PREGLEDNI RAD

UDK BROJEVI:
616.972:618.3
DOI: http://doi.org/10.5937/zdravzast50-30653

SIFILIS U TRUDNOĆI

Milan Bjekić[1]

[1] Gradski zavod za kožne i venerične bolesti, Beograd, Republika Srbija

SAŽETAK

U Srbiji je rani sifilis u porastu od 2010. godine i njegova zaraznost za seksualne partnere traje godinu dana od momenta inficiranja. Izuzetak čine trudnice koje infekciju mogu da prenesu na plod u toku četiri godine od inficiranja, ukoliko se ne leče. Sifilis u trudnoći može izazvati pobačaj, rađanje mrtvog deteta, deteta sa malom telesnom težinom ili nastanka kongenitalnog sifilisa. Cilj ovog rada je da prikaže kliničke manifestacije, laboratorijsku dijagnostiku i terapiju sifilisa u trudnoći, kao i da senzibiliše medicinske radnike na ovo oboljenje i na uvođenje obaveznih seroloških skrining testova za sifilis kod svih trudnica.

Ključne reči: sifilis, trudnoća, skrining test

Uvod

Rani sifilis predstavlja kontagioznu formu ovog oboljenja i prema prirodnom toku bolesti čine ga primarni, sekundarni i rani latentni stadijum koji traje godinu dana od dobijanja infekcije. Osoba sa ranim sifilisom zarazna je za seksualne partnere godinu dana od momenta inficiranja, a nelečena trudnica sa ranim sifilisom infekciju može preneti na svoj plod tokom naredne četiri godine od infekcije (1). Sifilis tokom trudnoće može izazvati ozbiljne komplikacije i dovesti do spontanog pobačaja, rađanja mrtvog deteta ili deteta sa znacima kongenitalnog sifilisa. Ako se infekcija trudnice blagovremeno otkrije i leči navedene komplikacije se mogu sprečiti, dok neotkrivene infekcije dovode do ozbiljnih sekvela.

Epidemiološka situacija početkom novog milenijuma ukazuje na značajan porast obolevanja od sifilisa u Republici Srbiji (2). Iako je većina obolelih pripadala muškarcima koji imaju seks sa muškarcima (2,3), beleže se infekcije i kod žena (4), a sve inficirane trudnice bile su Romkinje, kod kojih se sifilis češće javljao u odnosu na žene neromske populacije (5). U poslednjih pet godina kod nas je registrovan jedan slučaj kongenitalnog sifilisa (6). Podaci iz Evrope ukazuju da su najviše stope sifilisa kod žena registrovane u Bugarskoj, Litvaniji, Letoniji i na Islandu, a kongenitalnog sifilisa u Bugarskoj, zatim u Portugaliji, Rumuniji i Poljskoj (7). U toku 2017. godine u Sjedinjenim Američkim Državama zabeležen je najveći broj novorođenih sa sifilisom u poslednje dve dekade (8). Studije iz nekih Evropskih zemalja su pokazale da je preko 20% novoinficiranih žena sa sifilisom među trudnicama (9,10), a u Španiji (11) je pozitivan test kod trudnica bio dva puta i u Irskoj (12) šest puta češći u odnosu na opštu populaciju što bi se moglo objasniti povećanom primenom antenatalnog skrininga na sifilis.

Cilj ovog rada je da prikaže kliničke manifestacije, laboratorijsku dijagnostiku i terapiju sifilisa u trudnoći, kao i da senzibiliše medicinske radnike na ovo oboljenje i na uvođenje obaveznih seroloških skrining testova za sifilis kod svih trudnica.

Metode

U okviru ovog preglednog rada prikazali smo kliničke, laboratorijske, dijagnostičke i terapijske specifičnosti sifilisa u trudnoći dobijene na osnovu pretraživanja literature objavljene na engleskom jeziku preko PUBMED-a korišćenjem sledećih ključnih reči: sifilis, trudnoća i skrining test.

