Conference Summaries

National STD Curriculum Podcast

IDWeek 2024: Treatment and Prevention of Congenital Syphilis and Early Syphilis

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Season 5, Episode 6

This episode reviews four IDWeek 2024 oral abstracts about congenital syphilis, syphilis in pregnancy, the effectiveness of doxy-PEP, and the use of oral cefixime for early treatment.

Topics:

- Syphilis
- congenital syphilis
- Doxy-PEP
- cefixime

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Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
Consulting Fee: Innoviva Specialty Therapeutics

Transcript

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In this episode:

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introduction**[00:00] Introduction**

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STI [sexually transmitted infections] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STIs.

For this episode, we are going to review a few oral abstracts that were presented at the IDWeek conference, and it was held in October 2024. There were a few sessions that were focused on syphilis and congenital syphilis. And so, this episode will combine some of the presentations from these sessions. Again, please refer to our website for details on the presenters and the title of each abstract. First, I'm going to start out with some background about congenital syphilis, and I think that will help set the stage for the discussion of the

first two presentations.

background**[00:57] Background**

There has been a 222% increase in primary and secondary syphilis in adults over the last 10 years in the U.S., from 2013 to 2022, and this has resulted in over 200,000 cases of syphilis in 2022. That's a huge number! Now, while rates of primary and secondary syphilis remain higher among men, rates are actually increasing *faster* among women. For example, over a 5-year period, rates have increased 163% in men and 866% in women. What data suggests is that among women of reproductive age, rates are highest among those who ages 25 to 34 years old. With this increase of syphilis seen among women, there have been increases in congenital syphilis as well. So, from 2012 to 2022, there has been a tenfold increase of congenital syphilis cases, and this has resulted in 282 stillbirths and infant deaths related to syphilis in 2022. The highest absolute number of congenital syphilis cases occurred in Black or African Americans and the highest rates of congenital syphilis occurred in American Indian or Alaska Natives in 2022.

abstract-1**[02:11] Abstract 1**

Barbee L. *Preventing congenital syphilis by addressing missed opportunities in pregnancy*. Revenge of the syph(ilis) and other pediatric foes. Paper presented at: IDWeek 2024; October 19, 2024; Los Angeles, CA. Session 492. [**IDWeek**]

So, the first presentation we are going to review was given by Dr. Lindley Barbee from the CDC [Centers for Disease Control and Prevention], and Dr. Barbee works in the Division of STD Prevention. The title of this presentation was "Preventing congenital syphilis by addressing missed opportunities in pregnancy," and I'm going to spend a bit more time on this presentation.

1. In 2022, around 60,000 women were diagnosed with syphilis, and 17% of those women were pregnant at the time of syphilis diagnoses. While data indicate a potential congenital syphilis case was averted in 6 out of 10 pregnancies (so some progress has been made), there are missed opportunities to avert the rest of the congenital syphilis cases, especially with regards to timely testing and treatment. What they found is that no timely syphilis testing in pregnant women is one significant missed opportunity that was seen in 2022, and this occurred in 37% of congenital syphilis cases. Sometimes, it's related to no prenatal care, and that can account for most of these cases (about 70%), but 30% of the cases with no timely syphilis testing during pregnancy occurred in the pregnant women who had at least one prenatal care visit. And so, at this prenatal care visit, a syphilis test was just not done.
2. Some ways to address this have been proposed. So, for example, some open access low-barrier care clinics for prenatal care have been started, which might be an example of how to address at least one of these problems. For example, in California, Pregnancy Connections Clinic is a clinic for pregnant women experiencing homelessness or substance use, and it's based on a walk-in prenatal care model. The clinic was opened in January 2022 and of the 15 pregnant women who were diagnosed with syphilis, 14 of these cases (so 93%) of the congenital syphilis cases were averted. That's a very high number, especially for this underserved population, which can sometimes can be very difficult to engage in care.
3. Another opportunity is the education of providers through various resources, such as the STD Prevention Training Center and the National STD Curriculum. Many providers have not seen or dealt with a syphilis case before and they may not be aware of the increasing rates or how to diagnose or manage syphilis, including the staging and interpreting of serologies, which can sometimes be challenging.
4. Another missed opportunity is the late identification of seroconversion during pregnancy or not diagnosing syphilis that has been acquired while the woman has been pregnant. And so, this would make up about 5% of congenital syphilis cases or 196 cases. Now, one of the ways these cases can be averted or prevented is through third-trimester screening. A retrospective cohort of congenital syphilis cases that were diagnosed in Florida and Louisiana showed that 76 pregnant women who tested

negative for syphilis in the first trimester but with rescreening in the third trimester, 47% (or 36) of these pregnant women tested positive later in their pregnancy. This group was able to get 30 of those congenital syphilis cases prevented. Screening again in the third trimester actually made a large impact in this population, and a cost-effective analysis evaluating universal 28-week screening in all pregnant women in the U.S. found that it would meet criteria for cost-effectiveness given our current rate of syphilis among females in the reproductive ages.

