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SPECIAL ARTICLE

Elimination of Congenital Syphilis: What's New for Obstetricians in the 2020 Thai National Guideline?

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ABSTRACT

The goal of eliminating congenital syphilis in Thailand is to reduce new cases from 50 per 100,000 live births in 2015 to 5 per 100,000 live births in 2020. This remains a challenge because the incidence of syphilis in pregnant women is rising in many regions of Thailand. Therefore, the Ministry of Public Health of Thailand has revised the national guideline to control the situation by increasing the screening for Thai people with high risk of getting the disease; early detection and treatment of pregnant women with syphilis; suggesting pathological examination of placenta as well as identification of *Treponema pallidum*; enhancing the corporation between obstetricians and pediatricians; and emphasizing the post-treatment follow-up including contact tracing.

Keywords: elimination, congenital syphilis, Thai, obstetricians.

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การกำจัดซิฟิลิสแต่กำเนิด: มีอะไรใหม่สำหรับสูตินรีแพทย์ในแนวทางปฏิบัติของประเทศไทยปี 2563?

เจนจิต ฉายะจินดา, กิตติภูมิ ชินหิรัญ, สุรสิทธิ์ ชัยทองวงศ์วัฒนา, รสพร กิตติเยาวมาลย์, มานพชัย ธรรมคันโธ

บทคัดย่อ

เป้าหมายในการกำจัดซิฟิลิสแต่กำเนิดในประเทศไทยที่ต้องการลดจาก 50 รายต่อการเกิดมีชีพ 100,000 ราย ในปี พ.ศ. 2558 เป็น 5 ราย ต่อทารกเกิดมีชีพ 100,000 รายในปีพ.ศ. 2563 ยังคงเป็นเรื่องที่ท้าทาย เมื่ออุบัติการณ์ของหญิงตั้งครรภ์ที่ติดเชื้อซิฟิลิสสูงขึ้นในหลายภูมิภาคในประเทศไทย กระทรวงสาธารณสุขจึงปรับแนวทางปฏิบัติในการลดซิฟิลิสแต่กำเนิดเพื่อแก้ไขปัญหานี้ โดยเพิ่มการค้นหาผู้ที่เป็นโรค การวินิจฉัยและรักษาหญิงตั้งครรภ์ที่ติดเชื้อซิฟิลิสให้เร็วที่สุด สนับสนุนการตรวจรกเพื่อระบุเชื้อซิฟิลิส ส่งเสริมการประสานงานระหว่างสูติแพทย์กับกุมารแพทย์ และปรับแนวทางการตรวจติดตามภายหลังการรักษาให้เหมาะสม รวมถึงแนวทางการตรวจติดตามคู่เพศสัมพันธ์เพื่อรับการรักษาอย่างครบถ้วน

***คำสำคัญ**: กำจัด, ซิฟิลิสแต่กำเนิด, ประเทศไทย, สูติแพทย์*

Introduction

Congenital syphilis (CS) is caused by the transmission of *Treponema pallidum subsp. pallidum* from mother to fetus during pregnancy or delivery. Its consequences include miscarriages, dead fetus in utero, stillbirth, hydrops fetalis and infected infants. The diagnosis of CS at birth is categorized into two groups: confirmed cases, or fetus or infant with detection of the organism, and probable case, or those with high suspicion of CS without detected organism[1]. The data from Siriraj Hospital, which collected 195 pregnant women with syphilis who came to Siriraj Hospital from 2006-2015, showed the complications included 58 CS (29.7%), 5 miscarriages (2.4%) and 7 stillbirths (3.6%). Factors relating to CS were teenage pregnancy, receiving treatment for less than 4 weeks before delivery, or having never received any treatment[2]. Despite the fact that CS can be treated with the basic antibiotic like penicillin, permanent damage on infant's organs lasts much longer and can result in poor long-term outcomes.