Kliničke manifestacije sifilisa

Nakon prosečnog inkubacionog perioda od 3 nedelje na mestu ulaska treponeme palidum (lat. *Treponema pallidum*) javlja se tvrdi šankr (lat. *ulcus durum*), primarna lezija u vidu jasno

Health Care 50(1), 2021

REVIEW ARTICLE

UDK NUMBERS:
616.972:618.3
DOI: http://doi.org/10.5937/zdravzast50-30653

SYPHILIS IN PREGNANCY

Milan Bjekic[1]

[1] City Institute for Skin and Venereal Diseases, Belgrade, Republic of Serbia

SUMMARY

Early syphilis has been increasing in the Republic of Serbia since 2010 and its infectivity for sexual partners lasts for a year from the moment of infection. The exception is pregnant women who, if left untreated, can transmit the infection to the fetus within four years of infection. Syphilis in pregnancy can cause miscarriage, stillbirth, low birth weight or congenital syphilis. The aim of this paper is to present the clinical manifestations, laboratory diagnostics and therapy of syphilis in pregnancy, as well as to sensitize medical workers to this disease and the introduction of mandatory serological screening tests for syphilis in all pregnant women.

Keywords: syphilis, pregnancy, screening test

Introduction

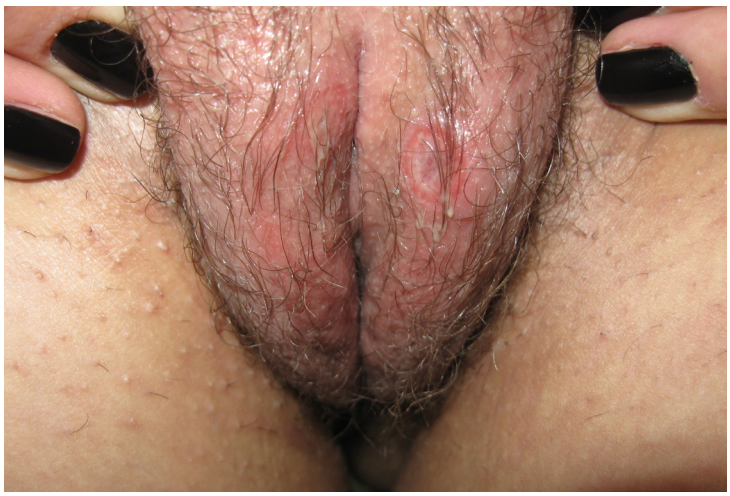
Early syphilis presents a contagious form of this disease and according to the natural course of the disease, it includes the primary, secondary and early latent stadium which lasts for one year from the moment of infection. A person with early syphilis is infectious for sexual partners one year from the moment of infection, while the untreated pregnant woman with early syphilis can transmit the infection to the fetus within four years from the moment of infection (1). Syphilis during pregnancy can cause serious complications and it can lead to miscarriage, stillbirth or childbirth with the signs of congenital syphilis. If the infection in a pregnant woman is discovered and treated timely, the above mentioned complications can be prevented, whereas the undiscovered infections lead to serious sequelae.

The epidemiological situation at the beginning of the new millennium has pointed to the significant increase of syphilis in the Republic of Serbia (2). Although the majority of people, who developed this disease, were men who had sex with men (2,3), the infection was recorded in women, as well (4), and all the infected pregnant women were Roma women, who were affected by syphilis more frequently in comparison to women who did not belong to the Roma population (5). In our country, one case of congenital syphilis has been registered during the last five years (6). Data from Europe point to the fact that the highest rates of syphilis in women have been reported in Bulgaria, Lithuania, Latvia and Iceland, while of congenital syphilis in Bulgaria, then Portugal, Romania and Poland (7). The largest number of newborns with syphilis for the last two decades was reported in The United States of America in 2017 (8). Studies from some European countries showed that more than 20% of newly infected women with syphilis were among pregnant women (9,10), while in Spain (11), the positive test in pregnant women was two times more frequent and in Ireland (12), six times more frequent in comparison to the general population, which could be explained by the increased application of ante-natal screening for syphilis.

The aim of this work is to present the clinical manifestations, laboratory diagnostics and therapy of syphilis in pregnancy, as well as to sensitize medical workers to this disease and the introduction of mandatory serological screening tests for syphilis in all pregnant women.