5. In 2024, ACOG (or the American College of Obstetricians and Gynecologists) recommended that all pregnant women should be tested for syphilis three times during pregnancy. Now, the USPSTF, or the U.S. Preventive Services Task Force, and the CDC recommend syphilis screening at the first prenatal visit and screening again in third trimester for individuals at increased risk. So, this makes it a little complicated because there are 18 states requiring third-trimester screening, but there are seven states in the U.S. with no screening laws for syphilis, and so that sometimes can be confusing for health practitioners.
6. Around 20% of syphilis testing in pregnant women that resulted in a congenital syphilis case occurred outside of the prenatal visit. For example, in emergency departments, jail intake settings, syringe services programs, or maternal and child health programs. So, these might be great settings for syphilis testing outside of the standard clinic. A study in Texas showed that opt-out screening and rapid point-of-care testing increased syphilis screening for pregnant women presenting to the emergency department from 2% to 56%. That's a huge increase! They were able to avert 3 congenital syphilis cases, and link 56 pregnant women to prenatal care, and 100% of the patients in the study said that they were satisfied and would recommend a point-of-care syphilis test.
7. The third missed opportunity is no treatment or inadequate treatment for someone who was diagnosed with syphilis during pregnancy, and this occurred in 51% of congenital syphilis cases (so around 1,900 cases) in 2022. Of these congenital syphilis cases, 40% had inadequate treatment of the pregnant woman and 11% had no documented treatment at all. Now, treatment completion could potentially increase with pairing with a rapid syphilis point-of-care test, as this would help to avoid loss to follow up. There are also some examples to help support treatment for syphilis in pregnancy outside of the clinic. For example, in Louisiana, the Syphilis Home Observed Treatment (SHOT) Protocol is a program they started to address their congenital syphilis crisis. In this program, a DIS, or disease intervention specialist, and a public health nurse visit the pregnant woman and the partner in the field or at home to administer syphilis treatment on that site. In Washington, the state law changed in March 2024, and it allows for medical assistants to provide intramuscular injections for syphilis treatment in the field with telehealth supervision. So, these are just a few examples communities and jurisdictions have utilized to help reverse congenital syphilis cases and address syphilis in pregnancy.
8. The CDC AtlasPlus app is available for providers to look up the syphilis rate in their county, and it's helpful to guide providers on whether they should be doing universal screening of all sexually active individuals ages 15 to 44 years old in their area for syphilis.

In summary, there has been a 10-fold increase in congenital syphilis cases in the past 10 years. And, an estimated 90% of congenital syphilis cases in 2022 could have been prevented through timely testing, follow-up of testing, and adequate treatment of the pregnant woman for syphilis.

abstract-2**[09:00] Abstract 2**

O'Callaghan K. *Bridging the treatment gap: Estimating the impact of widespread syphilis point-of-care testing*. Syphilis in the US: It's unrelenting. Paper presented at: IDWeek 2024; October 17, 2024; Los Angeles, CA. Session 73. [**IDWeek**]

The next presentation was by Dr. O'Callaghan at the CDC and is titled "Bridging the treatment gap: Estimating the impact of widespread syphilis point-of-care testing." As mentioned previously, timely syphilis testing and treatment during pregnancy could have prevented almost 90% of congenital syphilis cases, but there are gaps in the time it takes from testing to treatment, and it's this delay in treatment which can

account for some of these congenital syphilis cases.

