Programs for control of congenital toxoplasmosis

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Summary

Congenital toxoplasmosis can cause miscarriage and neurological and/or eye damage to the fetus. Since Austria and France established the prenatal screening, the prevalence of toxoplasmosis has declined from 50% to 35% and 84% to 44%, respectively. Other countries, such as the United Kingdom, have educational practices to reduce the risk of infection in seronegative pregnant women. In Brazil, prenatal screening is carried out in the states of Mato Grosso do Sul and Minas Gerais and the cities of Curitiba and Porto Alegre. In Londrina, state of Parana, the "Health Surveillance Program for Toxoplasmosis Acquired during Pregnancy and Congenital Toxoplasmosis" was established, which is based on serological screening, advising on prevention measures and quarterly serological monitoring in pregnant women that are initially seronegative, in addition to the monitoring of pregnant women and children with acute infection and case notification. In the first four years of implementation, the program evaluation showed a 63% reduction in the number of pregnant women and 42% in the number of children referred to reference services, resulting in the opening of vacancies for the care of patients with other diseases. As for medications, there was a 62% reduction in consumption of folic acid and 67% of sulfadiazine. Moreover, the definition of the protocols resulted in the standardization of care and safety for the decision-making by physicians. Therefore, as there are several protocols individualized in various departments and regions, the establishment of an ideal, consensual conduct with technical support, will result in implementing measures that will certainly save public resources, with the decrease in congenital toxoplasmosis.

Keywords: Toxoplasmosis, congenital; pregnant women; health programs and plans; primary prevention; secondary prevention; tertiary prevention.

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Introduction

Congenital toxoplasmosis has a major socioeconomic impact, especially if the child is affected by mental retardation and blindness[1]. The prenatal screening is carried out in some European countries, such as France, Austria, Slovenia, Germany, Switzerland, Italy and Belgium, and is based on the detection of IgG and IgM antibodies of the mother[2].

The analysis of cost and effectiveness of screening programs is important in public health policy decisions. Lappalainen et al.[3] performed a cost-benefit study in Finland, where the prevalence in pregnant women is 20.3% and the incidence of congenital toxoplasmosis is 2.4 per 1,000 and concluded that the prenatal screening associated with health education is economically viable when the incidence of maternal infection exceeds 1.1 per 1,000 pregnant women; however, the authors recommend screening even in countries with low incidence of the disease, due to the serious consequences of congenital toxoplasmosis. Countries with a congenital toxoplasmosis prevention program have low prevalence of the disease, confirming the importance of preventing infection in pregnant women[4].

Congenital toxoplasmosis and its sequelae can be avoided through primary prevention (information to susceptible pregnant women about the sources of infection), by serological prenatal screening (gestational toxoplasmosis identified as early as possible, followed by antibiotic treatment to prevent or limit the transplacental transmission and fetal diagnosis and treatment) and also by neonatal screening, followed by antimicrobial treatment of infected newborns to prevent clinical damage[5].

The primary prevention programs should be based on epidemiological and cultural characteristics of each region. Thus, determining risk factors in each population is of vital importance to determine health promotion strategies that should be based on the knowledge of factors that affect the behavior of pregnant women[6].

Suggestions made by the healthcare professionals to at-risk pregnant women are more effective than printed recommendations (magazines, brochures, posters), which are insufficient to change risk behaviors for toxoplasmosis[7,8]. Thus, it is essential that healthcare professionals be trained on prevention measures, in order to appropriately advise pregnant women[9]. Countries with high prevalence of toxoplasmosis successfully instituted secondary prevention programs through maternal serum screening[10].

The cost-benefit of prenatal screening is considered acceptable amidst the definition of the high prevalence in the population (above 40% of seroprevalence in women of childbearing age), whereas in areas of low prevalence, a screening test can be used[11].

Toxoplasmosis prevention strategies, adopted by the several public health systems, are not uniform across different countries or even inside a country. Countries with high incidence of infection, such as France[12], Austria[13] and Slovenia[4], implemented prenatal screening programs, whereas countries with low incidence of the disease have adopted neonatal screening, such as Denmark[14] and Poland[15]. The US[16] and the UK[17], where toxoplasmosis is rare, have no universal serologic screening program.

Programs for control of congenital toxoplasmosis in the world

Maternal screening programs

The maternal serum screening for detection of toxoplasmosis is an important tool, which allows the adoption of early prophylactic and therapeutic measures, thus reducing the rate of vertical transmission and/or fetal development impairment[18]. Therefore, it is essential to start the prenatal care in the first trimester of pregnancy, performing the serological screening, allowing the early identification of acute cases of gestational toxoplasmosis[19]. In cases of seronegativity, the test should be repeated in the second and third trimesters of pregnancy[4].