Methods

In this review article, we have presented clinical, laboratory, diagnostic and therapeutic specificities of syphilis in pregnant women, based on the literature that was published in the English

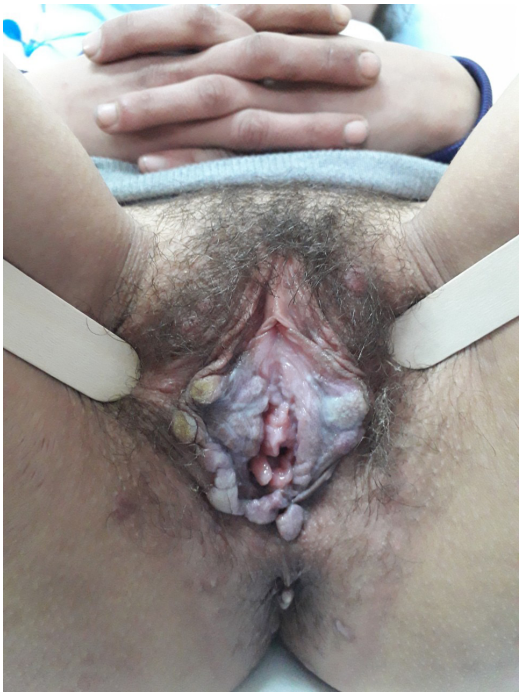


Slika 1. *Ulcus durum* vulve

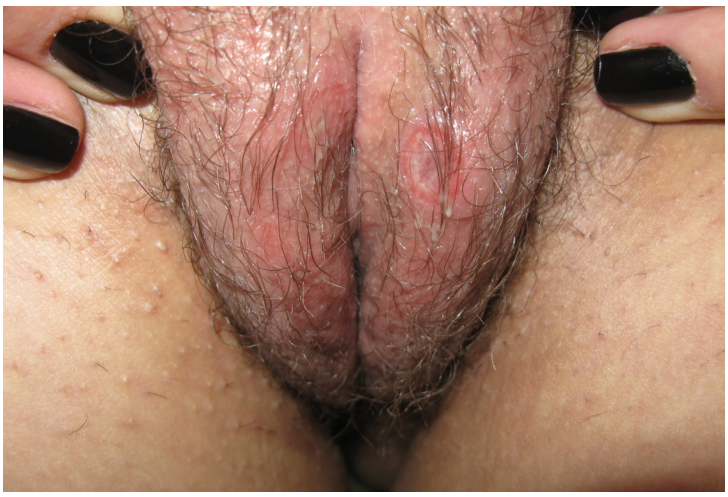
ograničene bezbolne uceracije tvrdih indurovanih ivica praćena bezbolnom regionalnom limfadenopatijom. *Ulcus durum* se može javiti na različitim mestima, kod vaginalnog seksa unutar vagine ili u predelu vulve (Slika 1), kod analnog seksa u analnom kanalu, završnom delu rektuma ili perianalno, a kod oralnog seksa na usnama ili u usnoj duplji (13). S obzirom na to da je šankr bezbolan i kod žena retko vidljiv, primarni stadijum infekcije se obično previdi, a bakterija se hematogenim putem širi po čitavom organizmu te nakon 2 do 10 nedelja nastaje sekundarni stadijum bolesti. On može biti praćen opštim simptomima, povišenom temperaturom, generalizovanom limfadenopatijom, kao i promenama po koži i vidljivim sluznicama (14).

Promene na koži su obično u vidu generalizovane makulozne ili papulozne ospe koja se često javlja i na dlanovima i tabanima. Ponekad nastaje alopecija u kapilicijumu koja može biti difuznog tipa ili u vidu sitnih alopecičnih polja, dok se u intertriginoznim regijama mogu javiti veoma infektivne papule – lat. *condylomata lata* (Slika 2). Promene u usnoj duplji su u vidu asimptomatskih mukoznih plakova prekrivenih beličastosivom hiperkeratotičnom membranom.

Pacijent je najinfektivniji u sekundarnom stadijumu bolesti. Ukoliko se obolela osoba ne leči oboljenje prelazi u ranu latentnu fazu koja je asimptomatska i traje do godinu dana od momenta infekcije. U ovoj fazi pacijent je i dalje in-



