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Incidence of toxoplasmosis in pregnancy in Campania: A population-based study on screening, treatment, and outcome

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ABSTRACT

Introduction: The aim of this study was to evaluate the incidence of toxoplasmosis infection during pregnancy and to describe the characteristics of the serological status, management, follow-up and treatment.

Material and methods: This is a population-based cohort study of women referred for suspected toxoplasmosis during pregnancy from January, 2001 to December, 2012. Suspected toxoplasmosis was defined as positive IgM antibody during pregnancy. Women with suspected toxoplasmosis during pregnancy were classified into three groups: seroconversion, suspected infection, or no infection in pregnancy. Women in the first and second group were treated according to local protocol, and amniocentesis with toxoplasmosis PCR detection and serial detailed ultrasound scans were offered. Neonates were investigated for congenital toxoplasmosis at birth and were monitored for at least one year after birth.

Results: During the study period, there were 738,588 deliveries in Campania. Of them 1159 (0.2%) were referred to our Institution for suspected toxoplasmosis during pregnancy: 183 (15.8%) women were classified as seroconversion, 381 (32.9%) were suspected infection, and 595 (51.3%) were not infected in pregnancy. Neonatal outcome was available for 476 pregnancies, including 479 neonates (3 twins, 473 singletons), out of the 564 pregnancies with seroconversion or suspected infection. 384 (80.2%) babies were not infected at birth and at follow-up, 67 (14.0%) had congenital toxoplasmosis, 10 (2.1%) were voluntary induced termination of pregnancy, 15 (3.1%) were spontaneous miscarriage, and 4 (0.8%) were stillbirth (of which one counted already in the infected cohort). Considering cases of congenital toxoplasmosis, the transmission rate in women with seroconversion was 32.9% (52/158), and in women with suspected infection was 4.7% (15/321).

Conclusions: Toxoplasmosis is uncommon in pregnancy with overall incidence of seroconversion and suspected infection in pregnancy of 0.8 per 1000 live births and incidence of congenital toxoplasmosis 0.1 per 1000 live births when applying a strict protocol of screening, follow-up, and treatment. 51.3% (595/1159) of women referred to our center for suspected infection were actually considered not infected.

Introduction

Toxoplasmosis is one of the common worldwide parasitic zoonosis caused by the intracellular protozoon Toxoplasma gondii. Maternal primary infection may cause congenital toxoplasmosis when acquired during pregnancy, because of the transplacental passage of the parasite [1]. The infection in

Abbreviation: VTP, voluntary termination of pregnancy.

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the fetus can cause miscarriage, stillbirth, intrauterine growth restriction, ocular and central nervous system abnormalities with auditory and visual disorders, and mental retardation in the infant [1,2].Vertical transmission increases with gestational age, while the severity of the symptoms in the fetus are inversely related [3].

Diagnosis of maternal infection almost completely relies on serological findings including IgM, IgG, and IgG Avidity. Seroconversion is demonstrated when IgM and IgG from negative become positive with both samples taken after conception [4].

The seroprevalence of the infection in women in childbearing age in Italy is considered to have deceased over the last 30 years. It was estimated 48.5% in the 1991 [5], 21.5% in the 2005 [6] and, recently, 22.3% in the 2011 [7]. On the other hand the risk of congenital toxoplasmosis in case of maternal infection can be as high as 70% in the third trimester [3], therefore the effectiveness of a policy of universal screening for toxoplasmosis infection during pregnancy is still subject of debate [8].

Objective

The aim of this study was to evaluate the incidence of toxoplasmosis infection during pregnancy in a population-based cohort study, and to describe the characteristics of the serological status, management, follow-up and treatment.

Material and methods

Study design

This is a population-based cohort study of women counselled for suspected toxoplasmosis infection during pregnancy between January, 2001 and December, 2012 in Campania, Italy.

In Italy, all pregnant women are screened for toxoplasmosis during pregnancy with IgG and IgM antibody at the first visit and, if both negative, every month until delivery. In Campania, Italy, all women who were found to have positive IgM antibody are referred for counselling and further evaluation at University of Naples Federico II, Naples, Italy.

At the first counselling visit, women undergo samples for IgG and IgM antibodies and IgG avidity at our reference laboratory at University of Naples Federico II, analyzed by enzyme immunoassays (EIAS). The results were expressed in international units per ml (IU/ml). IgM antibodies were considerate as negative if <0.55, borderline if included between 0.55 and 0.65, and positive if >0.65. IgG antibodies were considered as negative if <4, borderline if included between 4 and 8, and positive if >8. IgG avidity was considered as low if <0.200, intermediate if between 0.200 and 0.300, and high if >0.300.

