Sífilis Congénita: Algoritmo diagnóstico y terapéutico – es perfectible?

Pablo J. Sánchez, MD

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

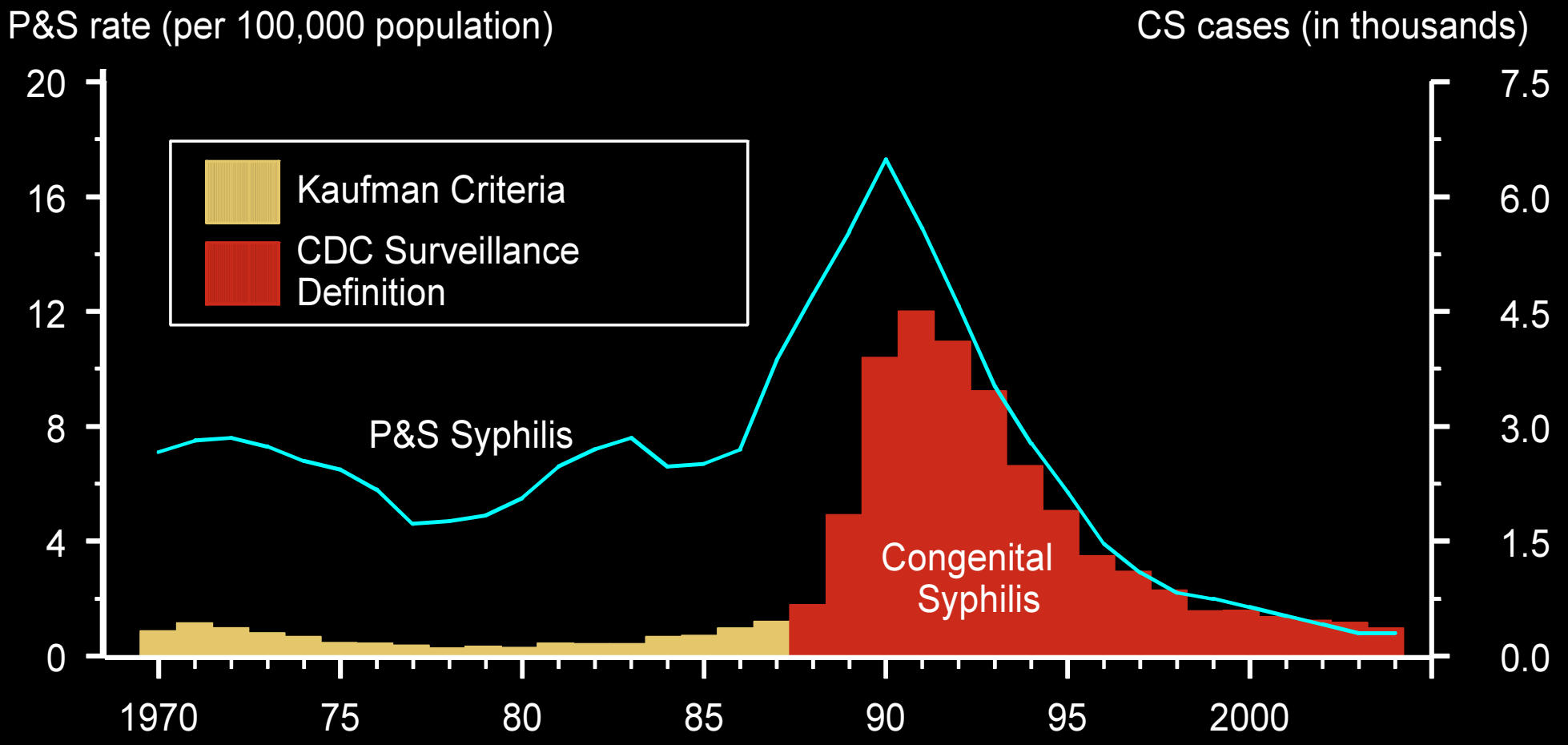
THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

39° Congreso Argentino de Pediatría
Rosario, Argentina; 9/26/19

EPIDEMIOLOGY

- Syphilis in pregnancy:
  - Hydramnios, spontaneous abortion
  - Preterm delivery → fetal syphilis, stillborn, nonimmune hydrops
  - Inadequate prenatal care:
    - Congenital cases

Congenital syphilis: Reported cases for infants <1 yr of age and rates of primary / secondary syphilis among women: United States, 1970–2004



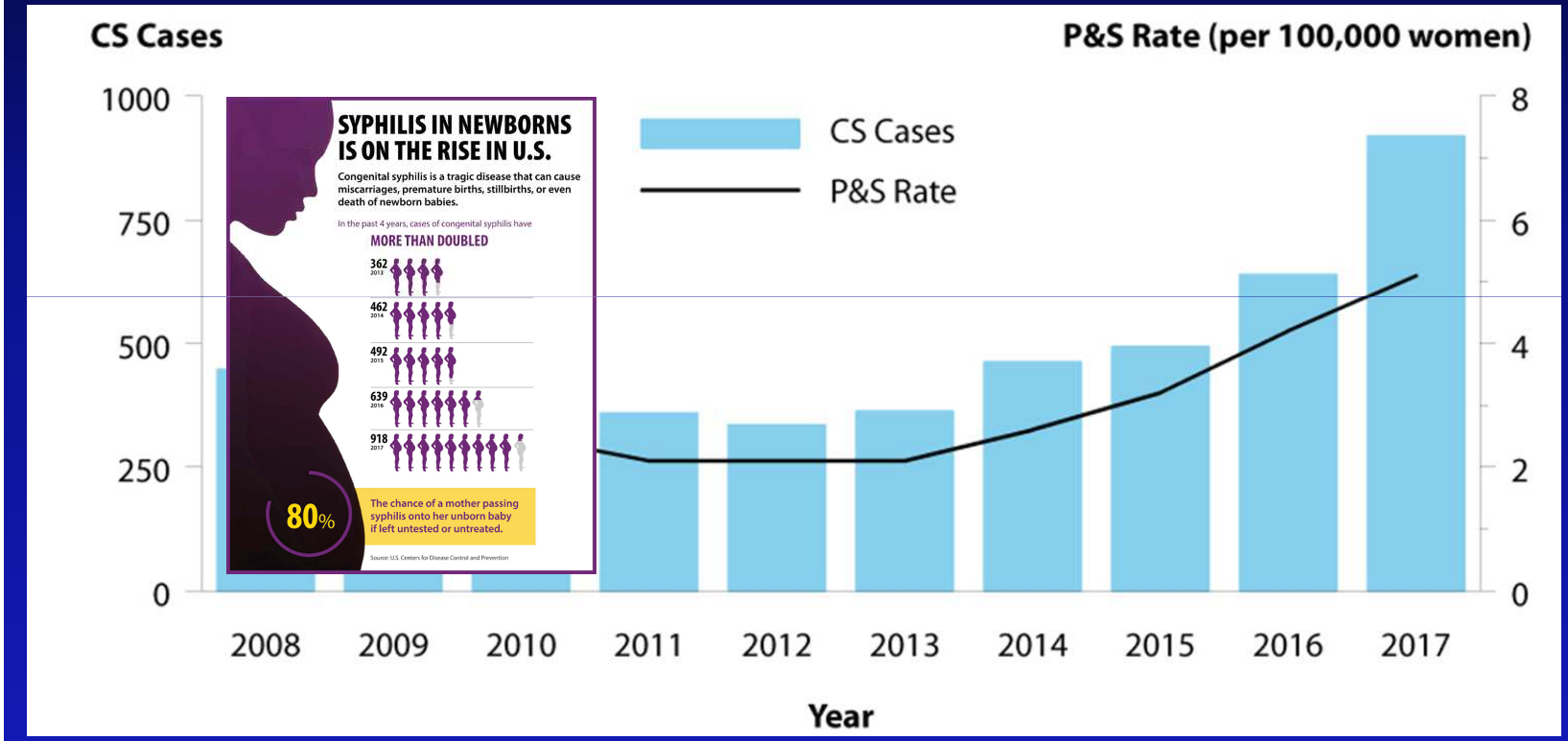
Note: The surveillance case definition for congenital syphilis changed in 1988.

SURVEILLANCE CASE DEFINITION: CONGENITAL SYPHILIS (1988*)

- Confirmed case: demonstration of *T. pallidum*
- Probable case:
  - Infant whose mother had untreated or inadequately treated syphilis at delivery
  - Reactive non-treponemal test and abnormal physical exam, long bone x-rays, or reactive CSF VDRL, elevated CSF cell count/protein
- Syphilitic stillbirth: fetal death at >20 wk gestation or BW >500 g and mother with untreated/inadequately treated syphilis

*CDC 2018

Congenital Syphilis — Cases by Year of Birth and Rates of Primary/Secondary Syphilis Among Women (15-44 yrs), United States, 2008–2017



2017:
918 cases;
64 stillbirths
13 infant deaths

Congenital syphilis increased 44% from 2016 and 153% from 2013, with a parallel 156% and 143% increase in all women and reproductive age women, respectively.