Slika 1. *Condylomata lata* vulve



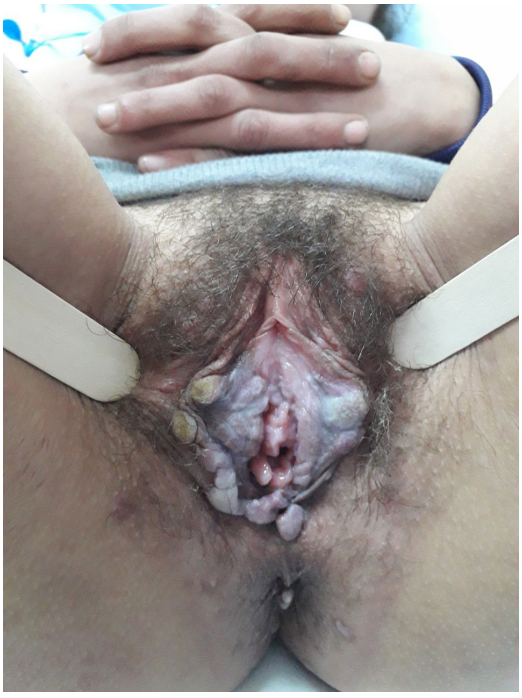
Picture1. *Ulcus durum* on the vulva

language and searched through PUBMED, using the following key words: syphilis, pregnancy, screening test.

Clinical manifestations of syphilis

After the average incubation period of three weeks, a firm chancre (lat. *ulcus durum*) occurs at the point of entry of *Treponema pallidum*, that is, a primary lesion in the form of clearly-defined painless ulceration with the hard indurated margins, followed by the painless regional lymphadenopathy. *Ulcus durum* can occur in different places, in vaginal sex inside the vagina or in the region of vulva (Picture 1), in anal sex in the anal canal, the last part of the rectum or in the perianal area, and in oral sex on lips or inside the mouth (13). Considering the fact that the chancre is painless and in women rarely visible, the primary stadium of infection is usually overlooked, and the bacteria spread to other parts of the body hematogenously, so the secondary stadium of disease occurs after 2 to 10 weeks. It can be followed by general symptoms, high temperature, generalized lymphadenopathy, as well as changes on the skin and visible mucosa (14).

Skin changes are usually in the form of macular and papular rash, which often appears on palms and soles. Alopecia sometimes appears in capillitium, and it can be diffuse or in the form of tiny alopecic patches, while in the intertriginous



Picture 2. *Condylomata lata* on the vulva

fektivan za svoje seksualne partnere. S obzirom na to da je sifilis „veliki imitator“, oboljenje često ostaje neprepoznato ili pogrešno lečeno. Iako se bolest seksualnim putem prenosi samo u prvoj godini od infekcije, nelečene žene su infektivne za plod naredne četiri godine. Infekcija se prenosi transplacentalno ili tokom porođaja usled kontakta ploda sa genitalnim lezijama majke. *Treponema pallidum* se može preneti putem placente već od 14. nedelje trudnoće, a rizik prenošenja se povećava sa napredovanjem trudnoće (15). Placentarna infekcija i smanjen dotok krvi u plod su najčešći razlozi fetalne smrti. Kod trećine inficiranih trudnica fetus se rađa sa kongenitalnim sifilisom. Kod skoro dve trećine novorođenčadi infekcija je asimptomatska, a mala fetalna težina može biti jedina manifestacija infekcije (16,17).

Kongenitalni sifilis se deli na rani u kome se znaci infekcije javljaju u prve dve godine života i na kasni kongenitalni sifilis u kome se promene javljaju posle druge godine. Spektar kliničkih manifestacija kongenitalnog sifilisa je širok (18) i nije predmet ovog rada.

Dijagnostika sifilisa

Direktna detekcija bakterije iz primarnog šankra ili sa vlažnih lezija sekundarnog stadijuma obavlja se na mikroskopu u tamnom polju, ali se zbog tehničkih nemogućnosti ova metoda godinama ne sprovodi u našoj sredini. Za potvrdu dijagnoze sifilisa u trudnoći najčešće se koriste serološki testovi: nespecifični VDRL (engl. *Venereal Disease Research Laboratory*) test, koji otkriva antitela na kardiolipin i specifični TPHA (engl. *Treponema Pallidum Hemagglutination Assay*) test (19). TPHA test postaje pozitivan 4 nedelje nakon infekcije, a VDRL test nešto kasnije u periodu od 4 do 6 nedelja. Dok specifični TPHA test ostaje pozitivan do kraja života, nespecifični VDRL test se nakon terapije vremenom negativizuje i koristi se za praćenje aktivnosti bolesti nakon lečenja.