Previously, Thailand was able to meet the definition of elimination of CS provided by the World Health Organization (WHO), which is fewer than 50 new cases per 100,000 live births, in 2015 and aimed to hit the target of fewer than 5 new cases per 100,000 live births[3]. In fact, the incidence was nearly four times higher from 2015 to 2018 (11.9 vs 42.6 cases per 100,000 live births). This finding was correlated with the rising prevalence of syphilis in pregnant women from 0.14 to 0.42 percent during the same time period. The impact was apparently demonstrated among teenage pregnant women who usually had the contagious stage of syphilis[4]. No return for blood-testing result, late/inadequate treatment and no/inadequate sex partners' evaluation and treatment are therefore the challenges of tackling the problem[4].

In 2020, with collaboration with multiple organizations, the Division of AIDS and STIs, Department of Disease Control of Thailand reviewed and revised the National Guideline on the management for the elimination of congenital syphilis in Thailand, 2015[3] in order to mitigate the problem. Apparently, obstetricians play an important role in this mission. Like the 2015 guideline, the 2020 guideline encourages thorough history-taking and physical examination. The routine blood testing for syphilis at the first antenatal care and at 28-32 weeks gestation is shifted from traditional sequence to reverse sequence. Same-day result testing using point-of-care tests are more highlighted in settings with high loss to follow-up rate. Couple counseling and testing for these infections in their husbands is recommended at first antenatal care. Additionally, safe sex is strongly suggested throughout pregnancy, especially when sex partners are promiscuous. In accordance with the WHO guideline, the treatment regimen for all stages of syphilis are clearly stated and the referral centers for pregnant women with penicillin hypersensitivity are provided.

Staging of syphilis

In general, syphilis is classified according to the stage as early stage consisting of primary, secondary, and early latent; and the late stage consisting of tertiary, late latent, and syphilis of unknown duration. Syphilis can also pass through blood-brain barrier leading to neurosyphilis. Instead of using two years to distinguish early from late syphilis as being suggested by the WHO[5], the Thai 2020 national guideline uses one year like the guidelines provided by the US Center for Disease Control and Prevention[6] and by the International Union against Sexually Transmitted Infections[7] for the benefit of higher treatment coverage. As known, the early stage of the disease in pregnant women was related to the higher probability of transmission[8].

Primary syphilis is the stage that the infection has just entered the body and causes a wound at its entry. The wound has an indurated edge and painless which can be spontaneous healing (hard chancre). Secondary syphilis is the stage after the infection enters the bloodstream and causes symptoms in various sites of the body such as moth-eaten alopecia, scaly-bordered rashes on the body, and multiple painless indurated edge rashes on genitalia, etc. Tertiary syphilis is usually the stage that the infection has been in the body for more than 10 years, causing the chronic destruction of organs such as arterioles. Both latent syphilis and syphilis of unknown duration have no symptoms.

Diagnosis of syphilis

The vast majority of pregnant women with syphilis have no symptom. Therefore, the diagnosis is mostly obtained by serological examination which is divided into two groups. Non-treponemal test includes rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL). Treponemal test includes *Treponema pallidum* haemagglutination assay (TPHA), *Treponema pallidum* particle agglutination assay (TPPA), chemiluminescence immunoassay (CMIA) and a rapid/ point-of-care syphilis testing which uses a chromatographic paper. As machine-based testing is not available in all settings, the chromatographic paper test has become more popular.

The serological diagnosis of syphilis requires the positive results of both treponemal and non-treponemal tests. Previously, the nontreponemal test was first performed and confirmed with a treponemal test (traditional sequence) but the disadvantage was the inability to diagnose very early syphilis or late syphilis. Therefore, at present, the reverse sequence, which uses an automated treponemal test followed by a non-treponemal test, is widely used all over the world. The King Chulalongkorn Memorial Hospital has changed to the reverse sequence algorithm for syphilis screening since 2011. With prevalence of syphilis of 1.98 in 1,000 pregnant women during February 2011 to January 2013, 69.6% of women with untreated syphilis would be missed diagnosed if the traditional algorithm was used[9].

