

Recovering Fetuses from Syphilis: Antenatal Care, Maternal, and Neonatal Outcomes

Fetüslerin Sifilizden Zarar Görmemesi: Antenatal Bakım, Maternal ve Neonatal Sonuçlar

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Abstract

Objective	Syphilis is a disease as old as human history. Untreated syphilis during pregnancy can cause serious prenatal adverse outcomes, including stillbirth, and congenital syphilis. World Health Organization, obstetrics and gynecology societies recommends screening syphilis at the first antenatal care visit. In this present study, it was aimed to discuss antenatal follow-up, maternal and neonatal outcomes of patients having syphilis infection during pregnancy.
Materials and Methods	Patients diagnosed with syphilis during pregnancy were included in the study. Patients were screened by a Non-Treponemal test and positive results were confirmed by the Treponemal test. Patients data including antenatal examinations, maternal and neonatal results, syphilis treatment, newborn examination findings, syphilis treatment follow-up were obtained and evaluated retrospectively through the hospital registry system and telephone interviews.
Results	The total number of patients who were screened with RPR in the first antenatal visit of the pregnancy over two and a half years period was 24427. Ten patients were diagnosed with syphilis by Treponemal test (TP-PA) confirmation. All patients were treated by three doses of Penicillin Benzathine G 2.4 million units via intramuscular route each at a one-week interval. All women gave birth at term without complication. Forty percent of patients diagnosed gestational diabetes mellitus. No congenital syphilis occurred. None of the patients had concomitant HIV and HCV infection.
Conclusion	Eradication is possible for syphilis. Early detection at the first antenatal visit and adequate treatment with penicillin would prevent maternal and congenital syphilis, and recover babies from adverse outcomes of syphilis.
Keywords	Syphilis; syphilis in pregnancy; Non-treponemal test; Treponemal test; Penicillin benzathine G

Öz

Amaç	Sifiliz insanlık tarihi kadar eski bir hastalıktır. Gebelikte tedavi edilmeyen sifiliz, ölü doğum da dahil ciddi prenatal sonuçlara ve konjenital sifilize neden olabilir. Dünya Sağlık Örgütü, obstetrik ve jinekoloji dernekleri ilk antenatal muayenede sifilizin taranmasını önermektedir. Bu çalışmada, gebeliğinde sifiliz enfeksiyonu saptanan hastaların, antenatal takipleri, maternal ve neonatal sonuçlarının tartışılması amaçlanmıştır.
Gereç ve Yöntemler	Gebelik sırasında sifiliz tanısı alan hastalar çalışmaya dahil edildi. Hastalar Non-Treponemal test (RPR) ile tarandı ve pozitif sonuçlar Treponemal test (TP-HA) ile doğrulandı. Antenatal bakılar, maternal ve neonatal sonuçlar, sifiliz tedavisi, yenidoğanın muayene bulguları, sifiliz tedavisi içeren hasta verileri retrospektif olarak hastane kayıt sistemi ve hasta telefon görüşmeleri ile elde edilerek değerlendirildi.
Bulgular	Yaklaşık 2.5 yıllık süreçte 24427 hasta gebeliğinin ilk antenatal muayenesinde sifiliz için RPR testi ile taranmıştır. On hastaya Treponemal test (TP-PA) ile doğrulanarak sifiliz tanısı konulmuştur. Tüm hastalara, 1 hafta aralıklarla 3 doz Penisilin Benzatin G 2.4 milyon ünite intramuskuler yolla tedavi uygulandı. Tüm kadınlar miadında, komplikasyonsuz olarak doğum yaptı. Hastaların yüzde 40'ü gestasyonel diyabetes mellitus tanısı aldı. Konjenital sifiliz bulgusu saptanmadı. Hiçbir hastada eşlik eden HIV ve HCV enfeksiyonu saptanmadı.
Sonuç	Sifiliz için eradikasyon mümkündür. İlk antenatal kontrolde erken tarama ve penisilin ile yeterli tedavi, maternal ve konjenital sifilizi ortaya çıkmasını engelleyecek ve bebeklerin sifilizin etkilerinden kurtarılmasını sağlayacaktır.
Anahtar Kelimeler	Sifiliz; gebelikte sifiliz; Non-treponemal test; Treponemal test; Penisilin benzatin G

