

# Perinatal Syphilis – Challenges in Clinical Management

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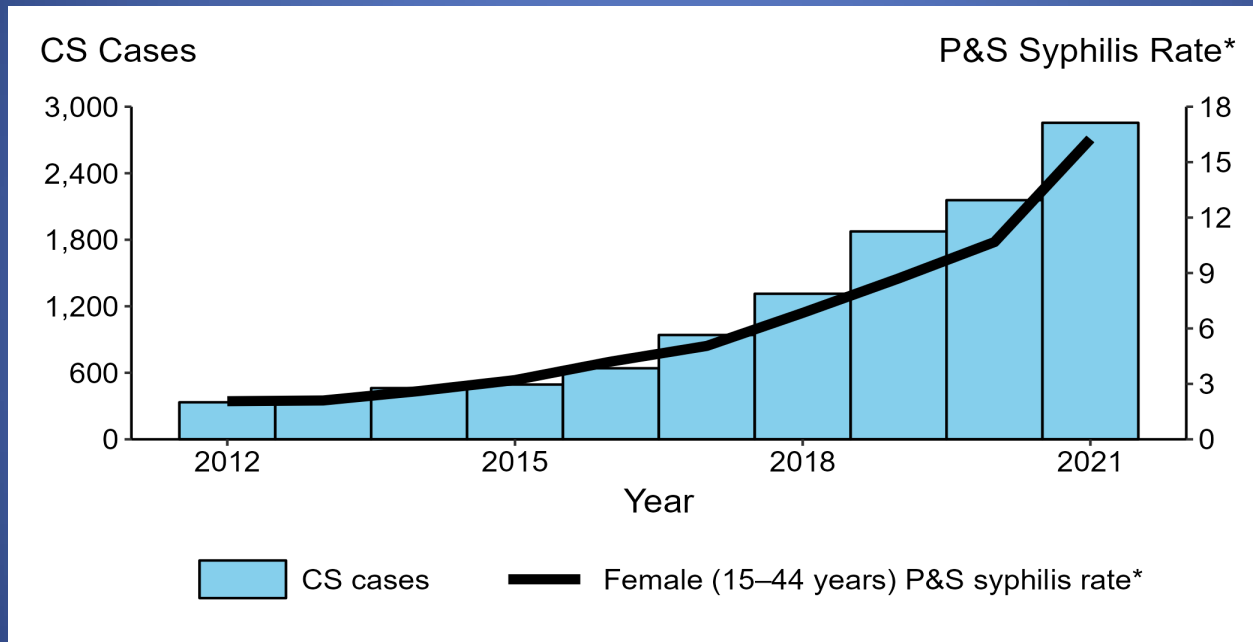
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# Background

## Reported Cases of Congenital Syphilis



In 2021, there were a total of 2,855 cases of congenital syphilis reported for a rate of 77.9 per 100,000 live births.

# Background

## Houston Health Department urges action as fetal deaths linked to congenital syphilis surge in Houston-area

Houston Health Department  
April 26, 2021

The US Centers for Disease Control and Prevention (CDC) recently released its [2019 STD Surveillance Report](#) showing that STD rates in the U.S. reached all-time highs for the sixth consecutive year. The National Coalition of STD Directors (NCSD) notes that even more concerning, the report found that a growing number of babies in the U.S. are dying as a result of syphilis passed from mother to child during pregnancy (congenital syphilis) – all because women are not receiving simple, CDC-recommended testing and treatment. Congenital syphilis is 100% preventable, but locally, preliminary 2020 data from the Houston Health Department (HHD) show a 250 percent increase in the number of fetal deaths linked to congenital syphilis.

- The number of fetal deaths in Houston and Harris County linked to congenital syphilis increased from four (4) cases in 2019 to 14 cases in 2020.
- 100% of fetal deaths in 2019 and 2020 were Black or Hispanic, highlighting stark disparities in testing and treatment.
- More babies are born with congenital syphilis in the Houston-area than any other part of the state.

**Medical providers play a vital role in preventing syphilis** in Houston and Harris County.

# Houston Health Department reports syphilis outbreak, begins rapid community outreach response

July 13, 2023

## Rise in cases among women, congenital syphilis attributed to outbreak

**HOUSTON** - The Houston Health Department is reporting a syphilis outbreak responsible for a 128 percent increase in cases among women and a nine-fold rise in congenital syphilis in Houston and Harris County.

