# NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

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# Definition of Neonatal Thrombocytopenia

- Mild 100-150 x $10^9$/L
  - 0.8% of newborns
- Moderate 50-100 x $10^9$/L
  - 0.5% of newborns
- Severe <50 x $10^9$/L
  - 0.2% of newborns

# Differential Diagnosis of Neonatal Thrombocytopenia

## Increased Consumption

- Immune mediated
  - NAIT
  - ITP
- Peripheral consumption
  - DIC
  - Giant hemangiomas (Kasabach-Merritt)
  - NEC
  - Hypersplenism

- Misc
  - Neonatal cord injury
  - Von Willebrand Dz

# Differential Diagnosis of Neonatal Thrombocytopenia

## Decreased Production

- TAR syndrome
- Wiscott-Aldrich syndrome
- Congenital leukemia
- Osteopetrosis

## Mixed Causes

- Infection
  - TORCH
  - bacterial sepsis
- ECMO
- Exchange transfusions
- Aneuploidy (T21 and T18)
- Drug toxicity

# Definition

- NAIT:

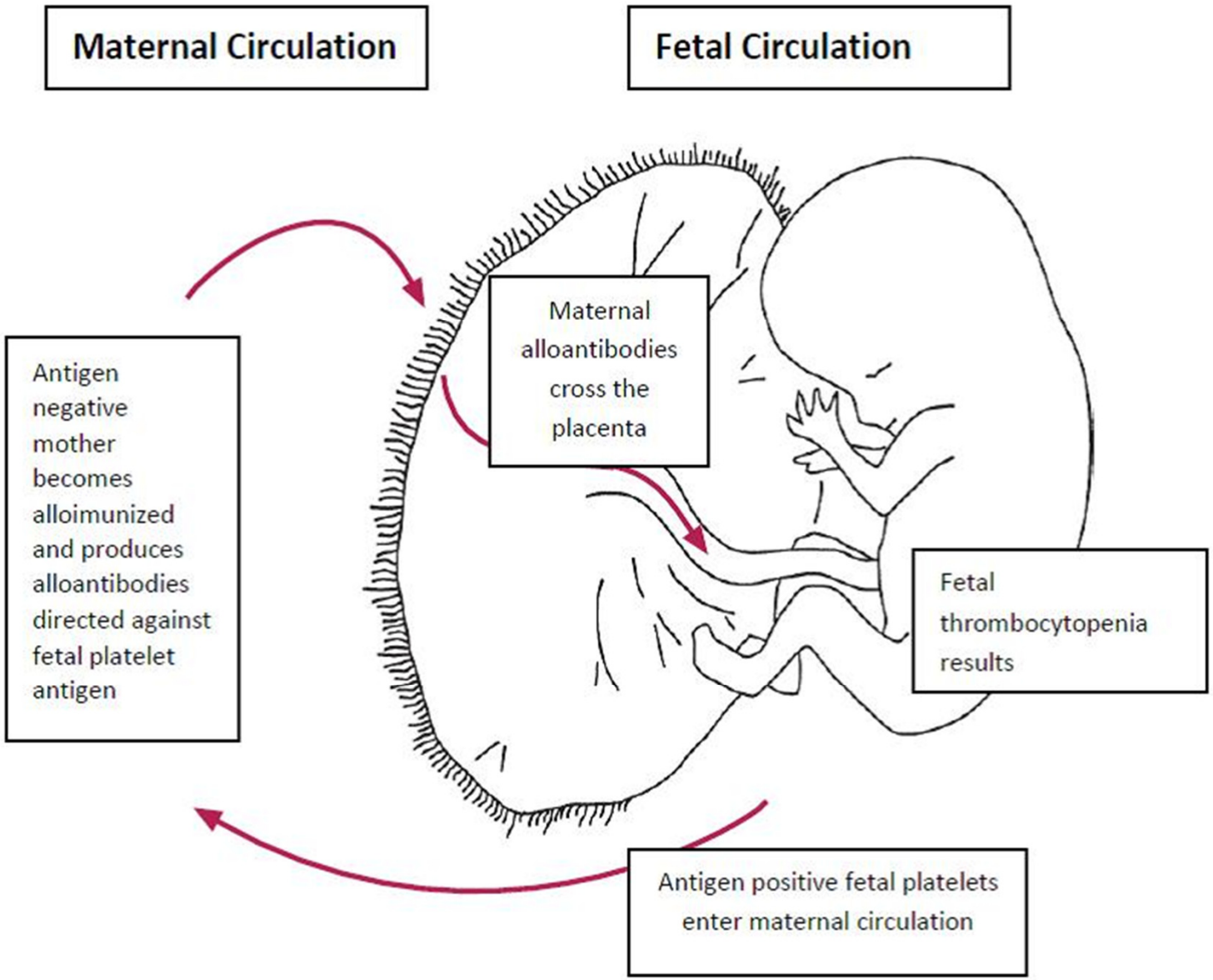
Platelet count <150 x $10^9$/l due to trans-placentally acquired maternal alloantibodies

