SYPHILIS

Prenatal syphilis infection is a possible cause of preterm delivery among immigrant women from eastern Europe

E Tridapalli, M G Capretti, V Sambri, A Marangoni, A Moroni, A D'Antuono, M L Bacchi, G Faldella

Sex Transm Infect 2007;83:102–105. doi: 10.1136/sti.2006.021352

See end of article for authors' affiliations

Correspondence to:
E Tridapalli, Department of Preventive Paediatrics and Neonatology, Istituto Clinico di Pediatria Preventiva e Neonatologia, Via Massarenti, 11, Bologna 40138, Italy; trida@med.unibo.it

Accepted 2 October 2006

Objective: To evaluate the prevalence of maternal syphilis at delivery and neonatal syphilis infection in an Italian urban area, in connection with the increased flow of immigration.

Study design: A prospective surveillance study was carried out in Bologna, Italy, from November 2000 to March 2006. All pregnant women were screened for syphilis at delivery. Infants born to seropositive mothers were enrolled in a prospective follow-up.

Results: During the study period 19 205 women gave birth to 19 548 infants. A total of 85 women were seropositive for syphilis at delivery. The overall syphilis seroprevalence in pregnant women was 0.44%, but it was 4.3% in women from eastern Europe and 5.8% in women from Central–South America. Ten women were first found positive at delivery, as they did not receive any prenatal care. Nine of these were from eastern Europe. All their infants were asymptomatic, but six had both reactive immunoglobulin (Ig)M western blot and rapid plasma reagin tests and were considered prenatally infected. Three of six were preterm (gestational age <37 weeks).

Conclusions: In Italy, congenital syphilis infection is strictly related to immigration from eastern Europe. Although it is asymptomatic, it could cause premature delivery. Therefore, it is necessary to perform serological tests during the third trimester in mothers coming from endemic areas to adequately treat syphilis in pregnancy and prevent congenital infection. If the mother's test results are not available at delivery, it is necessary to investigate the newborn, especially if it is born prematurely.

Congenital syphilis is mainly a consequence of lack of antenatal care and control of sexually transmitted infections. It can be prevented if infected mothers are identified and properly treated during pregnancy.¹ As congenital syphilis seemed to have disappeared from the Italian population, prenatal screening for syphilis is scheduled only during the first trimester of pregnancy in accordance with Italian legislation (Ministerial Decree, September 1998). However, congenital syphilis rates have been rising in many developed countries because of the large number of people immigrating from countries where syphilis is endemic. Also, in Italy, the number of immigrants has risen since the 1990s: there were 649 000 immigrants in 1991 and 1 341 000 in 2000. By the end of 2006, it is estimated that there will be three million immigrants in Italy. The aim of this study was to evaluate the prevalence of maternal syphilis at delivery and congenital syphilis infection, and related clinical manifestation in an Italian urban area in relation to the increased immigration flow from other countries.

MATERIALS AND METHODS

Study population

A prospective surveillance study was carried out at St Orsola Hospital in Bologna, Italy, from 1 November 2000 to 31 March 2006. All pregnant women were screened for syphilis at delivery: until 31 December 2004 we used syphilis screening recombinant EIA (Radim, Pomezia, Italy) as a screening test, whereas from 1 January 2005 we used the new recombinant chemiluminescence immunoassay LIAISON Treponema Screen (Diasorin, Saluggia, Italy), which yielded good values of sensitivity and specificity.² Positive samples were further analysed by the *Treponema pallidum* haemagglutination assay (Alfa Wasserman, Milan, Italy) and the *T pallidum* "in house" western blot³; if positive results were confirmed, the rapid plasma reagin (RPR) test (Radim) was also performed. A

maternal case history was obtained to identify high-risk pregnancies. We also investigated if mothers had already been correctly diagnosed during or before pregnancy, if and when they had been treated and if their non-treponemal serological test titres had decreased after treatment.