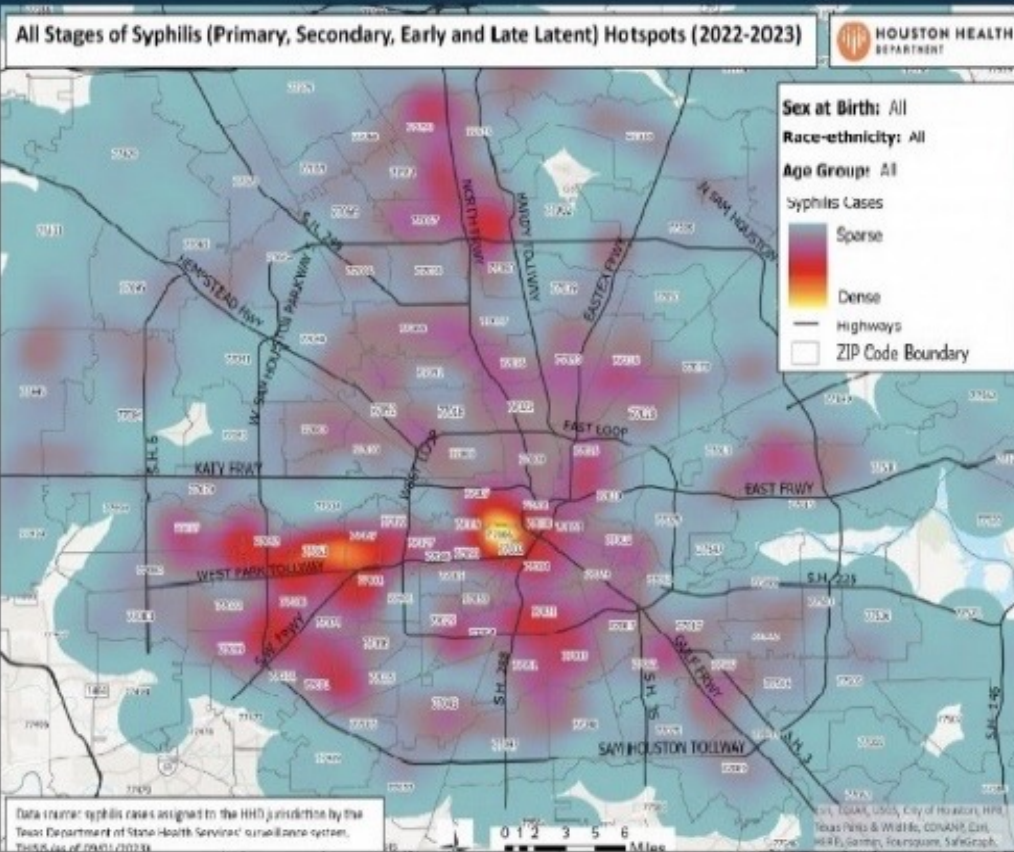
The department will launch a rapid outreach response that includes increasing screening opportunities, targeting hotspots and mobilizing community partners to curb new infections.

Statistics from the department indicate new infections rose from 1,845 in 2019 to 2,905 in 2022, a 57 percent increase.

Cases among women totaled 674 cases in 2022, up from 295 cases in 2019. Congenital syphilis soared from 16 cases in 2016 to 151 cases in 2021, the latest year for which statistics are available.

# Syphilis heat map 2023

## Hotspot Map (2022-2023)



## Syphilis - Houston

- A retrospective study of pregnant patients between 7/2019 – 4/2021 Houston County (Stafford, 2022; JAMA Net 2022)
- **Co-primary outcomes included:**
  - 1) Comparison of rates of individual and composite STI before the COVID-19 pandemic (7/2019 - 2/2020) to during the pandemic (3/2020 - 4/2021)
  - 2) Composite of adverse maternal and neonatal outcomes among individuals with individual and composite STI before and during the defined time periods
- Subgroup analysis rates of individual and composite STI according to COVID positive status during the pandemic

# Syphilis - Houston

Rates of STI and adverse outcomes pre and during COVID - Harris Health  
7/19-4/21 (N = 5,565)

	Pre-COVID – prior to 3/20 (%)	During COVID - after 3/20 N (%)	P- value	unadjusted RR (95% CI)	adjusted RR (95% CI)
<b>STI composite</b>	105/2412 (4.4)	162/3118 (5.2)	0.15	1.19 (0.94-1.52)	1.20 (0.94 - 1.54)
Chlamydia	36/2412 (1.5)	57/3115 (1.8)	0.33		
Gonorrhea	11/2412 (0.5)	16/3115 (0.5)	0.76		
<b>Syphilis</b>	<b>22/2412 (0.9)</b>	<b>48/3152 (1.5)</b>	<b>0.04</b>	<b>1.67 (1.01 – 2.75)</b>	<b>1.73 (1.04 -2.86)</b>
HIV	8/2412 (0.3)	8/3152 (0.3)	0.59		
Hepatitis B	34/2412 (1.4)	43/3152 (1.4)	0.89		