CDC.gov, 2019

CONGENITAL SYPHILIS: 2017

	Rank	No. of Cases	Rate / 100,000 Live Births
Louisiana			
Nevada			
California			
Texas			
Florida			
Arizona			
Maryland			
Arkansas			
N Carolina			
Georgia			
US Total			

West > South > Midwest > Northeast; Blacks > Hispanics

HP 2020 TARGET: 9.1

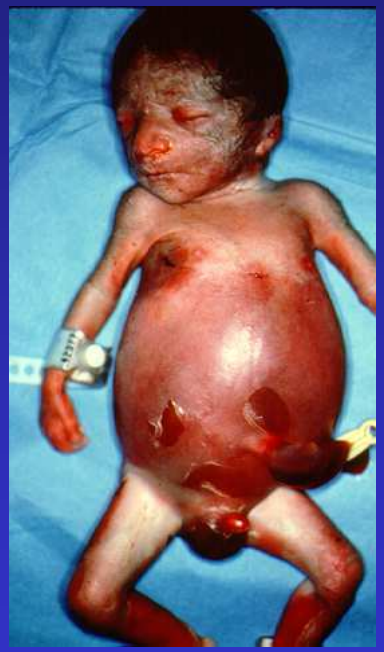
CONGENITAL SYPHILIS: 2017

	Rank	No. of Cases	Rate / 100,000 Live Births
Louisiana	#1	59	93.4
Nevada	#2	21	57.9
California	#3	281	57.5
Texas	**#4**	**176**	**44.2**
Florida	#5	93	41.3
Arizona	#6	30	35.5
Maryland	#7	20	27.3
Arkansas	#8	8	20.9
N Carolina	#9	23	19.0
Georgia	#10	23	17.7
US Total		922	23.2

West > South > Midwest > Northeast; Blacks > Hispanics HP 2020 TARGET: 9.1

CONGENITAL SYPHILIS: MORTALITY

- 1999-2013: 6383 cases of CS (decrease from 14,627 cases in 1992-1998; 56% decline)
- Neonatal mortality: 11.6/1000 live births
- 418 deaths, 342 (82%) stillbirths
- Case fatality rate: 6.5% (stable)
- 89% of deaths: untreated (73%) or inadequately treated during pregnancy
- Less prenatal care: ↑ risk of death
- 59% of deaths occurred by 31 wks of gestation



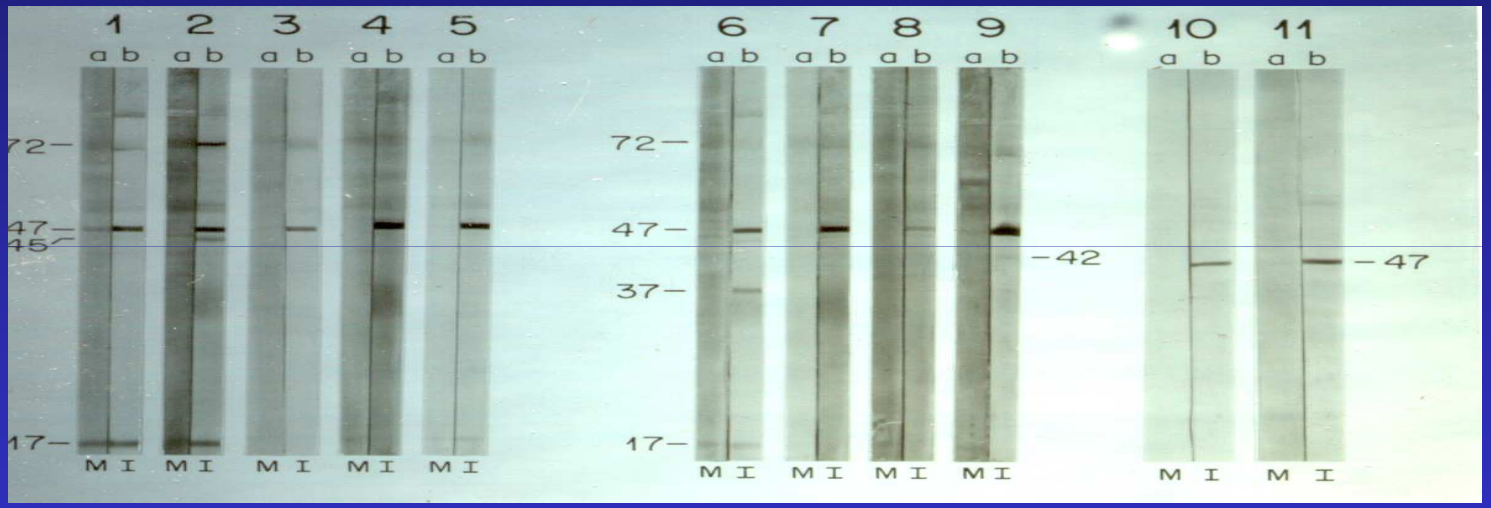
Su et al. *Am J Obstet Gynecol* 2015

PROBLEMS IN THE DIAGNOSIS OF CONGENITAL SYPHILIS

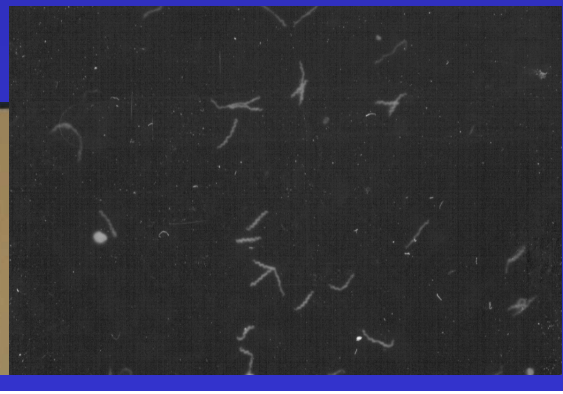
- Inability to detect or culture *T. pallidum* in neonatal clinical specimens
- Difficulty in interpretation of serologic tests due to transplacentally acquired maternal IgG
- Difficulty in identification of infants with CNS invasion by *T. pallidum*

DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- **IgM immunoblot:**



- **Rabbit infectivity test (RIT):**

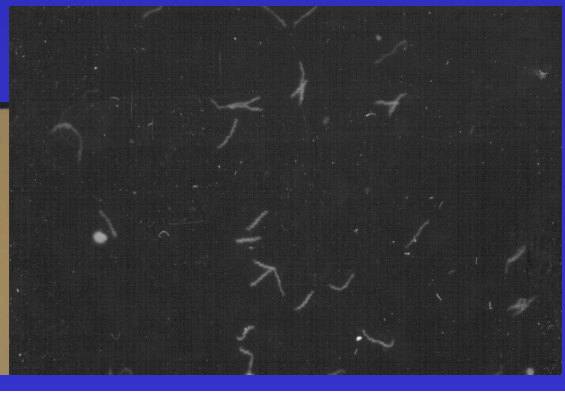


DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- IgM immunoblot:

NO COMMERCIALLY AVAILABLE SYPHILIS IGM TEST IS USEFUL!! DON'T DO THEM!!!

- Rabbit infectivity test (RIT):



DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- Mortality (35%)
- Vertical transmission
- “Asymptomatic” newborn
- Central nervous system invasion
- Evidence-based rationale for the management of infants born to mothers with reactive serologic tests for syphilis (CDC, AAP)

DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- "Asymptomatic" newborn
- Central nervous system invasion
- Evidence-based rationale for the management of infants born to mothers with reactive serologic tests for syphilis (CDC, AAP)

Mortality of Congenital Syphilis*

- Case-fatality rate:
  - Confirmed congenital syphilis: 35% (67/191)
    - Stillbirths: 79% of deaths (53/67)
    - Majority of stillbirths occurred before 28 weeks' gestation (74%)
  - CDC surveillance case definition: 11%
- CDC surveillance case definition under-estimated mortality by >300%

*PAS 2018

CONGENITAL SYPHILIS: VERTICAL TRANSMISSION

- *In utero*:
  - Transplacental route following maternal spirochetemia
- Intrapartum:
  - Contact with genital lesion

CONGENITAL SYPHILIS: INTRAUTERINE TRANSMISSION

- Isolation of the organism from umbilical cord blood and amniotic fluid
- The isolation of *T. pallidum* from as many as 74% of amniotic fluid specimens obtained from women with early syphilis also suggests that the organism is capable of traversing the fetal membranes, gain access to the amniotic fluid and result in fetal infection.

