Regular Review

Congenital toxoplasmosis

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The history of toxoplasmosis began in 1923 with the first published description of a human case, a congenitally infected baby. *Toxoplasma gondii* had been recognised 15 years earlier, but it was not until 1969 that the life cycle of this protozoan parasite was understood, with the discovery that the definitive host was any member of the cat family (fig 1).[1,2]

Despite extensive clinical and epidemiological reporting toxoplasmosis had a relatively low profile until the 1980s, since when it has attracted interest for two reasons. Firstly, it is an important cause of mortality and morbidity in HIV infected patients; secondly, the possibility of preventing or ameliorating its congenital form in the United Kingdom through introduction of a prenatal screening programme became the subject of professional and then public debate.[3-8] This review will focus mainly on the second issue because a recently published report by a multidisciplinary working group has recommended that such a programme should not at present be introduced, a conclusion which is likely to kindle further interest in toxoplasmosis.[9]

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Natural history and clinical features

Toxoplasmosis is a common infection throughout the world and is acquired principally via the oral route

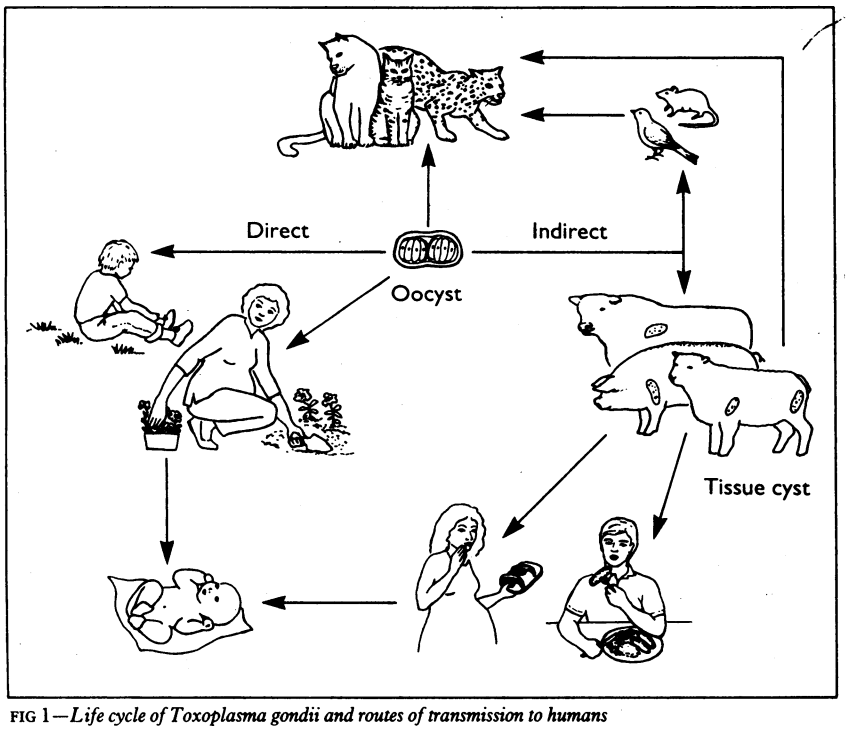
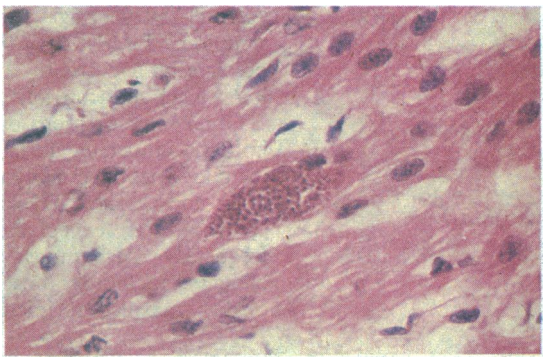


FIG 1—*Life cycle of Toxoplasma gondii and routes of transmission to humans*



Tissue cyst of Toxoplasma gondii in myocardium

or transplacentally. After initial acquisition there is a parasitaemia and widespread dissemination throughout the body. The acute stage of the infection then changes to the latent phase, during which the organism encysts in many tissues, particularly in skeletal and cardiac muscle and in the brain. These cysts contain viable toxoplasma and persist for life; they are not thought to affect the health of immunocompetent hosts—their existence is indicated only by the presence and persistence of IgG antibody specific for toxoplasma. However, if the immune system of the host is disturbed the cysts may reactivate, causing either disseminated infection, which may have such severe manifestations as encephalitis or myocarditis, or local tissue damage as in toxoplasmic retinochoroiditis.