Case definition

Study inclusion criteria were mothers with reactive serological tests for syphilis at delivery and lack of evidence of adequate treatment, the presence of clinical, laboratory or radiological evidence of syphilis in the infant, and maternal and infant serological titres compared using the same test and the same laboratory.^{4 5}

At birth, a clinical examination was performed: serological tests were obtained as well as a complete blood count, liver and pancreatic function, a cerebral ultrasonography, an auditory brain response test and a long-bone x ray. Infants with positive RPR tests at birth born to mothers who were not treated also received a cerebrospinal fluid analysis including Venereal Disease Research Laboratory (VDRL) testing (DADE Behring, Marburg, Germany), cell count and protein.

All seroreactive infants received careful follow-up examinations and serological testing at birth and after 3, 6, 9, 12 months or until the tests became negative.

Statistical analysis

Data were compared using Student's t test, χ^2 test and Fisher exact test; $p < 0.05$ was considered significant.

RESULTS

During the study period 19 205 women gave birth to 19 548 infants; 81% of mothers were Italian and the remaining 19%

Abbreviations: RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory

were foreigners. We found serological evidence of syphilis at delivery in 85 women, 75 of whom were found positive for syphilis during pregnancy, while the other 10 (11.7%) were found positive only at delivery as they did not receive any prenatal care.

Among the 75 women found seropositive during pregnancy, 46 had already been adequately treated before pregnancy, and their non-treponemal serological tests were non-reactive during pregnancy; 8 women knew of their syphilis infection before pregnancy but were advised to repeat the treatment during pregnancy because of persistent non-treponemal serological high titres that later decreased fourfold. Twenty one women had the first diagnosis of syphilis during pregnancy; these patients were immediately treated with benzathine penicillin intramuscularly, and their RPR titres showed a fourfold decrease by the end of the pregnancy.

The overall syphilis seroprevalence in pregnant women was 0.44%, with minor changes during the 5-year period (range 0.36–0.51%). However, immigrant women were more likely to be seropositive than Italian women (relative risk 28.17, 95% confidence interval (CI) 14.97 to 53.02, $p < 0.001$) (table 1).

Of the seropositive Italian women, 9 of 11 were treated before pregnancy, while the remaining 2 were treated during the first trimester of pregnancy. Women untreated at delivery were more likely to be from eastern Europe (9/10) than from other countries ($p < 0.05$); 4 women were from Romania, 3 from Moldova, 1 from Ukraine and 1 from Russia.

The mother's age ranged from 18 to 42 years. Untreated women with first-time diagnosis at delivery were younger than the adequately treated women (median standard deviation (SD) age 25 (4.6) v 29.2 (5.7) years; $p < 0.05$). Table 2 summarises the socioeconomic parameters of immigrant and native women.

A total of 95 infants were born to 85 seropositive mothers: there were 4 pairs of twins, and 6 seropositive women delivered twice during this period; 75 infants have completed the follow-up, as all their tests were negative, 12 infants are still being followed up and 8 infants were lost during follow-up.

A total of 10 (10.5%) infants were born to untreated mothers found to have syphilis at delivery, and all were asymptomatic. Despite the fact that their RPR titres were equal to their mothers' results, six of these infants were considered to have syphilis infection as they had a positive IgM western blot test (table 3). The infants received treatment with aqueous penicillin G 50 000 U/kg/dose intravenously every 8–12 h for 10–14 days. All six infants were born to mothers from eastern Europe. Three of the six were preterm (gestational age < 37 weeks) and two were extremely low birth weight; (birth weight < 1000 g). Whereas the rate of prematurity in infants born to all women from eastern Europe delivering in our

hospital during the study period was 9.4% (95% CI 7.2 to 11.5), it was 50% among infants with syphilis infection ($p < 0.005$).

Three of the six infants with syphilis infection were born at term (table 3): two of these had a VDRL test positive in cerebrospinal fluid and the third infant presented long-bone lesions at x-ray examination (transversal streaks of radiopacity about femoral distal metaphyses) no longer evident after treatment.