* Wendel et al. Obstet Gynecol. 1991;78:890
Nathan et al. J Ultrasound Med 1993;2:97
Hollier et al. Obstet Gynecol. 2001;97:947

CONGENITAL SYPHILIS: INTRAUTERINE TRANSMISSION

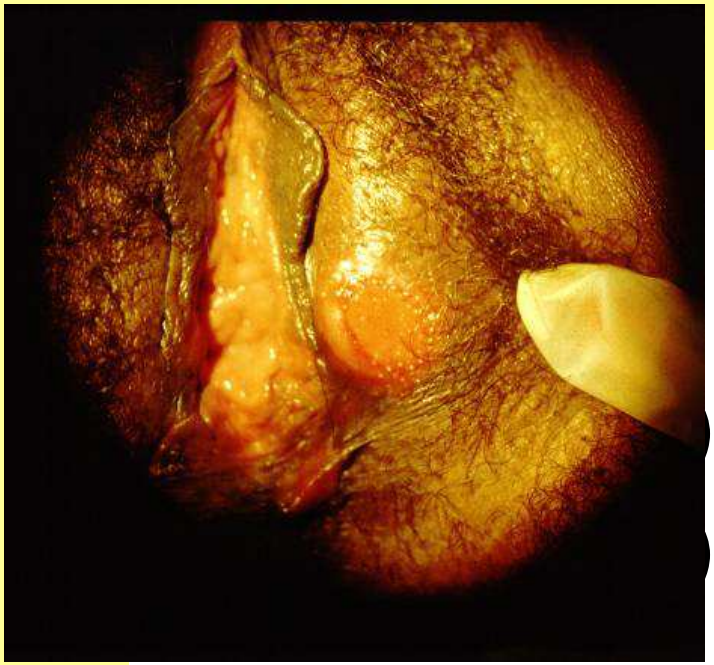
- Clinical disease *in utero* and at birth
- Detection of specific IgM antibody to *T. pallidum* in fetal serum obtained by cordocentesis and in neonatal serum obtained at birth

* Sanchez et al. J Infect Dis. 1989;159:508
Wendel et al. Obstet Gynecol. 1991;78:890

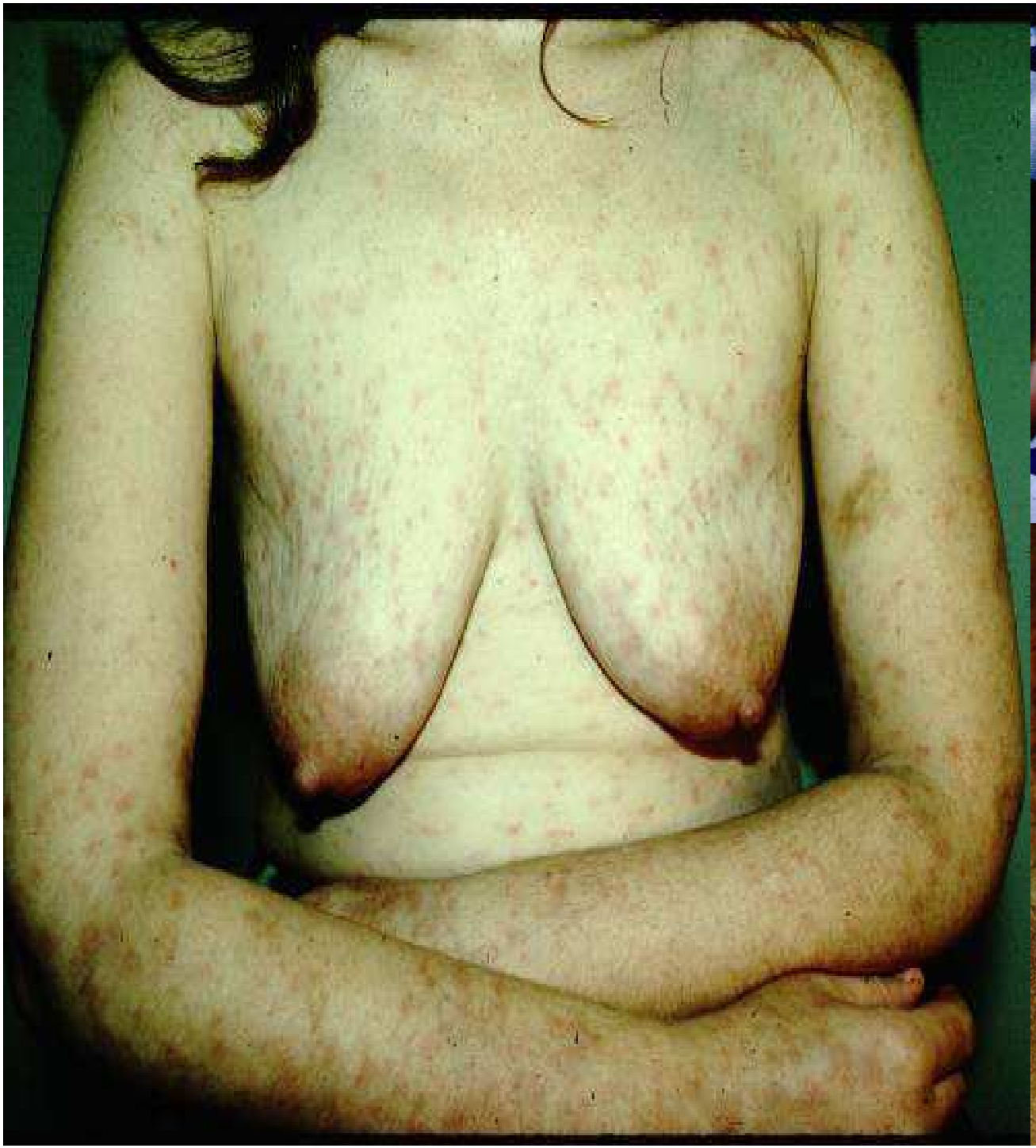
CONGENITAL SYPHILIS: VERTICAL TRANSMISSION

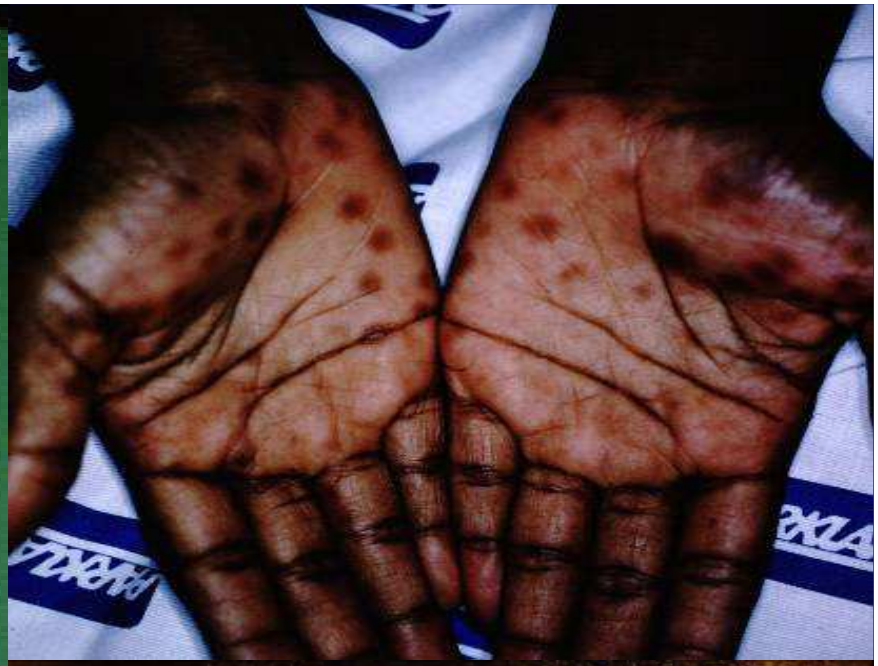
- Increases as stage of pregnancy advances but can occur at any time in gestation
- Related to stage of maternal syphilis

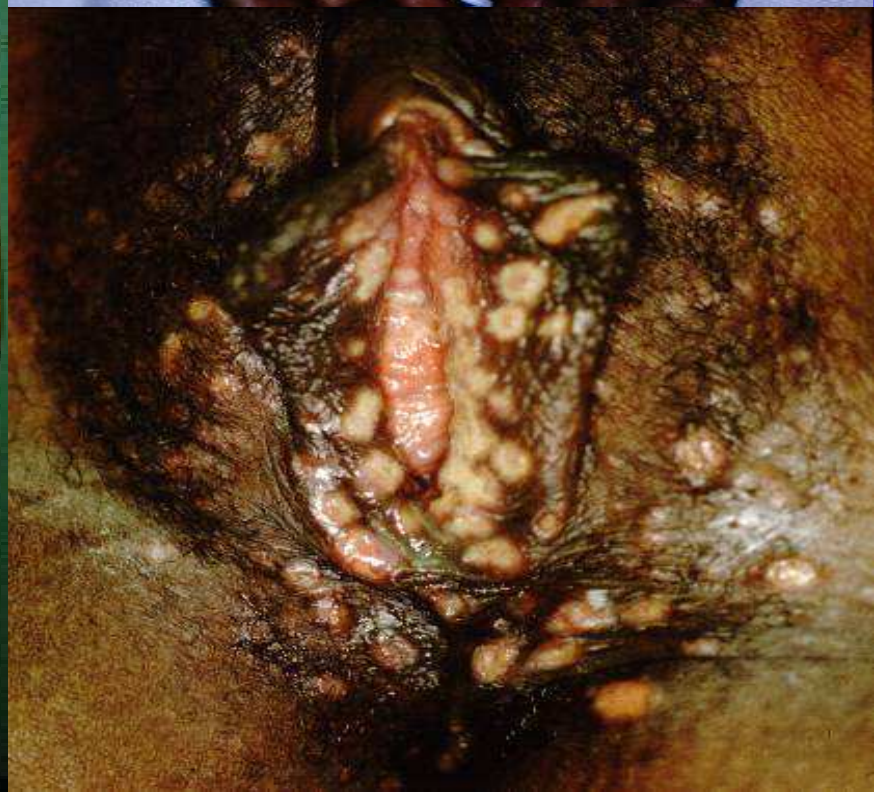
SYPHILIS IN PREGNANCY: THE PARKLAND EXPERIENCE (1988-1998)