ACQUIRED TOXOPLASMOSIS

Acute, postnatally acquired toxoplasmosis in immunocompetent subjects is difficult to diagnose because symptoms may be absent or non-specific and because the differentiation of acute from latent infection can be problematic. The proportion of total cases in whom the infection is truly asymptomatic is not known, but probably varies according to the strain of *T gondii* acquired and the degree of care with which a history of non-specific symptoms is sought. In the few outbreaks of toxoplasmosis which have been described about a quarter of the patients had no symptoms; however, studies of pregnant women interviewed after giving birth to a congenitally infected infant reported that most of the women were asymptomatic.[1,2]

Symptomatic acquired toxoplasmosis has various non-specific manifestations which may occur singly or in combination. These include a low grade fever, which may be persistent; generalised malaise and extreme tiredness; myalgia; and lymphadenopathy. Lymphadenopathy is an important sign—cervical nodes, both anterior and posterior, are most commonly

affected, but enlargement of suboccipital, axillary, inguinal, intra-abdominal, and intrathoracic nodes can occur; occasionally only one isolated node is affected. The enlargement may persist for up to six months or occasionally even longer; the nodes are usually firm; mobile; discrete; and, sometimes, initially tender.

Toxoplasmosis should also be considered in the differential diagnosis of glandular fever-like illnesses. Although this is an uncommon presentation, it can be indistinguishable from Epstein-Barr virus infectious mononucleosis, although sore throat and hepatosplenomegaly are less prominent features in toxoplasmosis.

Acute uveitis, typically retinochoroiditis, may be another manifestation of toxoplasmosis. Most such presentations are widely believed to be caused by reactivation of retinal cysts associated with congenital infection, but some authors are cautious about this assumption because acquired toxoplasmic uveitis has been described (albeit rarely) and because for most patients presenting without any accompanying symptoms for the first time in adulthood it is not possible with currently available laboratory tests to know when the acute infection took place.

Other manifestations of acquired toxoplasmosis in immunocompetent hosts are extremely rare; they include hepatitis, polymyositis, a range of skin rashes, lung and kidney involvement, encephalitis, and carditis. Both encephalitis and carditis are more frequently encountered in immunocompromised patients, including those with HIV infection and cardiac transplant recipients.

CONGENITAL TOXOPLASMOSIS

Most babies with congenital toxoplasmosis are asymptomatic at birth or have non-specific symptoms such as intrauterine growth retardation, hepatosplenomegaly, purpura, and jaundice. Some of these may, however, subsequently develop sequelae, of which retinochoroiditis is the most commonly recognised; this is reviewed in more detail below. A minority of congenitally infected neonates will have severe manifestations presenting at birth or during infancy; these manifestations include one or more components of the "classic triad" of congenital toxoplasmosis: hydrocephalus, intracranial calcification, and retinochoroiditis. Involvement of the central nervous system, occasionally with widespread tissue destruction, and also of the eyes, are the most important manifestations of symptomatic congenital toxoplasmosis, but there may also be extensive involvement of other organs including the liver, heart, and lungs.

Treatment

Acute acquired toxoplasmosis in immunocompetent, non-pregnant patients is not usually a serious illness, and specific treatment is not indicated. The indications for treatment are severe disseminated disease in immunocompromised patients, toxoplasmic uveitis affecting or threatening the macula, and maternofetal and neonatal congenital infections. The first two conditions require specialist care; maternofetal and neonatal congenital infections and aspects of methods of diagnosing toxoplasmosis are covered in this review because they are an integral part of approaches to preventing congenital toxoplasmosis.