According to Mitsuka-Breganó[20], there are several advantages in performing the universal prenatal screening in early pregnancy, namely: a) the possibility to recommend preventive measures to seronegative mothers; b) identification of pregnant women with asymptomatic acute infection and an appropriate treatment onset; c) increased care to the fetus and newborn; d) detection of maternal seroconversion by monitoring the serum of initially seronegative pregnant women; e) identification of pregnant women with chronic infection, who do not pose risks to the fetus.

Austria and France were the first countries to establish programs for prenatal screening of toxoplasmosis in 1975 with quarterly serological monitoring and in 1976, with monthly serological monitoring, respectively[13,21], both aiming at establishing preventive measures for seronegative women and ensure both diagnosis and early treatment of infection acquired during pregnancy. In these programs, if the serological screening indicated acute infection, maternal treatment starts with spiramycin in an attempt to prevent transmission to the fetus and, if fetal infection is confirmed by PCR of the amniotic fluid, spiramycin is substituted by a triple regimen consisting of pyrimethamine, sulfadiazine or sulfadoxine and folinic acid[21].

The French program was associated with a decline in both the incidence of congenital infection, as well as of severe disease detected at birth[22] and the prevalence of toxoplasmosis in pregnant women in that country decreased from 84% in the 1960s to 54% in 1995 to 44% in 2003[23]. The seropositivity among pregnant women in

Austria decreased from 50% at the end of the 1970s to 35% in the 1990s[24].

Since 2007, pregnancy and congenital toxoplasmosis surveillance has been performed by the French National Institute for Public Health Surveillance (InVS) of the National Reference Center for Toxoplasmosis, and aims to obtain information on cases of congenital toxoplasmosis diagnosed during pregnancy by amniocentesis or in newborns and children under one year whose mother seroconverted during pregnancy. Thus, one can estimate the overall prevalence of infection in France, follow the trends of prevalence and estimate the proportion of severe forms of infection (hydrocephalus, microcephaly, and retinochoroiditis)[23].

Other countries such as Slovenia, Germany, Switzerland, Italy and Belgium also perform extensive screening during pregnancy; however, it is not performed in the entire country[14].

The prenatal screening, although advocated by some experts as essential to reduce congenital toxoplasmosis[16], has some limitations. Serological tests that detect IgM antibodies, present in recent infections, are most often used for diagnosis of acute toxoplasmosis; however, the most modern methods detect minimal amounts for more than a year after the initial infection (residual IgM)[25], limiting its use. A false-positive IgM antibody result (residual IgM) brings much anxiety to the mother and her family and reduces the positive expectations regarding the new child[26]. Thus, this antibody should not be used as the only marker of acute infection, in order not to expose the mother and fetus to unnecessary risk for fetal diagnosis and treatment procedures.

There are also the medical risks of fetal diagnostic procedures, where the amniocentesis is required, and several reports have identified risk factors associated with fetal loss and other complications for both mother and the fetus, and the side effects of treatment[26,27].

Another disadvantage occurs in countries where the prevalence is lower, as they will have a higher cost of maternal screening due to the higher number of seronegative pregnant women who would need to repeat the serology during pregnancy. Based on these considerations, some experts recommend, for countries where the prevalence and incidence are low, to perform serological screening only in women at high risk of becoming infected by eating raw meat or having contact with soil, associated with primary prevention measures[28] or neonatal screening[14].

Some countries such as the United Kingdom, for instance, have adopted only educational practices in pregnant women considered to belong to high risk groups, according to the anamnesis, in order to reduce the risk of infection[17]. Primary prevention based on pre-natal education also proved to be effective, showing to be a good strategy to reduce congenital toxoplasmosis, as it does not interfere with any other prevention strategies (secondary and tertiary)[2].

Neonatal screening programs

The neonatal screening adopted in Poland[15], Denmark[14] and some US cities[29], countries with low prevalence of congenital toxoplasmosis, consists in the diagnosis of neonatal infection by detecting specific IgM to *Toxoplasma* in newborn screening test or "heel prick test". It is known that about 90% of infected children are asymptomatic at birth and clinical symptoms appear later[30,31].

In the US, Boyer et al.[16] and Montoya and Rosso[32] recommend that newborn screening be performed, as the incidence of congenital toxoplasmosis is equal or higher than other genetic and metabolic disorders (phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia), for which neonatal screening is mandatory by law in many states. In Massachusetts and New Hampshire, USA, all babies go through screening for toxoplasmosis since 1986, by the "New England Regional Newborn Screening Program." During the period from 1986 to 1992, of 635,000 newborns that underwent serological tests, 52 were infected with *Toxoplasma gondii*, which represented an infection rate of approximately one per 10,000 live births[33].

