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Original article

Results of the REIV-TOXO national survey on prenatal screening for toxoplasmosis in Spain

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ABSTRACT

Introduction: Currently, the status of serological screening for toxoplasmosis in pregnant women in Spain is unknown, and there is no official recommendation. The objective of this study is to show the current practice of gestational screening for toxoplasmosis in hospitals belonging to the Spanish Network for Research on Congenital Toxoplasmosis (REIV-TOXO).
Methods: An electronic survey was sent between April 2021 and September 2021 to investigators from 118 hospitals of REIV-TOXO, representing all Spanish regions. Nine items related to gestational screening for toxoplasmosis were collected. This information was compared with cases of congenital toxoplasmosis (CT) identified in REIV-TOXO to determine if these were diagnosed in the presence of gestational screening.
Results: During the study period, serological screening was performed in 53.3% (63/118) hospitals, with variations between regions and even among hospitals within the same region. Testing performed in each trimester was the most common practice (57.7%), followed by a single determination (24.4%). 89.4% of CT cases between January 2015 and September 2021 were diagnosed due to gestational screening.
Conclusion: The decision to perform gestational screening for toxoplasmosis in Spain is highly heterogeneous, with significant local and regional differences. Despite this, screening still allows the diagnosis of most CT cases. It is urgent to have current epidemiological data to inform decision-making in public health.

Resultados de la encuesta nacional de REIV-TOXO sobre el cribado gestacional de la toxoplasmosis en España

Palabras clave:
Niño
Infección congénita
Toxoplasma gondii
Cribado

RESUMEN

Introducción: En la actualidad se desconoce la situación del cribado serológico gestacional frente a toxoplasmosis en España, sin que exista una recomendación oficial al respecto. El objetivo del estudio es mostrar la práctica actual del cribado gestacional de la toxoplasmosis en los hospitales pertenecientes a la Red Estatal de Investigación en Toxoplasmosis Congénita (REIV-TOXO).

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Métodos: A través de una encuesta electrónica enviada entre abril y septiembre de 2021 a los investigadores de 118 hospitales de REIV-TOXO, pertenecientes a todas las comunidades autónomas (CCAA). Se recogieron 9 ítems relacionados con el cribado gestacional de la toxoplasmosis. Se contrastó la información obtenida con los casos de toxoplasmosis congénita (TC) identificados en REIV-TOXO para determinar si éstos fueron diagnosticados en presencia de cribado gestacional.
Resultados: En el periodo de estudio, el cribado serológico se realizaba en el 53,3% (63/118) de los hospitales, con variaciones entre CCAA y entre hospitales de una misma CCAA. La frecuencia trimestral era la práctica más frecuente (57,7%) seguida de la determinación única (24,4%). El 89,4% de los casos de TC entre enero de 2015 y septiembre de 2021 fueron diagnosticados gracias al cribado gestacional.
Conclusión: La decisión de realizar cribado gestacional para la toxoplasmosis en España es muy heterogénea, con diferencias locales y regionales importantes. A pesar de ello, el cribado sigue permitiendo diagnosticar la mayoría de los casos de TC. Urge disponer de datos epidemiológicos recientes que ayuden en la toma de decisiones en el ámbito de salud pública.

Introduction

Toxoplasmosis is considered a major zoonosis worldwide, and a third of the population is estimated to be chronically infected.[1,2] Congenital toxoplasmosis (CT) is the result of transplacental transmission to the foetus following primary infection in the pregnant woman, with a risk of miscarriage and foetal death, clinical manifestations of varying severity in the newborn (NB) and lifelong neurological and/or ophthalmological complications.[3,4]

The consequences of CT can be prevented or attenuated by early diagnosis and treatment during pregnancy.[4–6] As the pregnant woman may be asymptomatic, and clinical manifestations and ultrasound findings suggestive of CT have low diagnostic sensitivity and specificity, the only way to diagnose all *Toxoplasma gondii* infections in pregnancy is by serological screening.[4,7,8] However, there is no international consensus on the need to establish a screening programme for toxoplasmosis in pregnancy.[2,9] Consequently, toxoplasmosis prevention and detection programmes have not been implemented uniformly and each country has different preventive strategies depending on the incidence of the disease and the virulence of the pathogen in their respective regions. In fact, there are significant geographical variations in the impact of the disease due to differences in hygiene and dietary habits, climate, parasite virulence and the presence or absence of disease surveillance programmes. In Europe, some countries have universal prenatal screening programmes for toxoplasmosis, in contrast to the absence of surveillance in others (Fig. 1).[4,10–14]

In Spain, prenatal screening for toxoplasmosis is not currently included in the common portfolio of services of the National Health Service. Different scientific societies have opposing opinions on screening. While the Sociedad Española de Ginecología y Obstetricia (SEGO) [Spanish Society of Obstetrics and Gynaecology] does not recommend it systematically,[15] the Asociación Española de Pediatría (AEP) [Spanish Paediatrics Association] does. Despite these differences, prenatal screening is actively carried out in many hospitals in Spain.