The remaining four infants born to mothers with the first diagnosis of syphilis at delivery had a reactive RPR test with a titre lower than their mother's and a negative IgM western blot test at birth. The long-bone x-ray examination and cerebrospinal fluid analysis were normal. Three of these infants have completed follow-up as all the treponemal and non-treponemal tests were negative, whereas the fourth was lost to follow-up at the age of 4 months.

A total of 85 (89.5%) asymptomatic infants were born to mothers adequately treated before or during pregnancy, and none presented clinical, laboratory or radiological evidence of syphilis infection.

DISCUSSION

Syphilis is still a public health problem worldwide even in developed countries, and outbreaks have been reported recently in several European cities.⁶

The number of women that give birth each year in our hospital has not markedly changed since the 1990s, but the number of foreign women giving birth in our centre has increased considerably: they represented only 4.2% of all patients in 1991, whereas in 2004, the percentage of foreign immigrant women at delivery was 18%. Therefore, the prevalence of women with positive serological tests for syphilis at delivery increased fourfold from 1991 to the study period (0.11% v 0.42%).

Our study shows that in our area, syphilis in pregnancy and congenital disease are strictly related to the immigration flows. The maternal profile with the highest risk concerns young women from eastern Europe who did not receive adequate prenatal care owing to lack of knowledge of free healthcare services. Tikhonova *et al.*⁷ reported that maternal syphilis and the resulting congenital syphilis increased > 20 -fold from 1991 to 1999 in Russia. In our study, most cases of women at risk of transmitting syphilis to their infants were from Romania and Moldova, whereas only one woman was from Russia and another was from Ukraine.

In contrast with studies carried out in other developed countries,⁸ no women were HIV positive and a maternal history of drug misuse was present in only two cases.

When socioeconomic parameters of immigrants and natives were compared, we found that immigrants were more likely to

Table 1 Prevalence of maternal syphilis at delivery and prevalence of syphilis infection in the newborn according to mothers' origin

	Seropositive mothers according to their origin									Infants with highly probable congenital syphilis	
	n	%	n	%	RR	95% CI	p Value	HCV+			
Italy	11/15501	81	11	0.07	0.036	0.019 to 0.067	0.0001	2	2	0	0
Eastern Europe	47/1075	6	47	4.37	20.86	13.6 to 31.8	0.0001	3	0	6	0.55
South—Central America	14/239	1	14	5.85	15.65	8.95 to 27.36	0.0001	0	0	0	0
Africa	9/1010	5	9	0.89	2.13	1.07 to 4.24	0.05	0	0	0	0
China	2/242	1	2	0.82	1.88	0.46 to 7.63	0.676	0	0	0	0
Bangladesh	2/211	1	2	0.94	2.17	0.53 to 8.76	0.555	0	0	0	0
Others	0/927	5	0	0	—	—	—	0	0	0	0

HCV, hepatitis C virus; RR, women at greater risk of being seropositive according to country of origin

Table 2 Distribution of characteristics of 80 of 85 women seropositive for syphilis

	Mothers' origin, n (%)			
	Italy	Eastern Europe	South-Central America	Others
Education				
Primary school	—	2 (4.7)	2 (15.4)	1 (7.6)
Intermediate school	5 (45.5)	16 (37.1)	7 (53.8)	6 (46.2)
High school	4 (36.3)	19 (44.2)	2 (15.4)	6 (46.2)
Degree	2 (18.2)	3 (7.0)	—	—
Unknown	—	3 (7.0)	2 (15.4)	—
Employment				
Unemployed	—	5 (11.6)	3 (23.1)	—
Housewife	2 (18.2)	24 (55.8)	5 (38.4)	6 (46.2)
Employee	8 (72.7)	12 (27.9)	4 (30.8)	6 (46.2)
Freelancer	1 (9.1)	—	—	1 (7.6)
Unknown	—	2 (4.7)	1 (7.7)	—
Marital status				
Unmarried	5 (45.5)	23 (53.5)	4 (30.8)	1 (7.7)
Married	6 (54.5)	18 (41.8)	7 (53.8)	12 (92.3)
Unknown	—	2 (4.7)	2 (15.4)	—
Father's name on birth certificate				
Present	10 (90.1)	36 (83.7)	10 (76.9)	13 (100)
Not present	1 (9.9)	7 (16.3)	3 (23.1)	—
Citizenship				
Italian	11 (100)	—	—	—
Naturalised Italian	—	12 (27.9)	3 (23.1)	2 (15.4)
Foreign	—	31 (72.1)	10 (76.9)	11 (84.6)
Total seropositive women (n)	11	43	13	13

Values shown are the mean.

