Congenital toxoplasmosis: prevention, screening and treatment

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Summary: Congenital toxoplasmosis is an established cause of abortion, neonatal disease and ocular defects presenting in later life. Preventative options include health education, immunization and screening of pregnant women and infants with appropriate management of cases found to be at risk. Screening requires a knowledge of the disease, the test, the treatment and the administration of the proposed programme. Treatment can be directed towards the acutely infected mother, the infected fetus or infant and the patient with an acute exacerbation of ocular toxoplasmosis following congenital infection. Harm–benefit assessment of screening programmes designed to prevent congenital toxoplasmosis has produced conflicting results. Further research is required into the incidence of acute toxoplasmosis in pregnancy and subsequent congenital infection, the frequency of neonatal handicap, precise tests for the diagnosis of recent maternal infection and the presence of congenital toxoplasmosis and improved treatment of the infection.

Keywords: Congenital toxoplasmosis; prevention; screening; treatment.

Introduction

Toxoplasma infection of immune competent persons is a benign condition, usually asymptomatic but presenting with self-limiting lymphadenopathy and malaise in a minority of cases. In contrast, infection of immunocompromised individuals results in significant morbidity and mortality. Organ graft recipients, HIV-infected individuals and patients with malignancy may suffer life-threatening toxoplasmosis. However, the fetus represents the largest group of immunocompromised individuals in the population and congenital toxoplasmosis is an established cause of intrauterine death and severe neonatal disease. Late sequelae of congenital infection include ocular disease and mental retardation. In an attempt to reduce the incidence of congenital toxoplasmosis a number of countries, notably France and Austria, have introduced national prenatal screening programmes for this infection. More recently there have been calls from health care workers and lay groups that similar schemes be adopted in the UK and North America. In order to assess the merits of this debate it is necessary to consider the clinical condition that is congenital toxoplasmosis, putative preventative measures—particularly prospective screening—and specific treatment of infected mothers and their offspring.
Toxoplasmosis is primarily acquired by swallowing one of the life-forms of the parasite. Sporocysts are found in soil contaminated by infected cat faeces and may be carried to the mouth on poorly washed vegetables or fingers. Tissue cysts are present in meat derived from infected animals, notably pork and lamb, and remain viable when the meat is eaten raw or lightly cooked. Congenital toxoplasmosis occurs when the parasite establishes an infection of the placenta and subsequently crosses to reach the fetus. Conventional theory is that infection is only transmitted from mother to fetus when maternal toxoplasmosis is first acquired during, or shortly before, conception. This reflects the relatively brief period of parasitaemia after primary exposure when toxoplasma may be carried in the blood to the placenta. However, cases of congenital toxoplasmosis associated with maternal infection acquired prior to conception have been reported in both immune compromised and immunocompetent mothers. The incidence of this phenomenon is not established. Overall, 40–50% of untreated maternal infections acquired during pregnancy will be passed to the fetus. Transmission is more frequent later in pregnancy. However, the incidence of clinically severe congenital toxoplasmosis is greater when the mother is infected during the first trimester, so that only 10% of infected babies are markedly affected at birth (Figure 1).
In most countries the incidence of toxoplasmosis acquired in pregnancy and congenital infection is not established. Based on estimates of maternal infection of two per 1000 pregnancies, it was calculated that 30-40 seriously affected cases of congenital toxoplasmosis may occur in the UK each year. This estimate was found to be discordant with the observation of only 14 cases, not all seriously affected, reported to the British Paediatric Surveillance Unit between 1989-1990. Furthermore, there is evidence that the rate of community exposure to toxoplasma has fallen over recent years, possibly associated with changes in farming practice and the consumption of previously deep frozen meats (toxoplasma cysts are inactivated at low temperatures). Consequently the percentage of susceptible women acquiring toxoplasmosis in pregnancy may fall, although the susceptible population will have increased.

