

# **NEONATAL ALLOIMMUNE THROMBOCYTOPENIA**

## **Background**

1. Definition<sup>1</sup>
  - Neonatal Thrombocytopenia: Platelet count  $<150 \times 10^9/L$
  - Severe Neonatal Thrombocytopenia: Platelet count  $<50 \times 10^9/L$
2. General Information
  - Fetal/neonatal alloimmune thrombocytopenia (FNAIT) – most common and important cause of severe neonatal thrombocytopenia<sup>2</sup>

## **Pathophysiology**

1. Pathology of Disease
  - Maternal antiplatelet IgG antibodies cross placenta and attack fetal platelets at 14-16 weeks gestation<sup>3</sup>
  - Human platelet antigens (HPA) must be absent in mother and present in fetus (due to inheritance from father)<sup>3</sup>
  - By 18 weeks gestation, platelet antigens seen in fetus<sup>3</sup>
  - Transfer of antibodies increases as gestation progresses until maximum level is reached in late 3<sup>rd</sup> trimester<sup>1</sup>
  - Severity depends on<sup>1</sup>:
    - Concentration and subclass of maternal IgG allo-antibodies
    - Antigen density on fetal platelets
    - Phagocyte activity in fetal reticuloendothelial system.
    - Ability of fetal bone marrow to compensate for accelerated platelet destruction
2. Incidence, Prevalence<sup>1</sup>
  - HPA-1a found in 98% of Caucasian population
  - 2% of Caucasian pregnant women are HPA-1a negative and likely to carry a HPA-1a positive fetus
  - In Asians, HPA-4 most common cause of FNAIT
  - FNAIT Incidence: 1/600-1/5000
  - Anti-HPA-1a sensitization occurs only if mother's Human Leukocyte Antibody (HLA) type is DR52a.
3. Risk Factors
  - HPA incompatibility between father and mother<sup>3</sup>
4. Morbidity / Mortality<sup>1</sup>
  - Antenatal intracranial hemorrhage (ICH) in 10-30% of severe FNAIT
  - Death in 10% of ICH
  - Neurological sequelae in 10%-20% of ICH
  - 1/3 of infants with FNAIT and ICH die<sup>3</sup>

## Diagnosics

1. History<sup>1</sup>
  - Previous pregnancy of FNAIT
2. Physical Examination
  - Healthy appearing newborn born to healthy mother with normal maternal platelet count and uneventful pregnancy<sup>1</sup>
  - Within minutes to hours of newborn's life: petechiae, bruising, excessive bleeding, and mucocutaneous purpura appear<sup>3</sup>
  - ICH presentation: can vary from asymptomatic to seizures, retinal hemorrhage, lethargy, tense fontanel, altered consciousness, apnea, and bradycardia<sup>3</sup>
3. Diagnostic Testing
  - Diagnosis made after birth for first pregnancy<sup>3</sup>
  - CBC usually normal except for thrombocytopenia and anemia if excessive blood loss (always confirm true thrombocytopenia with second sample)<sup>3</sup>
  - Platelet count <20,000/ml when symptoms appear<sup>3</sup>
  - Must rule out infection, disseminated intravascular coagulation, bleeding disorders and maternal immune thrombocytopenia (ITP)<sup>1</sup>
  - Confirmatory test: presence of antiplatelet antibodies in maternal blood sample + maternal-paternal antigen incompatibility<sup>1</sup>
    - Mother and father should be screened for HPA-1, HPA-3, HPA-5 [+ HPA-4 if Asian]<sup>3</sup>
    - Maternal antiplatelet antibody testing accomplished via:
      - Monoclonal antibody-specific immobilization of platelet antigen test (MAIPA)
      - Platelet immunofluorescence test (PIFT)
      - Antigen-specific particle assay (ASPA)
    - Serologic testing for FNAIT recommended in following scenarios:<sup>1</sup>
      - severe thrombocytopenia (even when other causes of neonatal thrombocytopenia present)
      - ICH with significant thrombocytopenia
      - Family history of any transient neonatal thrombocytopenia
  - Diagnostic Testing in multiparous women with confirmed previous FNAIT
    - PCR from amniocytes or chorionic villi at 18 weeks gestation to determine fetal platelet type<sup>1</sup>
    - Fetal Blood Sampling to determine severity<sup>4</sup>
      - Use diminished because of significant risks
      - 1.3% fetal loss rate per procedure<sup>4</sup>
      - 5.5% loss rate per affected pregnancy<sup>4</sup>
4. Laboratory evaluation<sup>5</sup>
  - Commercial enzyme-linked immunosorbent antibody kits for initial screen followed by monoclonal antibody specific immobilization of platelet antigen assays and radioimmunoprecipitation assay for further antibody testing
5. Diagnostic imaging<sup>3</sup>
  - All neonates with confirmed FNAIT should be screened for ICH via cerebral ultrasound, CT, or nuclear magnetic resonance scan

