Secondary Syphilis with Giant Condyloma Acuminatum in Pregnant Women: A Report from a Limited Resource Area

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Abstract
Introduction: This report shows a case of secondary syphilis in pregnancy with Giant Condyloma Acuminatum (GCA) co-infection DD/condyloma lata which was resolved with alternative treatment of syphilis.
Case illustration: A 21-year-old, primigravid woman came to obstetrics outpatient clinic in rural SoE Hospital, East Nusa Tenggara, with a complaint of mass enlargement around vulva (minor and major labia) since 2 months before. Based on Last Menstrual Period (LMP), she was in 34 + 6 weeks of gestation. There were coin lesions in the palms. On genital examination, there was protruded mass sized around 15 x 10 cm, erythematous, and it easily bled on the center part which was suspected to be GCA. *Treponema Pallidum* rapid (TP-rapid) test using AIM© syphilis rapid test revealed positive results. The patient was diagnosed with secondary syphilis in pregnancy mixed with GCA with dd/condyloma lata and administered Ceftriaxone 1 g intramuscularly once daily for 14 days. She delivered at 41-42 weeks of gestation and a baby girl with 1,980 grams of body weight according to symmetric Intrauterine Growth Restriction (IUGR) was born. No clinical signs of congenital syphilis found.
Discussion: Vertical transmission which occurs in each stage of syphilis is related to the presence of spirochetes in the blood circulation. Infants born from syphilis pregnant women consist of 56% of jaundice, 14% of hearing impairment, 8% of renal disease, 8% of mental retardation, and 6% of IUGR or Small for Gestational Age (SGA).
Conclusion: Secondary syphilis coinfection with GCA in pregnancy is a rare case report. Syphilis is a significant public health problem globally, especially in Indonesia.

Keywords: syphilis, coinfection, giant condyloma acuminatum, intrauterine growth restriction

Sifilis Sekunder dengan Kondiloma Akuminata Besar pada Wanita Hamil: Sebuah Laporan dari Daerah dengan Keterbatasan Sumber Daya

Abstrak
Pendahuluan: *Kasus ini melaporkan sifilis sekunder pada kehamilan dengan kondiloma akuminatum besar dengan koinfeksi dd/kondiloma lata yang beresolusi setelah pemberian tatalaksana alternatif sifilis.*
Ilustrasi Kasus: *Seorang wanita primigravida berusia 21 tahun datang ke poliklinik obstetrik di RSUD SoE, Nusa Tenggara Timur dengan pembesaran massa sekitar vulva (labia minor dan mayor) sejak 2 bulan sebelumnya. Berdasarkan Hari Pertama Haid Terakhir (HPHT), usia kehamilan 34 + 6 minggu. Terdapat lesi pada telapak tangan. Pada pemeriksaan genital, terdapat massa ukuran 15 x 10 cm, eritema, mudah berdarah pada bagian tengah dengan kecurigaan kondiloma akuminatum besar. Hasil tes rapid Treponema Pallidum menggunakan tes rapid sifilis (AIM©) menunjukkan hasil positif. Pasien didiagnosis mengidap sifilis sekunder pada kehamilan dengan kondiloma akuminatum besar dengan koinfeksi dd/ kondiloma lata dan diberikan terapi seftriakson 1 gram intramuscular setiap hari selama 14 hari. Pasien melahirkan saat usia kehamilan 41-42 minggu dan lahir bayi 1.980 gram sesuai dengan Pertumbuhan Janin Terhambat (PJT) simetrik. Tidak ada tanda klinis sifilis kongenital yang ditemukan.*
Diskusi: *Transmisi vertikal dapat terjadi pada setiap tahap sifilis berkaitan dengan keberadaan spiroseta di sirkulasi darah. Bayi lahir dari wanita hamil sifilis biasanya menunjukkan tanda 56% kuning, 14% gangguan pendengaran, 8% gangguan ginjal, 8% retardasi mental, dan 6% PJT atau Kecil Masa Kehamilan (KMK).*
Kesimpulan: *Sifilis sekunder koinfeksi kondiloma akuminatum besar merupakan kasus jarang. Sifilis masih menjadi perhatian kesehatan global, khususnya di Indonesia.*

Kata kunci: *sifilis, koinfeksi, kondiloma akuminatum besar, pertumbuhan janin terhambat*