The aim of this study is to identify the extent of practice and the frequency of prenatal serological screening for toxoplasmosis in hospitals belonging to the REIV-TOXO (Red Estatal de InVestigación en TOXOplasmosis congénita [Spanish Network for Research on Congenital Toxoplasmosis]), a national research network made up of paediatricians from 118 hospitals in all of Spain's autonomous regions. REIV-TOXO collects anonymous information on CT cases detected in Spain, including epidemiological, clinical, diagnostic, therapeutic and follow-up characteristics of children infected with *T. gondii*.

Methods

We conducted a descriptive observational study by means of an electronic survey sent to the collaborating hospitals. The survey consisted of nine items, which gathered institutional data from the centre along with information on the presence and frequency of *T. gondii* serological screening in pregnant women, or the absence of serological screening and the year it was withdrawn (Appendix B Annex 1). The survey was sent to all investigators belonging to the 118 hospitals in the REIV-TOXO network, and remained open for two months (April and May 2021).

After that, REIV-TOXO coordinators contacted the REIV-TOXO investigators who did not respond to the survey by email to ask them directly about whether or not serological screening in pregnant women was practiced in their respective hospitals (June to September 2021).

Finally, the information obtained was compared with the cases of CT identified in REIV-TOXO, in order to determine whether the children with CT were diagnosed in the presence or absence of prenatal serological screening for toxoplasmosis.

Descriptive statistical analysis of the variables included in the survey was carried out using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

The study was part of the REIV-TOXO project, which received approval from the Independent Ethics Committee of Hospital Universitari de Girona Doctor Josep Trueta on 27 February 2018 (code CEIm 2018.027) as coordinating centre and from the other participating centres, and which has the scientific endorsement of the Sociedad Española de Infectología Pediátrica (SEIP) [Spanish Society of Paediatric Infectious Diseases] and the AEP.

Results

We received a response from 100% of the centres (118/118). In 97% of the cases the survey was completed by a paediatrician (two surveys were completed by a microbiologist and a gynaecologist respectively).

Of the hospitals that participated, 95.8% (113/118) were public or state-controlled and only 4% (5/118) were private. In terms of number of deliveries, 33.0% (39/118) of the hospitals reported more than 2000 deliveries/year, 48.3% (57/118) from 1000 to 2000 deliveries/year, 14.4% (17/118) less than 1000 deliveries/year and 4% (5/118) did not answer.

Serological screening for toxoplasmosis during pregnancy was performed in 53.3% (63/118) of the hospitals in the study period. Of these, 71% (45/63) reported the screening frequency. The majority