INTRODUCTION

A spirochete *Treponema pallidum* is a blameworthy factor causing syphilis that transmits via sexual intercourse. It is a public health problem from ancient times until today. Vertical transmission may manifest as perinatal adverse outcomes including preterm birth, intrauterine growth restriction, multiple anomalies, missed abortus, stillbirth or early perinatal death.¹ Easy separation and a high number of infected patients which 72% increased, from 5.5 cases to 9.5 cases per 100.000 population from 2013 to 2017 in the USA.² Pregnancy has no effect on the progression of syphilis however it can cause serious adverse outcomes of the pregnancy course. World Health Organization has reported that annually over 2 million pregnant women were infected with syphilis. About 65% of these patients would experience adverse pregnancy outcomes, that's why syphilis is the most common reason for congenital diseases.³ Syphilis has shown the progression of stages. The primary stage of syphilis exposes as a single painless chancre located where the *treponema pallidum* initially entered the body, especially located around the genitals, anus, or mouth. This lesion could disappear without treatment. After 6-8 weeks, the disease progresses to the secondary phase which occurs clinically as maculopapular lesions especially on palms and soles or as condyloma lata. These lesions could also disappear as painless chancre. Without having any of these lesions, some patients can progress the latent stage, which has no clinical findings, yet can be detected by serologic tests. If the duration of the disease is less than 1 year or more than 1 year, is called early latent stage and late latent stage respectively. The next stages are tertiary syphilis(cardiovascular or skeleton involvement) and Neurosyphilis. The frequency of vertical transmission is dependent on the amount of spirochetes in maternal blood circulation and stage of the disease; however, could be possible in every stage of the disease. Once the diagnosis has achieved, treatment is easy and feasible in every stage of the pregnancy. For that reason, screening tests were recommended by WHO and almost all societies at the first antenatal care of the pregnancy.^{4,5} Non-Treponemal

Tests(NTT) were used qualitatively for screening and quantitatively in the follow-up of treatment. Rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests detect the immune reaction against the lipoidal materials released from spirochete induced cell damage and cardiolipins released from spirochetes.⁶ On the other hand, treponemal tests, which are *Treponema pallidum* particle agglutination assay (TP-HA) and the fluorescent treponemal antibody absorption assay (FTA-ABS), are syphilis specific because, in these tests, *Treponema pallidum* (Nichols strain) is detected as an antigen.⁶ Non-Treponemal tests could be false-positive in hepatitis, infectious mononucleosis, viral pneumonia and other viral infections, malaria, and pregnancy. Thus, positive non-treponemal tests must be confirmed by Treponemal tests, before treatment. Benzathine penicillin G is utilized as a first-line treatment with high eradication rates in pregnant or non-pregnant patients.⁷

The purpose of this present study is the evaluation of pregnant patients with positive RPR test and determination of the antenatal care and obstetric outcomes of patients with syphilis.

MATERIAL and METHODS

A descriptive cross-sectional study was achieved reviewing patients admitted to polyclinics of obstetrics and gynecology in Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences between January 2017 and May 2019 after approval of the local ethic committee (Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences Date: 04.03.2020 Decision Number: 2011-KAEK-25 2020/03-14). Non-Treponemal Test-RPR- (Syphilis Ab Rapid Test Cassette- Zhejiang Orient Gene Biotech Co.; Ltd- Huzhou.Zhejiang, China) was performed qualitatively to all patients at the first antenatal visit of the pregnancy. Positive results of NTT were consulted to Infectious Diseases and Clinical Microbiology Clinic and re-evaluated by a Treponemal test (TP-HA: *Treponema Pallidum* Hemagglutination Assay; Omega