Prema preporukama Centara za kontrolu i prevenciju bolesti u Atalanti (engl. *Centers for Disease Control and Prevention - CDC*) rutinski serološki skrining test na sifilis (nespecifični i specifični) kod trudnica trebalo bi da se obavi prilikom prve prenatalne posete, a za pacijentkinje u riziku i u populacijama gde su visoke stope kongenitalnog sifilisa i oko 28 nedelje gestacije i u momentu porođaja (20). Kod žena koje su rodile mrtav plod nakon 20. nedelje gestacije takođe se savetuje testiranje na sifilis (21). Seropozitivne trudnice bi trebalo smatrati infektivnim ako ne postoji medicinska dokumentacija o ranijem lečenju ili su pak lečene ali nije došlo do četvorostrukog smanjenja titra VDRL testa za šest meseci od terapije.

Terapija sifilisa u trudnoći

Parenteralna primena penicilina je lek izbora u lečenju svih stadijuma sifilisa. Primena penicilina je efikasna kako u prevenciji transmisije sifilisa sa majke na plod tako i u tretmanu fetalne infekcije (22). Terapija trudnica se sprovodi prema protokolu lečenja u zavisnosti od stadijuma infekcije. U ranom sifilisu ordinira se intarmuskularno 2,4 miliona IJ benzatin penicilina G, mada postoje preporuke da bi trudnice trebalo da prime još jednu dozu istog leka za 7 dana (20). Aleksander i saradnici (22) su opisali da je kod 98% trudnica sa ranim sifilisom terapija benzatin penicilinom G sprečila prenošenje infekcije na fetus. Ako se dijagnoza sifilisa postavi u toku druge polovine trudnoće savetuje se ultrazvučni pregled fetusa radi procene znakova eventualnog kongenitalnog sifilisa (hepatomegalija, ascites, hidrops ili zadebljanje placente) koji povećava rizik za neuspešan tretman fetusa (23).

Terapija u drugoj polovini trudnoće povećava rizik prevremenog porođaja ili fetalnog distresa usled nastanka *Jarisch-Herxheimerove* reakcije pa se primena leka preporučuje u hospitalnim uslovima uz prisustvo akušera (24). Ova reakcija nastaje zbog oslobađanja endotoksina iz velikog broja raspadnutih treponema, a manifestuje se febrilnošću, glavoboljom i bolovima u mišićima u prva 24 sata od primene penicilina. Kod trudnica alergičnih na penicilin savetuje se desenzibilizacija, s obzirom na to da ne postoji alternativa ovom leku u trudnoći. Prvo serološko praćenje efikasnosti tretmana trebalo bi da se sprovode posle mesec dana, a uspeh terapije potvrđuje se četvorostrukim padom titra nespecifičnih seroloških testova 3 do 6 meseci nakon terapije ili osmostrukim padom nakon 12 meseci (20). Savetuje se testiranje svih trudnica sa sifilisom i na HIV infekciju.

Zaključak

Porast incidencije sifilisa u našoj zemlji, sekvele, koje neprepoznata infekcija ostavlja na plod, i vulnerabilnost mladih Romkinja na ovu infekciju ukazu-

regions very infectious papules can appear – lat. *condylomata lata* (Picture 2). Changes in the oral cavity appear in the form of asymptomatic mucous plaque covered with white-grey hyperkeratotic membrane.

A patient is the most infectious in the secondary stadium of disease. If the person affected by the disease is not treated, this disease develops to the early latent stage, which is asymptomatic and lasts for a year from the moment of infection. In this stage, the patient is still infectious for his sexual partners. Considering the fact that syphilis is the "great imitator", the disease often remains unrecognized or wrongly treated. Although this disease is sexually transmitted only during the first year from the moment of infection, untreated women are contagious for the fetus during the next four years. The infection is transmitted transplacentally or during birth when a baby has contact with mother's genital lesions. T*reponema pallidum* can be transmitted via placenta from about 14 weeks' gestation and the risk of transmission increases with gestational age (15). The placental infection and the reduction in blood flow to the fetus are the most common causes of fetal death. In one third of infected pregnant women, fetuses are born with congenital syphilis. In almost two thirds of newborns, the infection is asymptomatic, while low birth weight can be the only manifestation of infection (16,17).