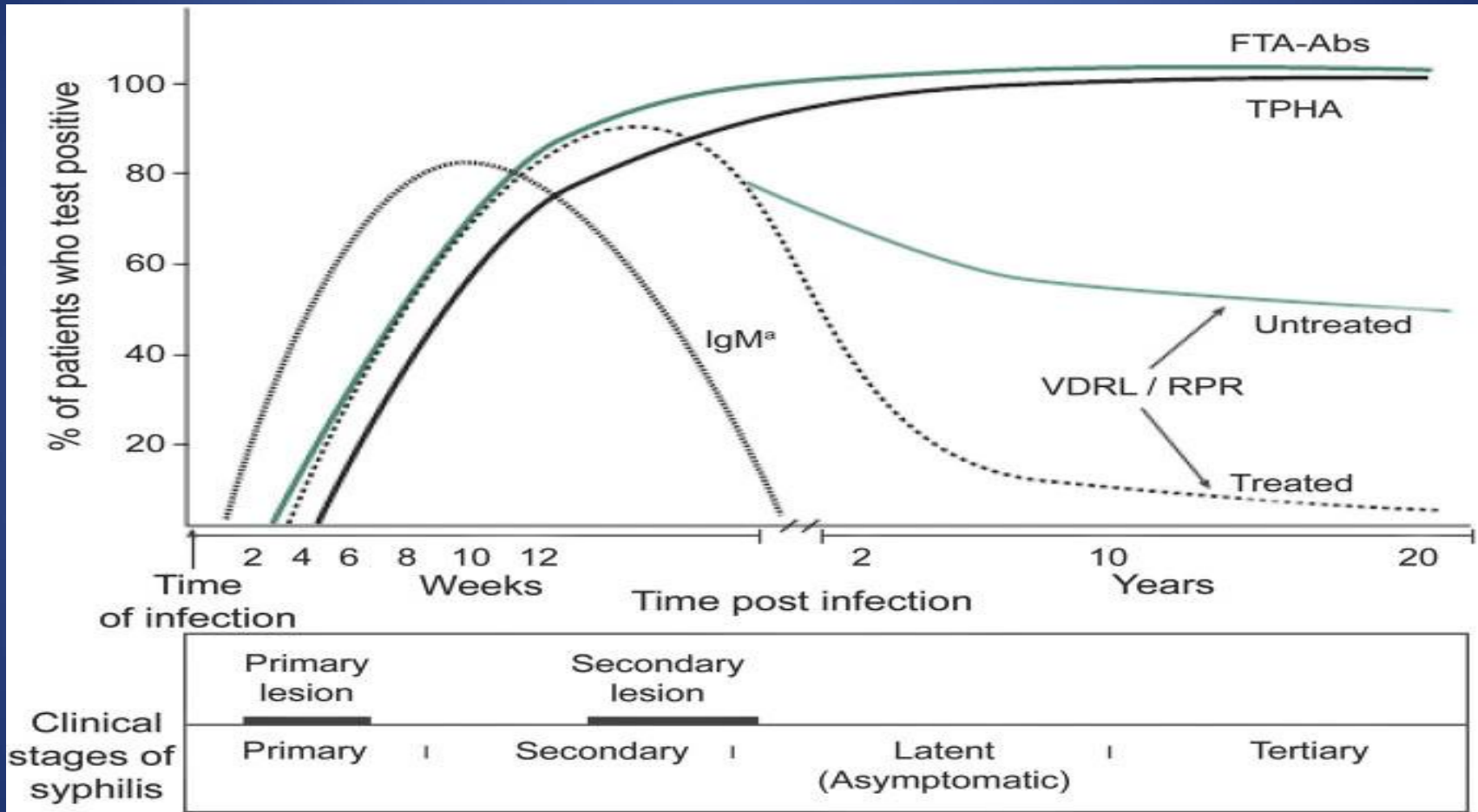
# Syphilis - Houston

Rates of STI and adverse outcomes in COVID positive - Harris Health 3/20 - 4/21 (n = 162)

		Covid – N (%)	Covid + N (%)	P- value	unadjusted RR (95% CI)	adjusted RR (95% CI)
	<b>STI composite</b>	144/2906 (5.0)	18/212 (8.5)	0.03	1.71(1.07-2.74)	1.48 (0.93-2.35)
	Chlamydia	51/2904 (1.8)	6/211 (2.8)	0.26		
	Gonorrhea	14/2904 (0.5)	2/211 (0.9)	0.30		
	<b>Syphilis</b>	<b>39/2936 (1.3)</b>	<b>9/216 (4.2)</b>	<b>0.01</b>	<b>3.13 (1.54 – 6.39)</b>	<b>2.82 (1.37-5.79)</b>
	HIV	8/2936 (0.3)	0/216 (0.0)	1.00		
	Hepatitis B	41/2936 (1.4)	2/216 (0.9)	0.77		



# Diagnosis – Adult and maternal diagnosis



Wicher V, 2001; Woods, CR, 2005; McFarlin BL, 1994

# Background

## Diagnosis – Same as adult diagnosis:

2021 current CDC 2021 STI Diagnosis and treatment guidelines based on serologic analysis and clinical staging

Reverse or Traditional screening algorithm (Treponemal or nontreponemal)