Several studies have demonstrated that the detection of anti-*T. gondii* IgM antibodies using the paper filter technique, identified about 85% of infected children[14,15,33]. However, Gilbert et al.[34] using various techniques for detection of IgM antibodies (ISAG, ELISA, immunofluorescence) and IgA antibodies (ISAGA, ELISA) reported that only 52 to 55% of newborns are IgM-reagents, varying according to the trimester in which the mother seroconverted.

Neonatal screening, when adopted as a single measure, is only responsible for the treatment of the newborn, failing to treat the mother, but this strategy when complementary to the maternal screening, becomes a beneficial tool for both.

Programs for control of congenital toxoplasmosis in Brazil

In Brazil, prenatal screening is suggested as a non-mandatory public policy due to the high prevalence of maternal toxoplasmosis (higher than 40%) being free of costs in some regions, with isolated experience and their own protocols, but without consistency in actions, such as Mato Grosso do Sul, Minas Gerais, São Paulo and Goiás, and the cities of Curitiba in Paraná and Porto Alegre in Rio Grande do Sul[5,25,35-38].

In Mato Grosso do Sul and Goiás, the prenatal screening program is based on a single test performed at the first prenatal consultation and the serological monitoring of initially negative women is not carried out[36,37]. The program in Belo Horizonte, state of Minas Gerais, includes a new serological test in the third trimester of gestation[25], whereas in Porto Alegre and Curitiba serology is repeated every trimester[5,35].

The "Curitiba Mother" program, one of the first implemented in Brazil by the Municipal Health Secretariat of Curitiba**,** state of Paraná, warrants special attention to the pregnant woman, establishing at which hospital the mother will give birth from their first prenatal consultation at the Basic Health Unit (UBS). Serology for IgG and IgM are performed at the first consultation and repeated in the second and third trimesters if the test result is nonreactive and if the patient is at high risk for acquiring the infection. If the pregnant woman is considered low risk, the serology is repeated between the 26th and 28th weeks of gestation. In cases of positive serology for IgG and IgM, the result is confirmed by the IgG avidity test[35].

The inclusion of toxoplasmosis in the Neonatal Screening Program, which complements the maternal screening in Brazil, has been suggested by several specialists[5,39]. Vasconcellos-Santos et al.[40] found 190 confirmed cases of infection in newborns of Minas Gerais, corresponding to a prevalence of 1 in 770 live births in this population.

The ophthalmologic assessment was decisive in 28 children (15.7%) who were suspected of congenital toxoplasmosis at the neonatal screening (positive or indeterminate IgM) disclosing retinochoroidal lesions, suggestive of toxoplasmosis, allowing confirmation that they had been, in fact, congenitally infected. The authors also emphasize that neonatal screening provides other advantages such as lower cost and relative simplicity, and allows the study of large samples.

Furthermore, many women still do not attend regular prenatal consultations and when the mother acquires the infection after the serology was performed, a stage in which the fetal transmission rate is higher, these cases can be detected by neonatal screening[20].

Health Surveillance Program for Pregnancy-Acquired and Congenital Toxoplasmosis in the city of Londrina

The Health Surveillance Program for Pregnancy-Acquired and Congenital Toxoplasmosis was implemented in the city of Londrina in 2006 and is based on the first serological screening in the prenatal consultation, offering recommendations on the prevention measures and serological monitoring every trimester in initially seronegative pregnant women for toxoplasmosis and the monitoring of pregnant women and children with acute toxoplasmosis, as well as case reporting.

A group of experts from various areas (Health Surveillance Secretariat of the Ministry of Health, Health Department of the State of Paraná, Londrina State University) established protocols for the diagnosis, treatment and conducts of mothers and children that were tested and validated in the public health system of this city. These protocols were included in the manual: "Pregnancy-acquired and Congenital Toxoplasmosis: Manual of Health Surveillance, Diagnosis, Treatment and Conducts" [41].

