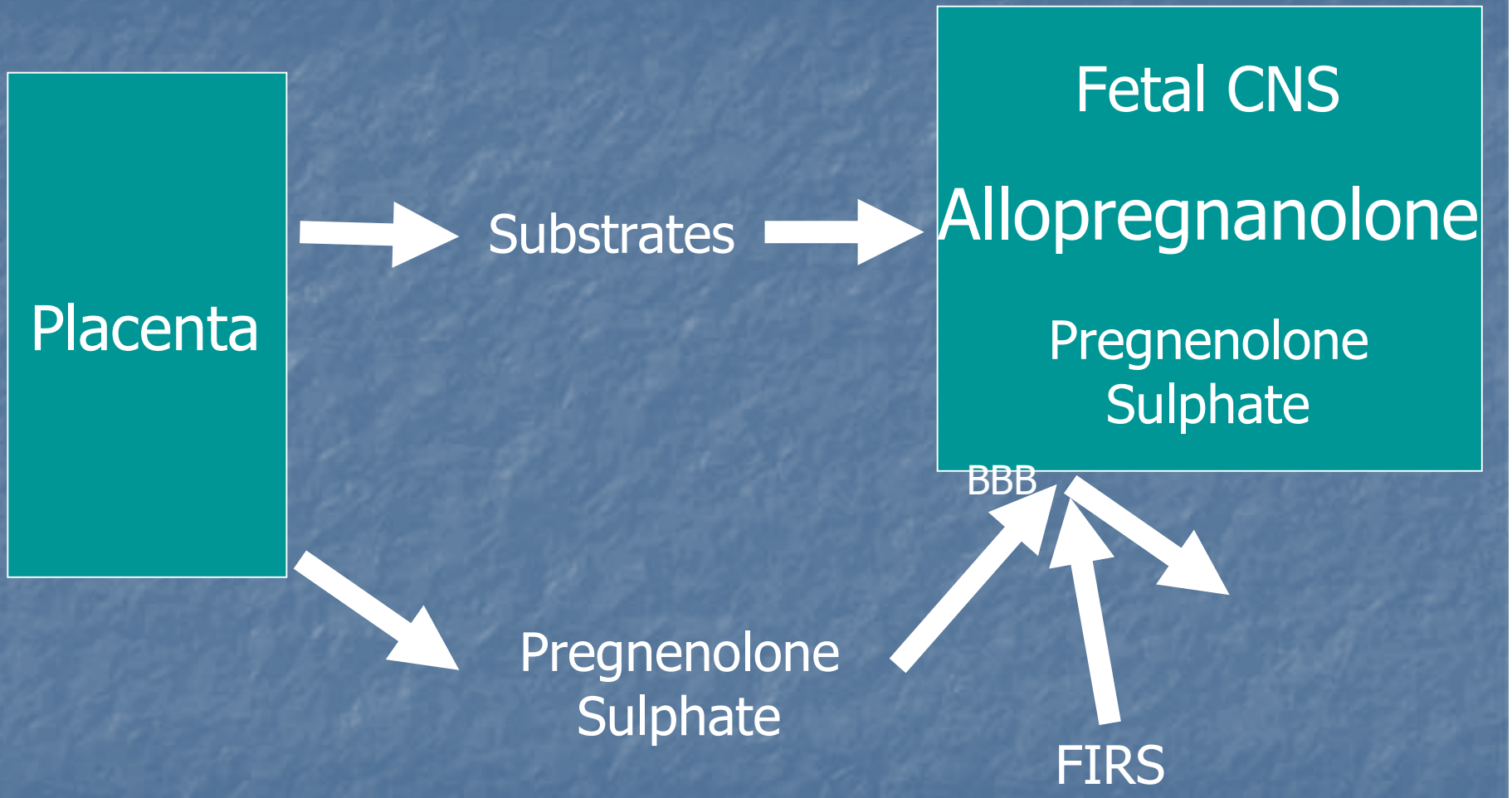
Neurosteroids

- Allopregnanolone
  - Brain levels induced by
    - Inflammatory mediators
    - Hypoxic ischemic insults
  - Protect against neuro-excitotoxicity
  - Marked anti-seizure actions
  - Raise seizure threshold
  - Induces somnolence