Primary toxoplasma infection of pregnant women is asymptomatic or accompanied by a mild, self-limiting non-specific illness of malaise and lethargy in over three-quarters of cases. As a result, acute maternal infection is rarely clinically apparent, unlike other infections which threaten the fetus such as rubella and varicella. Over 90% of congenitally-infected infants are asymptomatic at birth. The classical triad of congenital toxoplasmosis (hydrocephalus, intracranial calcification and choroidoretinitis) is very much the extreme and less usual clinical presentation. Non-specific signs of congenital toxoplasmosis include hepatosplenomegaly, jaundice, thrombocytopenia, growth retardation and rash, but these are rarely seen in the absence of the more characteristic features. Acute maternal toxoplasmosis can result in intrauterine death, particularly when acquired early in pregnancy. Cases of chronic maternal toxoplasmosis resulting in spontaneous abortion have also been described, but the incidence of these sequelae are not known. Long-term follow-up of initially asymptomatic children with congenital toxoplasmosis is vital to establish the frequency of late onset disease associated with the condition. Due to the low numbers of identified cases and the need to monitor for several decades, only a few, small studies have been completed. A Dutch study found that four of five symptomatic treated children, and four of six asymptomatic, untreated children developed ocular lesions, some appearing as late as 18 years after birth. In a second, North American study, seven of 13 asymptomatic children with congenital toxoplasmosis were treated prospectively. Of these 13 children three developed unilateral blindness, five showed bilateral retinitis and three developed unilateral retinitis. Five children developed neurological defects.

Prevention of congenital toxoplasmosis

Congenital infection may be prevented by intervention at a number of stages in the progression of the disease. Primary prevention seeks to eliminate toxoplasma infection of the pregnant women and could be achieved by vaccination or health education programmes. If maternal infection has
Figure 2. Prevention of congenital toxoplasmosis.

Vaccination
There are a number of approaches to the prevention of toxoplasmosis by vaccination. Live vaccines incorporate avirulent strains of toxoplasma attenuated by irradiation or temperature sensitivity. These preparations are more immunogenic than vaccines using extracts or homogenates of killed parasite. Heterologous immunization uses the cross-reactivity of closely related organisms, such as Hammondia hammondi, to induce resistance to toxoplasma infection. Other methods include induction of non-specific immunity with adjuvant preparations or the injection of toxoplasma nucleic acid. None of the vaccines is suitable for use in humans due to problems of chronic infection with subsequent reactivation, toxicity, or lack of solid long-lasting immunity to ‘wild strain’ infection. A temperature sensitive mutant of toxoplasma (S48) has been used to protect sheep in field trials and may limit one source of human infection.

Health education
Human toxoplasmosis is acquired by swallowing tissue cysts in raw or partially cooked meats or from ingestion of sporocysts contaminating soil

occurred, those pregnancies ‘at risk’ might be identified by systematic screening. Secondary prevention involves treatment or termination of pregnancies found to be at risk during systemic screening. Tertiary prevention attempts to identify the infected fetus or baby and to manage such cases by termination of pregnancy or specific treatment. At this level ‘prevention’ aims to reduce the number of affected cases rather than to reduce the incidence of infection. A programme aimed at reducing the incidence of clinically apparent congenital toxoplasmosis may include any or all of the measures indicated in Figure 2.
Congenital toxoplasmosis

Table I. Health education to reduce exposure to Toxoplasma gondii

<table>
<thead>
<tr>
<th>Objective:</th>
<th>Avoid swallowing the parasite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action:</td>
<td>Basic hygiene is sufficient</td>
</tr>
<tr>
<td>Specifics:</td>
<td>Wash hands after handling raw meat or gardening. Wear gloves if possible</td>
</tr>
<tr>
<td></td>
<td>Only eat meat which is well cooked. Do not eat raw or undercooked meat or drink unpasteurized milk</td>
</tr>
<tr>
<td></td>
<td>If possible let someone else clean cat litter trays. Otherwise, clean daily wearing gloves and wash hands immediately afterwards</td>
</tr>
</tbody>
</table>

Table II. Screening options for toxoplasmosis associated with pregnancy

<table>
<thead>
<tr>
<th>Population screened</th>
<th>Target group to be identified</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women pre-conception</td>
<td>Not exposed to toxoplasma</td>
<td>Health education (vaccination)</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Acute toxoplasma infection</td>
<td>Termination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal assessment</td>
</tr>
<tr>
<td>Neonates</td>
<td>Congenital toxoplasmosis</td>
<td>Specific therapy in early life.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ophthalmic supervision</td>
</tr>
</tbody>
</table>

or vegetables. The relative importance of the different routes of transmission are not established and may vary from one region to another.17 Broad health education with emphasis on good hygiene18 is offered to pregnant women in an attempt to reduce the incidence of acute toxoplasmosis (Table I). Although widely promoted, the efficacy of this approach is not fully evaluated. Appropriate health education can alter the behaviour of pregnant women in such a way as to reduce potential exposure to the parasite19 but the effect on the acquisition of toxoplasmosis has not been studied. Poorly designed information may be counterproductive by raising anxiety levels. Effective communication with the patient population requires planning, a selective content and must pay careful attention to the use of language. Illustrations are of lesser value.20

