Parvovirus B19 and Pregnancy

What We All Should Know

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Discussion Outline

- Disease Overview
- Epidemiology
- Pathophysiology
- Clinical Presentations
- Diagnostic Testing
- Treatment
- Prevention
- Summary
Parvovirus B19 Overview
B19 - Background & History

- 1975: Discovered accidentally by Yvonne Cossart & colleagues in London, England
- 1981: Linked to a disease state by John Pattison and colleagues during transient aplastic crisis in children
- Causative agent of “Fifth Disease”
  - “Slapped Cheek” Syndrome
  - Erythema Infectiosum
- 1984: 1st associated with non-immune hydrops fetalis / fetal death

• Single-stranded DNA virus (Parvoviridae family, erythrovirus genus)

• Protein coat made up of 2 antigens:
  – NS1: nonstructural protein- serves multiple replicative functions and is cytotoxic
  – Viral Proteins: VP1 = 5%  VP2 = 95%
  – All assays are based on detecting antibody to 1 or both of these proteins

• No lipid envelope - therefore survives heat & detergent treatment of blood products

• Named as the “fifth” pediatric disease reported (measles, scarlet fever, rubella, Duke’s (?), EI & roseola)

• Parvovirus B19 – pathogenic to humans

• 3 – 5 year epidemics

• Respiratory droplet spread

• Incubation period 4 – 20 days

• Viremia at 6 – 8 days, persisting 4 – 7 days

• Rash at approx. day 16 (non-infectious)

• Replicates rapidly in “erythroid progenitor” cells, but also on platelets, tissue of heart, lung, kidney, liver, endothelium and synovium

• Dependent on host cells to propagate
• Humans are only known hosts

• These are the cells that make Red Blood Cells (RBC’s). Parvovirus causes a drop in RBC’s and hemoglobin. This may result in severe anemia in certain patient groups.

Epidemiology
• Infections occur globally and are similar in U.S., Europe and Asia

• Outbreaks tend to be in Winter & Spring and are common in childhood

• Infection continues at a lower rate throughout adult life and >70% of the adult population is seropositive
  (Kerr et al., 1999)

• Epidemics follow a 3-4 year cycle.
  • Regional variations apply.
  • 50-70% adults are seropositive.

Pathophysiology
Viral Transmission
Native Virus Capsids

Image courtesy of the Wadsworth Centre - New York State Dept of Health
B19V and the erythroid progenitor cell receptors

2003 BLOOD : K. WEIGEL-KELLEY (alpha5 beta1= integrines),
2005 BLOOD : Y.MUNAKATA (Ku80 = auto-antigen =PN surface GRCD36, LBCD20 et LTCD3)
How is the virus spread?

- Respiratory
- Hand-to-mouth (resilient on surfaces)
- Infected blood products (esp. pooled factors VIII & IX)  
  Anderson et al., 1985; Lyon et al., 1989, Erdman et al., 1997
- Mother to fetus (vertical transmission)
- Infectious during 1\textsuperscript{st} 7-14 days only
  - During outbreaks 25\% & 50\% infection rates recorded in school & home
Pathophysiology of Fetal Disease

Human erythroid progenitor is natural host

Key is globoside or erythrocyte P antigen
- a neutral glycolipid that acts as a cellular receptor for virus and site of entry

Globoside is present in the placenta and fetal myocardium; also on some megakaryocytes and endothelial cells

Rare that erythrocyte lacks P antigen- means immunity

(Brown KE, Anderson SM, Young NS. Science 1993)
Pathophysiology of Fetal Disease

Maternal Infection & Viremia

↓

Transmission across placenta

↓

Virus attaches to erythroid cells

(P-globoside) fetal liver & myocardial cells

↓

Virus replicates resulting in cell death
Pathophysiology of Fetal Disease

Drop in RBC / Hb resulting in fetal anemia

Anemia leading to tissue hypoxia

Compensatory increase in cardiac output

High output cardiac failure & fetal hydrops

NB: B19V infection of fetal spleen, liver & heart may be a contributory cause of organ failure
Host Immune Response

- B19 infection → B cells divide to produce plasma and memory cells
- Plasma cells secrete IgM - detectable 7-10 days post-infection
- IgG is detectable ~15 days post-infection against VP1 & VP2
- Usually infection leads to lifelong protection due to the development of memory B cells
- APCs process virus and present peptides to Th cells secrete cytokines that mediate antiviral immunity BUT Th cells can also be associated with the pathogenesis of B19 (seen in chronic arthropathies, Mitchell et al., 2001.)
- Loss of Th response can cause serious infections in the immunocompromised host, Young, 1996, Kurtzman et al., 1989.
Antibody Response during Human Parvovirus B19 Infection