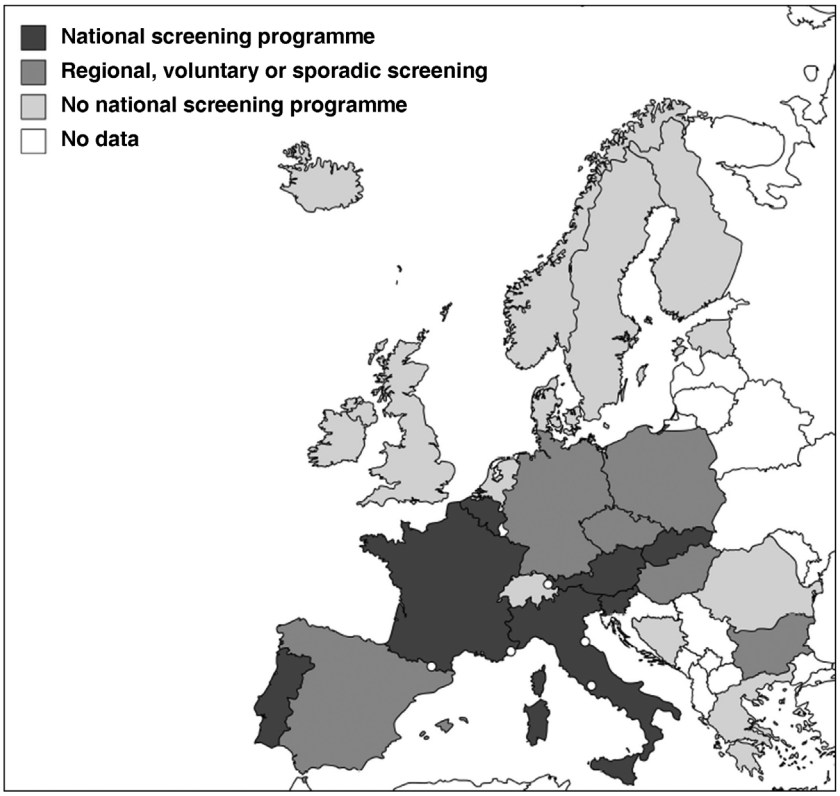

Fig. 1. Current status of prenatal toxoplasmosis surveillance programmes in Europe. Adapted from references.[4,10–14]

carried out screening on a three-monthly basis (26/45; 57.7%), the next most common being a single determination during pregnancy (11/45; 24.4%), and the rest reported screening at other frequencies (8/45; 17.7%). None of the hospitals carried out monthly screening.

Of the hospitals that did not perform prenatal serological screening, 24 reported the date it had been withdrawn: five hospitals before 2015, eight from 2016 to 2018 and 11 since 2019. The geographical distribution of prenatal screening in Spain in 2021 is shown in Fig. 2.

Of the 66 NB with CT detected by REIV-TOXO from 2015 to 2021, 89.4% (59/66) were diagnosed through the screening programme. The seven CT cases diagnosed in hospitals outside the prenatal screening period corresponded to six symptomatic cases and one whose clinical status is unknown due to lack of patient data entered in REIV-TOXO.

Discussion

The results of the national survey on prenatal screening for toxoplasmosis show that serological monitoring of toxoplasmosis in pregnant women in Spain is highly variable and heterogeneous. Most of Spain's autonomous regions have some hospitals that perform screening and others that do not. In general, screening is either carried out three-monthly or not at all in this country. Despite the current situation, the majority of CT cases are still diagnosed through prenatal serological screening.

In hospitals where serological screening is performed, there is a wide variability in the frequency of screening; from three-monthly to single determinations, not to mention centres that perform several determinations, but not three-monthly. We need to be aware that more frequent serological monitoring clearly increases the likelihood of early detection of primary infection and early initiation of treatment. The fewer the serological tests performed during pregnancy, the more complicated it is to interpret the results obtained in conflicting cases. In an immune pregnant woman with specific IgG tested at the beginning of pregnancy, it will not be necessary to repeat serology, but non-immune pregnant women should have continued monitoring. In the case of *anti-Toxoplasma* IgG seroconversion, prior test results (in addition to the IgG avidity result) will be essential to more accurately estimate the time of maternal infection, this being one of the most important factors for initiating early treatment and assessing the risk of transmission and potential morbidity of CT after the birth.

One limitation of this study is that the survey did not specifically include the serological screening strategy (specific IgG or IgG and specific IgM) or the laboratory technique used.

In Spain, the vast majority of CT cases diagnosed and treated come from hospitals that perform prenatal screening. In our study, the screening programme detected 89.4% of cases, enabling treatment of the mother and follow-up of the newborns. The cases followed up in hospitals that did not perform prenatal screening were either symptomatic cases or referred from hospitals that did perform such screening. These results reinforce the idea that the only way to diagnose all cases of CT is by screening, considering that the majority of children do not show symptoms at birth (75% in countries with systematic screening during pregnancy).[15,16] In our study, we found that of the hospitals where prenatal screening is no longer carried out, most have discontinued their programmes since 2016, probably due to the lack of support for screening in the pregnancy monitoring protocols of the institutions and scientific societies.[17–19]

Several arguments have been put forward for stopping prenatal screening. First is the low incidence of the disease. This has not been proven, due to the lack of recent epidemiological data and underreporting in the registries, despite the fact that toxoplasmosis is a notifiable disease (ISS 445/2015).[20] In 2013, the estimated incidence of CT was 2/10,000 live births, similar to the French, with an estimated median annual number of cases of 85 (IQR: 56–117).[21]