Congenital syphilis is classified into early syphilis, in which signs of infection appear in the first two years of life, and late congenital syphilis, in which changes appear after the second year of life. The spectrum of clinical manifestations of congenital syphilis is wide (18) and it is not the subject of this article.

Diagnostics of syphilis

Direct detection of bacteria from the primary chancre or from moisture lesions in the secondary stadium is performed with the help of dark field microscopy, but this method has not been conducted in our country for years due to technical incapacity. Serological tests are most commonly used to confirm the diagnosis of syphilis in pregnancy: the non-treponemal Venereal Disease Research Laboratory test (VDRL), which detects antibodies to cardiolipin, and the treponemal-specific Treponema Pallidum Hemagglutination Assay test (TPHA) (19). The TPHA test becomes positive 4 weeks after infection, while the VDRL test becomes positive a little bit later, 4 to 6 weeks after infection. The specific TPHA test remains positive for life, while after therapy the non-specific VDRL test becomes negative with time and it is used to follow disease activities after treatment.

According to the recommendations of the Centers for Disease Control and Prevention (CDC) in Atlanta, routine serological screening tests for syphilis (specific and non-specific) should be conducted in pregnant women during the first prenatal visit, while in patients who are at risk or in populations, where rates of congenital syphilis are high, at 28 weeks' gestation and at birth (20). In women, who gave birth to a stillborn child after 20 weeks' gestation, tests for syphilis are also recommended (21). Seropositive pregnant women should be considered infectious if there are no medical records about the previous treatment or if they were treated, but it did not come to a fourfold decrease in VDRL titers six months after therapy.

Therapy of syphilis in pregnancy

Penicillin, administered parenterally, is the treatment of choice in all stages of syphilis. The administration of penicillin is efficient in the prevention of syphilis transmission from mother to child, as well as in the treatment of fetal infection (22). The therapy in pregnant women is applied according to the protocol of treatment depending on the stadium of infection. In the early stage of syphilis, 2.4 million units of benzathine penicillin G are administered intramuscularly as a single dose, although there are recommendations that pregnant women should receive one more dose of the same drug 7 days after the initial dose (20). Alexander and associates (22) described that in 98% of pregnant women with early syphilis, the therapy of benzathine penicillin G prevented the transmission of infection to the fetus. If syphilis is diagnosed during the second half of pregnancy, the ultrasonographic fetal examination is recommended for possible signs of congenital syphilis (hepatomegaly, ascites, hydrops, placental thickness), which increases the risk of unsuccessful fetal treatment (23).

The therapy in the second half of pregnancy increases the risk of premature birth or fetal distress due to Jarisch-Herxheimer reaction, and there-

ju na potrebu skrininga na sifilis u trudnoći, naročito kod osoba pod povećanim epidemiološkim rizicima.