Screening

Screening for congenital toxoplasmosis can be performed in a number of ways, each with distinct objectives (Table II). Screening of women before conception attempts to identify those at risk of subsequent acute infection and to offer these persons appropriate health education or, in the future, vaccination. Screening of pregnant women is designed to recognize those
with acute toxoplasmosis who may benefit from specific therapy and can be offered further tests to determine the status of the fetus. Screening of samples from neonates tries to identify congenitally-infected babies who require drug therapy in early life, followed by ophthalmic supervision. The widely publicized French national screening programme is based on pre-conception testing of women, followed by periodic assessment of susceptible individuals throughout pregnancy looking for seroconversion. When acute infection is detected, ultrasound investigation and testing of fetal blood obtained by cordocentesis is performed. Fetal blood sampling is associated with significant morbidity and mortality and the general validity of this technique has been questioned. When applied to toxoplasmosis associated with pregnancy, the sensitivity of detecting congenital infection was found to be 93% and a lack of specificity has been reported.

When results of pre-conception tests are not available, difficulties arise in the estimation of the duration of maternal infection. The kinetics and magnitude of the individual's serological response to toxoplasma infection are variable, as are the sensitivity and specificity of different tests to detect acute infection. Consequently, women may be falsely reassured as being chronically infected or inappropriately managed as acutely infected in early pregnancy. At present there is no precise test of recent toxoplasma infection other than seroconversion; estimation of parameters such as IgM and IgG avidity are not sufficiently reliable for population screening. Postnatal screening for congenitally-infected infants has been performed in New England since 1986. Although this approach does not allow therapeutic intervention during the pregnancy it has the advantages of reduced screening costs and avoidance of controversy over therapeutic abortion. It is particularly appropriate in regions where immunity in the pregnant population is low. The New England programme is based on the detection of toxoplasma-specific IgM in neonatal blood samples obtained by heel-prick and stored on filter paper. The sensitivity and specificity of this approach has not been established, but the system would not be expected to identify asymptomatic cases of congenital toxoplasmosis which lack a detectable IgM response and which may constitute the majority of cases of congenital toxoplasma infection. An alternative system of postnatal screening has been established in Denmark. Here, first trimester maternal blood and neonatal Guthrie card samples are compared for toxoplasma IgG status in order to select instances of seroconversion. Children resulting from 'at risk' pregnancies are then investigated during the first year of life (Table III).

A major defect of all screening models for congenital toxoplasmosis has been the failure to achieve satisfactory case compliance. In a UK study only 50% of self-selected, motivated women, found to be at high risk of congenital transmission, completed an investigation procedure leading to a final diagnosis of the status of the child. Indeed, in the absence of enhanced specialist intervention, this figure fell to 25%. In France, 133
Table III. *Screening procedures for toxoplasmosis associated with pregnancy*

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Pre-conception IgG</td>
<td>High sensitivity and specificity due to precision of IgG tests</td>
<td>Poor compliance with pre-conception testing</td>
</tr>
<tr>
<td></td>
<td>IgG status during pregnancy</td>
<td>Early intervention for 'at risk' pregnancies</td>
<td>Costs of multiple tests during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Confirmation of seroconversion by IgM measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3, 25, 41</td>
<td>IgG ± IgM status in early pregnancy</td>
<td>Improved compliance</td>
<td>Poor specificity of IgM as a measure of recent infection</td>
</tr>
<tr>
<td></td>
<td>IgG and/or IgM assessment during pregnancy</td>
<td>Early intervention for 'at risk' pregnancies</td>
<td>Costs of multiple tests during pregnancy</td>
</tr>
<tr>
<td>27</td>
<td>IgG status in early pregnancy</td>
<td>High sensitivity and specificity due to precision of IgG tests</td>
<td>Does not allow intervention prior to delivery</td>
</tr>
<tr>
<td></td>
<td>IgG status on cord blood</td>
<td>Improved compliance</td>
<td>Reduced costs</td>
</tr>
<tr>
<td>26</td>
<td>IgM testing of cord blood</td>
<td>Much reduced costs</td>
<td>Poor sensitivity as IgM-negative infected babies are not identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full compliance</td>
<td>Does not allow intervention prior to delivery</td>
</tr>
</tbody>
</table>