Women were therefore classified into three groups according to antibody status:

1 Group 1: Seroconversion.

One or more samples taken with IgG-/IgM- followed by another sample with IgG+/IgM+. The time of seroconversion (first, second, or third trimester) was calculated as the midpoint between the last IgG-/IgM-, and first IgM+/IgG + test or 14 days before the first IgM + if IgG- test [3].

2 Group 2: Suspected infection:

IgG+/IgM + at first sample taken in pregnancy. This subset of women was further classified according to the IgG avidity results (low, intermediate, and high avidity). Women with IgG+/IgM + at first sample taken in pregnancy but with high avidity before 12 weeks were excluded from this group and were classified in Group 3.

3 Group 3: No infection in pregnancy:

Susceptible: IgG-/IgM-

Past infection: IgG+/IgM- and/or maternal preconception seropositive sample

Persistent IgM antibodies: IgM + without appearance of IgG

IgG+/IgM + at first sample taken in pregnancy with high avidity before 12 weeks

Maternal management and follow-up

Women in group 3 were discharged from follow-up.

Women in the first and second group were treated according to a local protocol. Amniocentesis for the presence of Toxoplasma DNA by polymerase chain reaction (PCR) was offered starting from 20 0/7 weeks and until 23 6/7 weeks of gestation, at least after 6 weeks following seroconversion in case of group 1 woman, and in selected cases in case of group 2. Women were also offered detailed ultrasound scan every 4 weeks after routine anatomy scan, in order to look for ultrasound signs suggestive of fetal infection (i.e. fetal abnormalities including ventriculomegaly, brain or hepatic calcifications, cataract, hepatosplenomegaly, ascites, severe IUGR) [9].

Local protocol included:

- Amniocentesis positive regardless of the group: pyrimethamine (50 mg every 12 h for 2 days, then 50 mg daily) with sulfadiazine (75 mg/kg followed by 50 mg/kg every 12 h, respecting a maximum of 4 g/day), and folinic acid (10–20 mg daily) until 38 weeks.
- Amniocentesis negative regardless of the group: Spiramycin 3000 IU every 8 h until delivery.
- Amniocentesis not performed: Spiramycin 3000 IU every 8 h until delivery in case of group 2 women; pyrimethamine (50 mg every 12 h for 2 days, then 50 mg daily) with sulfadiazine (75 mg/kg followed by 50 mg/kg every 12 h, respecting a maximum of 4 g/day), and folinic acid (10–20 mg daily) from 22 weeks until 38 weeks, in case of group 1 women.
- Ultrasound signs of infection regardless of the group and regardless of the amniocentesis result: pyrimethamine (50 mg every 12 h for 2 days, then 50 mg daily) with sulfadiazine (75 mg/kg followed by 50 mg/kg every 12 h, respecting a maximum of 4 g/day), and folinic acid (10–20 mg daily) until 38 weeks.

Neonatal management and follow-up

All babies born from women in group 1 and 2 were followed by a team of selected pediatricians. The protocol for neonatal and children surveillance offered in our center has already been described in a previous report [10]. In summary, babies were considered infected in case of presence of IgG antibodies beyond age 12 months without specific treatment.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA).

Data are shown as means, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the *t*-test to test group means by assuming equal within-group variances. Odds ratio (OR) with 95% confidence interval (CI) was

calculated. A 2-sided P value less than 0.05 was considered significant.

Positive and negative likelihood ratio and sensibility and specificity of ultrasound and amniocentesis were also calculated

This study was reported following the Strengthening The Reporting of Observational studies in Epidemiology guidelines [11].

Results

Population characteristics

During the study period, there were 738,588 deliveries in Campania. Of them 1159 (0.2%) were referred to University of Naples for suspected toxoplasmosis during pregnancy, defined as positive IgM antibody during pregnancy. After confirmed sample in our reference laboratory, 183 (15.8%) women were classified as seroconversions, 381 (32.9%) were suspected infection and 595 (51.3%) were not infected in pregnancy (Fig. 1).

Out of the 183 women with seroconversion, 79 (43.2%) were first-trimester seroconversion, 88 (48.1%) second-trimester, and 16 (8.7%) third-trimester. Out of the 381 women classified in the Group 2: 220 (57.7%) had low avidity, 161 (42.3%) had intermediate avidity or high avidity after 12 weeks.

Finally, out of the 595 women classified in group 3: 18 (3.0%) were susceptible, 120 (20.2%) were past infection, 27 (4.5%) were persistent IgM, and 430 (72.3%) were high avidity before 12 weeks.