Literatura

1. Garnett GP, Aral SO, Hoyle DV, Cates W, Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis 1997; 24(4):185-200.
2. Bjekić M, Šipetić-Grujičić S, Begović-Vuksanović B, Rafailović N, Vlajinac H. Syphilis resurgence in Belgrade, Serbia in the new millennium: an outbreak in 2014. Centr Eur J Public Health 2017: 25(4):277-281.
3. Bjekić M, Šipetić S. Epidemiološke i kliničke karakteristike obolelih od sifilisa. Zdravstvena zaštita 2014; 43(1):1-5.
4. Bjekić M, Vlajinac H, Begović-Vuksanović B. Karakteristike sifilisa u populaciji Beograda u periodu od 2009. do 2018. godine. Zdravstvena zaštita 2020; 49(1):9-14.
5. Bjekić M, Vlajinac H, Šipetić-Grujičić S. Characteristics of gonorrhea and syphilis cases among Roma ethnic group in Belgrade, Serbia. Braz J Infect Dis 2016; 20(4):349-353.
6. Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“. Izveštaj o zaraznim bolestima u Republici Srbiji za 2017. godinu. Beograd: Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“, 2018.
7. European Centre for Disease Prevention and Control. Syphilis and congenital syphilis in Europe –A review of epidemiological trends (2007–2018) and options for response. Stockholm: ECDC, 2019.
8. The Lancet. Congenital syphilis in the USA. The Lancet. 2018; 392(10154):1168.
9. Serwin AB, Unemo M. Syphilis in females in Bialystok, Poland, 2000-2015. Przegl Epidemiol 2016; 70(2):273-80.
10. Pala S, Conti C, Goldoni P, Silvaggio D, Nicolai M, Schiariti E, et al. A five year retrospective study on Syphilis in the Sexual Transmitted Disease Centre (STDC) of the teaching Hospital Umberto I in Rome. Ann Ig 2018; 20(1):66-70.
11. Burgos A, Romero DP, Gálvez R, Ramos R, García SS, Martínez AL, et al. Analysis of serological tests in almeriense pregnant women in the last year. J Perinat Med 2015; 43(S1):P-0363.
12. Lutomski JE, Shiely F, Molloy EJ. The prevalence of syphilis at childbirth in Ireland: a six-year review. J Matern Fetal Neonatal Med 2014; 27(17):1823-5.
13. Lautenschlager S. Cutaneous manifestations of syphilis: recognition and management. Am J Clin Dermatol 2006; 7(5):291-304.
14. Bjekić M. Secondary syphilis in patients treated at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2014. Serb J Dermatol Venereol 2015; 7(2):53-60.
15. Hawkes S, Matin N, Broutet N, Low N. Effectiveness ofinterventions to improve screening for syphilis in pregnancy:a systematic review and meta-analysis. Lancet Infect Dis 2011; 11(9):684-691.
16. Sheffield JS, Sánchez PJ, Morris G, Maberry M, Zeray F, McIntire DD et al. Congenitalsyphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol 2002; 186(3):569-573.
17. Watson-Jones D, Changalucha J, Gumodoka B, Weiss H. Rusizoka M, Ndeki L, et al. Syphilisin pregnancy in Tanzania. I. Impact ofmaternal syphilis onoutcome of pregnancy. J Infect Dis 2002; 186(7):940-947.
18. Cooper JM, Sánchez PJ. Congenital syphilis. Semin Perinatol 2018; 42(3): 176-184.
19. Clyne B, Jerrard DA. Syphilis testing. J Emerg Med 2000; 18(3):361-367.
20. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines. 2015. MMWR Recomm Rep 2015; 64 (no. RR-3):34-51.
21. Wendel GD Jr, Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sánchez PJ. Treatment of syphilis in pregnancyand prevention of congenital syphilis. Clin Infect Dis 2002; 35(2):S200-209.
22. Alexander JM, Sheffield JS, SánchezPJ, Mayfield J, Wendel GD Jr. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999; 93(1):5-8.
23. Hollier LM, Harstad TW, Sánchez PJ, Twickler DM, Wendel GD Jr. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol 2001; 97(6):947-953.
24. Klein VR, Cox SM, Mitchell MD, Wendel GD Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet Gynecol 1990; 75(3 Pt 1):375-380.

fore, the therapy should be administered in hospital conditions in the presence of obstetrician (24). This reaction is caused by the release of treponemal endotoxin-like compounds, and it is manifested in the form of fever, headache, myalgia during the first 24 hours after receiving penicillin. Pregnant women, who are allergic to penicillin, should be desensitized because a suitable alternative in pregnancy does not exist. The first serological testing of the treatment efficiency should be conducted after one month, while the success of therapy is confirmed by the fourfold decline in non-treponemal antibody titers 3 to 6 months after therapy, or by the eightfold decline after 12 months (20). All pregnant women with syphilis should be tested for HIV infection, as well.

Conclusion

The increase in the incidence of syphilis in our country, the unrecognized infection leading to fetal sequelae, as well as the vulnerability of young Roma women to this infection point to the need for screening for syphilis in pregnancy, especially in persons who are at increased epidemiological risks.