(41%) of 326 infants with suspected congenital toxoplasmosis were not followed up for more than six weeks.29

**Treatment**

Management of toxoplasmosis associated with pregnancy can be directed toward the mother, the fetus and the baby (Figure 2). Once infection is established no treatment is curative because none of the currently available anti-toxoplasma drugs have reliable activity against the cyst form of the parasite.30 Consequently, treatment of the mother aims to prevent fetal infection while treatment of the fetus and infant aims to limit physical damage due to infection.

When a pregnancy is found to be at risk due to acute toxoplasma infection
many women will opt for termination even though the majority of babies in such cases are not infected and an even smaller number would be affected by toxoplasmosis. Detailed counselling is required prior to screening to ensure such decisions are based on an informed opinion. Women who elect to continue the pregnancy should be offered spiramycin therapy in the first instance. Spiramycin is a macrolide drug, similar to erythromycin, which concentrates in the placenta and reduces the incidence of maternal–fetal transmission of toxoplasmosis.\textsuperscript{31} It is without serious side-effect in pregnancy but the efficacy of the drug has not been assessed in a double-blind placebo controlled trial.\textsuperscript{17} Many health workers are of the opinion that such a trial would now be unethical due to the established reduction in placental infection after spiramycin therapy.\textsuperscript{32} Prospective studies suggest that maternal spiramycin treatment results in a 60\% reduction in congenital toxoplasmosis.\textsuperscript{1} When radiology or fetal serology indicates congenital infection has been established, a late termination of pregnancy can be considered. Otherwise a sulphonamide, such as sulphadiazine, plus pyrimethamine with folinic acid supplementation may be given in short courses alternating with courses of spiramycin until delivery. One study found that the placenta was infected in 77\% of women given spiramycin against 42\% of women who received combination therapy, suggesting improved efficacy as a prophylactic measure.\textsuperscript{33} Due to the toxicity of the combined therapy and the teratogenic potential of pyrimethamine, many authorities reserve combined treatment for cases where there is substantive evidence of fetal infection.\textsuperscript{22} This approach may result in fewer cases of clinical disease after congenital infection.\textsuperscript{33,34}

Postnatal treatment of infants born after acute maternal toxoplasmosis depends on the clinical, radiological and serological status of the child. If the child is asymptomatic with normal radiology of the skull, no detectable specific IgM or IgA and a failure to isolate the parasite from the placenta or neonatal blood, management consists of periodic serological assessment to monitor the removal of passively-acquired IgG of maternal origin. No specific therapy is indicated. When the child has clinical, serological or parasite isolation evidence of congenital infection, specific therapy comprises alternating courses of spiramycin followed by a combination of sulphonamide with pyrimethamine plus folinic acid.\textsuperscript{22,33} Some paediatricians also give systemic steroids if neurological damage is severe. Treatment is continued through the first 12 months of life in an attempt to limit tissue damage until the child’s immune system matures sufficiently to control the infection.\textsuperscript{30} Comparison of the outcome of treated infants with those of historical controls suggests postnatal therapy may reduce the incidence of sensorineural hearing loss.\textsuperscript{35} Active exacerbation of ocular toxoplasmosis in later life subsequent to congenital infection requires short-course antiparasite and anti-inflammatory therapy.\textsuperscript{30}
Table IV. *Principles of screening*

| Disease: | The disease should be an important health problem with a well-described natural history and identifiable early stage |
| Test: | There should be a suitable diagnostic test, acceptable to the target population |
| Treatment: | Treatment at the early stage of the disease should be of greater benefit than delayed treatment |
| Administration: | There should be adequate facilities for diagnosis and effective treatment of cases identified |
| Harm:benefit ratio: | Screened individuals should have a lower risk of physical or psychological harm than the chance of benefit |