Introduction

Syphilis, known as "the great imitator", is a Sexually Transmitted Infection (STI) caused by *Treponema pallidum sub. pallidum* with various manifestations and clinical stages.[1] In Indonesia, until September 2020, there were 1.7 million cases with 500,000 new cases in 2020.[2] In our province in East Nusa Tenggara, an estimation of 1,520 cases of syphilis were reported in 2020.[3]

World Health Organization (WHO) estimates that almost 1.5 millions of pregnant women are infected with active syphilis each year.[4] Syphilis infection in pregnancy is associated with pregnancy complication such as miscarriage, stillbirth, or neonatal death up to 30% of cases.[5] There were around 350,000 adverse pregnancy outcomes related to syphilis including 143,000 stillbirths, 62,000 neonatal deaths, 44,000 preterm or low birth weight, and 102,000 infected infants in 2012.[4] Untreated syphilis, especially in primary and secondary stages will affect pregnancy outcomes. Early congenital syphilis manifests as bone deformities, rashes, jaundice, lethargy, and anemia. On the other hand, late congenital syphilis contributes to neurological impairment, sensorineural deafness, and blindness.[6] According to high prevalence and serious morbidity in both mothers and babies, Indonesia has conducted triple elimination infection screening on pregnant women in all health care facilities, namely syphilis, HIV, and hepatitis B.[7] To establish STI diagnosis, it needs careful physical examination combined with additional comprehensive diagnostic examination.

This report shows a case of secondary syphilis in pregnancy with Giant Condyloma Acuminatum (GCA) co-infection DD/ condyloma lata which was resolved with alternative treatment of syphilis and the influence of fetal morbidity after delivery.

Case Illustration

A21-year-old, primigravid woman came to our obstetrics outpatient clinic in rural SoE Hospital, East Nusa Tenggara with a complaint of mass enlargement around vulva (minor and major labia) since 2 months before. She had history of unprotected sex with multiple heterosexual partners. Her last sexual partner was an intercity driver. She also complained of having vaginal discharge. Based on Last Menstrual Period (LMP), she was in 34 + 6 weeks of gestation. There were no complaints regarding her pregnancy such as contraction, water leakage, or vaginal bleeding. On physical examination, there were coin lesions in the palms (figure 1a). On genital examination, there was protruded mass sized around 15 x 10 cm, erythematous, and it easily bled on the center part (figure 1b). Meanwhile, there was lesion in the distal part of vagina (figure 1c). There was no colposcopy or biopsy facility in our rural hospital. *Treponema Pallidum* rapid (TP-rapid) test using AIM© syphilis rapid test revealed positive result and there was no Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test procedure in our hospital. Other triple eliminations such as HIV and hepatitis B showed negative results. Ultrasound examination depicted fetal biometry corresponding to 31-32 weeks of gestation with estimated fetal body weight of 1,200 grams. We diagnosed her with secondary syphilis in pregnancy mixed with Giant Condyloma Acuminatum (GCA) with dd/condyloma lata. We could not establish a definite diagnosis due to the unavailability of biopsy in our hospital. Based on WHO Sexual Transmitted Infection (STI) guidelines, the recommended treatment for secondary syphilis is Benzathine Penicillin G of 2.4 million units once intramuscularly (strong recommendation); however, it was out of stock. Other treatment such as Procaine Penicillin was also not available, while

Erythromycin was not supported by national health insurance. Thus, we treated the patient with Ceftriaxone 1 g intramuscularly once daily for 14 days (conditional recommendation) and the patient was in-hospitalized.

After 14 days of treatment, the patient came with an improvement of the mass (figure 2). She was advised to take antenatal care in hospital and planned for elective cesarean section in 39 weeks of gestation due to the giant condyloma acuminatum that would block the birth canal. Unfortunately, she was lost to follow up. Thereafter, she came back to our hospital due to regular contraction in 41-42 weeks of gestation based on third trimester of ultrasound scan. On the examination, there was complete dilatation without amniotic membrane and head on station +3. She delivered a baby girl with 1,980 grams of body weight, 47 cm, 30 cm, and 32 cm of body length, Head Circumference (HC), and Abdominal Circumference (AC), respectively. The Ballard score showed 42 weeks. The HC/AC ratio described 0.9 meaning symmetric Intrauterine Growth Restriction (IUGR). No clinical signs of congenital syphilis were found on physical examination such as jaundice, hepatosplenomegaly, or skin rash. There was no availability of non-treponemal serologic titers (RPR or VDRL). Since the neonate had normal physical examination, there was no serum quantitative non-treponemal serologic titer, and the mother was inadequately treated, it was classified as possible congenital syphilis. After delivery, no coin patch erythematous was found on the palms and the condyloma around the vulva shrank (fiture 3a and figure 3b).