			Early Latent	Late Latent
No. of Mothers			145	27
Outcome (%):				
Stillbirth			31 (21)	1 (4)
Congenital Syphilis			21 (14)	1 (4)
Total	6 (23)	32 (60)	52 (36)	2 (7)







SYPHILIS: SEROLOGIC TESTS

- **Nontreponemal tests**: RPR / VDRL
  - **Antigen**: lecithin, cholesterol and cardiolipin (diphosphatidylglycerol); detects an antibody against cardiolipin that is present in sera of patients with syphilis
  - **Quantitative tests**: Useful to assess adequacy of treatment and to detect reinfection (fourfold difference, e.g. 1:8 vs. 1:32)

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- **Nontreponemal tests**: RPR / VDRL
  - **Quantitative tests**: Useful to assess adequacy of treatment and to detect reinfection (fourfold difference, e.g. 1:8 vs. 1:32)
  - Diagnosis of congenital syphilis is supported by infant's RPR / VDRL ≥ 4x maternal RPR / VDRL

SYPHILIS: SEROLOGIC TESTS

- RPR: more sensitive than VDRL; preferred for screening of pregnant women
- Perform the same nontreponemal test on the infant that was performed on the mother

RPR/VDRL ON INFANT: SERUM OR UMBILICAL CORD BLOOD (UCB)?

- AAP: serum; UCB: false ⊕ (5-10%) and false-neg (5-20%) results can occur
- CDC: serum; UCB: contamination with maternal blood may yield a false ⊕ result
- UCB: Easy to obtain; readily available
  - Avoid contamination
  - DON'T use for screening!

SYPHILIS: SEROLOGIC TESTS

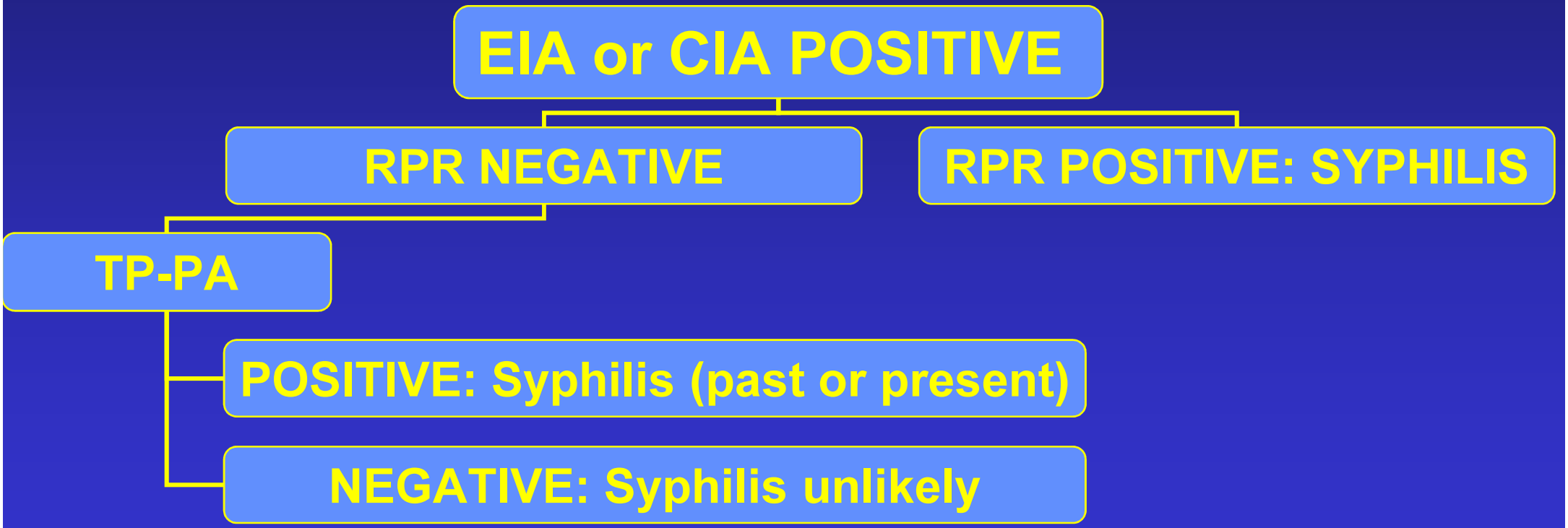
- **Treponemal tests:**
  - Detect antibody (IgG) to *T. pallidum*
  - Confirm reactive nontreponemal test result
    - **TP-PA**: hemagglutination test (lysate of *T. pallidum*)
    - FTA-ABS (lyophilized *T. pallidum*)
    - Enzyme / chemiluminescence immunoassays (EIA / CIA)

CONGENITAL SYPHILIS: PREVENTION

Screening with treponemal test?

“Reverse Sequence Screening”

"REVERSE SEQUENCE" SCREENING: CDC RECOMMENDATIONS



MMWR, 2/2011

SYPHILIS: SEROLOGIC TESTS

- **Treponemal tests:**
  - **Non-quantitative tests**
  - **Remain reactive indefinitely**
  - **Not useful for distinguishing active infection from past infection or assessing adequacy of treatment**
  - **Not useful in evaluation of newborn**

STD 2015

www.cdc.gov

CONGENITAL SYPHILIS

- **Early** manifestations (< 2years of age):
  - Due to hematogenous spread of organism and resultant inflammatory response in various organs and tissues
  - Extramedullary hematopoiesis
  - Immune-mediated
- **Late** manifestations (>2 years of age):
  - Scarring or stigmata from early disease
  - Reaction to persistent inflammation
  - Noninfectious

LATE CONGENITAL SYPHILIS

- Central nervous system, bones, and joints, teeth, eyes, and skin:
  - Interstitial keratitis* (5-20 years of age); eighth cr  ss* (10-40 years of age); H peg-shaped, notched nulberry molars, anterior l ontal bossing, saddle n ioral fissures), Clutton joints (symmetric, painless swelling of knees)
- Prevented by early treatment!

*Hutchinson triad

LATE CONGENITAL SYPHILIS

- , bones, and joints,

  5-20 years of age);
  leafness* (10-40 years
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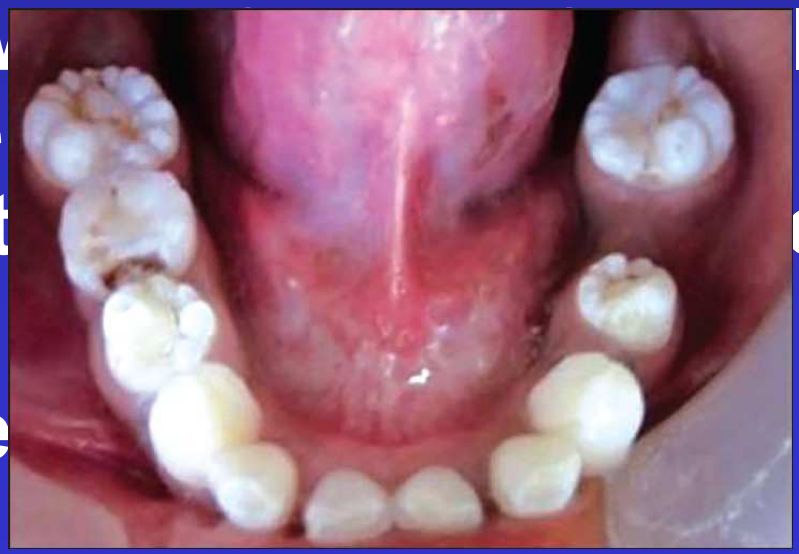

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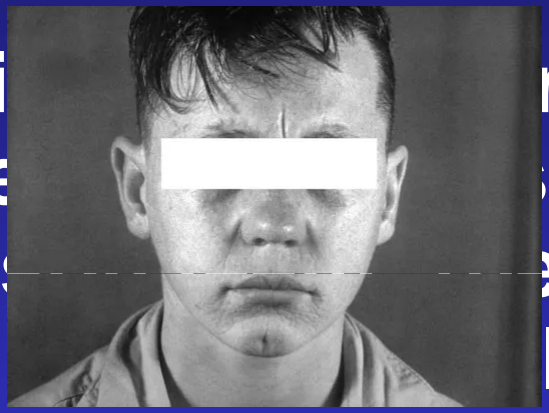
GENITAL SYPHILIS