Data regarding the remaining 5 women (4 from Eastern Europe and 1 from South America) are not available as they gave up their babies for adoption.

be unemployed or housewives than native women ($p = 0.009$); no significant differences were found in their marital status or education.

None of the infants with syphilis infection had any evident clinical signs at birth, therefore congenital disease would have been missed if serological tests had not been performed for both mother and infant at the time of delivery. Prematurity was the only non-specific clinical manifestation: although the aetiology of prematurity among high-risk pregnant women varies, congenital syphilis is a well-documented cause.⁹ A recent study on congenital syphilis¹⁰ carried out in Russia found that prematurity is more likely to occur in affected infants born to untreated women.

Although in Italy prenatal screening for syphilis is scheduled only during the first trimester of pregnancy, a closer prenatal care programme and screening is advisable for immigrant women (ie, serological tests should be repeated at the third trimester and at delivery) to prevent congenital syphilis and the related premature delivery with its overall social costs. We believe that when the results of syphilis testing of foreign women are not available at delivery, it is mandatory to serologically investigate the newborns, especially if they are premature.

In this study, we investigated the characteristics of women giving birth to infants with probable congenital syphilis in our Italian urban area. As risk factors can vary in different regions, it would be interesting to identify the general profile of pregnant women at high risk and to update data on the prevalence of congenital syphilis in Italy. For these reasons, a large National Surveillance Study is currently being conducted, and the initial results are scheduled for next year. As previous articles illustrate,^{11, 12} research is needed to compare situations found in different hospitals. Evaluations could also identify problems and solutions associated with under-reporting and incomplete report forms.

Finally, as also underlined by a recent report,¹³ antenatal screening results should be reviewed by a multidisciplinary team with experience in the management of syphilis. This enables a full evaluation of the mother to be carried out during the pregnancy and a plan made for treatment and follow-up of the infant. In our experience, close collaboration between paediatricians, microbiologists and clinicians dealing with sexually transmitted infections has led to the identification of many cases of congenital syphilis that would otherwise have been missed.

Table 3 Characteristics of the six infants with highly probable congenital syphilis at birth and at last visit during follow-up

	Birth						Follow-up			
	GA, weeks	BW, g	IgM WB	RPR	VDRL CSF	Long-bone x ray	Age, months	RPR	IgM WB	IgG WB
Case 1	24	695	+	+	Not performed	Normal	10	—	—	+
Case 2	26	495	+	+	Not performed	Normal	12	—	—	—*
Case 3	34	2150	+	+	—	Normal	4 (lost)	Weakly reactive	—	+
Case 4	40	3660	+	+	+	Normal	10	—	—	—*
Case 5	39	3250	+	+	+	Normal	24	—	—	+
Case 6	38	2800	+	+	—	Abnormal	3	—	—	+

BW, birth weight; CSF, cerebro spinal fluid; CGA, gestational age; Ig, immunoglobulin; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory; WB, western blot; +, positive; —, negative.

*These babies became seronegative as a possible consequence of early antibiotic treatment.

Key messages

- Congenital syphilis has reappeared in the Italian population in recent years; this phenomenon is related to immigration flows from underprivileged countries.
- The maternal profile with the highest risk of transmitting congenital syphilis concerns young women from eastern Europe who did not receive adequate prenatal care owing to lack of knowledge of free healthcare services.
- A closer prenatal care programme and screening is advisable for immigrant women (ie, serological tests should be repeated at the third trimester and at delivery) to prevent congenital syphilis.
- The close collaboration between paediatricians, microbiologists and clinicians dealing with sexually transmitted infections led to the identification of cases of congenital syphilis.