Discussion

Syphilis can be classified into several stages, namely primary, secondary, latent, and tertiary syphilis. Pregnancy does not change the clinical manifestation of syphilis. Inadequate treatment of syphilis in pregnant women can contribute to fetal morbidity and mortality, especially congenital syphilis.[1,8] Good physical examination combined with laboratory support can help doctors establish the diagnosis. Vertical transmission which occurs in each stage of syphilis is related with the presence of spirochetes in the blood circulation. Primary and secondary syphilis have a higher risk of transmission than latent and tertiary syphilis. As catastrophic consequences of congenital syphilis, it can be manifested based on gestational age, stage of maternal syphilis, maternal treatment, and immunological response to fetus.[9] Congenital syphilis can be divided into two characteristics: early and late congenital syphilis. Early congenital syphilis is diagnosed within two years of life with clinical symptoms such

Figure 1a (left): Coin Patch Erythematous Lesion on Palms; Figure 1b (center): Condyloma on Labia; Figure 1c: Condyloma on Distal Vaginal

Figure 2 Improvement of the Mass after 14-Day Treatment

Figure 3a (Left): No Coin Lesions Found on Palms; Figure 3b (Center): Condyloma Resolution after Delivery

as hepatosplenomegaly, desquamating skin rash, rhinitis, anemia, thrombocytopenia, and osteochondritis. Meanwhile, late congenital syphilis is characterized by notched teeth (Hutchinson's teeth), deafness, interstitial keratitis, development delay, hydrocephalus, seizures, nerve palsies, and bone deformities.[1]

Untreated syphilis in pregnancy will affect >70% of infants and 40% of fetal or perinatal death.[10] The rate of fetal infection depends on the stages of syphilis including 50%, 67%, and 83% for primary, secondary, and early latent infection, respectively.[11] However, more than two-thirds of live neonates do not show any symptom at first. A study from Korea shows that outcomes of infant born from syphilis pregnant women consist of 56% of jaundice, 14% of hearing impairment, 8% of renal disease, 8% of mental retardation, and 6% of IUGR or Small for Gestational Age (SGA).[10] In our case, we could find only symmetric IUGR. The exact mechanism is still mysterious. In animal models, Th1 response is triggered in primary syphilis and changed to Th2 response as disease progression in secondary stage of syphilis. The increase in inflammatory cytokines such as IL-2, IFN-gamma, TNF-alpha, and prostaglandin due to fetal infection is associated with activation of macrophages which is considered related to fetal death, preterm delivery, and severe IUGR in primary or secondary syphilis.[11]

Management of syphilis pregnant

women aims to reduce the risk of congenital syphilis in neonates. Diagnosis of congenital syphilis is not easy because maternal non-treponemal and treponemal immunoglobulin G (IgG) antibodies can be transferred through placenta so that it will be confusing in the interpretation, especially in infants less than 30 days old. The treatment of neonates should be based on identification of syphilis in the mother, adequacy of maternal treatment, presence of clinical, laboratory, and radiographic evidence of syphilis in neonate, and comparison of maternal and neonatal serologic titers. A treponemal (TP-rapid) test on neonatal serum is not recommended because it can detect signs of maternal antibodies for >15 months. The neonate in our case possibly had congenital syphilis based on CDC classification.[12] Unfortunately, there was no available penicillin G and the evidence was insufficient to administer ceftriaxone to treat congenital syphilis in neonates with jaundice.

Guidelines from CDC state that a neonate that is not treated because congenital syphilis is less likely, non-treponemal antibody titers would decrease by age of 3 months and be non-reactive at the age of 6 months, indicating passive transfer from maternal IgG antibody. At the age of 6 months, if the test is non-reactive, the follow-up is no longer needed, meanwhile, if the test is still reactive, the infant is likely infected and should be treated.[12] Unfortunately, in our district hospital, non-treponemal antibody titer was not available.