Days post inoculation

- Virus
- IgM
- IgG
Various Clinical Presentations of Parvovirus B19
Different Disease Manifestations of Parvovirus B19

- “Fifth Disease” or Erythema Infectiosum
- Hydrops Fetalis and congenital infection
- Arthropathies
- Transient Aplastic Crisis
- Persistent Infection
- Assorted syndromes (less common and not proven)
  - Seronegative hepatitis, chronic fatigue syndrome, vasculitides, meningitis, encephalitis

Parvovirus B19 in Pediatrics and Pregnancy
First phase- fever and non-specific viral symptoms occur early- *high viral shedding and transmission*

Second phase- Childhood exanthem of “slapped cheek rash”—no transmission at this time

Cutaneous eruption and rheumatic symptoms occur two weeks after viral infection—correspond to appearance of viral antibodies

Rash likely due to formation of immune complexes—usually IgM +/- IgG

Rash can be lacy, reticular or evanescent and recur with exposure to sunlight, heat, emotion or exercise
Pathogenesis of B19V & Clinical Presentation
Typical presentation of slapped cheek syndrome
Fifth Disease in Pregnancy

- Usually asymptomatic - can see exanthema & arthralgia
- may cause fetal hydrops; may resolve spontaneously
- may lead to severe fetal anemia and hydrops
- may cause stillbirth and spontaneous abortion
- B19 infects fetal erythroid precursor cells
- Lytic infection results in anemia
- development of generalized fetal hydrops with massive edema
- cause of fetal death: acute cardiac failure
Recent Statistics

• 4 million births in Europe or US per annum

• 30% of women non-immune, therefore 1.2 million women at risk

• Conservative estimate of fetal loss per annum is 3000

Risk of Infection

• 50-60% of women of child-bearing age are immune

• If seronegative
  – 1% overall risk of infection
  – 13.5% during epidemics
  – 50% if direct household contact
  – 20 –30% from school exposure
  – Overall fetal loss rate after infection is between 2% and 10%.

B19 Infection in Pregnancy

• 1/3 of infected mothers will pass the virus on to their baby

• B19 affects 1/400 pregnancies

• Greatest risk during 2nd trimester
  – Fetal RBC’s have 45-70 day life span and RBC mass increases by 3-4x between 3-6 months gestation

• When to test?
  – Following suspected rash exposure or symptoms
  – May be included in “TORCH” panel
  – During suspected outbreaks
Fetal Complications

- Fetal Death usually occurs 4-6 weeks post-infection, but can go out 12-20 wks (Hedrick, 1996, Miller et al., 1998)

- Greatest risk during 2nd trimester
  - May be most vulnerable because fetal RBC’s have a shortened 45-70 day life span and RBC mass increases by 3-4x between 3-6 months gestation (Rodis et al., 1988)

- B19 replication with erythroid progenitor cells which leads to apoptosis and ultimately inhibits erythropoiesis causing severe anemia (Morey et al., 1993)
Fetal Complications

- In 1984, Fetal Hydrops was first associated with B19
- Up to 20% of NIHF is felt to be related to B19
- Anemia is the underlying factor in the development of hydrops
- Rare and controversial cause of third-trimester fetal loss
Making the Diagnosis

When to test?
What test to order?
How do I interpret the results?
What do I do with the results?
What do I tell my patients?
When is imaging necessary?
What interventions are out there?
Laboratory Testing

- High index of suspicion and the timing of B19 testing is critical
- Pre-natal screening is an option- allows you to assess prior exposure, current infection or past infection
- “routine screening for symptoms of B19 infection or [evidence] of seroconversion would overcome this problem” [ of overlooking B19]


- Use most sensitive assays available to avoid false-positives and negatives
- Can follow msAFP, but normals are less predictive especially after 20 wks (Murphy J, Jones D. OBG Management Nov 2000.)
Diagnosis

- Complete history, including occupational and recent viral syndromes
- IgM- & IgG-
  - No infection / susceptible- repeat testing in 2 weeks
- IgM- & IgG+
  - Immune- reassure your patient- no risk
- IgM+ & IgG+ infection in last 7-120 days
  - Current infection- HIGH FETAL RISK requires fetal surveillance with weekly ultrasounds for 10-12 weeks
- IgM+ & IgG- infection in last 7 days
  - Current infection- HIGH FETAL RISK requires fetal surveillance with weekly ultrasounds for 10-12 weeks
Laboratory Testing