Neurosteroids

- Pregnenolone and pregnenolone sulphate
  - Placenta also secretes
  - Excitatory action in the brain
  - Cross the blood brain barrier
    - Normal – slow
    - Abnormal BBB – rapid transfer
    - Inflammation
    - Hypoxic ischemic insult

Neurosteroids



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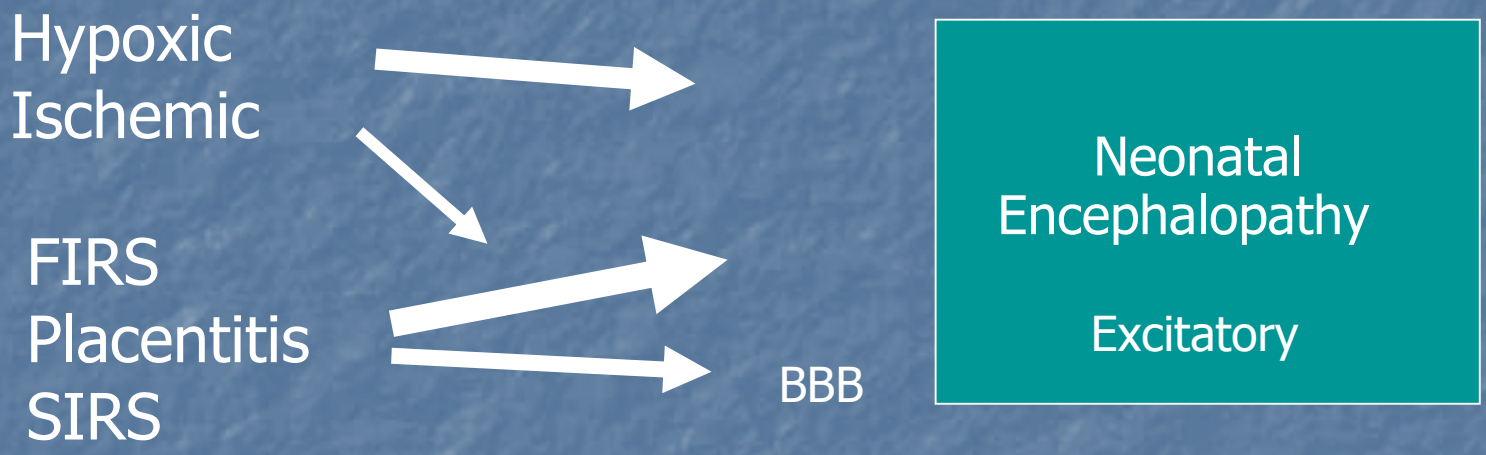