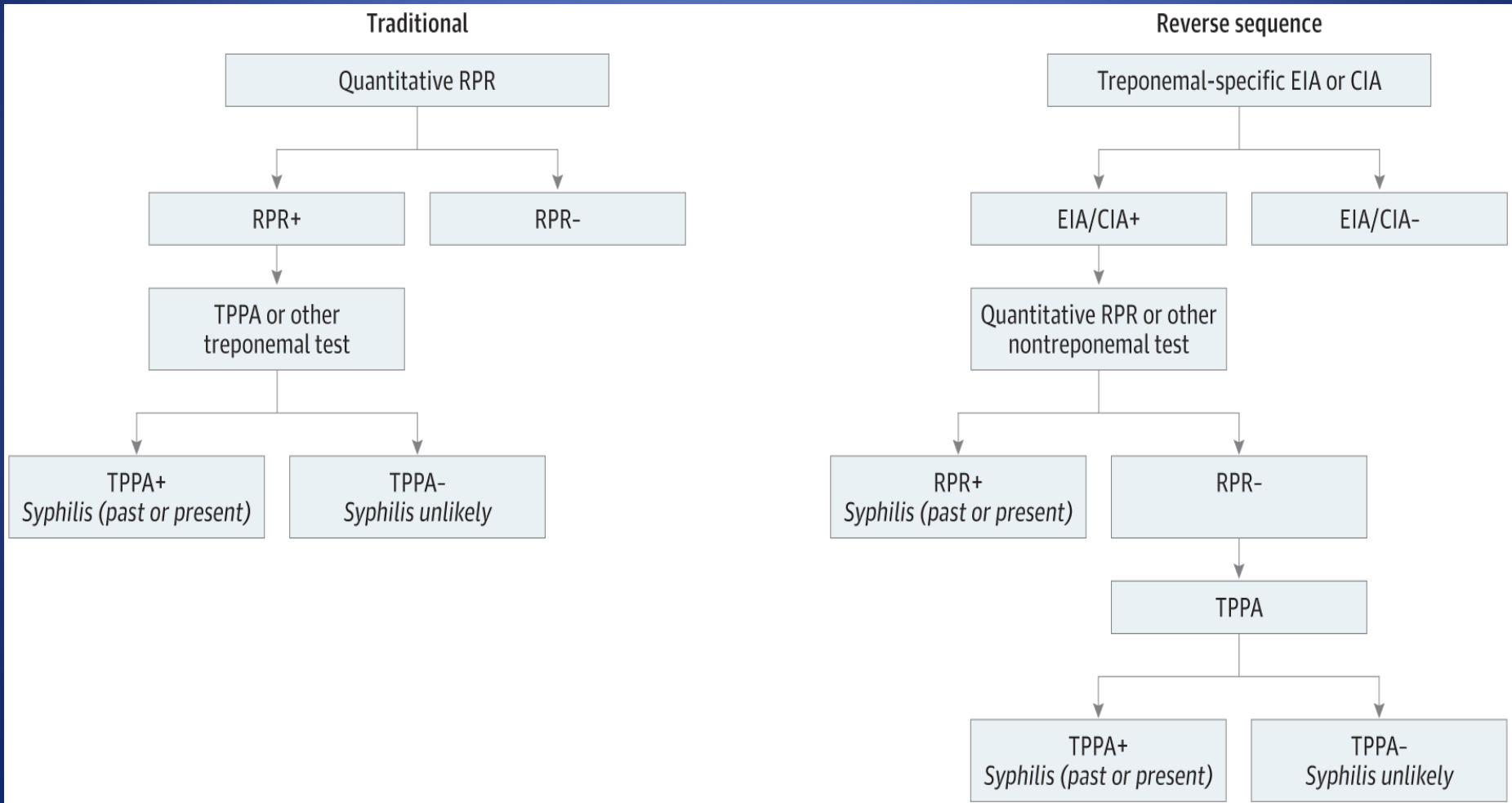
*CDC. 2021 STD Treatment Guidelines; Syphilis During Pregnancy.*

The nontreponemal assay is **recommended** for determining serological activity

15% of patients remain positive for life – same for pregnancy

# Diagnosis – Same as adult diagnosis:

2021 current CDC 2021 STI Guidelines



# Early Syphilis

- (Primary) Painless Chancre - Chancre resolves in 3–8 weeks without treatment
- (Secondary) Non-suppurative lymphadenopathy
- 4–10 weeks after chancre appears
- Dermatologic (90%)
  - Diffuse macular rash
  - Plantar and palmar target-like lesions
- **High congenital infection rate**
- **70 percent with early infection!**



A circular ulceration on the surface of a tongue in a patient with primary syphilis.

Source: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. [www.cdc.gov/std/syphilis/images.htm](http://www.cdc.gov/std/syphilis/images.htm)



A sharp-edged circular ulceration at the right corner of the mouth in a patient with primary syphilis.

Source: Centers for Disease Control and Prevention, Public Health Image Library (Robert E. Sumpter); National STD Curriculum <https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all>.

# Latent Syphilis

- Sero-reactivity without other evidence of disease (asymptomatic at time of treatment)
- Early latent: acquired syphilis < 1 year
- Late latent or unknown duration: > 1 year or unable to determine
- **Congenital infection risk remains high in early latent (30–40%)**
- **Late latent – lower ~15%**

# Background

Treatment - The dosage and the length of treatment for pregnant women **SAME** as adults:

- 1) Dependent on the stage & clinical manifestations of the disease
- 2) Adequate treatment of maternal syphilis requires a 4- fold reduction of nontreponemal titers over 6 -12 months following treatment
- 3) Check every 8 weeks during pregnancy (closer interval if indicated)

**\*\* NOT > 9 DAYS** apart for late latent pregnant

Followed by Dept of Health, titers and treatment schedule documented

# Follow-Up

- Repeat titers every 4 – 6 wks in pregnancy (CDC 8 wks).
- If signs persist or recur or a 4-fold increase in non-treponemal test titer (i.e., compared with the max or baseline titer at time of treatment) probably failed treatment or were re-infected.
- **Failure of titers to decline 4-fold within 6 months** after therapy might be indicative of probable treatment failure.

# *Jarisch-Herxheimer* reaction is an acute febrile reaction:

- Headache, myalgia, and other symptoms that occur the first 24 hrs after therapy for syphilis (as high as 45%).
- May induce early labor or fetal distress in pregnant women, should not prevent or delay therapy.
- The fetus can experience the JH reaction too!