51.3% (595/1159) of women (Group 3) referred to our center for suspected infection were therefore considered as not infected in pregnancy after analysis of serology in previous pregnancies, when available, and confirmed sample in our reference laboratory, and were therefore discharged with no further follow-up.

In the remaining 564 women (Group 1 and Group 2), amniocentesis was performed in 256 (45.4%) cases. 47 (18.4%) cases were positive.

Management and follow-up

All women in group 1 and 2 received treatment during pregnancy. 75% (423/564) of the women received prophylaxis with spiramycin, 3.5% (20/564) received treatment with

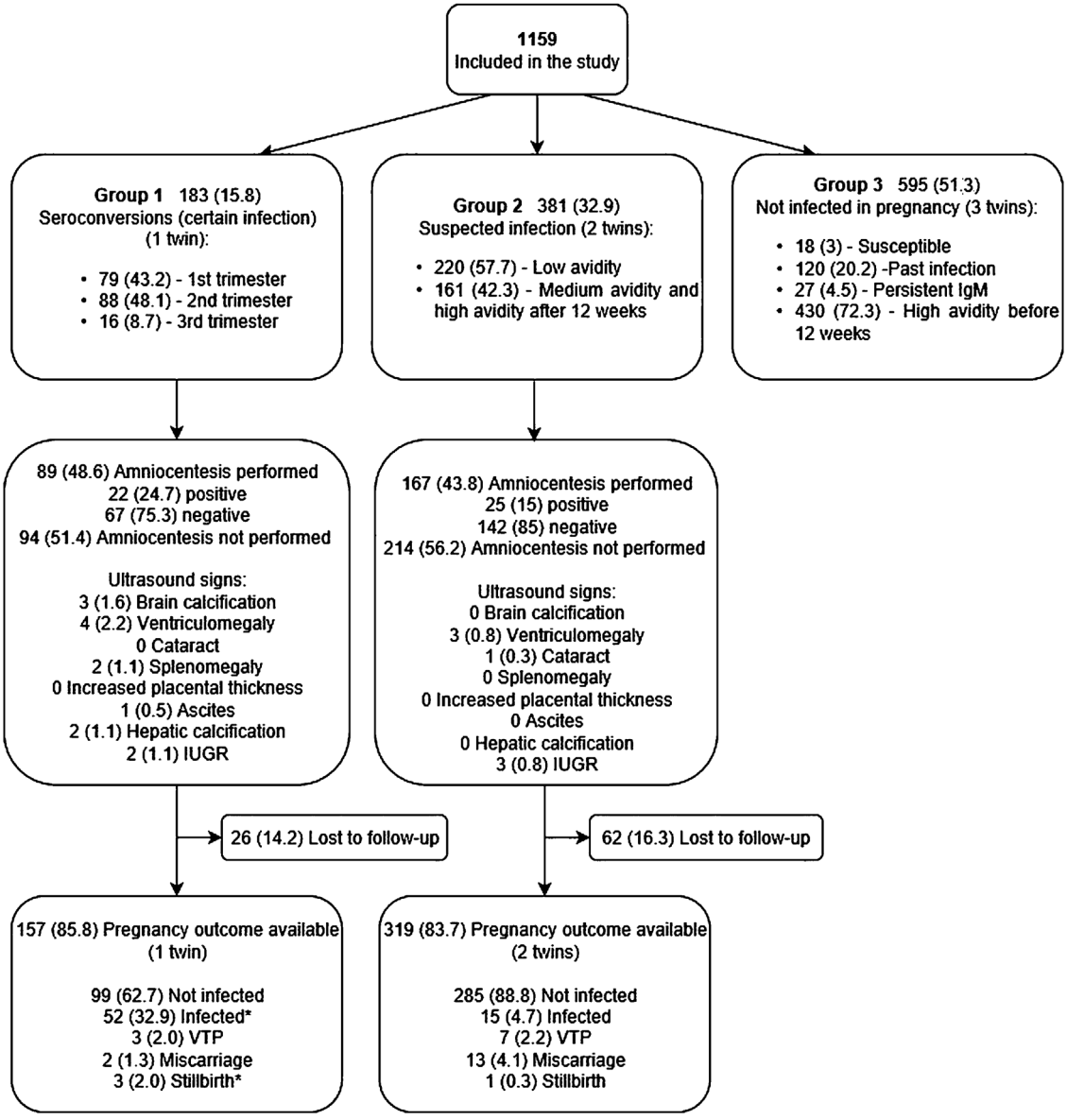

Fig. 1. Study flow chart.