In the 2020 guideline, the reverse sequence is officially recommended. There are two algorithms for two different healthcare settings. Algorithm 1 is for those with negligible rate of loss to follow-up; (Fig. 1) and algorithm 2 is for those with high tendency of loss to follow-up cases (Fig. 2). Algorithm 1 has long been a universal practice in use all over the world. The 2020 guideline favors CMIA as the first screening tool for its affordability and high sensitivity. Algorithm 2 uses a rapid diagnostic test as the primary test followed by RPR because both of them can be reported on the same day. If the rapid test is positive but RPR is negative, another treponemal test must be done. In the 2020 guideline, either TPPA or TPHA is recommended to be the second treponemal test. As both of them take a few days to report and are not available in some local hospitals, the 2020 guideline suggests starting immediate treatment. If the second treponemal test is negative, the treatment course will be stopped. In contrast, if TPHA/TPPA is positive but the patients do not return, the benefit of the given dose of penicillin outweighs the risk of penicillin overuse[8,10]. Moreover, to date, *Treponema pallidum* has no report to be penicillin-resistant.

Treatment guidelines for syphilis in pregnant women (Table 1.)

Penicillin is the only drug that can evidently prevent CS. The desired concentration of penicillin in maternal serum for killing *T. pallidum* is ≥ 0.018 µg/mL. One dose of 2.4 million units benzathine penicillin G aims to reach the treponemicidal level for at least one week. However, 36% of the infected pregnant women had the level at < 0.018 µg/mL by day 7[11]. Another study showed that 4.8 million units of benzathine penicillin G can result in serum penicillin level at ≥ 0.20 µg/mL for 30 days after treatment[12]. The large cohort study by Zhu, et al showed that out of 535,537 pregnant women in Shanghai, China during 2002-2006, there were 1,471 maternal syphilis cases. Of them, 12.5% had CS infants despite the complete treatment; and the incidence appeared more remarkable if maternal RPR titer was ≥ 1:16 and treatment was commenced after gestational age 20 weeks[13]. As a result, some experts suggest an additional 2.4 million units intramuscular injection of benzathine penicillin for pregnant patients[6]. From our experience, pregnant women whose skin lesions are not resolved within two weeks after the treatment are the candidates to receive the second dose.

Since the use of this drug is greatly reduced, benzathine penicillin is often out of stock. Some patients with a history of penicillin allergy require an alternative drugs. Although only 10 percent of people with a history of penicillin allergy are confirmed as being allergic to the drug, penicillin remains contraindicated. Desensitization is an option for this group of population but it requires a well-trained teamwork among obstetricians, allergist, and a team of skilled nurses with fully-equipped life-saving setting. In accordance with treatment guideline provided by WHO[14], the recommended treatment regimen is in Table 1.

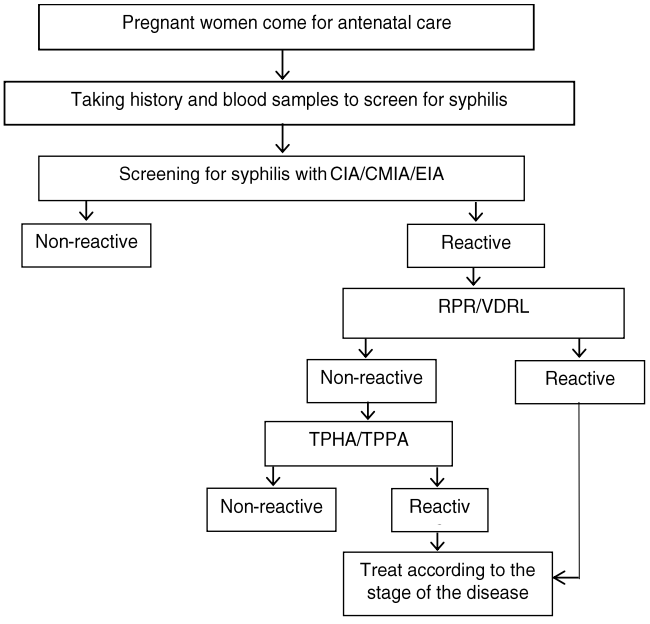

Fig. 1. Diagnostic method using automated machine.