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anterior bowing of shins, frontal bossing, saddle nose, rhagades (perioral fissures), Clutton joints (symmetric, pa
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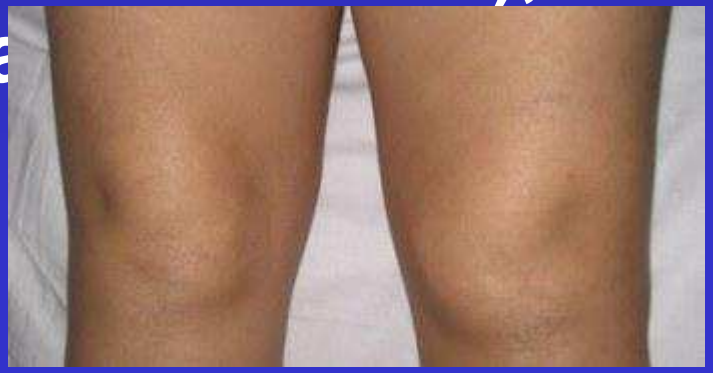


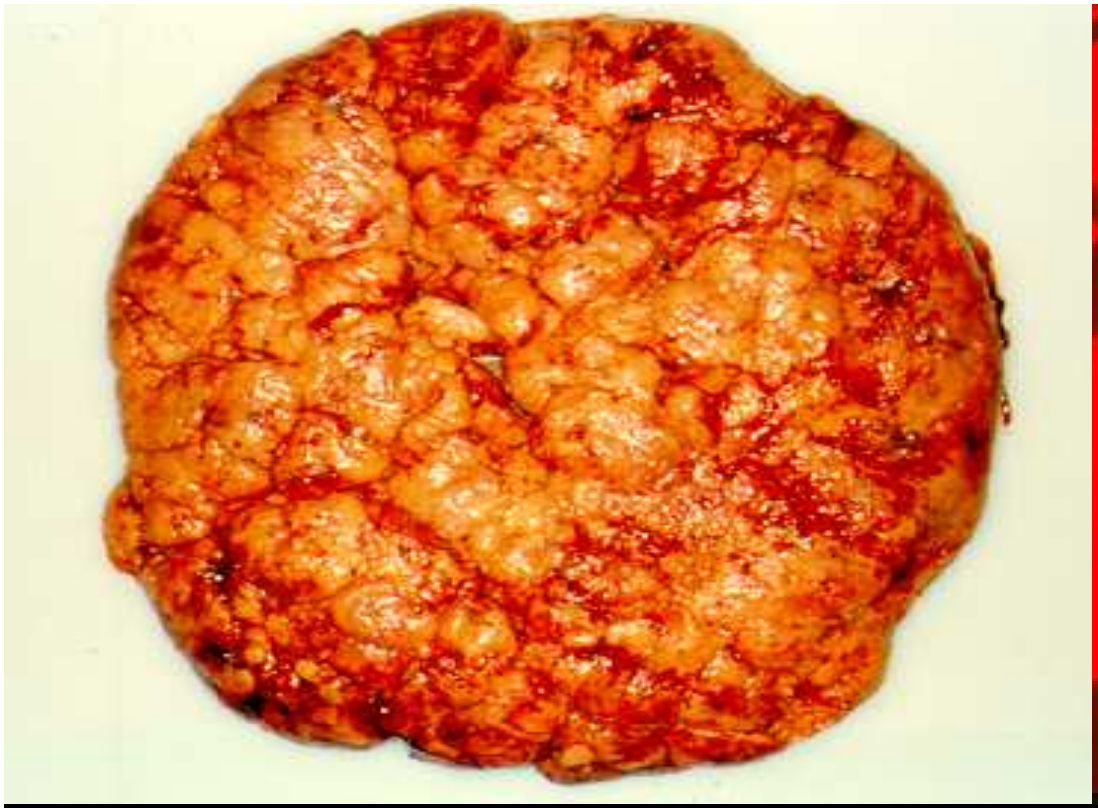
- Prevented by early treatment!

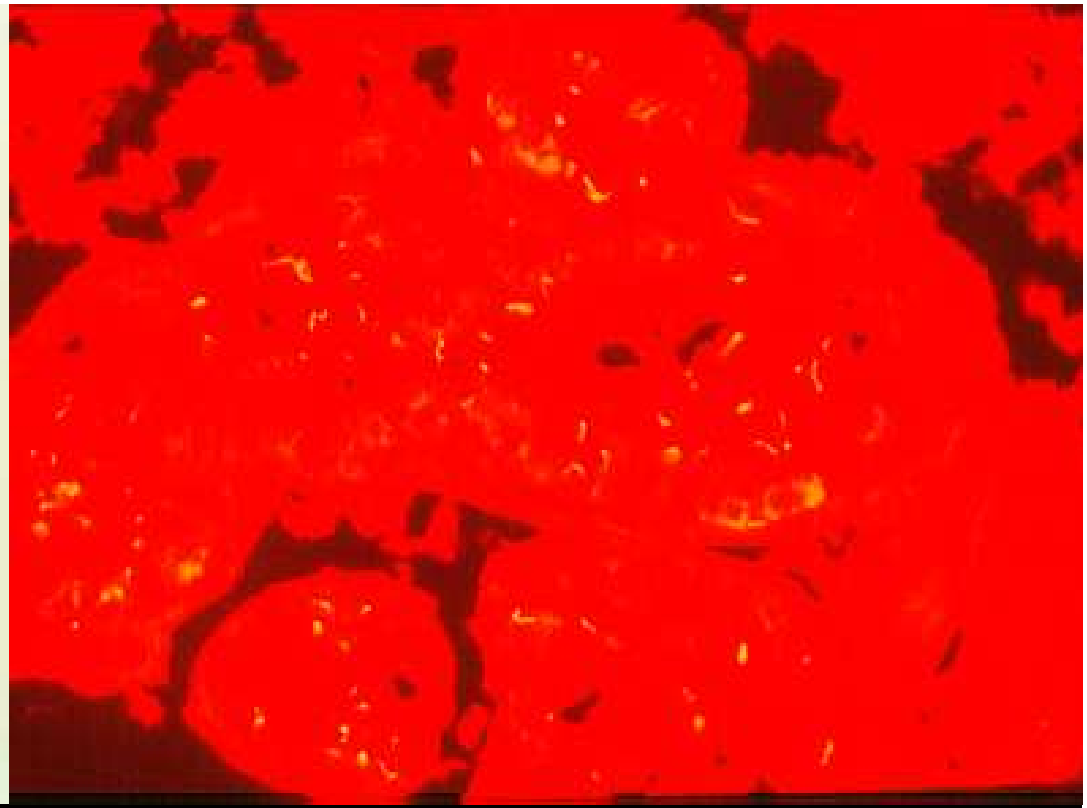
Evaluation and Treatment of Infants During the First Month of Age