Authors' affiliations

E Tridapalli, M G Capretti, G Faldella, Department of Preventive Paediatrics and Neonatology; St Orsola Malpighi General Hospital, University of Bologna, Bologna, Italy

V Sambri, A Marangoni, A Moroni, Section of Dermatology, DMCSS; St Orsola Malpighi General Hospital, University of Bologna, Bologna, Italy

A D'Antuono, Section of Microbiology, DMCSS, St Orsola Malpighi General Hospital, University of Bologna, Bologna, Italy

M L Bacchi, Institute of Cardiology; St Orsola Malpighi General Hospital, University of Bologna, Bologna, Italy

Competing interests: None declared.

Contributors: ET designed the study plan, organised the multidisciplinary collaboration among the various participants in the study, carried out the clinical follow-up of the infants born to seropositive mothers and contributed to the drawing up of the paper, MGC contributed to designing

the study plan, she collected the data and contributed to the drawing up of the paper, VS designed the serological follow-up of the seropositive mothers and their children, AMa carried out the serological follow-up of the participants in the study and contributed to the drawing up of the paper, AMo carried out the serological follow-up of the participants in the study, AD'A carried out the clinical follow-up of the seropositive women attending the centre for sexually transmitted diseases, MLB conducted the statistical analyses of study results, and GF contributed to designing the study plan and the drawing up of the paper and reviewed the paper.

REFERENCES

- 1 Walker DG, Walker GJ. Forgotten but not gone: the continuing scourge of congenital syphilis. *Lancet Infect Dis* 2002;**2**:432–6.
- 2 Marangoni A, Sambri V, Accardo S, et al. Evaluation of LIAISON® Treponema Screen, a novel recombinant antigen-based chemiluminescence immunoassay for the laboratory diagnosis of syphilis. *Clin Diagn Lab Immunol* 2005;**12**:1231–4.
- 3 Sambri V, Marangoni A, Eyer C, et al. Western Immunoblotting with five *Treponema pallidum* recombinant antigens for serological diagnosis of syphilis. *Clin Diagn Lab Immunol* 2001;**8**:534–9.
- 4 Goh BT, van Voorst Vader PC. European Branch of the International Union against Sexually Transmitted Infection and the European Office of the World Health Organization. European guideline for the management of syphilis. *Int J STD AIDS* 2001;**12**(Suppl 3):14–26.
- 5 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Recomm Rep* 2002;**51**:1–78.
- 6 Saloojee H, Velaphi S, Goga Y, et al. The prevention and management of congenital syphilis: an overview and recommendations. *Bull World Health Organ* 2004;**82**:424–30.
- 7 Tikhonova L, Salakhov E, Southwick K, et al. Congenital syphilis in the Russian Federation: magnitude, determinants, and consequences. *Sex Transm Infect* 2003;**79**:106–10.
- 8 Genc M, Ledger WJ. Syphilis in pregnancy. *Sex Transm Infect* 2000;**76**:73–9.
- 9 Goldenberg RL, Culhane JF, Johnson DC. Maternal infection and adverse fetal and neonatal outcomes. *Clin Perinatol* 2005;**32**:523–59.
- 10 Salakhov E, Tikhonova L, Southwick K, et al. Congenital syphilis in Russia. The value of counting epidemiologic cases and clinical cases. *Sex Transm Dis* 2004;**31**:127–32.
- 11 Beltrami J, Berman S. Congenital syphilis: a persisting sentinel public health event. *Sex Trans Dis* 2006;**33**:675–6.
- 12 Simms I, Ward H. Congenital syphilis in the United Kingdom. *Sex Transm Infect* 2006;**82**:1.
- 13 Cross A, Luck S, Patey R, et al. Syphilis in London circa 2004: new challenges from an old disease. *Arch Dis Child* 2005;**90**:1045–6.