**Harm -- benefit assessment**

The evaluation of a systematic programme of prevention, screening and treatment of toxoplasmosis associated with pregnancy must apply certain criteria.\(^36\) It is necessary to establish basic facts about the disease itself, the diagnostic tests to be used, the treatment of the condition and the administrative structure of the programme. Overall the benefits of the programme must outweigh the associated harm (Table IV). In the context of congenital toxoplasmosis, a number of problems exist when evaluating intervention programmes. The size of the problem remains uncertain in most countries.\(^8\) Most importantly the degree of handicap due to congenital toxoplasmosis has not been defined and calculations based on disease presentation prior to the development of modern medical management may be inappropriate.\(^6\) The precision of toxoplasma serology tests may not be adequate when applied to a large population with a low incidence of infection\(^25\) so that excessive numbers of false-positive and false-negative findings may occur. Patient acceptance of diagnostic and management for toxoplasma in pregnancy has been assumed despite a number of studies indicating that compliance is, in reality, relatively low.\(^28,37\) In many countries there are insufficient resources for the patient counselling, detailed laboratory testing and fetal blood sampling required in a screening programme. The efficacy of drug therapy of acute toxoplasmosis in pregnancy, fetal infection and during the postnatal period has not been subjected to vigorous, controlled trials. These limitations indicate that any calculation of the harm: benefit ratio is speculative at best.

Benefits of screening for congenital toxoplasmosis include: a reduction in the numbers of babies born with overt disease and of those who develop ocular problems in later life; a reduction in the severity of damage in some infected individuals; the provision of reassurance to pregnant women found to be immune to the infection; and the satisfaction of parental demand for
the screening process itself.\textsuperscript{20} Harm associated with screening includes: wastage of uninfected or infected but undamaged fetuses;\textsuperscript{6} psychological damage to the parents when the programme fails and a child with congenital toxoplasmosis is born; maternal concern generated by the necessary delays and decision-making involved during testing;\textsuperscript{38} and the complications of drug therapy and termination of pregnancy.\textsuperscript{39} Calculations of the financial costs of screening and the savings in health expenditure resulting from the prevention of handicap are complex and imprecise. Some studies have concluded that UK costs would outweigh savings\textsuperscript{40} while others found the reverse situation in Scotland.\textsuperscript{41} Global consideration of the harm:benefit ratio have led some authorities to promote screening in the US,\textsuperscript{5} France\textsuperscript{42} and the UK.\textsuperscript{4,20} Others have considered the same data and concluded that screening should not be introduced in the UK\textsuperscript{43} and questioned its continuation in France.\textsuperscript{17} As a result, \textit{ad hoc} testing on demand takes place in the absence of organized screening programmes in most countries while Austria and France remain committed to prenatal screening despite suboptimal evaluation of this approach.\textsuperscript{6}

\textbf{Future prospects}

Given the present unsatisfactory position, which is the way forward? Firstly, a clear understanding that the pregnant woman with an illness compatible with toxoplasmosis should be investigated. In the UK the well but worried woman should be given careful counselling as to the benefits and potential harm that could be generated by screening and only selected individuals should proceed to testing. Routine screening of a pregnant population is not indicated outside of ethically approved, properly funded, scientific studies.\textsuperscript{43} All pregnant women should be given simple health education concentrating on the value of good hygiene. Those interested in the subject must recognize that the onus of proof lies with those who believe routine screening should be introduced. Any programme must be regarded as experimental research until the value and safety of that approach has been confirmed.\textsuperscript{44} Directed research is required into the incidence of toxoplasmosis in pregnancy and of congenital infection, the frequency of physical or mental handicap due to congenital toxoplasmosis,\textsuperscript{43} development of screening tests for the infection with enhanced precision and the introduction of efficacious, safe treatment, particularly drugs which eradicate the cyst form of the parasite.

Health care workers and lay groups must accept full responsibility for the sequelae of their actions. The general practitioner, obstetrician or midwife who orders toxoplasma serology testing of a pregnant woman must appreciate that this action may result in a child being subjected to repeated investigations in early life. Patient help groups who promote routine screening and claim credit for a beneficial outcome should share the responsibility when harm results. Most importantly perhaps, those for and
against screening should cooperate towards the common goal of improved health care. The two sides have been portrayed as the ‘evangelists’ marching towards the holy grail of universal screening and the ‘snails’ studiously considering the problems along the route. The enthusiasm of one group should be combined with the logic of the other to secure progress through good research.

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References