Diagnostics, UK). The stage of syphilis and treatment modalities were reviewed. Patients' antenatal care visits, second-trimester ultrasound reports, glucose tolerance test results, concomitant diseases, mode of delivery, neonatal APGAR scores, admission to NICU were recorded. All patients' data were obtained through the hospital registry system. All patients were telephoned and informed about the present study. Patients who were willing to answer the questions and accepted being participants, included in the study. During the telephone interview, questions were asked about the health condition of the baby, any adverse effect during treatment, the latest visit with infectious diseases specialist, the query of primary or secondary lesions of syphilis.

RESULTS

The total number of patients who were screened with RPR was 24427. Among these patients, the number of patients whose results were positive was 36. These patients were examined by Treponemal test (TP-HA). Ten patients were reported as positive over 2.5 years. Distributions of the cases by years were 3, 2 and 5 respectively in the years 2017, 2018 and 2019.

None of the patients had any characteristic dermatological features on the date of the syphilis diagnosis which could be referred to as the primary or secondary phase of the disease. All pregnant women were postulated as the latent stage of infection. The telephone interview has exposed that all patients had single painless chancre which healed without treatment. Two of them experienced palmar local mucocutaneous lesions. Patients can not state the proper time of these lesions, thus early or late phase separation could not be distinguished adequately. All of the patients were utilized 3 doses of Benzathine penicillin G 2.4 million units via intramuscular route 3 times each at 1-week interval. All patients were treated adequately.

Nine patients were diagnosed in first trimester, and 1 in the 20th week of gestation. None of the characteristic ul-

trasonographic views of congenital syphilis had detected in the second trimester ultrasound examination. Four of these patients were diagnosed with gestational diabetes mellitus. All gave birth at term without complication. Only 1 newborn was admitted to NICU due to transient tachypnea of the newborn. None of the babies had any sign of congenital syphilis. The characteristics and properties of all the patients were determined in table 1.

Table 1: Evaluation of the characteristic properties, antenatal care, neonatal outcomes, and approach to the syphilis

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.
Age	39	37	21	27	24	26	25	20	21	22
Gestational week at diagnosis	20	8	8	8	8	6	6	6	5	5
Fetal Anomaly	No	No	No	No	No	No	No	No	No	No
Concomitant disease	No	GDM	No	GDM	No	No	No	GDM	No	GDM
Type of birth	VB	CS	VB	VB	CS	VB	VB	CS	VB	VB
Complication	No	No	No	No	No	No	No	No	No	No
Delivery week	37	37	38	39	39	40	37	38	41	38
Birth weight (gram)	2750	4050	3000	3780	3150	3950	2900	2930	3745	2850
HIV or HCV	No	No	No	No	No	No	No	No	No	No
APGAR 1 st min.	8	9	9	8	8	8	9	9	9	8
APGAR 5 th min.	10	10	10	8	9	9	10	10	9	8
NICU Admission	None	Yes	None	None	None	None	None	None	None	None
Primary lesion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Secondary lesion	No	No	Yes	No	No	No	No	Yes	No	No
Disease Stage	Latent	Latent	Latent	Latent	Latent	Latent	Latent	Latent	Latent	Latent
Dose of Penicillin	3	3	3	3	3	3	3	3	3	3
Affected Baby	No	No	No	No	No	No	No	No	No	No
Treatment failure or adverse effect	No	No	No	No	No	No	No	No	No	No

GDM: Gestational Diabetes Mellitus, NICU: The Neonatal Intensive Care Unit, HIV: Human immunodeficiency virus, HCV: Hepatitis C Virus
 VB: Vaginal Birth CS: Cesarean Section, min: Minute