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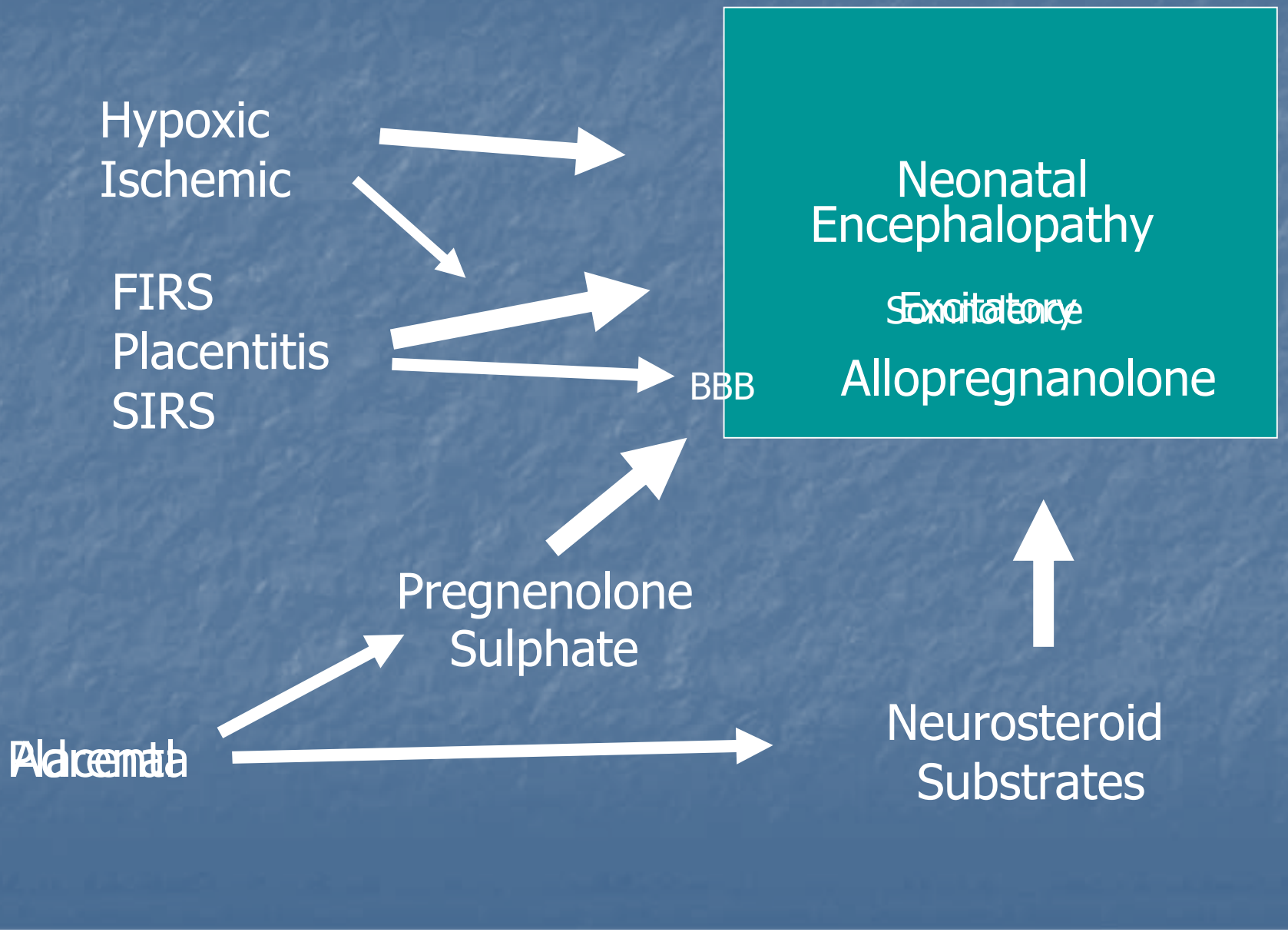

Typical Clinical Course

- Born near normal behavior
- Initial signs – excitatory
  - Constant activity – wandering, not lie down
  - Hyper-responsiveness
  - Hypertonus
  - Culminating in tonic-clonic seizure-like behavior
- Onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induces neurosteroids
  - Healing period
- Recovery

Typical Clinical Course

- Born seizure-like behavior
  - Less placental steroidogenesis
    - Lower levels protective neurosteroids
  - Inflammatory mediators
    - Induced blood brain barrier deficits
    - Allow sulfated neurosteroids into CNS
- With neonatal stress onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induced CNS neurosteroids
  - Healing period