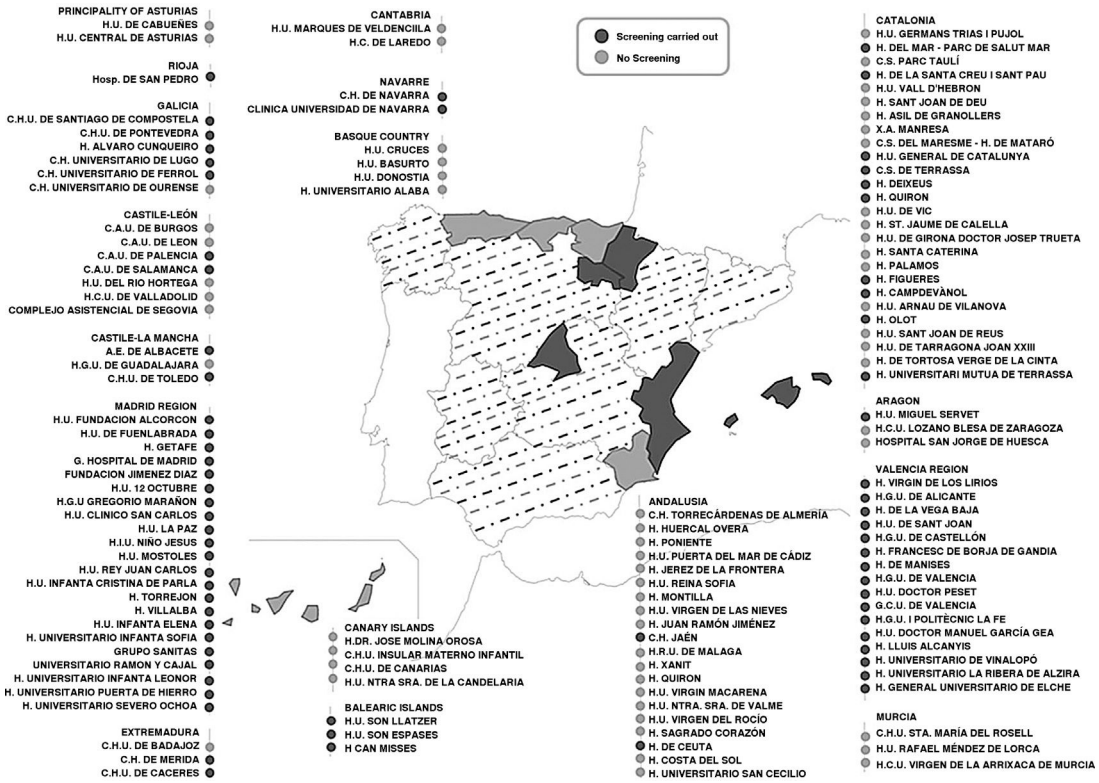

Fig. 2. Geographical distribution of prenatal screening for toxoplasmosis (April–September 2021).
The striped areas correspond to zones with coexistence of the two strategies.

We should point out that other diseases such as syphilis and rubella, with a lower incidence, have well-established prenatal screening programmes in Spain.[22]

Another reason has been the suspected possible decline in the number of cases in recent years, which could compromise the cost-effectiveness of screening programmes. But key to its assessment is knowledge of the incidence and burden of the disease.[23] In Spain, without robust epidemiological data and an accurate assessment of the long-term consequences of CT, this is impossible to determine. In fact, recent cost-effectiveness studies in countries in our region using their own data have been favourable to screening.[24–26]

Another argument which has contributed to screening being discontinued is the complexity of interpreting serological test results in certain cases, but this has been minimised by the existence of better diagnostic methods, guidelines that facilitate interpretation and the support of reference laboratories and experts. In the monitoring of pregnant women, when a primary infection is detected, amniocentesis is recommended after 18 weeks of gestation to try to identify whether or not transmission to the foetus has occurred and to initiate the most appropriate treatment. The potential complications of amniocentesis, an important diagnostic tool in the approach to toxoplasmosis, have also played a role, although the risk appears to be very low and lower than initially described.[27,28] Last of all, despite the available evidence in favour of the beneficial effect of prenatal treatment,[5,6] doubts about its efficacy remain and have contributed to the withdrawal of screening. In contrast, the introduction of monthly screening and amniocentesis in France facilitated early prenatal treatment and significantly reduced symptomatic cases, neurological sequelae and subsequent death.[29]

In conclusion, whether or not to screen remains the most controversial issue in the field of toxoplasmosis. The status of prenatal screening for toxoplasmosis in Spain needs to be rapidly addressed. We believe that the arguments used for phasing out prenatal screening have been lacking in sufficient evidence. It is known that without screening, most cases of CT cannot be detected and treated early, as they are often initially asymptomatic or have non-specific symptoms. In our view, the debate should focus more on determining the frequency and technique for screening than on whether or not prenatal screening is necessary. There is a need to standardise the approach to prenatal toxoplasmosis in order to offer the same possibilities to all pregnant women. To this end, there is an urgent need for epidemiological data in Spain to assist in public health decision-making.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Appendix B. Supplementary data

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