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Case report of eight pregnant women with syphilis

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Authorship

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ABSTRACT

Congenital syphilis may lead to severe sequelae in affected infants. The prevalence of syphilis in women of childbearing age has increased worldwide. From 2015 to 2018, we encountered eight pregnant women with syphilis including six with late latent and two with early latent syphilis. Seven pregnant women with syphilis received antibiotic therapies of oral amoxicillin, intravenous penicillin G, or the both. The syphilotherapies in four cases were considered effective, because rapid plasma reagin titers decreased. None of the seven pregnant women who received syphilotherapies had congenital syphilis. The remaining one woman who did not undergo a maternity checkup or syphilotherapy delivered a stillbirth with congenital syphilis at 29 gestational weeks.

Keywords: amoxicillin, congenital syphilis, penicillin G, pregnancy, syphilis

Introduction

Syphilis in pregnancy may cause adverse pregnancy outcomes, including miscarriage, preterm delivery, stillbirth, neonatal death, and congenital syphilis. Congenital syphilis causes severe sequelae in infected infants, including cerebral palsy, hydrocephalus, sensorineural hearing loss, and musculoskeletal deformity. The prevalence of syphilis in women of childbearing age has increased worldwide. In the United States, the rate of women with primary and secondary syphilis increased by 22% from 2012 to 2014, and the rate of congenital syphilis also increased by 38% in the same period [1]. In Japan, increases in the rate of women with syphilis were also observed from 2010 to 2018 [2].

Here, we report eight pregnant women with syphilis. One pregnancy ended in a stillbirth with congenital syphilis.

Case Report

From October 2015 to November 2018, eight pregnant women with syphilis were referred to the Kobe University Hospital. **Table 1** shows the clinical characteristics and serological findings for the eight pregnant women with syphilis and their newborns.

In the university hospital, 24 million units of penicillin G (PCG) daily are administered intravenously for 2–3 weeks in pregnant women with untreated syphilis. If pregnant women refuse treatments with intravenous PCG, 1500 mg of amoxicillin (AMPC) per day are administered orally for 4 weeks. Pregnant women who received syphilotherapies underwent serial fetal ultrasound examinations throughout pregnancy to detect evidence of congenital syphilis, including fetal growth restriction, ascites, and hepatosplenomegaly. When the rapid plasma reagin (RPR) titers at 3 months after treatment decreased by a quarter in card tests or by half in automated tests compared with the RPR titers before treatments, the syphilotherapies were considered effective. The workup for congenital syphilis was performed in newborns born to mothers with syphilis. When newborns had clinical findings associated with congenital syphilis, or the RPR titers of newborns were four-fold higher than those of their mothers at birth, or serum fluorescent treponemal antibody absorption (FTA-ABS) IgM were positive, they were diagnosed with congenital syphilis.

Of the eight pregnant women with syphilis, seven were administered antibiotics from median 14 (range, 9–19) gestational weeks (GW). Cases 1 and 2 were administered with an insufficient dose of oral AMPC (750 mg/day) at the previous hospitals. In the two cases, the RPR titers did not decrease, and therefore, they were referred to the university hospital. Thereafter, Cases 1 and 2 were administered with an adequate dose of oral AMPC (1500 mg/day) for 7 weeks and intravenous PCG (24 million units/day) for 3 weeks, respectively. Case 3, who had early latent syphilis, was administered intravenously with PCG (24 million units/day) for 2 weeks. Case 4, 5, and 6, who had late latent syphilis, were administered intravenously with PCG (24 million units/day) for 3 weeks. Case 7 was administered with an adequate dose of oral AMPC (1500 mg/day) for 13 weeks at the previous hospital, but the RPR titers did not decrease. Case 7 was referred to the university hospital and administered with double-dose oral AMPC (3000 mg/day) for one week and intravenous PCG (24 million units/day) for 3 weeks, nonetheless the RPR titers did not decrease.

In four of the six cases (66.7%), wherein the efficacy of syphilotherapies were evaluated, the treatments were considered effective (Table 1). None of the seven pregnant women with syphilis who received syphilotherapies had congenital syphilis of their newborns.