# Background – Fetal Infection

- The fetus:

Fetal infection during pregnancy:

Premature birth, spontaneous abortion, stillbirth, hydrops, perinatal death 30-40%

# Background – Fetal Infection

- Congenital Syphilis - Pathophysiology:

Hematologic dissemination and transplacental passage of *T. pallidum*

ALL stages and trimesters \**T. pallidum* found in abortus 6 – 8 weeks

- Early syphilis – up to 70% fetal infection

- Late latent – unknown - 15% fetal infection

Lack of data regarding trimester specific timing of infection, stage at infection and adverse neonatal outcomes

# Background – Fetal Infection

## Congenital Syphilis - Pathophysiology

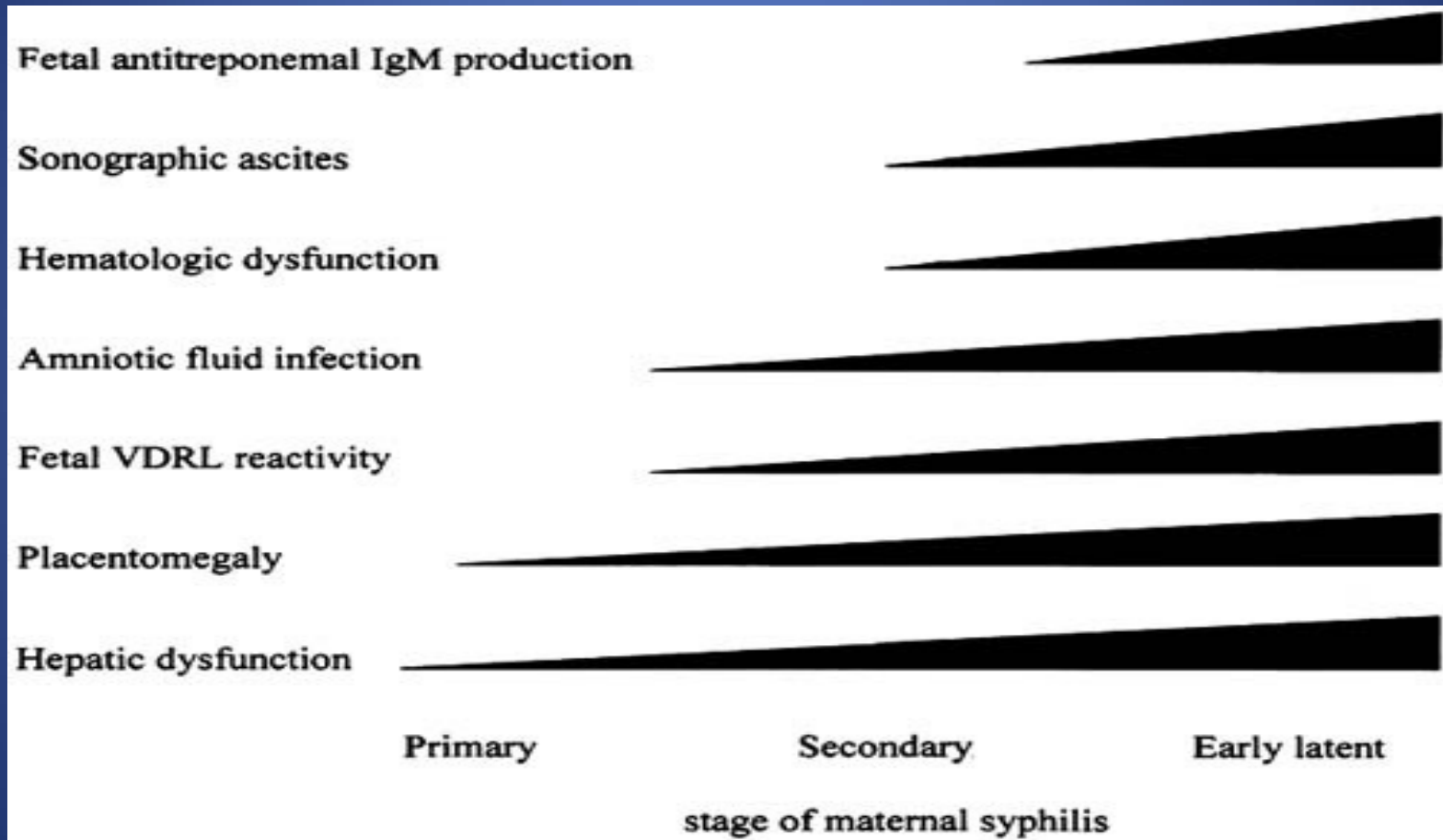
MASS inflammation to all organs, “system inflammatory response”

## Extra-medullary hematopoiesis

Fetal red blood cells are produced in extramedullary sites such as the liver and spleen

- Start in yolk sac, placenta and fetal liver
- Secondary to destruction of precursor RBC

# Progression of Fetal Infection



# • **Congenital Syphilis** – Fetal Infection

Antenatal Diagnosis:

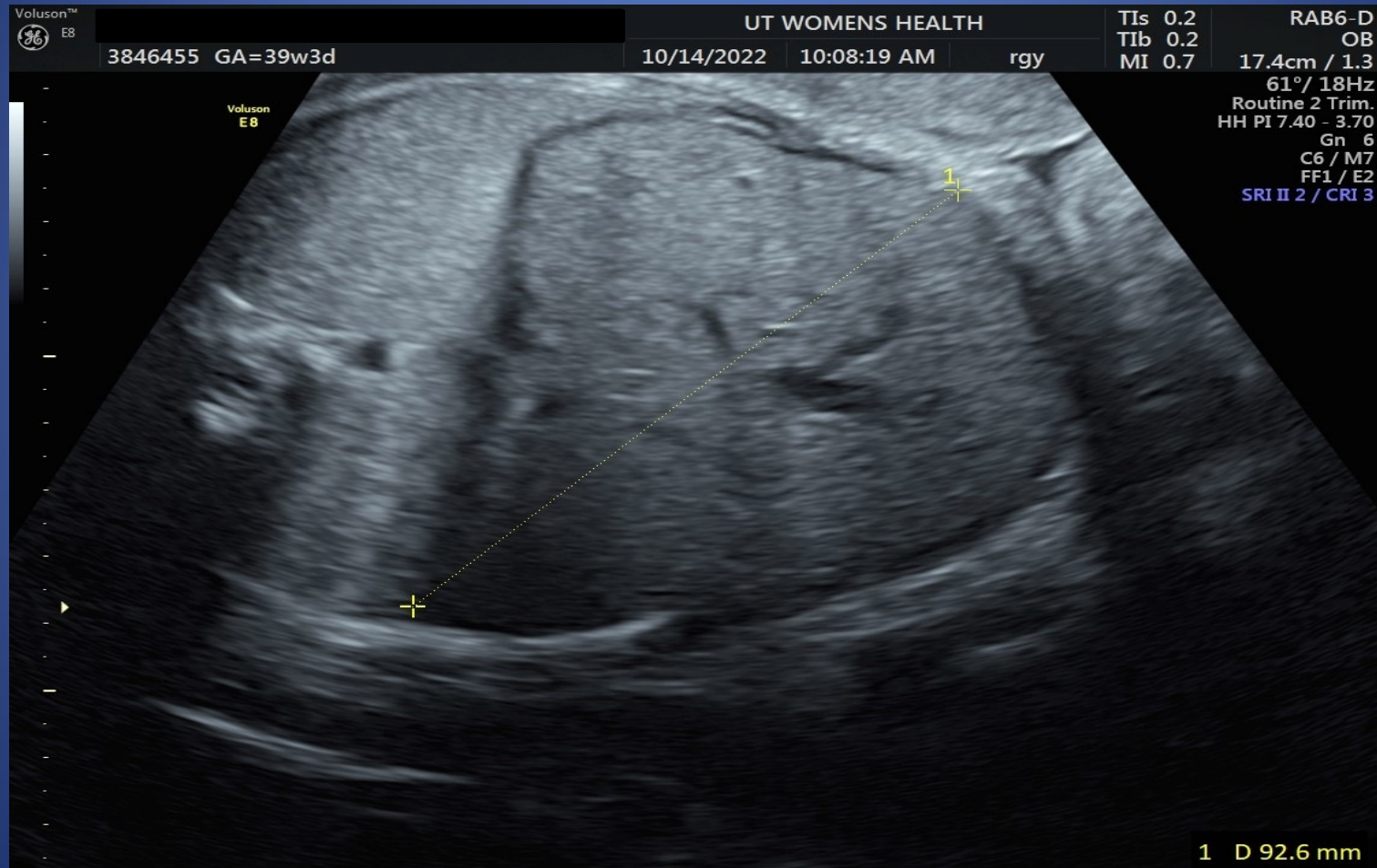
Sonographic markers

Sonographic stigmata of syphilis represented by inflammatory damage to organs and hematopoietic cell line destruction

- Placental thickness, hepatomegaly, elevated MCA velocities, stillbirth : (39% detection of CS, missed diagnosis 15%, Rac 2015)