# Pathogenesis

- Fetus has platelet antigen that is absent on maternal platelets
- Antigen positive fetal platelets pass into circulation of antigen negative mother
- This prompts maternal production of IgG antibodies against ‘foreign’ antigen

# Pathogenesis continued…

- Maternal IgG antibodies cross placenta and enter the fetal circulation
- Within the fetal circulation maternal antibodies bind to fetal platelets and and cause destruction by phagocytes in the RE system
- Fetal thrombocytopenia results


Maternal Circulation
Fetal Circulation
Antigen negative mother becomes alloimunized and produces alloantibodies directed against fetal platelet antigen
Maternal alloantibodies cross the placenta
Fetal thrombocytopenia results
Antigen positive fetal platelets enter maternal circulation

# Human Platelet Alloantigens

- HPAs are glycoproteins found on the surface of platelets
- An alloantigen is an antigen that is present in a proportion of the population and absent in the rest of that population
- 24 platelet specific alloantigens

| Nomenclature | | Glycoprotein (GP) localization | Phenotype frequency (%)* | |
|---|---|---|---|---|
| 'New' | 'Old' | | Caucasian | Japanese |
| HPA-1a | $Zw^a$, $PI^{A1}$ | IIIa | 97.9 | 99.9 |
| -1b | $Zw^b$, $PI^{A2}$ | IIIa | 26.5 | 3.7 |
| HPA-2a | $Ko^b$ | Ibz | 99.3 | ND |
| -2b | $Ko^a$, $Sib^a$ | Ibz | 14.6 | 25.4 |
| HPA-3a | $Bak^a$, $Lek^a$ | IIb | 87.7 | 78.9 |
| -3b | $Bak^b$ | IIb | 64.1 | 70.7 |
| HPA-4a | $Pen^a$, $Yuk^b$ | IIIa | 99.9 | 99.9 |
| -4b | $Pen^b$, $Yuk^a$ | IIIa | <0.2 | 1.7 |
| HPA-5a | $Br^b$, $Zav^b$ | Ia | 99.2 | 99.8 |
| -5b | $Br^a$, $Zav^a$, $Hc^a$ | Ia | 20.6 | 8.7 |
| HPA-6bW | $Tu^a$, $Ca^a$ | IIIa | $\ll 1^{**}$ | ND |
| HPA-7bW | $Mo^a$ | IIIa | $\ll 1^{***}$ | ND |
| HPA-8bW | $Sr^a$ | IIIa | $\ll 1^{****}$ | ND |
| HPA-9bW | $Max^a$ | IIb | $< 1^{*****}$ | ND |
| HPA-10bW | $La^a$ | IIIa | $< 1^{******}$ | ND |
| HPA-11bW | $Gro^a$ | IIIa | ND | ND |
| Other | $Va^a$ | IIb/IIIa | $\ll 1^{*******}$ | ND |