DISCUSSION

Syphilis as a sexually transmitted disease has characterized with the finest detail because of accompanying humanity until ancient times. Just like a curse spreading through the populations making the diagnosis compelling due to imitating several diseases, caused to name as “The Great Pretender”. Penicillin, which is assumed as the invention of the 20th century, has made syphilis a treatable and preventable disease approximately 70 years ago. However, syphilis continues to threaten public health, spreading all over the world in the 21st century. Number of patients has increased in Turkey from 281 in 2012 to 2430 in 2018 which meant 3.12 cases per 100.000 in 2018.⁸ These results could seem favorable; however, in a study in 2010 had depicted that about only 25% of the syphilis cases were notified to the government statistical data.⁹ The present study is the first unique study exhibiting the data of the preg-

nant patients with syphilis in Turkey. Over 24000 results of the RPR test were reviewed and 10 pregnant patients have diagnosed syphilis with TP-HA. All patients were treated without complications and no congenital syphilis case has occurred in our cases. That’s why we use recovering of the fetuses from syphilis at our title of the study.

The coexistence of sexually transmitted diseases is a well-known reality. Syphilis facilitates not only transmission but also the acquisition of HIV. Patients diagnosed with syphilis should also be examined for HIV, and vice versa. None of the patients in our study had HIV or HCV concomitantly.

The most important feature of syphilis which distinguishes it from many other prenatal diseases is that the mother and the fetus can be treated properly with one medication.

The most crucial part is to perform diagnostic tools for patients. Some studies investigated the cost-effectivities of prenatal syphilis screening to all patients.^{10,11}; however one should aware of the disastrous consequences to the fetus and syphilis as being a public health problem, none of these calculations on that subject ought to be performed. In Turkey; the price of the rapid NTT costs about 55 cents and the TP-HA test costs about 140 cents which were covered by social insurance of the state. As aforementioned, major deficiency in preventing syphilis is to diagnose, thus asymptomatic patients especially pregnant women should be examined with a rapid NTT screening test. Ten of 10 patients had stated that they had a primary lesion healed without treatment. Thus; all patients should be questioned whether they had a history of any lesions related to syphilis during all admittance to any physician and performed rapid test if necessary to prevent this disease. If the incidence keeps raising, screening the whole population could be considered. To date, in Turkey all patients have been screening before marriage, during pregnancy and before making an application to driving license examination.

Approximately 52% of untreated pregnant women with syphilis would experience adverse outcomes such as miscarriage, preterm labor, hydrops fetalis, intrauterine growth restriction, stillbirth, neonatal death, and several deformities in neurologic development, musculoskeletal, gastrointestinal or urogenital system.^{1,12,13} Perinatal adverse outcomes are associated with stage of the disease, gestational week of the patient, utilization of treatment and interval between treatment and the birth. The total number of patients with syphilis was declared and the number of the patients with the primary and secondary stage of syphilis was also declared individually in the USA because the highest spirochete *Treponema pallidum* in maternal circulation exist in these stages.^{2,14} which causes the highest possibility of vertical transmission and fetal infection; however, every stage of the disease could induce fetal infection and congenital syphilis.¹⁵

Eponyms, which means giving the name of a specific property in an illness, were introduced frequently for syphilis. In a study, eighteen of them were described specifically.¹⁶ Kassowitzs law is one of them, describes the decreasing the severity of the adverse outcome and the possibility of vertical transmission, as through the greater duration between the infection and consecutive pregnancies. It has been postulated in a contemporary study, which was published in 1975 evaluated children with congenital syphilis, that transmission rates decrease from 70-100% to 10% during primary and late latent syphilis respectively.¹⁷ Syphilis could harm at any time of the pregnancy at any stage of the disease, nonetheless, ultrasonographic findings could not be detected before the 20th week of gestation due to the fetal immune system immaturity. All the patients were diagnosed before the 20th week of gestation in our study. That could be the reason that no ultrasonographic findings occurred. Hepatic and placental involvement would cause increasing the volume of these organs and disrupted erythrocyte production causes anemia findings like elevated peak systolic velocity of the middle cerebral artery, polyhydramnios, ascites, and hydrops fetalis.^{18,19} After the administration of maternal treatment, fetal healing could be monitored by ultrasound. It was depicted that anemia dissolves firstly, hepatomegaly and placentomegaly dissolves lastly.^{18,20} In our present study, none of the patients experienced adverse perinatal outcomes. The major reason for this glamorous success was the detection of the patients in an early gestational age, late latent stage of the disease and adequate utilization treatment.