SCENARIO 1:
PROVEN OR HIGHLY PROBABLE
SYPHILIS

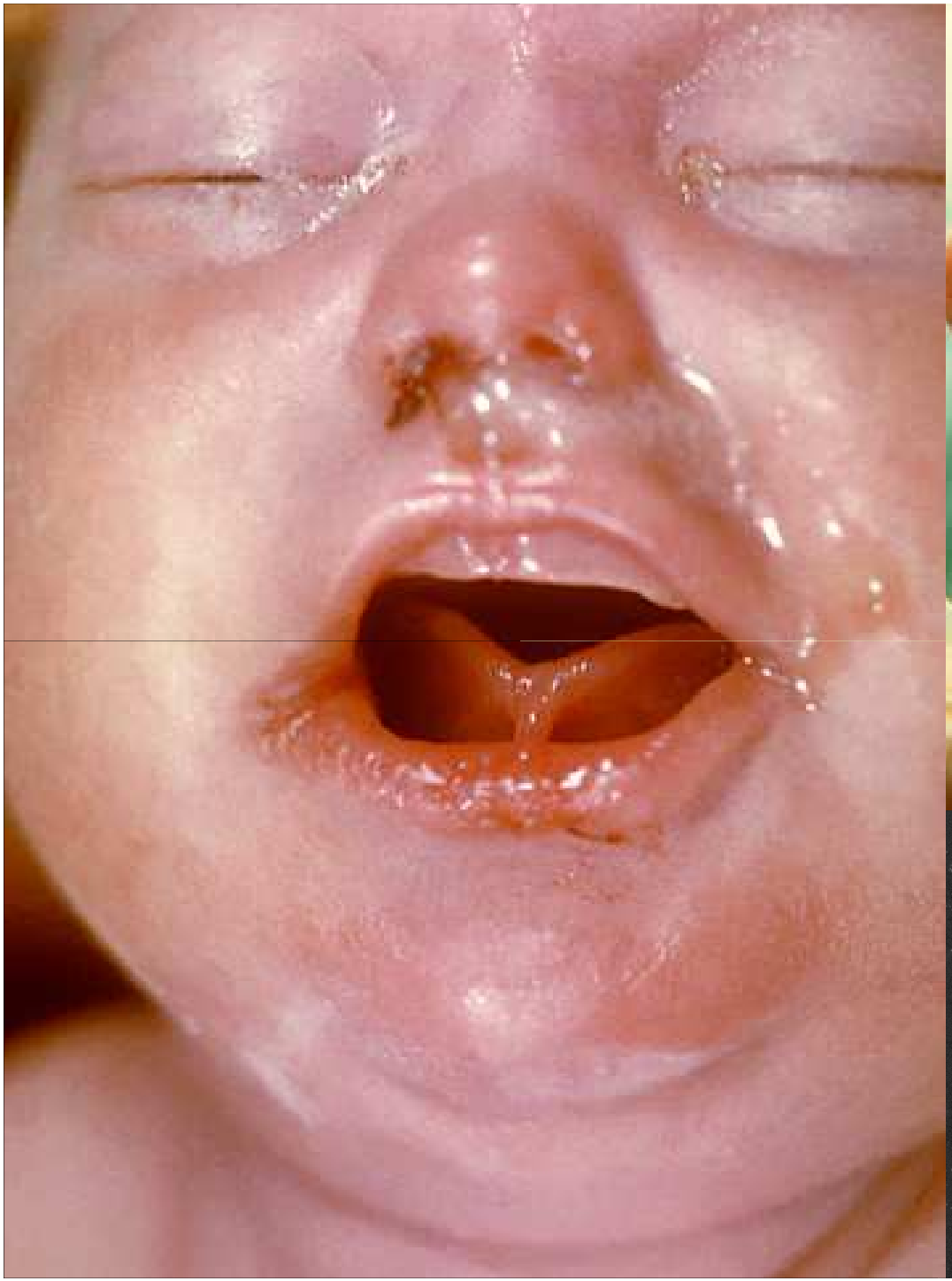
PROVEN OR HIGHLY PROBABLE SYPHILIS

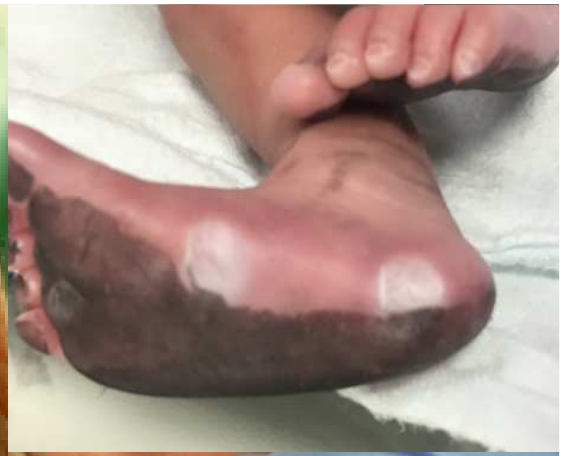
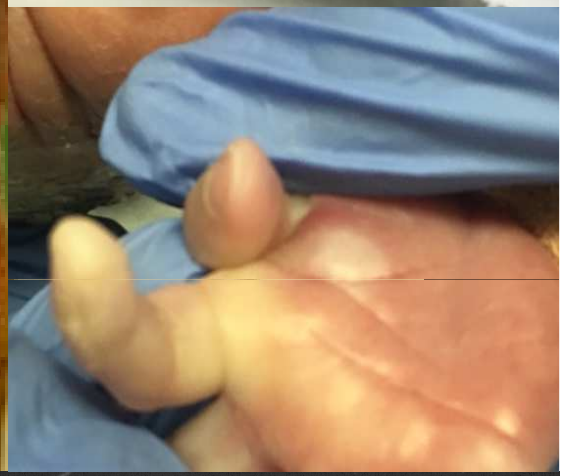
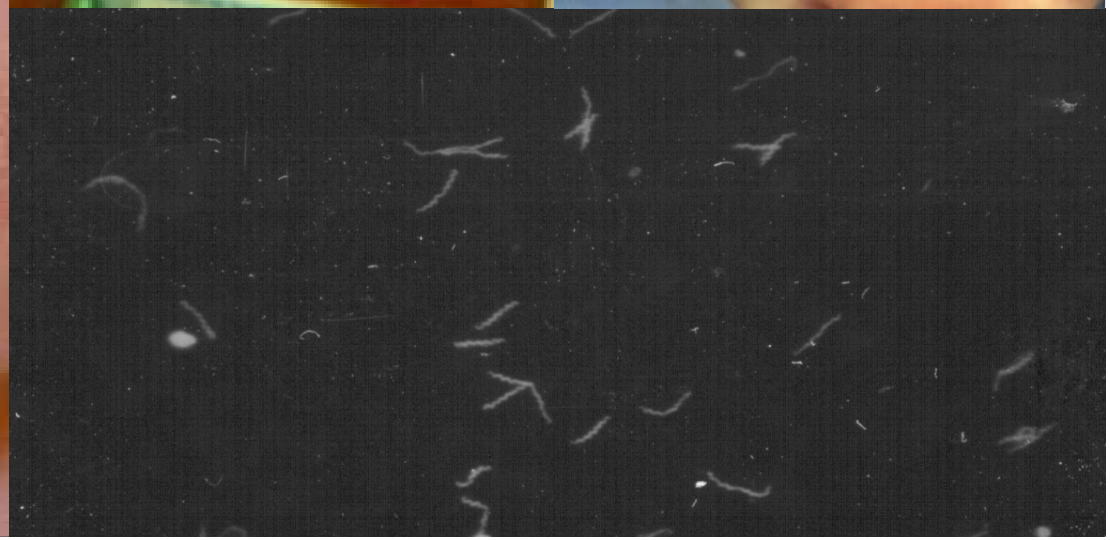
- Infant physical exam abnormal
- Serum VDRL/RPR ≥4x maternal titer
- Positive darkfield or fluorescent antibody test of body fluid(s) or tissue

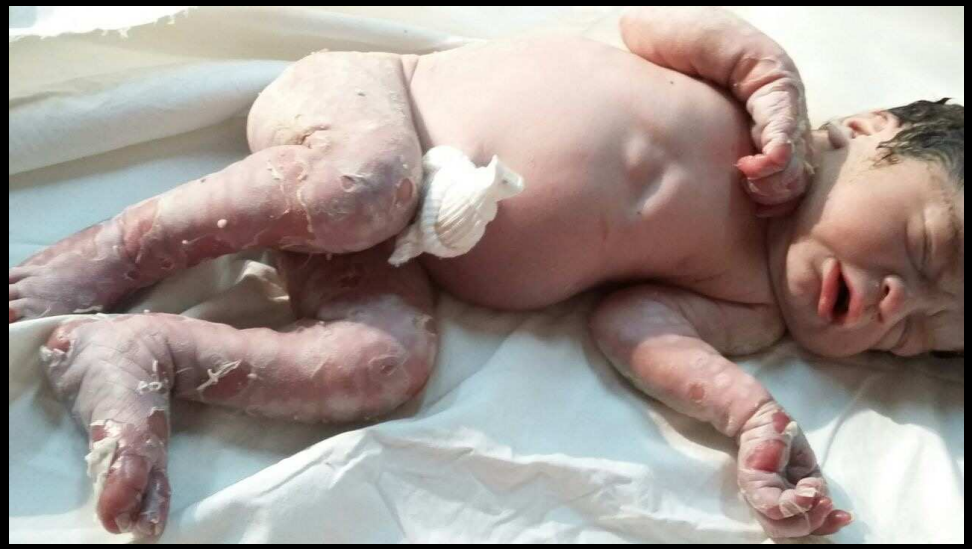


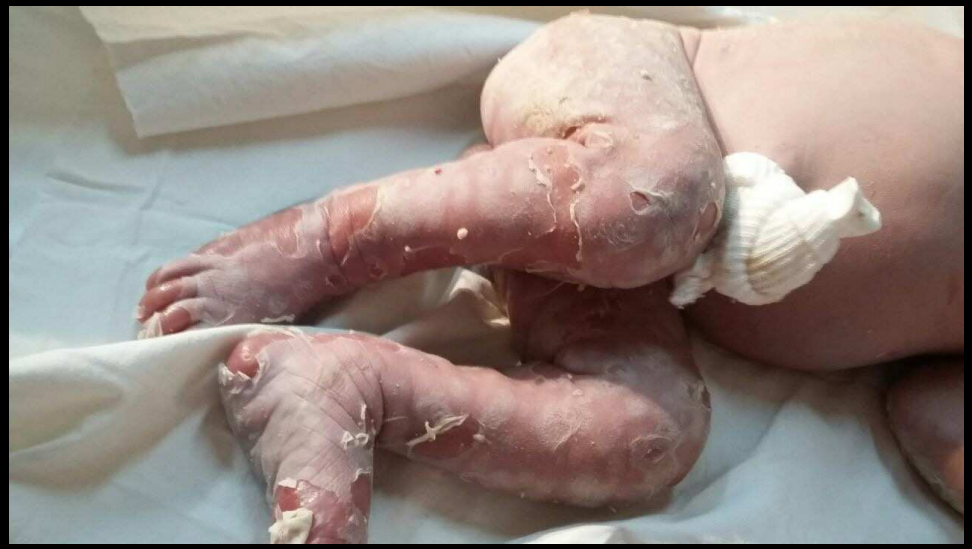


- **Histopathology**: necrotizing funisitis, villous enlargement, acute villitis
- **Increased detection** of congenital syphilis from 67% to 89% in live-born infants, and 91% to 97% in stillborns (Obstet Gynecol 2002:100:126)