## Differential Diagnosis

### 1. Key Differential Diagnoses<sup>3</sup>

- FNAIT seen in healthy newborns versus thrombocytopenia seen in a sick newborn. Newborn thrombocytopenia seen in the following:
  - Maternal Idiopathic Thrombocytopenia purpura (2<sup>nd</sup> most common cause of neonatal thrombocytopenia)
  - Neonatal Drug Exposure: Heparin, Quinine
  - Thrombocytopenia – absent radius syndrome
  - Congenital Amegakaryocytic Thrombocytopenia
  - Maternal Factors:
    - Penicillin, Dioxin, Phenytoin, Indomethacin, Phenytoin, Heparin exposure;
    - History Pregnancy Induced-Hypertension
  - Chromosomal abnormalities: Trisomy 18, 13, 21, Turner's
  - Wiskott-Aldrich Syndrome
  - Fanconi's anemia
  - Kasabach-Merritt syndrome
  - Cardiac anomalies
  - Placental insufficiency

### 2. Extensive Differential Diagnoses<sup>1</sup>

- Congenital infections: CMV, Syphilis, Toxoplasmosis, Rubella, HIV, Parvovirus B19
- Severe Rhesus disease
- Disseminated intravascular coagulation
- Perinatal infection: GBS, *E.coli*, *Listeria*

## Therapeutics

### 1. Acute Treatment in Neonate

- Treat based on newborn's condition<sup>1</sup>
  - Asymptomatic with mild to moderate thrombocytopenia<sup>1</sup>
    - No treatment necessary
  - Neonatal Bleeding or Severe Thrombocytopenia
    - First Line Therapy: Transfusion of HPA compatible platelets ASAP<sup>1</sup>
      - Transfusion of 1 dose (10 mL/kg) usually increases platelet count by  $100 \times 10^9/L$  within 1 hour
    - If HPA compatible platelets not available, then either<sup>1</sup>
      - Transfusion of HPA-1a-negative and HPA-5a-negative platelets or
      - Transfusion of maternal platelets
        - Need gamma-irradiated and washed to minimize transfer of maternal antibodies.
    - Until matched platelets available, acceptable to give unmatched platelet concentrates<sup>1</sup>
    - IVIG and/or steroids when severe thrombocytopenia and/or hemorrhage persists<sup>1</sup>