Blanchette, 2000

# Human Platelet Alloantigens

- HPA-1a most common
  - Synonyms include: $Zw^a$, $PL^{A1}$
  - Located on GPIIIa platelet glycoprotein
  - Responsible for >80% NAIT cases
- HPA-5b $2^{nd}$ most common in Caucasians
- HPA-4 is the most common in Asians

# Incidence

- Relatively rare
- Reports vary from 1 in 500 to 1 in 5000 live births

# Incidence: Expected vs Observed

- HPA-1a negativity aprox 2% in mothers
- 75% of males are homozygous and 25% are heterozygous
- Would expect 85% of these couples to be at risk
- However only 10% of HPA-1a negative moms exposed to HPA-1a positive platelets become immunized
- Protective nature of HLA types

# Diagnosis

- Abnormally low platelet count
- Feto-maternal incompatibility for a platelet associated antigen
- Maternal platelet alloantibodies against the antigen
- Clinical response to compatible antigen negative platelets

# Clinical Presentation

- 40-60% are first borns
- Appropriate for gestational age birthweight
- Full term infants
- Unexpected thrombocytopenia
- Hemorrhagic symptoms

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- Mother is unaffected and asymptomatic

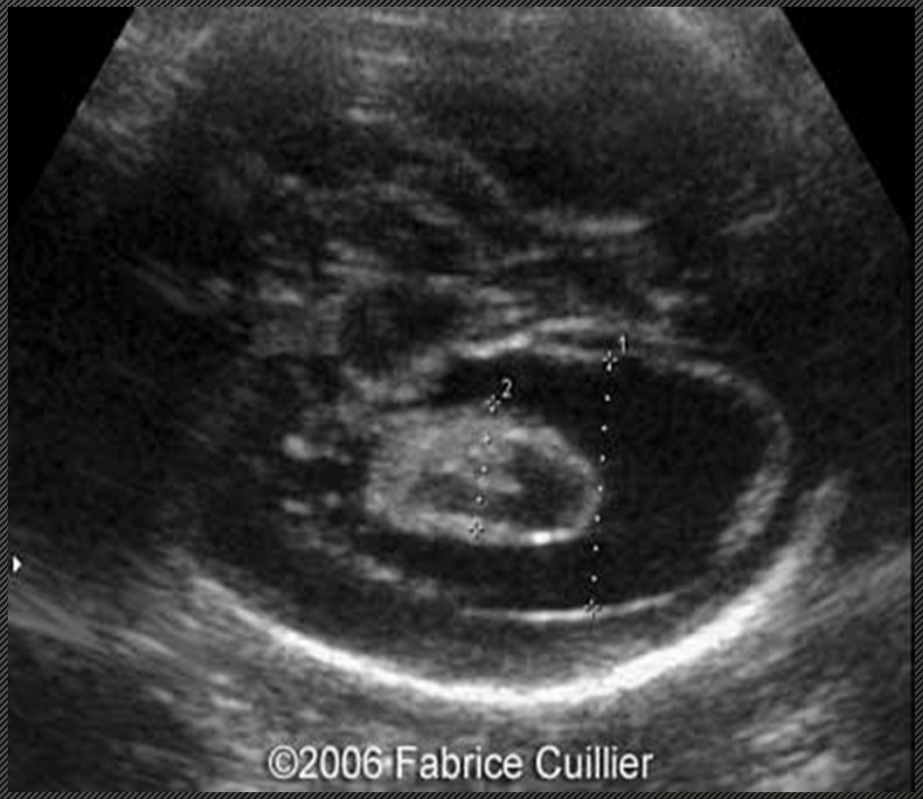
# 88 Neonates with NAIT

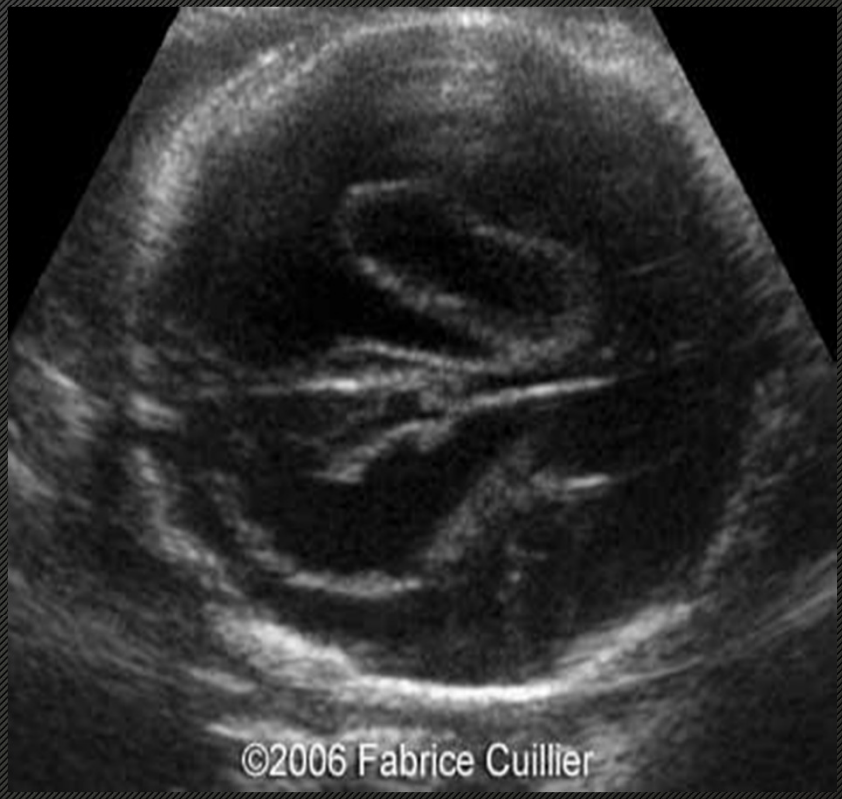
| Hemorrhagic Symptoms | N | % |
|---|---|---|
| Petechiae/Purpura | 79 | 90 |
| Hematoma | 58 | 66 |
| Gastrointestinal | 26 | 30 |
| Melena | 24 | 27 |
| Hematemesis | 2 | 2 |
| Hemoptysis | 7 | 8 |
| Hematuria | 3 | 3 |
| Retinal Hemorrhage | 6 | 7 |
| CNS Hemorrhage | 12 | 14 |
| No symptoms | 9 | 10 |