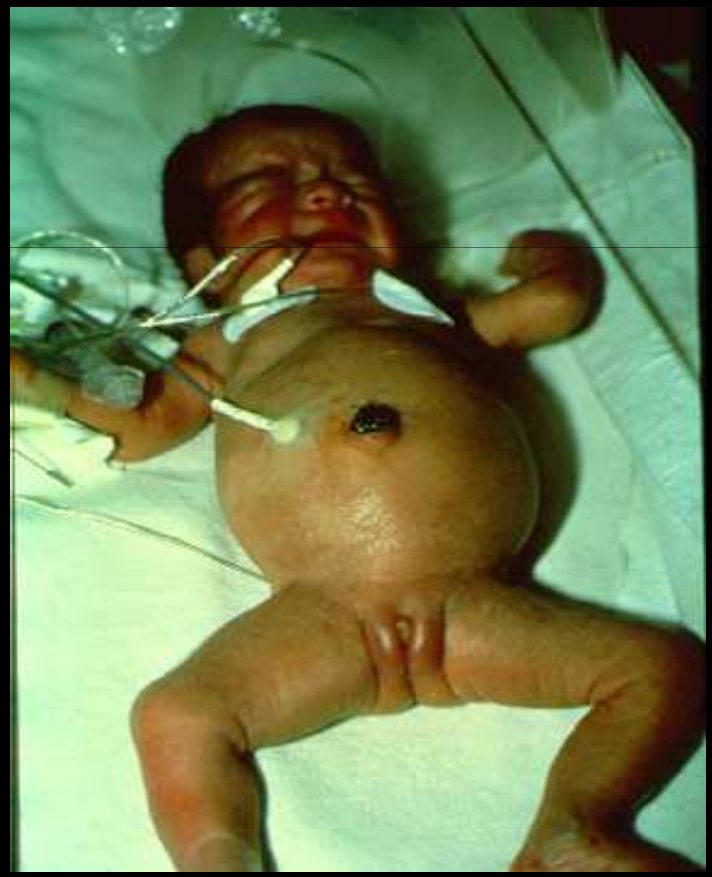




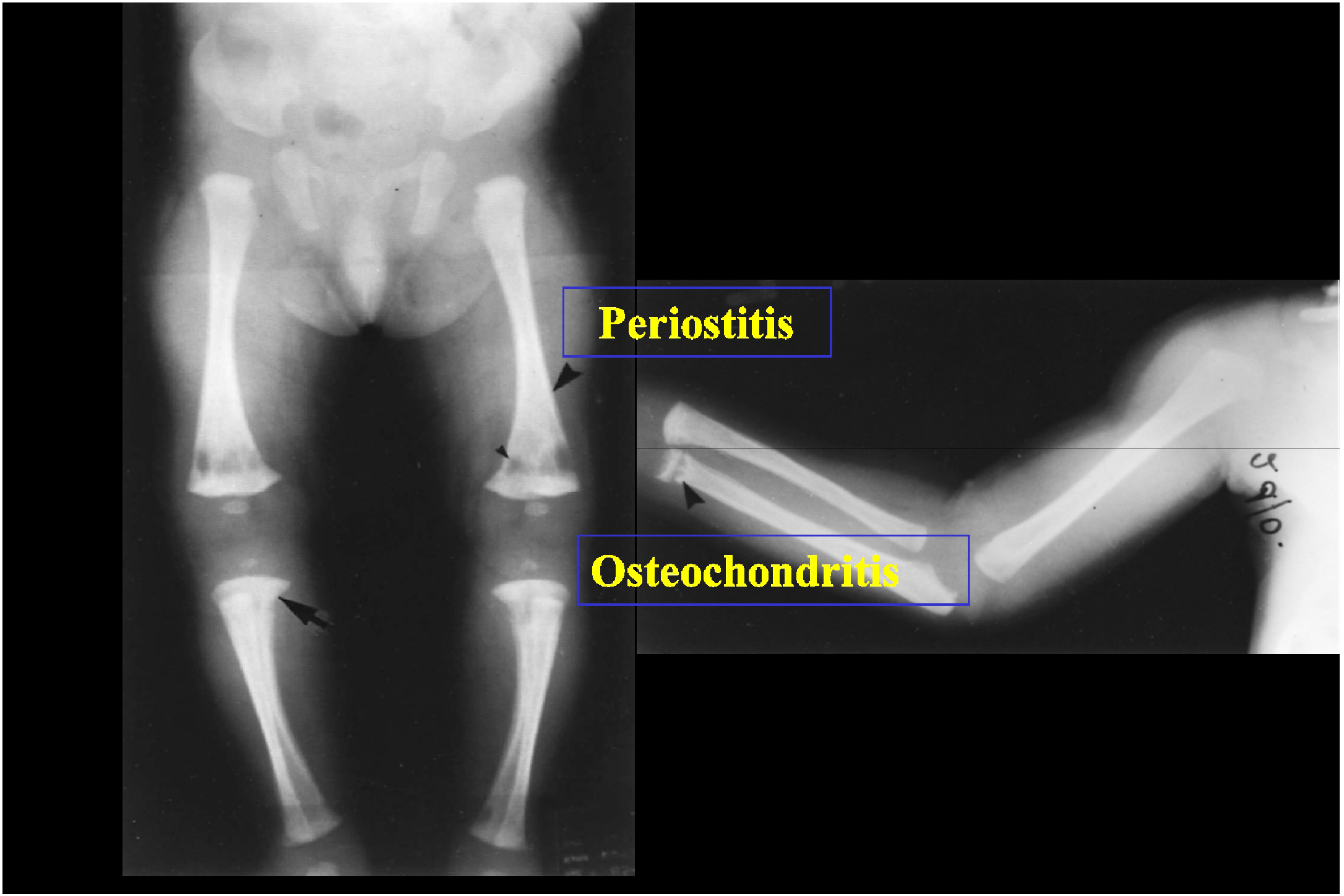




EARLY CONGENITAL SYPHILIS: CLINICAL MANIFESTATIONS

- Hepatosplenomegaly
- Anemia
- Thrombocytopenia
- Hydrops fetalis
- Pneumonia
- Nephrotic syndrome




Periostitis
Osteochondritis

CONGENITAL SYPHILIS: *SYMPTOMATIC* INFANTS

	SERUM/BLOOD (n=46)	CSF (n=39)
POS IgM	98%	41%
POS RIT	57% (20/35)	47% (16/34)

*Grimprel et al. J Clin Microbiol 1991;29:1711

CENTRAL NERVOUS SYSTEM INFECTION IN CONGENITAL SYPHILIS

76 INFANTS, CSF RIT: 17 POS, 59 NEG

- Sensitivity; Specificity:

Reactive CSF VDRL:	53%; 90%
CSF Pleocytosis:	38%; 88%
Elevated CSF Protein:	56%; 78%

Michelow et al. NEJM, 2002

CENTRAL NERVOUS SYSTEM INFECTION IN CONGENITAL SYPHILIS

- 22% (17/76): positive CSF RIT
- 41% of those with abnormal clinical, laboratory, or radiographic evaluation
- 60% of those with abnormal PE
- 100%, +serum IgM; 94%, +blood PCR; 65%, +CSF PCR
- 3 infants: +CSF RIT, normal CSF indices (2 abn evaluation, 1 pos IgM)

Michelow et al. NEJM, 2002

CONGENITAL SYPHILIS: TREATMENT

- Infant VDRL/RPR ≥ 4x Maternal VDRL/RPR OR Physical Exam is *ABNORMAL* OR ⊕ TP body fluid:
  - Aqueous PCN G 50,000 U/kg IV q 8-12 hr x 10 d, or
  - Procaine PCN G 50,000 U/kg IM q day x 10 d

CONGENITAL SYPHILIS: TREATMENT

- Penicillin dosed missed > 1 day, restart course
- Alternative therapy: NONE
  - ?Ampicillin: no data, penicillin should be used, and if not, close serologic follow-up required

SCENARIO 2

The "*ASYMPTOMATIC*" infant: Why? What is the likelihood that this infant has congenital syphilis?

CONGENITAL SYPHILIS: ASYMPTOMATIC INFANTS BORN TO MOTHERS WITH UNTREATED SYPHILIS

	SERUM/BLOOD (n=86)	CSF (n=68)
POS IgM	16%	3% (2/62)
POS RIT	7%	2% (1/62)

*Grimprel et al. J Clin Microbiol 1991;29:1711

MATERNAL TREATMENT ≤ 4 WKS BEFORE DELIVERY: ASYMPTOMATIC INFANTS

	Blood	CSF
No. of Infants:	23*	21*
⊕ IgM	30%	5%
⊕ RIT	5%	0/19

* 1 Mother HIV-Ab ⊕

CONGENITAL SYPHILIS: EVALUATION AND TREATMENT

- Infant physical exam normal AND VDRL/RPR <4x maternal titer:
  - **Maternal Rx**:
    - None, inadequate, unknown
    - Erythromycin, azithromycin, non-penicillin drug
    - ≤ 4 wks before delivery
  - Mother re-infected (RPR ↑ 4x)

QUESTION

- Full term infant born to mother with no prenatal care and no history of syphilis. At delivery, RPR is 1:32, TP-PA is reactive. Infant exam is normal, and serum RPR is 1:16. What do you do?
  1. Full evaluation (CBC/platelets; bone x-rays; LP) and treat for 10 days of IV penicillin
  2. Full evaluation and if normal, treat with single dose of benzathine penicillin
  3. No evaluation but treat with 10 days of IV penicillin
  4. Follow-up only

CONGENITAL SYPHILIS: "*Asymptomatic*" INFANT

- Physical exam normal; VDRL/RPR reactive and <4x maternal titer (cont):
  - **Evaluation:** CBC, platelets, LP, bone X-rays
  - **Treatment: options**
    - **Penicillin G** (aqueous/procaine) x 10d: evaluation optional; evaluation abnormal, not done or incomplete
    - **Benzathine PCN G** 50,000 u/kg IM: normal CBC, platelet, lumbar puncture, bone x-rays and follow-up certain

CONGENITAL SYPHILIS: "*Asymptomatic*" INFANT

- Evaluation and Treatment:
  - Full evaluation (LP, bone x-rays, CBC, platelets) MUST be performed and be completely normal if benzathine PCN used.
  - Complete evaluation unnecessary if aqueous PCN G/procaine PCN x 10 d, but tests may be performed to document CSF abnormalities or support a diagnosis of syphilis.