Table 1
Characteristics of pregnancies ended with adverse outcome including voluntary termination of pregnancy (VTP), miscarriage, and stillbirth.

	Total		Group		Amnio positive/ tot amnio	Ultrasound sign present/ tot ultrasound
VTP	10	3 (30)	**Group 1**	*3 seroconversion I trim*	0	0/11
		7 (70)	**Group 2**			
Miscarriage	15	2 (13.3)	**Group 1**	*2 seroconversion I trim*	1/2 (50%)	0/16
		13 (86.7)	**Group 2**			
Stillbirth	4	3 (75)	**Group 1**	*1 seroconversion I trim, 1 seroconversion II trim, 1 seroconversion III trim*	1/2 (50%)	1/4 (25%) brain and hepatic calcifications, hepatosplenomegaly, ventriculomegaly
		1 (25)	**Group 2**			

Table 2
Ultrasound signs suggestive of congenital toxoplasmosis in infected and not infected fetuses.

	Infected	Not infected	Tot	P value	OR (CI)
	67 (16.5)	384 (83.5)	451		
At least one US sign	7 (10.4)	6 (1.6)	13	0.001	7.4 (2.4 to 22.6)
Brain calcification	3 (4.5)	0 (0)	3 (0.7)	0.003	
Ventriculomegaly	4 (6)	3 (0.8)	7 (1.6)	0.011	8.1 (1.8 to 38.9)
Cataract	0	1 (0.3)	1 (0.2)	0.851	
hepatosplenomegaly	2 (3)	0	2 (0.4)	0.022	
Ascites	1 (1.5)	0	1 (0.2)	0.149	
Hepatic calcification	2 (3)	0	2 (0.4)	0.022	
IUGR	2 (3)	2 (0.5)	4 (0.9)	0.107	5.1 (0.8 to 42.5)

IUGR, intrauterine growth restriction; US, ultrasound; OR, odds ratio; CI, confidence interval.
Data presented as number (percentage).

pyrimethamine and sulfadiazine, 21.3% (120/564) received first spiramycin followed by pyrimethamine and sulfadiazine, and one patient refused the treatment at all because intended to terminate the pregnancy.

Ultrasound follow-up was performed in all 183 women of group 1 and those 381 of group 2 (Fig. 1). The most common ultrasound sign suggestive of congenital toxoplasmosis was ventriculomegaly, present in 4 (2.2%) fetuses of group 1 and in 3 (0.8%) of group 2.

Neonatal outcomes

Neonatal outcome was available for 476 pregnancies, including 479 neonates (3 twins, 473 singletons), out of the 564 pregnancies with seroconversion or suspected infection. 384 (80.2%) babies were not infected at birth and at follow-up, 67 (14.0%) had congenital toxoplasmosis, 10 (2.1%) were voluntary induced termination of pregnancy, 15 (3.1%) were spontaneous miscarriage, and 4 (0.8%) were stillbirth (of which one counted already in the infected cohort).

Pregnancies with adverse outcome

Characteristics of pregnancies ended with adverse outcome, including voluntary termination of pregnancy, miscarriage and still birth are shown in Table 1. Ultrasound signs suggestive of congenital toxoplasmosis in infected and not infected fetuses are shown in Table 2.

10.4% of the fetuses with of congenital toxoplasmosis had at least one ultrasound sign suggestive of infection compared with 1.6% not infected fetuses (p value 0.001, OR 7.4, CI 2.4 to 22.6). Fetuses with congenital toxoplasmosis had statistically significant higher risk of having brain calcification, ventriculomegaly, hepatosplenomegaly, hepatic calcification compared to not infected fetuses (Table 2).

Sensitivity and specificity of ultrasound and of amniocentesis

Overall positive and negative likelihood ratio of ultrasound were respectively 5.7 (95% CI 1.9 to 17.2) and 0.9 (95% CI 0.9 to 1), sensitivity was 9% and specificity was 98.4%. Furthermore, positive and negative likelihood ratio of amniocentesis were respectively 11.9 (95% CI 7 to 10.1) and 0.2 (95% CI 0.1 to 1.4), sensitivity was 86.2% and specificity was 92.8%.

Prevalence of toxoplasmosis

Considering cases of congenital toxoplasmosis, 52 children were born from women in group 1 resulting in a transmission rate of 32.9%; 17.6% (12/68) of children had congenital toxoplasmosis in case of seroconversion in the first trimester, 40.5% (32/79) in the second trimester and 53.3% (8/15) in the third trimester. The remaining 15 children were born from women in group 2 with a transmission rate of 4.7%.