Mueller-Eckhardt, et al, Lancet, 1989

# Intracranial Hemorrhage

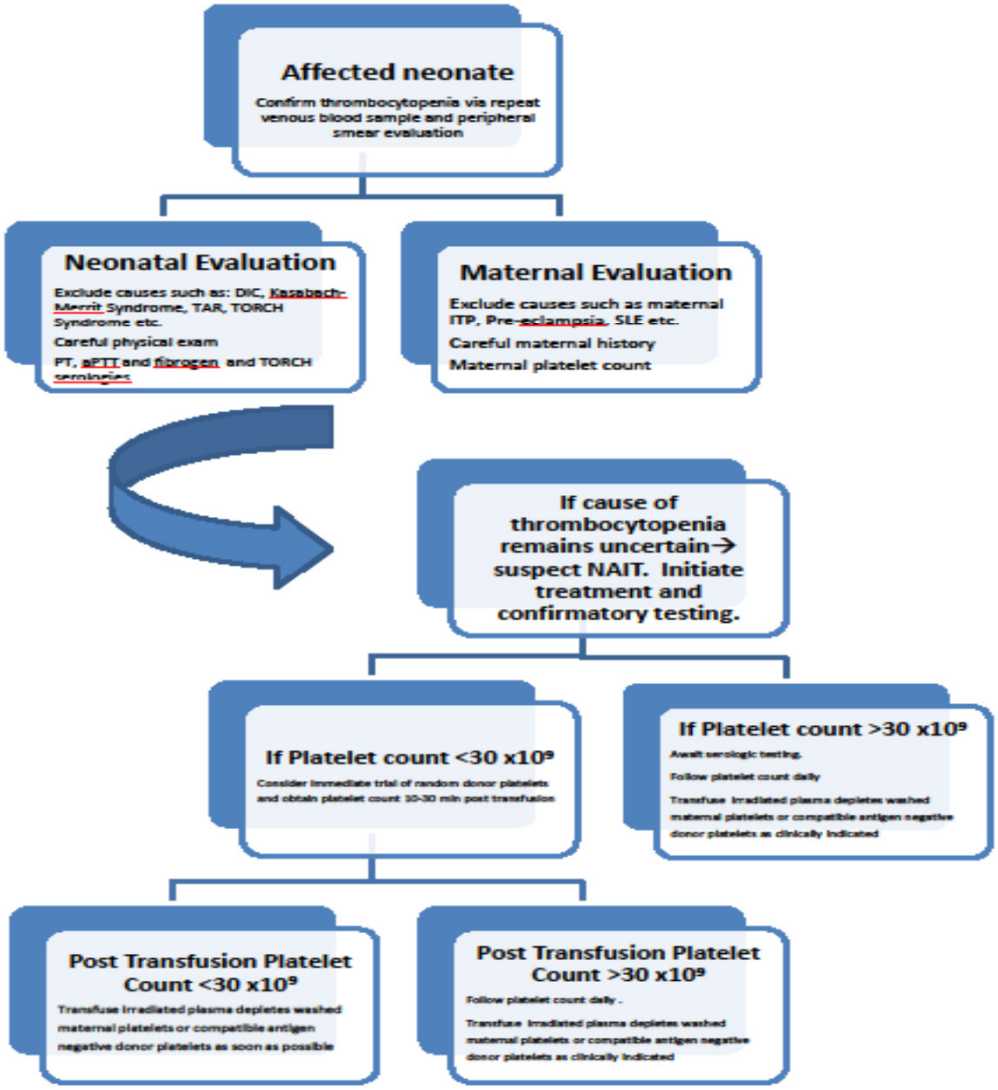
- Reported incidence 8-22%
- 75% of bleeds are antenatal
- Risk Factors:
  - Platelets <20 x $10^9$/L
  - Sibling with intracranial hemorrhage
- Death or neurologic impairment will occur in up to 25% of cases




# Fetal Intracranial Hemorrhage on Ultrasound

# Postnatal Management



# Subsequent Pregnancies

- Very high recurrence risk
  - ~100% in homozygous father
- Usually more severe in subsequent pregnancies
- Earlier nadir of platelet count

# Prenatal Management

Suspect NAIT if:

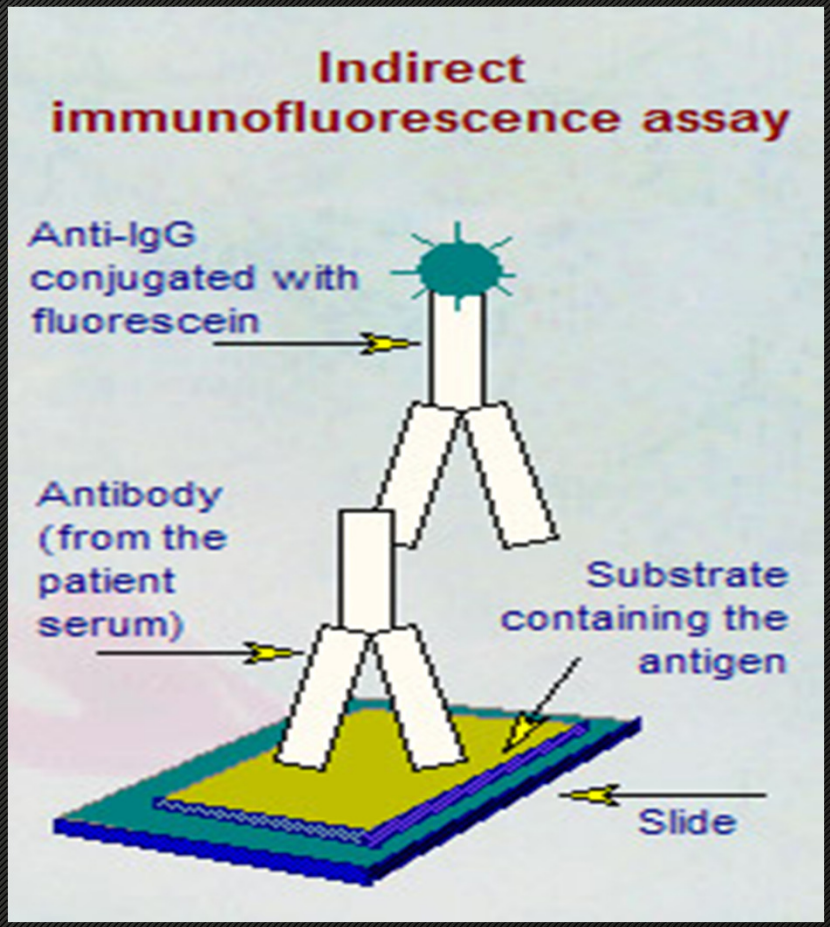
- previously affected infant
- history of pregnancy with unexplained fetal death, hydrocephalus or hemorrhagic symptoms
- Finding of hydrocephalous or evidence of bleed on US in current pregnancy

# Prenatal Diagnosis

- Parental Platelet Antigen typing
- Fetal platelet genotyping via CVS or amniocentesis

# Laboratory Diagnosis

- Maternal & paternal platelet antigen testing looking for HPA incompatibility
- Screening of maternal serum for antibodies



# Treatment Options

- Maternal IVIG
- Maternal Glucocorticosteroids
- In-utero platelet transfusions
- Early delivery?

# Risk Stratification

- Standard Risk:
  - Previous sibling with isolated thrombocytopenia
- High Risk
  - Previous sibling with peripartum ICH
- Very High Risk
  - Previous sibling with antenatal ICH or IUFD

# Standard Risk Management

Starting at 20 weeks GA give either:

- IVIG 1 g/kg/week
- Prednisone 0.5 mg/kg/day

# High Risk Management

Starting at 20 weeks GA give both:

- IVIG 1 g/kg/week
- Prednisone 1 mg/kg/day

# Very High Risk Management

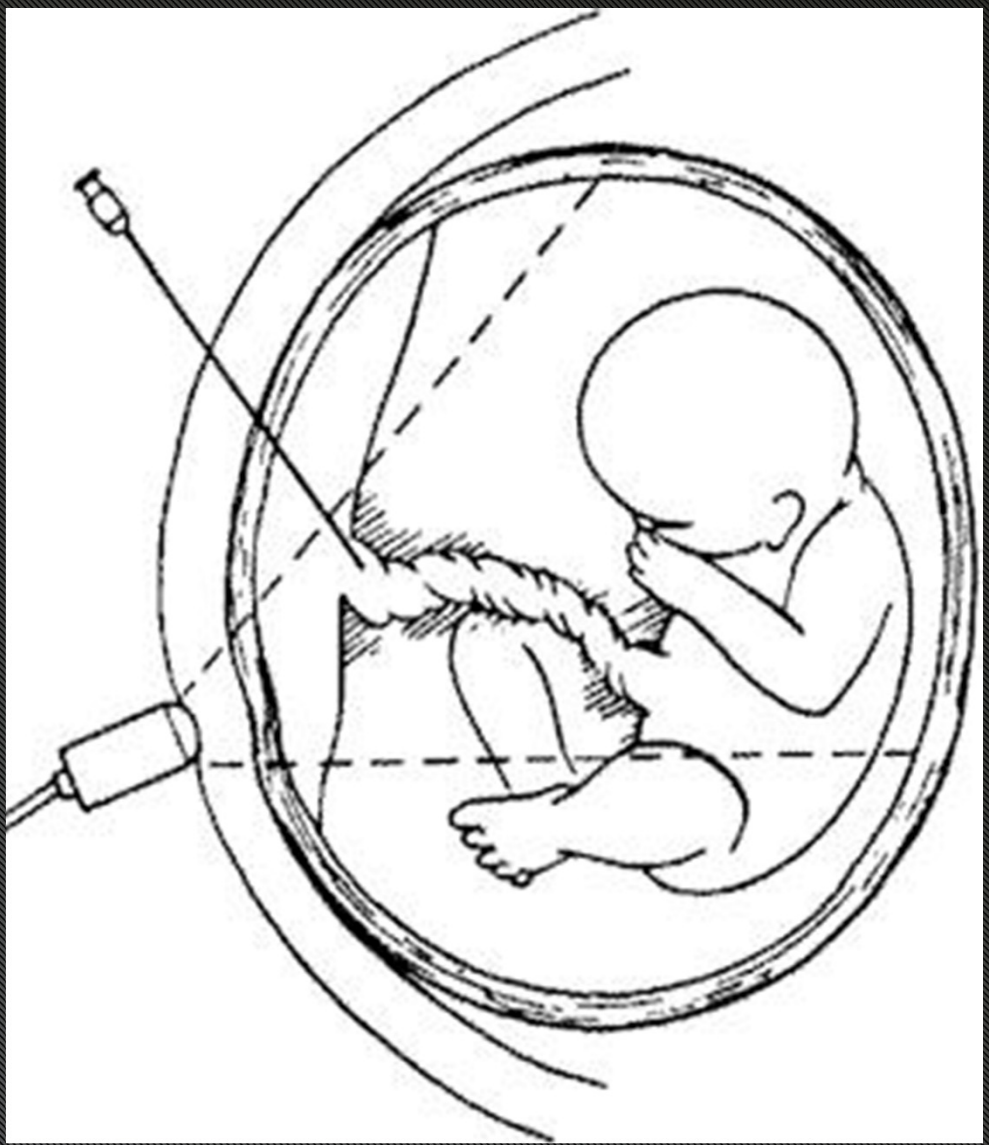
Starting at 12 weeks give:

- IVIG 1 or 2 g/kg/week

After 20 weeks consider:

- +/- Fetal Blood sampling
- Increase IVIG dose
- Add Prednisone

# Intrauterine Platelet Transfusion



# FBS and In-utero Platelet Transfusion

- Overton, et al, AJOG, 2002
  - 12 pregnancies
  - Weekly Fetal blood sampling starting after 20 weeks
  - 84 transfusions of compatible antigen-negative platelets
  - 2 Intrauterine fetal deaths

  - attributable PRLR 1.2% per procedure
  - 8.3% per pregnancy (2' repeat procedures)
  - No ICH in survivors

# Preparation of Platelets for IUT

- Compatible antigen-negative platelet concentrate
- Irradiated to deplete leukocytes
- CMV, Hep B & C, HIV tested

# In-utero Platelet Transfusions

## Volume Transfused =

$$\frac{\text{Estimated Fetoplacental Volume (ml) x (target final-initial Plt Count) x2}}{\text{Plt Count of transfused Concentration}}$$

- **Empiric**
  - 1-5 ml <30 weeks
  - 5-10 ml >30 weeks

- Half-life 3 days
- Goal platelet count 300-500K post procedure to achieve a weekly nadir at 30-50K at time of next procedure expected

# Mode of Delivery

- C-section indicated unless fetal platelet count:
  - >50 x $10^9$/L at time of delivery
  - >100K at 32 weeks
- Delivery before term not supported unless treatment failure

# Thank you!