Benzathine penicillin G is an effective and safe treatment option for syphilis. Doxycycline and tetracycline are contraindicated during pregnancy thus, even if the patient is allergenic to penicillin, desensitization is recommended before utilization under control of immunologist. One single dose of Benzathine penicillin G 2.4 million units via intramuscular route is suggested for the primary, secondary or early latent phase of syphilis. Three doses of Benzathine penicillin G 2.4 million units via intramuscular

route each with a one-week interval is suggested for late latent syphilis, unknown duration of infection, and tertiary syphilis.²¹⁻²³ In cases of shortage of penicillin in some countries like Brazil where the incidence is high in pregnant women, ceftriaxone 1gr via the endovenous route was utilized and resulted in good consequences.¹⁴ Penicillin treatment could cause pyrexia, myalgia, malaise, hypotension, headache, preterm labor, uterine contraction, fetal heart rate decelerations or even stillbirth, which is called Jarisch-Herxheimer Reaction(JHR) that occurs about 40% of patients.^{24,25} It is a therapeutic shock syndrome due to an inflammatory reaction to the lipoid materials that were released after the rapid kill of spirochetes. Treatment is supportive and if fetal heart rate decelerations or uterine contractions do not respond to medical treatment, delivery should be performed.^{24,25} Patients should be hospitalized and motorized at least 24 hours after penicillin administration. Each patient should be evaluated individually and routine obstetrics management should be followed up to decide delivery or medical treatment for JHR. To postpone treatment in the third trimester of the pregnancy to avoid Jarisch-Herxheimer reaction is not recommended. The most appropriate treatment outcomes can be achieved for congenital syphilis when the penicillin treatment is utilized at least 30 days before the delivery of the baby.^{5,12,21}

About 40% of the participants were diagnosed with Gestational diabetes mellitus. There have not existed recent studies investigating these phenomena. There are some studies depicted there is a relationship between diabetes mellitus and syphilis however they have been reported in 1944, 1892, and 1917.²⁶ A recent study has reported an association between neurosyphilis and diabetes mellitus.²⁶ Our findings should be kept in mind that pregnant women diagnosed with syphilis could have gestational diabetes mellitus more often. That was the only information about the possible relationship between syphilis in pregnancy and gestational diabetes mellitus in literature.

There is no vaccine and the treated people do not acquire a specific immunity for syphilis; re-infection is possible.²⁷

Treatment follow-up is crucial. Turkey Ministry of Health recommends reexamination of Non Treponemal Test quantitatively with 3-6 months interval until these test would be negative. The treatment of the partner is obligatory.²⁸

The limitation of the study is being a retrospective nature and having only 10 syphilis positive patients. Pre-treatment quantitative results of NTT and post-treatment results could not be obtained. Patients' statements in the telephone interview were taken into consideration about treatment follow up and neonatal examinations.

In conclusion

Syphilis is a treatable and preventable disease. Devastating consequences are inevitable unless it is treated during pregnancy. Screening all pregnant patients at the first antenatal care is crucial without considering cost-effectiveness. Penicillin is beneficial and highly efficient for maternal and congenital syphilis treatment. Continuity of antenatal care after treatment and detailed examination of the newborn is essential. It should be kept in mind that gestational mellitus could be more often in these patients.

The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences ethic committee in 04.03.2020 with a decision Number: 2011-KAEK-25 2020/03-14).

There are no conflicts of interest to declare.

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