Literature

1. Garnett GP, Aral SO, Hoyle DV, Cates W, Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis 1997; 24(4): 185-200.
2. Bjekic M, Sipetic-Grujicic S, Begovic-Vuksanovic B, Rafailovic N, Vlajinac H. Syphilis resurgence in Belgrade, Serbia in the new millennium: an outbreak in 2014. Centr Eur J Public Health 2017: 25(4):277-281.
3. Bjekic M, Sipetić S. Epidemiological and clinical characteristics of syphilis cases. Health Care 2014; 43(1):1-5.
4. Bjekic M, Vlajinac H, Begovic-Vuksanovic B. Syphilis characteristics in Belgrade population in period from 2009 to 2018. Health Care 2020; 49(1):9-14.
5. Bjekic M, Vlajinac H, Sipetic-Grujicic S. Characteristics of gonorrhea and syphilis cases among Roma ethnic group in Belgrade, Serbia. Braz J Infect Dis 2016; 20(4):349-353.
6. Institute of Public Health of Serbia „Dr Milan Jovanović Batut". Report on communicable diseases in the Republic of Serbia for 2017. Belgrade: Institute of Public Health of Serbia „Dr Milan Jovanović Batut", 2018.
7. European Centre for Disease Prevention and Control. Syphilis and congenital syphilis in Europe –A review of epidemiological trends (2007–2018) and options for response. Stockholm: ECDC, 2019.
8. The Lancet. Congenital syphilis in the USA. The Lancet. 2018; 392(10154):1168.
9. Serwin AB, Unemo M. Syphilis in females in Bialystok, Poland, 2000-2015. Przegl Epidemiol 2016; 70(2):273-80.
10. Pala S, Conti C, Goldoni P, Silvaggio D, Nicolai M, Schiariti E, et al. A five year retrospective study on Syphilis in the Sexual Transmitted Disease Centre (STDC) of the teaching Hospital Umberto I in Rome. Ann Ig 2018; 20(1):66-70.
11. Burgos A, Romero DP, Gálvez R, Ramos R, García SS, Martínez AL, et al. Analysis of serological tests in almeriense pregnant women in the last year. J Perinat Med 2015; 43 (S1): P-0363.
12. Lutomski JE, Shiely F, Molloy EJ. The prevalence of syphilis at childbirth in Ireland: a six-year review. J Matern Fetal Neonatal Med 2014; 27(17):1823-5.
13. Lautenschlager S. Cutaneous manifestations of syphilis: recognition and management. Am J Clin Dermatol 2006; 7(5):291-304.
14. Bjekic M. Secondary syphilis in patients treated at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2014. Serb J Dermatol Venereol 2015; 7(2):53-60.
15. Hawkes S, Matin N, Broutet N, Low N. Effectiveness ofinterventions to improve screening for syphilis in pregnancy:a systematic review and meta-analysis. Lancet Infect Dis 2011; 11(9): 684-691.
16. Sheffield JS, Sánchez PJ, Morris G, Maberry M, Zeray F, McIntire DD et al. Congenitalsyphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol 2002; 186(3):569-573.
17. Watson-Jones D, Changalucha J, Gumodoka B, Weiss H. Rusizoka M, Ndeki L, et al. Syphilisin pregnancy in Tanzania. I. Impact ofmaternal syphilis onoutcome of pregnancy. J Infect Dis 2002; 186(7):940-947.
18. Cooper JM, Sánchez PJ. Congenital syphilis. Semin Perinatol 2018; 42(3): 176-184.
19. Clyne B, Jerrard DA. Syphilis testing. J Emerg Med 2000; 18(3):361-367.
20. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines. 2015. MMWR Recomm Rep 2015; 64 (no. RR-3):34-51.
21. Wendel GD Jr, Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sánchez PJ. Treatment of syphilis in pregnancyand prevention of congenital syphilis. Clin Infect Dis 2002; 35 (2):S200-209.
22. Alexander JM, Sheffield JS, SánchezPJ, Mayfield J, Wendel GD Jr. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999; 93(1): 5-8.
23. Hollier LM, Harstad TW, Sánchez PJ, Twickler DM, Wendel GD Jr. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol 2001; 97(6):947-953.
24. Klein VR, Cox SM, Mitchell MD, Wendel GD Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet Gynecol 1990; 75(3 Pt 1): 375-380.

Sukob interesa: Nije prijavljen.
Primljen: 31.01.2021.
Revizija: 11.02.2021.
Prihvaćen: 17.02.2021.

Autor za korespondenciju: prim. dr sc. med. Milan Bjekić, Gradski zavod za kožne i venerične bolesti, Džordža Vašingtona 17, 11 000 Beograd, Srbija; e-mail: milinkovski@gmail.com

Conflict of interest: None declared.
Received: 01/31/2021
Revised: 02/11/2021
Accepted: 02/17/2021

Corresponding author: Chief Physician Milan Bjekic, MD, PhD, City Institute for Skin and Venereal Diseases, Dzordža Vasingtona 17, 11 000 Beograd, Srbija; e-mail: milinkovski@gmail.com