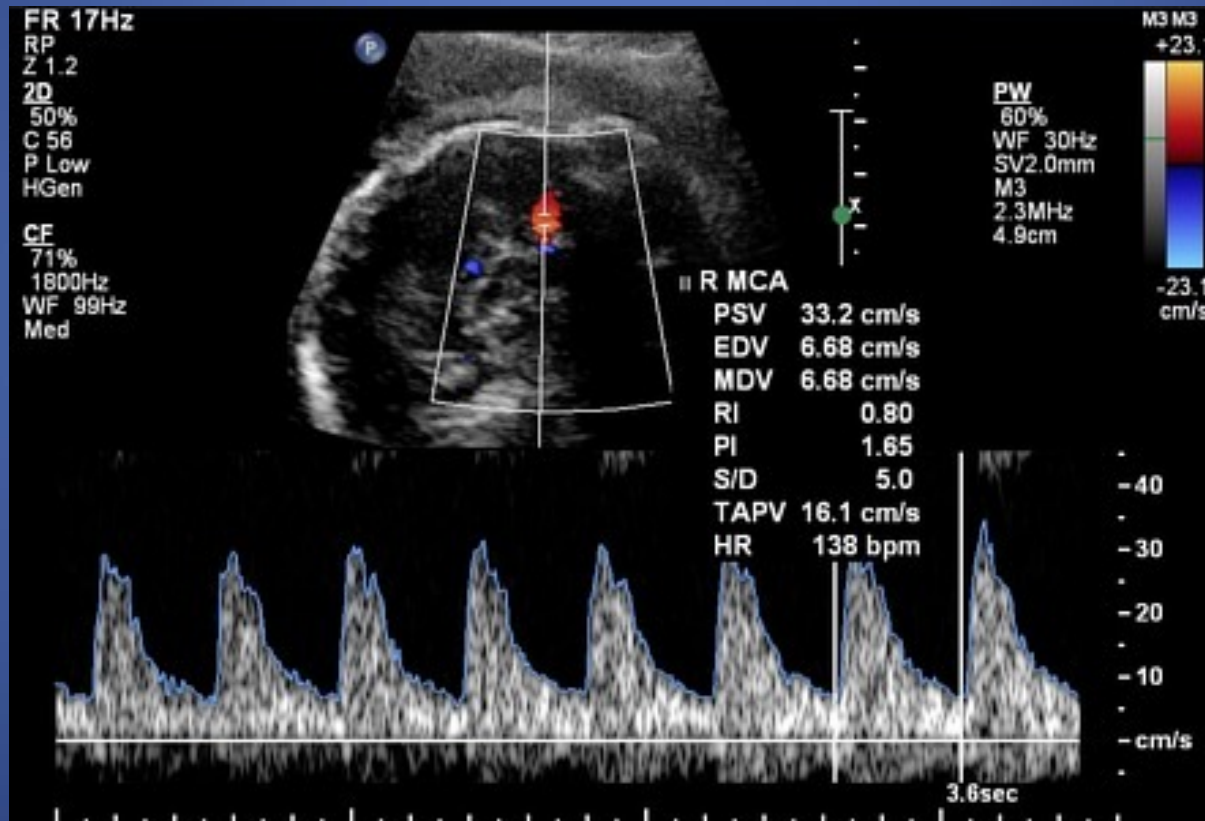
# Congenital Syphilis - Diagnosis

## Antenatal sonographic markers: fetal liver



# Congenital Syphilis - Diagnosis

Antenatal sonographic markers: MCA velocities



# Congenital Syphilis - Diagnosis

## Antenatal sonographic markers

- The role of specialized ultrasound conducted by fetal specialists for the detection of congenital syphilis is warranted
- UT Health FC performing a prospective cohort study evaluating fetuses of infected mothers > 18 weeks using specialized sonogram to increase detection of congenital infection from 37% to 65%
- CNS neurosonology, spectral analysis, posterior fossa, cardiac function, spleen volumes, UA and DV velocities, bone density calculations
- Ongoing, N = 64



# Congenital Syphilis – Diagnosis

## Diagnosis at Birth:

Placental pathology 76%, with special immunohistochemistry  
89% liveborn, > 97% IUFD (Sheffield J, 2002; Herremans T, 2010)

Early polymerase chain reaction (PCR) technology sensitivity at  
78-86% - lesion (primary, secondary lesion exudate, hematologic)

Sheffield JS, 2002; Nathan L, 1997; Sanchez PJ, 1992; Arnold SR, 2000; Wendel GD, 2002;  
Herremans T; 2010; Vintzileos AM, 1985

# • Congenital Syphilis – Diagnosis

## At Birth:

IgM platforms: the IgM 19S FTA-A BS tests, IgM immunoblots and IgM ELISA -83% sensitive

Can be false negative in early infection - newborns

- The treponemal tests, TP-PA test, the FTA-ABS test, EIA and CIA - high false positive, persistent positive despite treatment

*Herremans T, 2010; Stoll BJ,1993; 2015 Sexually Transmitted Diseases Treatment Guidelines; Congenital Syphilis.*

- **Congenital Syphilis - Diagnosis at Birth:**

- Given poor diagnostics for the newborn, the nontreponemal tests, VDRL/ RPR test, are currently used for diagnosis of congenital syphilis in the newborn
- Nontreponemal tests are only 14% sensitive at birth and can be maternal passive IgG transfer for up to 15 months
- Herremans T, 2010; Bvallejo C, 2013; Wozniak PS, 2017; Stoll BJ,1993; *2021 STD Treatment Guidelines; Congenital Syphilis*

- **Congenital syphilis – Diagnosis at Birth**

Because of the **poor diagnostic sensitivity** of these tests,

- Diagnostic algorithm for newborn is also based on:
  - Maternal treatment history (adequate and 30 days < delivery)
  - Antenatal sonographic findings consistent with infection\*
  - Newborn signs/symptoms, bone and lab abnormalities
  - Serology – considered infected if > 4 fold mothers, or mothers do not decrease

Sheffield J, 2002; Herremans T, 2010; Bvallejo C, 2013; Wozniak PS, 2017; Stoll BJ,1993; 2021 STD Treatment Guidelines; Congenital Syphilis.