*According to Thai MOPH, syphilis screening is recommended at the first antenatal care visit and during 28-32 week gestation.

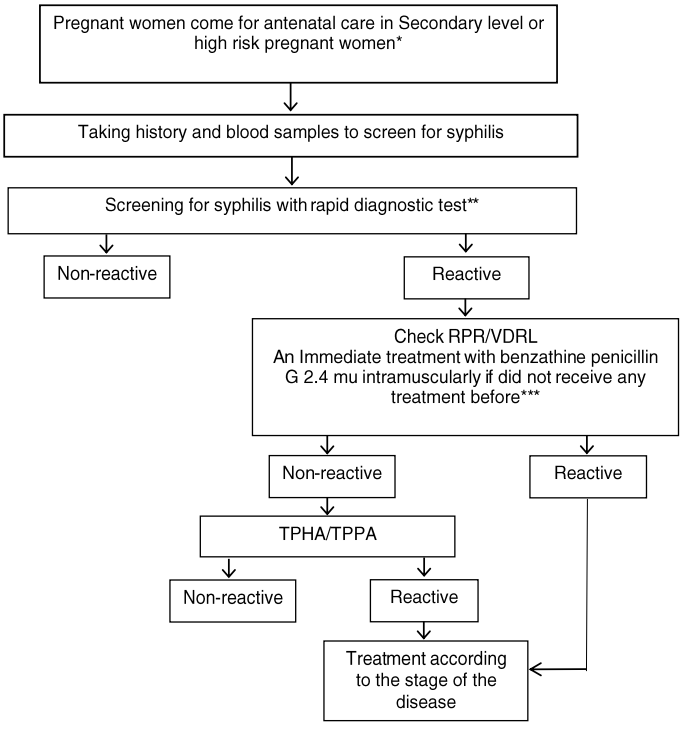

Fig. 2. Diagnostic method using a rapid test.

* High risk pregnant women means teenage pregnancy, pregnancy with late ANC etc.

** Rapid diagnostic tests must have reports for efficacy in at least 2 accepted journals in the WHO list of qualification testing or Department of Medical Science and have a sensitivity of at least 95%.

*** Immediate treatment can be commenced provided the result of RPR/VDRL cannot be retrieved on the same day; or TPHA/TPPA needs to be done.

Table 1. Treatment guidelines.

	Treatment
Early syphilis	**Recommended Regimen**
	- Benzathine penicillin G 2.4 million units intramuscularly in a single dose, divided into 1.2 million units per buttock
	- Follow-up 3 months after treatment by blood testing for RPR/VDRL, if there is a suspicion of treatment failure.*
	o No history of risk of re-infection: benzathine penicillin G 2.4 million units intramuscularly weekly for 3 doses
	o Having a history of risk of re-infection, benzathine penicillin G 2.4 million units intramuscularly in a single dose
	- Treat all sex partners according to the stage of syphilis**
	- The RPR/VDRL must be checked before starting every new treatment.
	Alternative Regimen
	- Erythromycin base (except estolate) 500 mg orally 4 times a day for 14 days
	- Ceftriaxone 1 g intramuscularly or intravenously once a day for 10 days
	- Azithromyzin 2 g orally single dose
Late syphilis	**Recommended Regimen**
	- Benzathine penicillin G 2.4 million units intramuscularly weekly for 3 consecutive doses, divided into 1.2 million units per buttock. Treatment interval can be extended up to 14 days, otherwise a new course will be required.
	- Follow-up 3 months after treatment by blood testing for RPR/VDRL, if there is a suspicion of treatment failure.*
	o No history of risk of re-infection
	- Presence of neurosyphilis symptoms and signs*** or being HIV-seropositive: Treat as neurosyphilis
	- No neurosyphilis symptoms and signs or HIV-seronegative: benzathine penicillin G 2.4 million units intramuscularly weekly for 3 doses
	o Having an obvious history of new infection: benzathine penicillin G 2.4 million units intramuscularly in a single dose
	- Treatment of the husband/sex partner only if the serological test results are positive
	- The RPR/VDRL must be checked before starting every new treatment.
	Alternative Regimen
	- Erythromycin base (except estolate) 500 mg orally 4 times a day for 30 days
Neurosyphilis	**Recommended Regimen**
	- Aqueous crystalline penicillin G 18–24 million units per day intravenous, administered as 3–4 million units every 4 hours or continuous infusion, for 10–14 days
	- Treatment of the husband/sex partner only if the serological test results are positive
	- Lumbar puncture should be avoided in pregnant women.