Contrary, Case 8, who had a history of roseola 2 months before referral, had never received a maternity checkup. She was transferred to the university hospital due to preterm premature rupture of the membranes at 29 GW. She delivered a stillbirth of congenital syphilis weighing 705 g with saddle nose and hepatosplenomegaly.

All eight pregnant women were diagnosed as having syphilis by serological tests for the first time during pregnancy. However, three pregnant women (Case 3, 5, and 8) were considered to have skin manifestations of syphilis, which spontaneously disappeared after a few weeks without syphilotherapies.

Discussion

From 2015 to 2018, eight pregnant women with syphilis were referred to Kobe University Hospital. When they visited the university hospital, six of the eight women had late latent syphilis, and the remaining two had early latent syphilis. Seven of the eight pregnant women with syphilis received syphilotherapies. One woman was treated with oral AMPC alone, four with intravenous PCG alone, and two with the both. The antibiotic treatments in four of the six patients (66.7%) were considered effective, except for Case 3 who had extremely low RPR titers before treatment (Table 1). None of the seven pregnant women who were treated with antibiotics had congenital syphilis of their newborns. Contrary, one woman received no medication and delivered a stillbirth with congenital syphilis.

In the United States, the rate of women with primary and secondary syphilis increased by 22% from 2012 to 2014, and the rate of congenital syphilis also increased by 38% in the same period [1]. In Japan, increases in the rate of women with syphilis were also observed from 2010 to 2018[2]. In addition, it is estimated that 250 Japanese pregnant women have syphilis annually [3]. In Hyogo Prefecture, the number of women with syphilis increased from 1 in 2010 to 78 in 2018 [4]. The Centers for Disease Control and Prevention (CDC) guideline recommends antibiotic treatments for syphilis in

pregnancy based on the stage of the disease as early in the pregnancy as possible [5]. For example, in the guideline, pregnant women with late latent stage of syphilis are treated with intramuscular administration of 2.4 million units of benzathine penicillin G (BPG) weekly for 3 weeks. However, BPG is not available in Japan; therefore, oral AMPC (1500 mg/day × 4 weeks) is used instead of intramuscular administration of BPG. However, completing antibiotic treatment with oral AMPC for 4 weeks is difficult because of poor patient adherence. Therefore, we recommend intravenous administration of PCG (24 million units/day × 2–3 weeks) for pregnant women with syphilis based on the treatment regimen for patients with neurosyphilis in the CDC guideline. In this report, six pregnant women with syphilis were administered with PCG intravenously. Because of the extremely low RPR titers before syphilotherapy in Case 3 (automated tests: <0.2 R.U., card tests: 2 times), RPR titers did not decrease after syphilotherapy. Except Case 3, in three of the five (60%) pregnant women with syphilis treated with intravenous administration of PCG regimen, a four-fold decline in RPR titers in card tests was observed (Cases 2, 4, and 5). A recent retrospective review suggested that a four-fold decline in RPR titers in card tests until delivery could be observed in only 38% patients [6]. Therapeutic efficacy of intravenous administration of PCG among pregnant women with syphilis may not be inferior to that of

intramuscular administration of BPG.

By contrast, the degree of decrease in maternal RPR titers after syphilotherapy is not associated with the incidence rates of congenital syphilis after syphilotherapies [6]. Indeed, in the present report, maternal RPR titer decline was not observed in three of seven pregnant women treated with antibiotics (Cases 3, 6, and 7), nontheless none of them had congenital syphilis of their newborns.

Previous studies demonstrated that pregnant women who delivered infants with syphilis tended to have no prenatal care [5, 7]. The risk of congenital syphilis has been reported to be correlated with the stage of disease with primary and secondary syphilis, conferring the highest risk of adverse pregnancy outcomes [5, 8]. Case 8 received no prenatal care and had a history of roseola 2 months before referral to the university hospital. It was likely that she acquired secondary syphilis before 21 GW, and her stillbirth had congenital syphilis, because saddle nose is one of the typical symptoms of congenital syphilis [9].