- \* *If sono findings antenatally – AAP recommendations treat as case at birth*

- **Congenital Syphilis – Diagnosis at Birth**
- Symptoms:

Symptomatic newborn – seizures, exam, abnormal lab/radiologic studies. Neurosyphilis occurs in 60% of symptomatic newborns

# Congenital Syphilis – Diagnosis at Birth

## Symptoms:

Asymptomatic newborns – 60% of infected newborns are asymptomatic at birth, regardless of titers

If newborn treated/not treated – longitudinal follow up needed until negative **up to 15 – 18 months**

- Majority of newborns with congenital syphilis have equivocal titers

# Congenital syphilis

- **CURRENT ALGORITHM – 5% of discharged newborns readmitted for persistent infection** TXDH data. CDC.
- Delayed diagnoses and treatment = adverse health outcomes.
- 70% lost to follow up with possible persistent infection
- No funded programs in most states to follow newborns

# Challenges to follow up for mother baby dyad- Houston

N = 26 mother-baby dyads – (Single Center 2017 -2021)

	Appropriate Surveillance n/N (%)	Relative Risk (95% CI)
<b>Age</b>		
<25	4/9 (44.4)	1.51 (0.46, 5.12)
>=25	5/17 (29.4)	
<b>Race</b>		
Black	7/13 (53.9)	<b>3.5 (1.01, 32.76)</b>
Non-Black	2/13 (15.4)	
<b>Ethnicity</b>		
Hispanic	2/11 (18.2)	0.39 (0.10, 1.53)
Not Hispanic	7/15 (46.7)	
<b>Language of preference</b>		
English	7/15 (46.7)	<b>2.57 (0.74, 24.10)</b>
Spanish	2/11 (18.8)	
<b>Parity</b>		
<=3	4/11 (36.6)	1.10 (0.33, 3.85)
>3	5/15 (33.3)	
<b>Prenatal Care</b>		
>3 visits	6/15 (40.0)	<b>1.47 (0.47, 10.61)</b>
<3 visits	3/11 (27.3)	



# Challenges to follow up for mother baby dyad- Houston

N = 26 mother-baby dads – (Single Center 2017 -2021)

- Appropriate surveillance
- Relative Risk

	n/N (%)	Relative Risk (95% CI)
<b>GA at delivery</b>		
<37	1/5 (11.1)	0.53 (0.02, 2.29)
>=37	8/21 (88.9)	
<b>Mode of Delivery</b>		
Vaginal/OVD	5/17 (29.4)	0.66 (0.20, 2.18)
C-Section	4/9 (44.4)	
<b>Any STI</b>		
Yes	4/14 (28.6)	0.69 (0.24, 1.99)
No	5/12 (41.7)	
<b>Any psychiatric diagnosis</b>		
No	7/17 (41.2)	<b>1.85 (0.55, 17.44)</b>
Yes	2/9 (22.2)	



# CDC 2021 STD Guidelines

- What to do with allergy to penicillin:
- 1) Get medical history, including prior exposures to penicillin or other  $\beta$ -lactam antibiotics
- 2) performing a skin test evaluation (**SAFE in pregnancy**) and
- 3) among those who have a negative penicillin skin test, give 250 mg amoxicillin before giving IM benzathine penicillin (or low risk allergy)
- **What is a low-risk allergy?**

# CDC 2021 STD Guidelines

- Low-risk penicillin allergy:
- low-risk history of IgE-mediated PCN allergy includes: symptoms such gastrointestinal intolerance, headache, fatigue, or nonspecific pruritus, or family history only.
- **In these cases, an oral challenge of amoxicillin 250 mg can be administered to document the absence of allergy.**
- **After 30 min OK to give IM benzathine penicillin.**

- If skin testing positive - oral or IV/IM penicillin desensitization protocol
- Oral desensitization protocol: Wendel, G D; et al. NEJM 1985

Step	Oral				Intra-venous			
	Penicillin concentration (mg/ml)	Amount (ml)	Dose (mg)	Cumulative dose (mg)	Penicillin concentration (mg/ml)	Flow-rate (ml/h)	Dose (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05	0.01	6	0.015	0.015
2	0.5	0.2	0.1	0.15	0.01	12	0.03	0.045
3	0.5	0.4	0.2	0.35	0.01	24	0.06	0.105
4	0.5	0.8	0.4	0.75	0.1	50	0.125	0.23
5	0.5	1.6	0.8	1.55	0.1	10	0.25	0.48
6	0.5	3.2	1.6	3.15	0.1	20	0.50	1.0
7	0.5	6.4	3.2	6.35	0.1	40	1.0	2.0
8	5.0	1.2	6.0	12.35	0.1	80	2.0	4.0

85% of IGE mediated resolve by adulthood (1% per year without exposure)

# CDC 2021 STD Guidelines

- Persons with a history of severe adverse reaction (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis) and other severe non-IgE-mediated reactions (e.g., interstitial nephritis, and hemolytic anemia) and anaphylaxis within 6 hrs of ingestion are not candidates for penicillin skin testing or challenge.
- **NEED inpatient IMU/ICU with multidisciplinary team support.**

# CDC 2021 STD Guidelines

- If evidence of congenital syphilis on ultrasound (enlarged fetal liver, thickened placenta or evidence of fetal anemia – elevated MCA velocities) and  $>$  than 23 weeks gestation, **CONSIDER:**
- Admission for 23 -hour observation to give 1st dose with fetal monitoring (DO not delay treatment for sonographic evaluation)
- If NO evidence of congenital syphilis on ultrasound, give benzathine penicillin outpatient

# Future Directions

- **Improve screening practices:** standardize screening recommendations, mandates
- **Best Practice Alert (BPA) EHR** – improved appropriate screening 65% in Houston in 6 months (SMFM 2024)
- **OPT-Out Testing in nontraditional settings** – ED, triage with presumptive treatment





- Thank you!
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