Considering the 738,588 deliveries in Campania from January 2001 to December 2012, the overall incidence of seroconversion and suspected infection in pregnancy was 0.8 per 1000 live births and incidence of congenital toxoplasmosis was 0.1 per 1000 live births.

Discussion

Main findings

Our study showed that 51.3% (595/1159) of women referred for suspected toxoplasmosis during pregnancy were considered not infected after analysis of serology in previous pregnancies, and confirmatory test at reference laboratory. These data highlighted the importance to standardize techniques and tests for toxoplasmosis in the laboratories, and also the need to refer these cases to centralized centres where there are trained doctors in this specific field for further evaluation and counselling. The reason for this is

that in cases other than seroconversion, where the diagnosis of maternal infection in pregnancy is uncertain, is difficult to quantify the risk of fetal adverse outcome. This may lead to unnecessary tests, and couple anxiety associated with uncertainty on baby's prognosis that can induce unnecessary interventions including termination of pregnancy [12,13].

Nowadays the ability to identify toxoplasmosis infection is primarily based on serological assay (detection of IgM, IgG, and IgG avidity). Consistently presence of IgM antibodies are a transient marker of recent acute infection, however they may persist for a longer period of time [14]. On the other hand the high avidity test can help confirm chronic infections, but low or intermediate levels do not confirm a recent infection because they can persist for a longer time [14–17].

In our cohort we identified 183 women with documented seroconversion in pregnancy and 381 women with suspected infection in pregnancy due to presence of both IgM and IgG and low or intermediate avidity or high avidity after 12 weeks.

Ultrasound follow up was extensively performed in all these pregnancies, but signs of infection were uncommon. Only 7 (10.4%) fetuses with congenital toxoplasmosis had at least one ultrasound sign suggestive of infection. Manderlbrot et al. documented similar result, they reported only cerebral ultrasound signs of infection which were present in 4.2% of fetuses with congenital toxoplasmosis [18]. In our cohort when ultrasound signs of infection were detected, 57.1% of women were undergoing treatment with spiramycin and 42.9% with pyrimethamine and sulfadiazine.

256 amniocentesis were performed, with sensitivity of 86.2% and specificity of 92.8%. In other studies was reported a higher sensitivity and specificity close to 100% [19,20]. This discordance in the result could be explained by worst quality control in laboratory performance, a reduction of parasite load due to maternal treatment or delayed in transmission.

The rate of transmission was overall 32.9% (52/158) in women with documented seroconversion in pregnancy. The rate of congenital toxoplasmosis increased comparing the trimester of seroconversion, according to literature [3], subdivided as: 17.6% (12/68) of children had congenital toxoplasmosis in case of seroconversion in the first trimester, 40.5% (32/79) in the second trimester and 53.3% (8/15) in the third. The remaining 15 children were born from women with suspected infection in pregnancy with a transmission rate of 4.7%. Rate of congenital toxoplasmosis in women with suspected infection has been recently documented to be as high as 56% by Avelino et at. [21], and much lower as 0.8–4.8% in other studies in women with IgM+/IgG + and low avidity [22,23]. This wide difference in rate of congenital toxoplasmosis could be explained by poor antenatal screening with delay in first trimester screening in the study by Avelino et al. This difference in rate of congenital toxoplasmosis when comparing women with seroconversion with women with suspected infection in pregnancy highlights the importance of proper counselling of the parents and strategy of management of the pregnancy according to the risk. To date, many studies are not clear about case definition and tent to evaluate seroconversion together with cases with suspected infection in pregnancy [23–30]. A direct comparison between studies is rather difficult, because of different screening programs for toxoplasmosis, different treatment schemes and risk groups analyzed.

The most important limitation of our study is the retrospective approach. We do acknowledge that several biases may be highlighted due to the study design. Women positive to toxoplasmosis in pregnancy could be not referred to our institution. Women could be not screened during pregnancy. Only one fetus among those with induced termination of pregnancy, miscarriage and stillbirth cases was tested for toxoplasmosis infection. Pregnancy outcomes were available for only 476 pregnancies.

Conclusion

In conclusion, 50% of women referred for suspected toxoplasmosis during pregnancy were considered not infected in pregnancy after appropriate analysis of serology. The incidence of congenital toxoplasmosis was as low as 0.1 per 1000 live births. The incidence of congenital toxoplasmosis was statistically significant higher in women with seroconversion compared to those with suspected infection, respectively 32.9% (52/158) and 4.7% (15/321). These findings should question about benefits and cost-effectiveness of universal screening policy for toxoplasmosis in pregnancy.

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Declaration of Competing Interest

The authors report no conflict of interest.

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