* Treatment failure is defined as any of the followings: no improvement in clinical symptoms, or a 4-fold rising in RPR/VDRL at 3 months after treatment, or decline in RPR/VDRL < 4-fold or 1:8 or greater after 6 months of treatment.

** Treat all sex partners according to the stage of syphilis: having sexual relation with the patients within 3 months for primary syphilis, 6 months for seconady syphilis and two years for early latent syphilis. Diagnostic approach of sex partners is similar to that of pregnant women (Algorithm 1, 2).

*** Neurosyphilis symptoms and signs include eye pain, redness, photophobia, sensorineural hearing loss, etc.

Care during labor

The 2020 guideline underlines the importance of good collaboration between obstetricians and pediatricians during labor. A history of incomplete or no treatment, or high non-treponemal titer before delivery (VDRL ≥ 1:8 or RPR ≥ 1:4) after treatment, or received non-penicillin drug treatment are considered as a high-risk factors for the vertical transmission. It is always necessary to notify the pediatrician before delivery. In addition, the 2020 guideline recommends sending placenta for pathological report and for *T. pallidum* detection.

Follow-up guideline

Only one non-treponemal test, either RPR or VDRL, is used throughout the process of follow-up. The 2015 guideline recommended pregnant women with early syphilis to return for VDRL/RPR testing at 1, 2, 3, 6, 9, 12, 18, 24 months. Generally, if the response to treatment is good, VDRL/RPR will decline to at least 4 times at 6 months of treatment. Moreover, too many follow-up visits during first three months post-treatment are impractical. At the Siriraj Female STI Clinic, only 20% could adhere to the protocol. Moreover, considering 6-month visit as the adequate post-treatment follow-up, 59.5% did not hit the target and 14% had not a single visit. The associating factors included age of 19 years or younger, lower education than primary school, and living in a nuclear family[15]. Therefore, the 2020 guideline recommends the first follow-up visit be at 3 months post-treatment with a highlight that VDRL/RPR should be done on the treatment day. In addition, maternal blood testing for VDRL/RPR is recommended on the delivery day for the comparison between maternal VDRL titer and infant's VDRL/RPR blood titer. For pregnant women receiving initial treatment as late syphilis, they often have a low initial VDRL/RPR, so it is difficult to follow the decline of VDRL/RPR.

The data from the Siriraj Female STI Clinic support that 3-month VDRL monitoring can detect more than 60% of patients diagnosed with syphilis who have good treatment response. Of 386 women with syphilis at the Clinic during 2007-2017, 201 (52.1%) were pregnant. Among pregnant patients, 101(50.2%) had initial VDRL titer ≥ 1:8 but only 60 (59.4%) came for 3-month VDRL monitoring. Thirty-nine patients (65.0%) had four-fold decline at 3 months. There were 31 patients (30.7%) came for VDRL titer monitoring at 6 months. Apart from those who had four-fold decline at 3 months, six did at 6 months. Among non-pregnant patients, only 57(30.8%) had initial VDRL titer ≥ 1:8. Of them, 34 (59.6%) came for 3-month VDRL monitoring and 21/34 (61.8%) had four-fold decline of VDRL. There were 18 patients coming for the 6-month VDRL monitoring and five had four-fold decline of VDRL.

Conclusion

The reduction of CS incidence to less than 5 cases per 100,000 live births in Thailand remains a challenge. The promising way is that all stakeholders work harmoniously to increase Thai people's awareness of self-protection, to strengthen screening program in all population, to give adequate treatment and post-treatment follow-up.

Potential conflicts of interest

The authors declare no conflict of interest.

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