Buschke-Loewenstein tumor or GCA as a coinfection of STI in our patient is a rare disease with prevalence of only 0.1%. GCA is associated with infection by Human Papilloma Virus (HPV), immunodeficiencies, poor hygiene, multiple sexual partners, and chronic genital infection.[13] Extended surgical excision with reconstruction of skin is still the best option for the treatment of GCA. The management GCA during pregnancy is more complicated due to the awareness to both the mother and the fetus.[14] Vaginal delivery is not an option because it can block the birth canal and increase risk of vertical transmission to infant such as laryngeal papilloma.[15] In our case, the patient was planned for elective CS; she was lost to follow-up and came to hospital with second stage of labor. Surprisingly, the GCA shrank with minimal remaining lesion on vagina. Until now, there have been no reported studies regarding spontaneous shrinkage of GCA in pregnancy. Meanwhile, for condyloma lata, it disappeared due to syphilis stages' conversion from secondary to latent syphilis.

As the standard treatment of syphilis during pregnancy, benzathine penicillin G is highly effective with the successful rate reaching 98.2% in the prevention of congenital syphilis.[16,17] Unfortunately, our case was found in an area with limited resources, where benzathine penicillin is not always available. Therefore, we administered intramuscular ceftriaxone 1 gram for 14 days to treat secondary syphilis. Case series in Japan revealed a successful use of intramuscular ceftriaxone in pregnancy to prevent congenital syphilis.[18,19] In second case series, secondary syphilis obtained a 10-day course of intramuscular ceftriaxone 250 mg which was repeated at 28 weeks of gestation.[17,19] However, a randomized controlled trial is still needed to determine the use of ceftriaxone in pregnant patient to prevent congenital syphilis. WHO STI guidelines recommend using erythromycin 500 mg orally four times daily for 14 days or intramuscular ceftriaxone 1 gram once daily for 10-14 days or oral azithromycin 2 gram once, unless benzathine or procaine penicillin is available.[4]

To monitor the adequacy of therapy, the Ministry of Health of the Republic of Indonesia suggests clinical and serological monitoring every 3 months in the first year and every 6 months in the second year using

T. pallidum hemagglutinin test (TPHA) and VDLR/RPR titer for primary and secondary syphilis. Unfortunately, neither of them were not available in our district. Meanwhile, TP-rapid test can only be used for screening because the test cannot differentiate whether the infection is active or not. Therefore, it was not possible to evaluate the treatment progress, which could cause overtreatment.[7] Until now, both the patient and the baby were monitored by obstetricians and pediatricians to find out the syphilis stage and complication of late congenital syphilis.

In 2016, WHO released *Global Health Sector Strategy on Sexually Transmitted Infections 2016-2021* with the purpose of reducing the number of congenital syphilis to 50 cases per 100,000 live birth rates in 80% countries in 2030. WHO has developed elimination criteria of syphilis transmission from mothers to babies that have to be achieved in order to get validation from WHO. The criteria are that the number of congenital syphilis cases is less than 50 cases per 100,000 live birth rates and meets 3 service coverage targets: (1) 95% of pregnant women get ANC; (2) 95% of pregnant women who get ANC are tested for syphilis; and (3) 95% of pregnant women who are tested positive for syphilis get adequate treatment with benzathine penicillin. Our area does not have comprehensive diagnostic tests and adequate treatment, so it is deeply regretted that we still could not meet the elimination criteria.[3] In Indonesia, the Ministry of Health states that every pregnant woman should be tested for syphilis as early as possible and be repeated at third trimester and during delivery. In areas with limited resources without the availability of RPR/ VDRL and TPHA tests, TP-rapid test can be used, and all positive results are considered as active syphilis.[7] It needs a commitment and collaboration among obstetricians, pediatricians, dermatovenereologists, and public health offices. Unfortunately, RPR/ VDRL and TPHA test as well as benzathine penicillin as a drug of choice are not easily available in rural areas in Indonesia. Therefore, it needs the government's role to cope with this problem in reaching the target from WHO.

Conclusion

Secondary syphilis coinfection with GCA in pregnancy is a rare case report. Syphilis is a significant public health problem globally, especially in Indonesia. To increase the accuracy of diagnosis and treatment for elimination of STI in pregnancy, Indonesian government needs to provide the diagnostic test and effective treatment using benzathine penicillin in all health care facilities in Indonesia.

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