Neonatal Encephalopathy: The sepsis connection

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Previously Neonatal Encephalopathy (NE) has been thought to be almost exclusively caused by hypoxic ischemic insults. Indeed, many practitioners continue to refer to NE as Hypoxic Ischemic Encephalopathy (HIE). However there is little evidence that most neonates with NE have had a prenatal hypoxic ischemic insult.[1] Currently the best evidence in experimental models and human neonatology suggests that NE is a result of Septic Encephalopathy (SE), Hypoxic Ischemic Encephalopathy (HIE) or the interaction of the two, modified by innate protective mechanisms.[2] SE may be mediated by inflammatory mediators originating from maternal systemic inflammatory response syndrome (SIRS)[3] or from fetal inflammatory response syndrome (FIRS).[3,4] The most common source of maternal inflammation in the mare is maternal placentitis and FIRS in the foal is maternal or fetal placentitis. In fetal circulation proinflammatory cytokines, prostaglandins, or lipopolysaccharide[5] may change the blood brain barrier permeability[2] resulting in the "leak" of mediators into the brain or the mediators may attach to cytokine receptors in areas devoid of the blood brain barrier[5] resulting in up-regulation of proinflammatory cytokines[5] and activation microglia/macrophages[5] resulting in fetal brain SIRS (neuroinflammation). In central inflammation, microglia activation is a key feature, which will lead to the release of cytokines as well as trophic factors.[5] The neuroinflammatory response depends on level and mix of inflammatory messengers.[3,5] Low levels of messengers may result in "preconditioning" leading to protection for repeat exposure to higher levels of mediators or for hypoxic ischemic insults but more commonly the result is "sensitization" (sometimes referred to as negative preconditioning) which makes the neonate more susceptible to the effects of repeat exposure of inflammatory messengers or to even mild hypoxic ischemic insults.[2,5] The neuroinflammatory response may result in changes in dendritic structure, catecholamine homeostasis, neuronal and glial proliferation, CNS vulnerability to other insults and in some circumstances brain lesions.[2,5] These changes may result in cognitive limitations, behavioral problems, visuospatial difficulties as well as other signs we see in foals with NE.[3,4]

The relationship between placentitis and the occurrence of neonatal foal diseases including neonatal encephalopathy has not been completely explored. Even though it is common clinical practice to treat placentitis in the late term mare with the goal of improving foal outcome, the effectiveness of these interventions in naturally occurring equine placentitis has not been well described. We report on a preliminary observational retrospective study of the relationship between occurrence of placentitis and neonatal encephalopathy and the effect of treatment for placentitis.

Clinician notes from foals and their mares admitted to the Graham French Neonatal Section, Connelly Intensive Care Unit for neonatal intensive care or to the high risk pregnancy program from 1997 through 2008 were reviewed. All cases which had a complete fetal membrane evaluation and the resulting foal was hospitalized allowing for clinical evaluation by the first author (JEP) were included. The following information was extracted: presence of placentitis based on gross and histologic findings; retained fetal membranes (retained placenta defined as > 3 hours postpartum); prepartum therapy; occurrence of dystocia; premature placental separation (PPS); need for birth resuscitation; occurrence of Neonatal Encephalitis (NE); Neonatal Nephropathy (NN); Neonatal Gastroenteropathy (NG); clinical prematurity; intrauterine growth restriction (IUGR), sepsis, bacteremia, outcome and weights of fetal membranes, foal at birth and mare before and after parturition. At the time this abstract is being written the data from this study is still being analyzed.

Although the full data set has not been analyzed as of this writing, analysis of a subset (108 cases) shows a strong association of placentitis and several neonatal diseases including NE, but only when untreated cases are considered (OR 3.4, 95% CI 1.1-9.8). If this strong association is present in the full data set, it supports the hypothesis that placentitis is an important cause of NE. In addition prepartum treat of the mare for placentitis appears to protect against development of NE. The commonly utilized therapy of antimicrobials, NSAIDs and progestins all seemed to contribute to this protective affect. These associations will be confirmed as more cases are added to this data set. Mares with suspect placentitis should be treated prepartum to decrease the likelihood of development of NE.

1. Nelson KB. Is it HIE? And why that matters. *Acta Paediatrica* 2007;96:1113–1114.

2. Ugwumadu, A. Infection and fetal neurologic injury. *Curr Opin Obstet Gynecol* 2006;18:106–111.

3. Dammann O, Leviton A. Inflammatory brain damage in preterm newborns—dry numbers, wet lab, and causal inferences. *Early Human Development* 2004;79:1–15.

4. Gomez R, Romero R, Ghezzi F, et al. The fetal inflammatory response syndrome. *Am J Obstet Gynecol* 1998;179:194-202.

5. Hagberg H, Mallard C. Effect of inflammation on central nervous system development and vulnerability. *Curr Opin Neurol* 2005;18:117–123.