- Cost of blood tests and sonograms to patient and healthcare system is an issue
  - IgM EIA- $95- serum/speckled tube
  - IgG EIA- $95- serum/speckled tube
  - IgG/IgM EIA- $190- serum/speckled tube
  - B19 DNA by PCR- $162- lavender-top & frozen
- These are approximate costs provided by Quest Diagnostics®
- Somewhere between 70%-100% of the cost is covered by insurance. WARN YOUR PATIENTS THAT THEY MAY GET A BILL.
Treatment Options

• “Wait & see” - expectant management
  – Weekly monitoring by ultrasound
  – Monitor middle cerebral artery-peak systolic velocity (MCA-PSV)- if >95th percentile higher risk of anemia
  – If anemia present, the blood is less viscous and has higher velocity;
  – Delivery of the fetus
    – Only an option post-34 weeks gestation

• Intrauterine transfusion
  – Post 18-20 weeks gestation
  – 83.8% success rate!
  – Review of literature puts survival between 50% and 90%.

Hydropic Fetus

Typical presentation of hydrops fetalis associated with Parvovirus B19 infection
Fig. 2. Fetal ascites (1) and enlargement of fetal liver (2) and fetal heart (3).
Arthritic Joint with Rash
Clinical Manifestations of Parvovirus B19 Infection. Panel A shows typical cutaneous eruptions in fifth disease, including “slapped” cheeks in children and a more generalized lacy, reticular pattern of erythema. Panel B shows a bone marrow aspirate with no mature erythroid precursors and with characteristic giant pronormoblasts. In Panel C, hydrops fetalis is evident in an infant who was infected in utero in midtrimester (courtesy of Dr. O. Caul).

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Fetal hydrops
Treatment Options

- 5-10 day course of (0.4g/kg) IVIG for fetal hydrops reduces viral burden and can improve anemia (Selbing et al., 1995; Alger, 1997)

- Spontaneous resolution may occur, but difficult to predict - 54% observed vs. 83.5% transfused survival rate (Rodis et al., 1998)

- If hydrops is found than percutaneous umbilical blood sampling (PUBS) is indicated to assess fetal blood prior to RBC transfusion
  - 1% complication rate (fetal hemorrhage)
  - Determines MCV, Hct, plts, WBC and viral DNA
Prevention Strategies

- Educate the medical provider and the patient
- Take a good history and assess risk
- Screen patients up front and when there is risk of exposure
- Vaccines are in development, but are not currently available (available in animals)
- Currently not recommended by ACOG “that high risk groups” be excluded from the workplace during epidemics (day care, school), but opinions vary and decided on a case-by case basis (ACOG practice bulletin Sept 2000)
- Screening the blood supply- not always routinely done, but most manufacturers do
Websites

Fifth Disease - General Information:

http://www.fifthdisease.org
http://kidshealth.org/parent/infections/bacterial_viral/fifth
http://www.drreddy.com/shots/fifth.html
http://www.emedicinehealth.com/articles/15841-1.asp

Medline Plus:

Medicine.net:
http://www.medicinenet.com/Fifth_Disease/article.htm
http://www.biotrin.com
Websites

**Fifth Disease And Pregnancy:**

http://www.fifthdisease.org

**Medline Plus:**


**New York State Dept of Health:**

http://www.health.state.ny.us/nysdoh/communicable_diseases/en/fifth.htm
Websites

Treatment and Diagnosis:

Health Link USA:

http://www.healthlinkusa.com/cgi-bin/foxweb.exe/hl/linkindex1?searchtext=Fifth+Disease&words=all&fromrelated=519

E medicine:

http://www.emedicinehealth.com/articles/15841-1.asp
http://www.emedicine.com/derm/topic136.htm
http://www.caringforkids.cps.ca/whensick/FifthDisease.htm
http://www.mayoclinic.com/invoke.cfm?id=DS00437
http://www.ivillage.com/topics/health/0,,296127,00.html?arrivalSA=1&cobrand=0&arrival_freqCap=1&pba=adid=10506657
Summary

- Educate yourself and the patient
- High-index of suspicion
- Order and interpret tests appropriately
- Refer to high-risk OB/GYN if fetal compromise suspected