- Therapeutic effect of platelet count delayed for 24-48 hrs; neonate remains at risk for ICH
  - Fresh Frozen Plasma<sup>3</sup>
    - Contains 1 international unit of clotting factors for every 10-15 mL/kg
    - Dose: 10-20 mL/kg to prevent bleeding with severe thrombocytopenia of unknown origin
- 2. Antenatal Treatment in history of FNAIT sibling
  - Recommend non-invasive management over invasive<sup>1</sup>
    - Non-Invasive Management
      - Weekly maternal gamma globulin infusion - IVIG (1 g/kg/wk) with or without steroids (0.5 mg/kg/d)<sup>1</sup>
        - Gamma globulin has following actions:
          - suppresses platelet antibody synthesis
          - blocks antiplatelet antibody transfer
          - competitively inhibits platelet binding to maternal antibodies and/or interferes with phagocyte-mediated immune clearance by reticulo-endothelial system<sup>1</sup>
        - Peak maternal IgG level decreases by 50% after 72 hrs<sup>1</sup>
        - IVIG prevents ICH and increases platelets in 55%-85% of cases<sup>1</sup>
        - Side effects: Aseptic meningitis, acute renal failure, thrombosis, anaphylaxis, headaches, febrile reactions, nausea, malaise, and myalgia<sup>1</sup>
        - Side effects minimized by slowing infusion rate<sup>1</sup>
        - Optimal management with IVIG alone or IVIG plus steroids remains unclear.<sup>2</sup>
      - Steroids as sole treatment controversial<sup>1</sup>
        - Efficacy variable, and chronic steroid therapy associated with oligohydramnios
        - Mechanism of action: suppression of Fc receptor function of macrophages and possible interference with antibody synthesis
    - Invasive Management<sup>2</sup>
      - Fetal blood sampling and intrauterine platelet transfusion
        - Previous initial approach but no longer commonly used because of the increased risk of fetal death
        - Only used as an option when mother does not respond to noninvasive management
  - Mode of Delivery<sup>1</sup>
    - Delivery plan based on patient's risk category, response to treatment, and most recent fetal platelet count.
    - Cordocentesis, to determine fetal platelet count as delivery considered, not associated with fetal bleeding
    - Appropriate gestation age for delivery has not been determined

- Cesarean Delivery alone not effective in preventing antenatal or perinatal hemorrhage
  - Vaginal Delivery<sup>1</sup>
    - Reasonable if fetal platelet  $> 50 \times 10^9/L$
    - If platelets  $< 50 \times 10^9/L$ , platelet intrauterine transfusion can protect against bleeding (must weigh risks of transfusion)
    - No evidence to suggest increased risk of ICH in vaginal deliveries with platelets  $< 50 \times 10^9/L$
    - Avoid instrumental vaginal delivery, fetal scalp electrodes, and fetal scalp blood samples
    - Neonatal care team should be present and compatible platelets prepared by blood bank
3. Further Management (24 hrs)
- Observe and follow platelet counts daily<sup>5</sup>
  - Maternal antibodies start to leave infant's circulation at 48 hours of age<sup>3</sup>
  - Resolution of FNAIT usually occurs by 2 weeks of age with complete normalizing of platelet count by 4 weeks<sup>3</sup>
  - Platelet count should be kept  $> 100 \times 10^9/L$  if bleeding occurred and maintained at  $> 50 \times 10^9/L$  for 1 to 2 weeks<sup>5</sup>
4. Recommended Antenatal Therapy:<sup>1</sup>
- Weekly maternal IVIG infusions (1 g/kg/wk) with or without oral steroids (0.5 mg/kg/d)
  - Begin treatment 4 to 6 weeks earlier than when ICH or severe thrombocytopenia occurred in previous pregnancy
    - If information unavailable begin therapy at 30 weeks

### **Follow-Up<sup>3</sup>**

1. Outpatient follow-up includes platelet levels for rare but possible thrombocytopenia recurrence
2. Developmental/neurological follow-up is necessary if ICH occurred
3. Close maternal follow-up with high risk obstetrics and early prenatal care if history of confirmed FNAIT pregnancy

### **Prognosis**

1. FNAIT occurs earlier and is more severe in subsequent pregnancies<sup>1</sup>
2. Recent studies show that high 3<sup>rd</sup> semester antibody titers ( $> 1:32$ ) and high IgG3 subclass titers may predict severe thrombocytopenia. This has yet to be confirmed.<sup>6</sup>
3. Best noninvasive predictor = in utero ICH in sibling<sup>1</sup>
  - 70-80% recurrence rate of ICH if prior sibling affected<sup>1</sup>
4. Quick and proper treatment reduces the risks of death and long-term disabilities<sup>3</sup>

### **Patient Education<sup>1</sup>**

1. Must provide preconceptional counseling for patients with history of pregnancy with FNAIT
2. <http://naitbabies.org/>

## References

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