QUESTION

- Full term infant born to mother with no prenatal care. At delivery, TP EIA positive, RPR NR, but TP-PA reactive. Physical Exam is NORMAL and serum RPR nonreactive. What do you do?
  1. Full evaluation (CBC/platelets; bone x-rays; LP) and treatment
  2. Full evaluation and treat if only abnormal
  3. No evaluation but treat with single dose of benzathine penicillin
  4. Follow-up only

CONGENITAL SYPHILIS: "*Asymptomatic*" INFANT

- **Physical Exam NORMAL and serum VDRL/RPR nonreactive (cont):**
  - **Evaluation: none (no CBC, x-rays, LP)**
  - **Treatment:**
    - **Benzathine PCN G 50,000 u/kg IM**

Wozniak et al, *J Perinatology* 2017
Peterman et al, Sexually Transmitted Diseases, 2013

Do Women with Persistently Negative Nontreponemal Test Results Transmit Syphilis during Pregnancy?

- 1991-2009 (CDC): 23,863 infants reported with CS
- 86 mothers: negative nontreponemal tests and had no infant with confirmed syphilis and no syphilitic stillbirths
- 1 mother: negative nontreponemal test result 27 days after delivery of a child with “positive x-rays” and elevated CSF cell count or protein, but details unavailable

Peterman et al, *Sexually Transmitted Diseases*, 2013

"*Asymptomatic*" Infant: Physical Exam Normal and Serum RPR/VDRL NR

- 115 infants (1984-2002) at PMH, Dallas:
  - 14, mothers treated <4 weeks before delivery: none had abnormal laboratory or radiographic evaluation
  - 87, untreated mothers: 5% (2/37) had anemia, 2% (1/47) had elevated ALT, 1/28 had direct hyperbilirubinemia (Down syndrome)
  - 5 infants:
    - Positive serum IgM: 3/49
    - Positive serum PCR: 2/53
    - Mothers: untreated (4) or treated < 4 wks (1)

Wozniak et al, J Perinatology 2017

SCENARIO 3

CONGENITAL SYPHILIS: "*Asymptomatic*" INFANT

- **Maternal Treatment:**
  - During pregnancy, appropriate for stage of infection, > 4 wks before delivery
  - No evidence of reinfection or relapse
- Infant PE normal; RPR <4x maternal titer
  - **No evaluation; Treatment:**
    - Benzathine penicillin G IM x 1
    - "Some experts": close serologic follow-up only

*Alexander et al. *Obstet Gynecol*. 1999;93:5
Sheffield et al. *Am J Obstet Gynecol*. 2002;186:569

SCENARIO 4

CONGENITAL SYPHILIS: "ASYMPTOMATIC" INFANT

- Infant physical exam normal AND VDRL /RPR <4x maternal titer:
  - **Maternal Rx**: Before pregnancy, no evidence of re-infection or relapse
  - Infant: **No evaluation, follow-up only**
    - ? Benzathine PCN IM x1 if F/U uncertain

Evaluation and Treatment of Older Infants and Children

EVALUATION

- CSF analysis
- CBC / platelet count
- Other tests (long bone radiographs, chest radiograph, eye exam, LFTs, abdominal ultrasound, ABR, neuroimaging) as clinically indicated

TREATMENT

- Aqueous PCN G 50,000 U/kg IV q4-6 hr x 10 d
- "Some specialists" suggest giving a single dose of benzathine penicillin G 50,000 U/kg IM after the 10-day course
- If child has no clinical manifestations of disease, the CSF exam is normal, and the CSF VDRL test result is negative, some specialists would treat with up to 3 weekly doses of benzathine penicillin G 50,0000 U/kg IM

Special Considerations

- HIV infection: infants born to mothers coinfected with HIV do not require different evaluation, therapy, or follow-up for syphilis
- Penicillin shortage: penicillin G, procaine penicillin, benzathine penicillin, ceftriaxone

  www.cdc.gov.nchstp/dstd/penicillinG.htm/

CONGENITAL SYPHILIS: FOLLOW-UP

- Serologic testing (RPR) q 2-3 months until nonreactive. Persistent, stable titer beyond 1 yr: retreat?
- Treponemal test: Reactive beyond 18 months indicates congenital infection
- Initial CSF abnormal: Repeat at 6 months? if abnormal, retreat

CONGENITAL SYPHILIS: PREVENTION

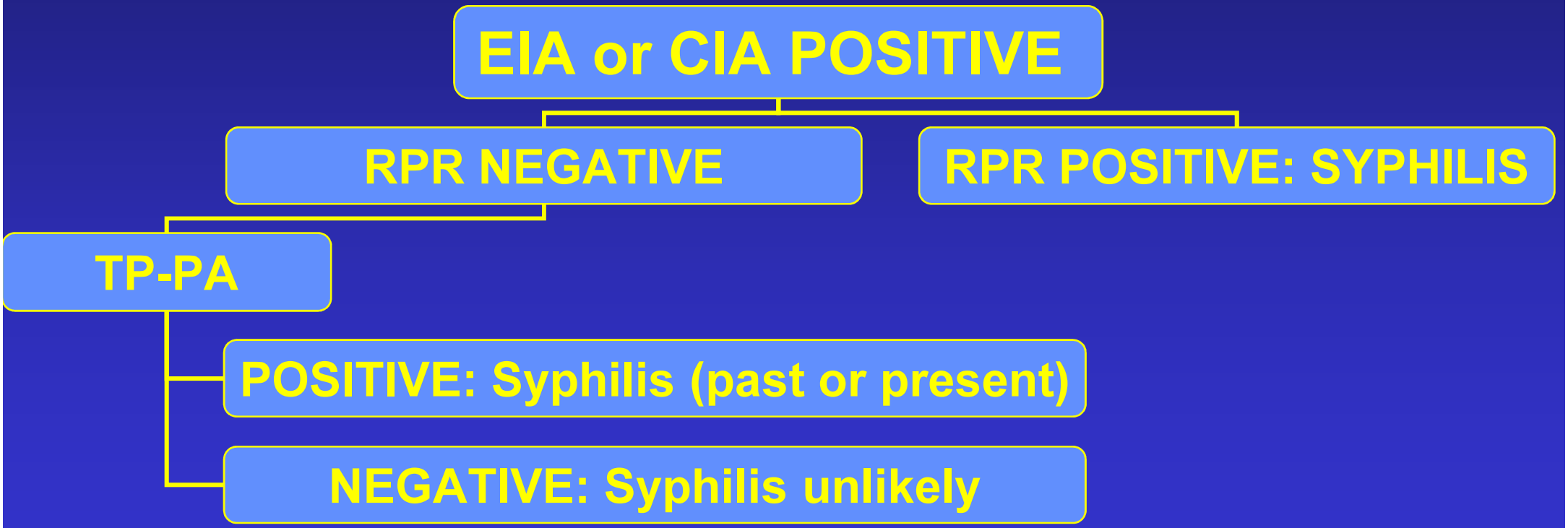
- Ensure adequate universal prenatal care
- Serologic screening (RPR):
  - 1st prenatal visit
  - In high-risk areas:
    - Repeat at 28-32 wks and delivery

CONGENITAL SYPHILIS: PREVENTION

Screening with treponemal test?

“Reverse Sequence Screening”

"REVERSE SEQUENCE" SCREENING: CDC RECOMMENDATIONS



MMWR, 2/2011

Discordant Syphilis Immunoassays: Pregnancy (Mmeje et al. CID 2015)

- Pregnant women at Kaiser Permanente Northern California: 8/2007-8/2010
- Reverse screening: chemiluminescence (CIA)
- Discordant: CIA+/RPR-; TP-PA then performed
- 194 pregnant women:
  - 20% (38): CIA+/RPR-/TP-PA+
  - 80% (156): CIA+/RPR-/TP-PA-
    - 53% of 77 women became CIA-
  - No differences in birth outcomes

CONGENITAL SYPHILIS: PREVENTION

- Do not discharge infant without maternal serologic status documented at least once during pregnancy
- Report all cases to Health Dept. for contact tracing and identification of core populations and environments

CALL THE SYPHILIS LINE

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214-621-1068 (cell)
614-355-6638 (office)
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Nationwide Children's Hospital

Center for Perinatal Research

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