The program is currently implemented in other cities of Paraná such as Rolândia, Cambé, Cascavel, Palotina and Jesuítas, and undergoing implementation in Ibiporã and Maringá. The implementation process is divided into four phases:

1. Adequacy of the program actions: based on the definition of the flow chart of activities, laboratories that will perform the serological screening (for IgG and IgM) and confirmatory (IgG avidity test up to 16 weeks of gestation), of the reference ambulatories that care for pregnant women and children with toxoplasmosis; of the notification system and drug supply for each participating municipality.
2. Training workshops: Training workshops addressing aspects of the life cycle of the parasite, with emphasis on transmission and prevention, laboratory diagnosis and program actions to be implemented. The workshops should be directed at three target groups that care for pregnant women and children: physicians (gynecologists, pediatricians, infectologists, ophthalmologists, neonatologists), nurses that work at the epidemiological surveillance department of the municipality and the FHP (Family Health Program) teams; biochemists in charge of the serological screening and confirmation, and community health and nursing assistants.
3. Start of activities in the basic health units (UBS): implementation of the program in all UBS, managed by a coordinator appointed by the Health Department of the Municipality and with the technical support of the project participants. To give recommendations on the preventive measures, materials will be made available for the pregnant women (booklets, brochures, video animation and posters).
4. Program monitoring and evaluation: monitoring of program activities carried out through visits and regular meetings in the municipalities participating in the program for the detection and resolution of problems and difficulties.

The program evaluation in Londrina showed a 63.9% reduction in the number of pregnant women and 42.6% in the number of children referred to reference services (HU/UEL) for the treatment of toxoplasmosis, resulting in the increase of beds/treatment for pregnant women and children with other diseases. As for drugs, there was a reduction of 62.3% in the use of folinic acid and 67.4% of sulfadiazine. Moreover, the definition of the protocols resulted in the standardization of care and safety for the decision-making by the physicians[20].

After the implementation of the "Health Surveillance Program for Pregnancy-Acquired and Congenital Toxoplasmosis" in Londrina, a study was conducted with pregnant women seeking care in the public health system and

who started prenatal care in the first trimester of pregnancy and seropositivity of 49.2% of anti-*T. gondii* IgG antibodies was found in a sample of 492 pregnant women. Among the variables analyzed, an association was observed with the low *per capita* income, low educational level, the presence of a cat in the residence and the habit of eating raw vegetables. There was no association with the ingestion of raw or undercooked meat and contact with soil[42].

In another study carried out in Londrina, with all pregnant women treated at a UBS between January and July 2007, totaling 634 pregnant women, the authors observed a 50.5% prevalence of anti-*T. gondii* IgG antibodies and a significant association with residing in rural areas, more than one pregnancy, low educational level (< 8 years of schooling) and low *per capita* income.

In Rolândia a 54.4% prevalence of anti-*T. gondii* IgG antibodies was observed and association with residing in rural areas, more than one pregnancy, low educational level, low *per capita* income, age (< 20 years) and a trend towards statistical association with the consumption of untreated water was found.

The pregnant women in Cambé had a prevalence of 46.4% of anti-*T. gondii* IgG antibodies and association only between low educational level and low *per capita* income. In Cascavel, the authors found a 53.0% prevalence of anti-*T. gondii* IgG antibodies and a significant association with age, more than one pregnancy and low *per capita* income.

In the city of Palotina, a prevalence of 61.3% of anti-*T. gondii* antibodies was found and the association between low education level, more than one pregnancy, the presence of cats in the residence and the habit of eating the colonial salami, which is typical of this region, was observed.

This model of health surveillance program for toxoplasmosis can be implemented in any Brazilian city, and based on it, one can obtain epidemiological data, which associated with the geographic, sociodemographic and cultural characteristics, contribute to define strategies for disease control. The Ministry of Health is using this program as a model to implement toxoplasmosis surveillance at national level.

Final considerations

As the maternal, fetal and neonatal diagnostic parameters are complex and difficult to interpret, and there is no technique standardization, interpretations are discordant and the lack of awareness of the limitations of the various techniques for detecting antibodies further complicates the diagnosis. There are several individualized protocols in different departments and regions which adopt different diagnostic and therapeutic measures without evaluating the results. In addition, there is no standardized set of measures that aims to give preventive guidance to such extension in order to reach the healthcare system entrance. The establishment of an ideal and consensual conduct with technical support will result in the adoption of measures which will certainly result in cost decrease for the Public Health System and the reduction in congenital toxoplasmosis.

Moreover, it is essential that each country or each region have its own epidemiological information to establish control programs, particularly for pregnant women, as the incidence and prevalence of toxoplasmosis vary from region to region within the country. This variation is related to dietary habits, contact with the soil, presence of cats, ruralization of domiciles and other less well-established factors. The access to epidemiological data allows the evaluation of the cost-effectiveness of measures, including direct and indirect health costs, considering the prevented fetal and neonatal infections.

Recently, the Ministry of Health has approved Decree# 2472 of 31 August 2010, Annex III, which establishes the list of Compulsory Notification in Sentinel Units (LNCS), including notification of gestational acute and congenital toxoplasmosis, which will allow the evaluation of control programs and will provide data for the implementation of a nationwide program.

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