1. A study evaluating syphilis treatment among women who are pregnant in the U.S. found that the median duration from the first syphilis test to documentation of the first dose of treatment was actually nine days. Now, some of these delays are due to the average turnaround time for the results of syphilis testing, and this is something many of us have seen as practitioners ordering syphilis testing. You order the syphilis test but it takes a while before those results return. One of the questions is whether there is a way to improve this time gap and provide earlier treatment. For example, can a point-of-care test help reduce the interval from a positive syphilis test to treatment for the patient? And, would rapid tests allow for the treatment during that same visit?
2. There are two point-of-care tests that are available in the U.S.: the *Chembio HIV-Syphilis* tests and the *Syphilis Health Check*. Both of these test for treponemal antibodies only, and this means that they're not helpful in those with a prior history of treated syphilis but are helpful in those with no history of syphilis.
3. Dr. O'Callaghan remarks that point-of-care tests would be helpful in a variety of settings. These might include for persons who travel far to a clinic setting to return for treatment. For example, those who are living in rural communities or in communities with a low health care access. They also might be helpful for persons who might be lost to follow-up, let's say, given housing instability or substance use. Or, in medical encounters that have a short time window to provide medical services, such as emergency departments or correctional facilities. Rapid point-of-care tests in these settings can allow for treatment during these same clinic or medical visits.
4. So, one of the questions is: What is the potential impact of large-scale implementation of point-of-care testing for syphilis with immediate treatment options? Now, using the national congenital syphilis case notification data from 2022, the National Syphilis and Congenital Syphilis Syndemic Federal Task Force evaluated pregnant women who received a timely syphilis test, but did not receive any treatment or received the first dose of treatment late within pregnancy, for example, within 30 days of delivery. In 2022, there were 3,761 cases of congenital syphilis and 521 cases (or 14%) received inadequate or delayed treatment despite a syphilis test performed at the recommended time in pregnancy. In addition, there were 423 cases of congenital syphilis (or 11%) that were due to the pregnant woman receiving no treatment at all for syphilis. So, a total of 25% of cases of congenital syphilis may have benefited from a rapid point-of-care test on the day of testing of that pregnant woman. That's a lot of cases. From their analysis, 452 (or 12% of these cases) would have been adequately treated for syphilis had they received a reactive rapid test and one dose of benzathine penicillin on the day of testing. This would not only have effectively treated the pregnant woman for syphilis but also prevented congenital syphilis in that child.
5. The benefit of point-of-care testing and treatment would affect 26% of cases in American Indian and Alaska Native persons and 27% of Black and African American persons, which is much higher number compared to 13% of cases in Asian persons.

In summary, test-to-treatment gap is critically important and it's possible that 25% of pregnant women would have benefited from same-day point-of-care testing and treatment. There are differences in the impact of point-of-care testing programs, and showing a greater benefit in some groups compared to others. Point-of-care testing may provide a benefit to curb the epidemic of congenital syphilis. What would be really nice is to have a point-of-care nontreponemal syphilis test, and that would help to identify new cases of syphilis in those with a past history of treated infection. Further work is needed to figure out implementation and selection of optimal sites of point-of-care testing.

abstract-3**[13:27] Abstract 3**

Cannon C. *Can doxy-PEP implementation reverse syphilis trends?* Syphilis in the US: It's unrelenting. Paper presented at: IDWeek 2024; October 17, 2024; Los Angeles, CA. Session 73. [**IDWeek**]

I'll next review a talk that was given by Dr. Chase Cannon from the University of Washington. This was titled

“Can doxycycline postexposure prophylaxis (or doxy-PEP) implementation reverse syphilis trends?” This was a nice summary of the literature supporting this topic. If you’d like to hear more about doxycycline postexposure prophylaxis (or doxy-PEP), please visit our episode from April of 2024 where Dr. Cannon discussed management of doxy-PEP.

Now, the guidance from the CDC is for providers to counsel all men who have sex with men with at least one bacterial STI in the last 12 months about the benefits and harms of doxy-PEP and then offer this prevention tool through shared decision-making. There are a variety of clinical sites which have implemented doxy-PEP to priority populations.

1. The first question is whether doxy-PEP reduces syphilis. Dr. Cannon mentioned a meta-analysis of studies evaluating doxy-PEP, and it showed that this method reduces syphilis by 77%. Data from San Francisco showed population-level syphilis declines after doxy-PEP guidelines were released. For example, there was an overall 51% decrease in early syphilis cases in MSM [men who have sex with men]. Multiple other cities and jurisdictions have shown declines in syphilis in those persons using doxy-PEP. For example, clinics in San Francisco, Seattle, New York City, and Boston have shown 40% to 70% declines in syphilis for those persons using doxy-PEP. And these variable percentages depend on the city, the clinic, and the population that they’re evaluating.
2. So, the next question is: What about doxy-PEP to reduce congenital syphilis rates? Now, here, we don’t have too much data. There is some observational data on the efficacy of Doxy-PrEP use in Japanese sex workers. Doxy-PrEP would be doxycycline preexposure prophylaxis. In 40 women who took Doxy-PrEP, there was a 64% reduction in overall STIs. The incidence of syphilis in women who started Doxy-PrEP went down from eight cases prior to starting Doxy-PrEP to zero after starting Doxy-PrEP. So, in this small study, it indicates that Doxy-PrEP might be effective in women to prevent syphilis.
3. Dr. Cannon mentioned some studies showed that there might be some implementation challenges of doxy-PEP specific to women in clinical settings. For example, the participants who were part of the doxy-PEP study in Kenya, which included women, highlighted barriers to doxy-PEP use. These barriers included side effects, privacy concerns, social perception, and forgetting to take doses. Other concerns, such as safety in pregnancy and food insecurity, might also arise.
4. Now, there are some concerns about unintended consequences of using doxy-PEP. And, one of those concerns is antimicrobial resistance. The San Francisco city clinic showed rising tetracycline resistance in *Neisseria gonorrhea*cultures from 2019 through 2023. They did see this resistance prior to doxy-PEP guidelines being released, and so this might be due to widespread doxycycline use for other reasons, for example, for community-acquired pneumonia or to treat chlamydia infection.
5. Dr. Cannon talked about different settings to provide doxy-PEP outside of the traditionally organized medical clinics, which might be helpful. These might include nurse-led models, mobile health units, health fairs, Pride events, HIV PrEP and HIV clinics, but then also prenatal care settings, and urgent care settings, among others.
6. Some questions about doxy-PEP still remain. For example, how do we more effectively reach out to other populations? Can we better understand why people decline to use doxy-PEP, or are there messaging strategies to increase uptake in young people? And then, how do we implement doxy-PEP into already busy clinic settings and what enables sustained doxy-PEP use?