In addition, syphilis mismanagement, e.g., unrecognized disease and inadequate treatment, is one of the important risk factors for not only heterosexual syphilis, but also congenital syphilis [7, 10, 11]. Although Cases 1 and 2 were administered inadequate syphilotherapies (oral AMPC 750 mg/day), they had no congenital syphilis of newborns.

Improving knowledge about adequate diagnosis and treatment of syphilis in pregnancy among clinical practitioners is critical for preventing the occurrence of congenital syphilis.

Vertical transmission rates in early and late latent syphilis are known to be significantly lower than those in primary and secondary syphilis [12]. In the present report, all pregnant women with syphilis who were intravenously administered with PCG had latent syphilis; therefore, it was unclear whether intravenous administration PCG regimen was truly effective for preventing congenital syphilis.

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Conflict of interest

None.

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Table 1. Eight pregnant women with syphilis and their babies

Case	Age (years old)	Gravidity / Parity	Clinical symptom (timing of onset)	GW at syphilis diagnosis	GW at antibiotic treatment	RPR titers before treatemts		TPHA (S/CO)	Stage of syphilis	Antibiotic treatment	RPR titers at 3 months after treatments		Efficacy	GW at delivery	Birth weight (g)	Clinical findings of the infants	Serological tests for syphilis in the inafants			
						Automated tests (R.U.)	Card tests (times)				Automated tests (R.U.)	Card tests (times)					Automated RPR tests (R.U.)	TPHA (S/CO)	FTA -ABS IgG (times)	FTA-ABS IgM (times)
1	23	2/0	None	10	14	90	N.D .	6340	Late latent	AMPC p.o. 750 mg/d x 6w + 1,500 mg/d x 7w	8.6	8	Effective	39	3712	None	<0.4	19.4	N.D.	N.D.
2	36	5/2	None	9	9	>20	64	1.33	Late latent	AMPC p.o. 750 mg/d x 1w→ PCG d.i.v. 24 million/d x 3w	2.1	2	Effective	38	2410	None	<0.4	>20	+	-
3	24	1/0	Localized skin rash (6months before pregnancy)	13	15	<0.4	2	14.89	Early latent	PCG d.i.v. 24 million/d x 2w	<0.4	2	N.A.	40	3254	None	<0.4	3.81	N.D.	N.D.
4	24	1/0	None	10	11	>20	32	>20	Late latent	PCG d.i.v. 24 million/d x 3w	6.4	8	Effective	36	2518	None	<0.4	>20	N.D.	N.D.
5	26	2/0	Genital ulcers (3years before pregnancy)	11	12	>20	64	19.8	Late latent	PCG d.i.v. 24 million/d x 3w	17.6	16	Effective	39	2610	None	1.9	>20	N.D.	N.D.
6	27	1/0	None	11	19	6	4	15.74	Late latent	PCG d.i.v. 24 million/d x 3w	3.8	4	Ineffective	37	3158	None	<0.4	14.2	N.D.	N.D.
7	21	1/0	None	12	14	>20	64	>20	Late latent	AMPC p.o. 1500 mg/d x 13w →AMPC p.o. 3000 mg/d x 1w →PCG d.i.v. 24 million/d x 3w	74	64	Ineffective	38	2060	None	2.3	4890	N.D.	-
8	39	6/4	Roseola (21GW)	29	N.A.	>20	64	>20	Early latent	None	N.A.	N.A.	N.A.	29	704	Stillbirth, hepatospleno-megaly, saddle nose	N.D.	N.D.	N.D.	N.D.

Abbreviations: GW, gestational weeks; RPR, rapid plasma regain; TPHA, Treponema pallidum haemagglutination assay; FTA-ABS, fluorescent treponemal antibody absorption; Ig, immunoglobulin; AMPC, amoxicillin; p.o., per os; PCG, penicillin G; div, drip infusion in vein; N.D., not determined; N.A., not applicable.