So, this was a great review of doxy-PEP. Now, whether doxy-PEP implementation will reverse syphilis trends, I would say the answer to this question is possibly and we’ll see. The high uptake of doxy-PEP in MSM alone might not be sufficient to reverse congenital syphilis. There are some studies focusing on doxy-PEP implementation as well as the impact on antimicrobial resistance in different cities, so stay tuned for further research in this area.

abstract-4**[17:47] Abstract 4**

Keith K. *Preliminary results from a clinical trial comparing the efficacy of cefixime versus penicillin g for the treatment of early syphilis*. Intimate insights: Sexually transmitted infection studies. Paper presented at:

IDWeek 2024; October 17, 2024; Los Angeles, CA. Session 217. [**IDWeek**]

The next presentation we'll review was given by Kori Keith from USC and titled "Preliminary results from a clinical trial comparing the efficacy of cefixime versus penicillin G for the treatment of early syphilis."

So, let's start out with some background. From 2018 to 2020, there was a small pilot study evaluating cefixime 400 mg orally twice a day for 10 days versus one dose of intramuscular benzathine penicillin G 2.4 million units to treat early syphilis. In this small study, they found that 87% of participants were successfully treated in the cefixime arm compared to 93% in the penicillin arm. So, the presentation at IDWeek reviewed preliminary results from a bigger clinical trial to evaluate oral cefixime as an alternative to treat early syphilis compared to one dose of intramuscular benzathine penicillin G. Now, of note, due to the penicillin shortage during this time, the protocol was modified to also include doxycycline in place of benzathine penicillin for the treatment of early syphilis. The intended plan for the study is to enroll 400 participants across 11 clinical sites in the U.S.

1. The outcome of interest is a 4-fold or greater decrease in the serum RPR (or rapid plasma reagin) at 3 or 6 months after treatment completion. Enrollment is still ongoing, and these are the preliminary results that they have found so far in 145 participants.
2. What they've seen is that in the cefixime arm, 88% of the participants were successfully treated for syphilis. This is compared to 90% in the benzathine penicillin G arm and 100% in the doxycycline arm. Now, this is interesting and I wouldn't have expected lower treatment success in the benzathine penicillin arm when compared with doxycycline.
3. But, they haven't yet fully analyzed the data or done an in-depth analysis., and these are pending. So, for example, they noted that some patients might have a 4-fold response in RPR titer after 6 months, or some patients might have had an increase in RPR titer due to reinfection, not necessarily due to failure of treatment, so this might account for the 90% efficacy seen in the benzathine penicillin G arm thus far and these results might be clarified once a detailed analysis has been completed.

But I liked this study because preliminary results from this trial suggests that oral cefixime might be a viable alternative to treat early syphilis. I look forward to seeing the final in-depth analysis once available, as alternative treatments for syphilis are sorely needed.

summary**[20:25] Summary**

To conclude, I'd like to summarize some key points from this session:

1. From 2012 to 2022, there has been a tenfold increase of congenital syphilis, resulting in 282 stillbirths and infant deaths.
2. Missed opportunities to prevent congenital syphilis include no timely testing, not identifying seroconversion during pregnancy, or lack of appropriate treatment.
3. Opportunities for intervention include low-barrier care prenatal clinics, provider education, third-trimester screening, and rapid point-of-care testing of pregnant women.
4. Rapid point-of-care syphilis testing may decrease time to treatment and possibly prevent loss to follow up.
5. Now, it's possible doxy-PEP might have an impact on syphilis trends. There has been a decrease in syphilis in MSM who are taking doxy-PEP, but further studies are still needed in women, as well as evaluating unintended consequences of doxy-PEP, such as antimicrobial resistance.
6. Oral cefixime might be an alternative antimicrobial agent to treat early syphilis. Final results are pending from a large clinical trial.

credits**[21:31] Credits**

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Transcripts and references for this podcast series can be found on our website, the National STD Curriculum at www.std.uw.edu. Thank you for listening and have a wonderful day.

congenital-syphilis-early-syphilis