Congenital toxoplasmosis: opportunities for prevention

Figure 2 summarises the ways of preventing congenital toxoplasmosis; the principles of primary, secondary, and tertiary prevention can apply to any infection which, if acquired in pregnancy, may be transmitted to the fetus. There is, however, an important difference between toxoplasma and many other fetopathic organisms, which is its susceptibility to chemotherapy. The most commonly used agents are spiramycin (a macrolide antibiotic which concentrates in the placenta, but whose efficacy once fetal infection is established is questioned[2]) and combination therapy of pyrimethamine and a sulphonamide (also used in treating acquired infection in non-pregnant patients, when appropriate), which do readily cross the placenta.[1,2] If maternal parasitaemia is diagnosed in time chemotherapy may therefore be possible to prevent transplacental transmission of the organism (secondary prevention) or, if this has occurred, to limit tissue damage in an infected fetus or neonate (tertiary prevention). Because screening involves secondary and tertiary prevention it will always be a less satisfactory approach than primary prevention.

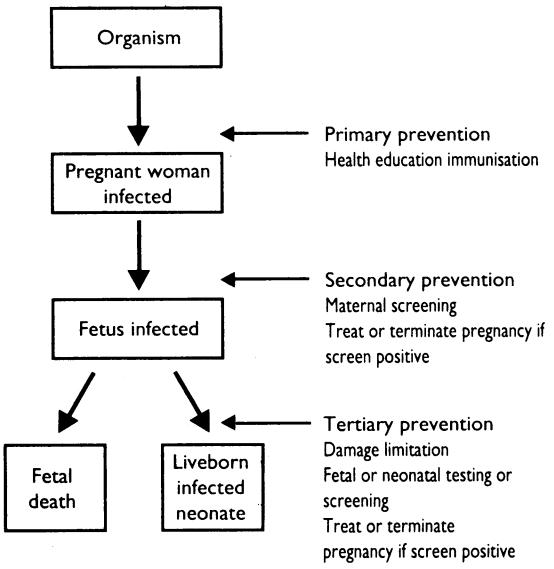


FIG 2—*General scenarios for prevention of disease caused by intrauterine infection*

Primary prevention

Although research is in progress, there are no immediate prospects of a human vaccine against toxoplasma[1,10] (animal vaccines, however, have been developed[11]). Elimination of environmental contamination by cats' faeces, though desirable, is impractical on a wide scale, so health education to avoid risk behaviour is currently the main option for primary prevention.

Unfortunately it is not known how most toxoplasma infections are acquired. It is, however, inferred from the life cycle of the parasite (fig 1) that this occurs mainly through the oral route, either from raw or undercooked meat containing tissue cysts or from environmental sources contaminated by the oocyst phase of the parasite.[12] Oocysts are shed for about two weeks in the faeces of cats who have recently acquired the infection; animals destined to be eaten as meat and humans may become infected from this source and develop tissue cysts. There is also evidence that infected animals shed the organism in milk and that this can be a vehicle of infection for humans.[13] At least one waterborne outbreak of toxoplasmosis has been recognised,[14] but the contribution of this route to sporadic cases has not been fully explored. There has been little published evaluation of the effectiveness of health education programmes in preventing maternofetal toxoplasmosis.[2] It is essential, however, to assess the impact of this approach because if primary preven-

tion proved to be ineffective then secondary and tertiary prevention through prenatal or neonatal screening could assume greater importance.

Secondary prevention

PRENATAL SCREENING ALGORITHMS AND TESTS

Prenatal screening for toxoplasmosis has existed in France and Austria for many years, and the programmes based in Paris have been described in detail.[15 16] Figure 3 outlines the principles: they centre on determining by antibody measurement whether a pregnant woman has a current infection (screen positive) or latent infection (immune) or has not yet been exposed (susceptible). The success of the programme in achieving secondary or tertiary prevention depends on the validity of the belief that only maternal infection acquired for the first time since conception poses a risk to the fetus (which is questioned later in this review). It also depends on correctly identifying such infection in time to intervene with chemotherapy; this may be followed by fetal diagnosis at an appropriate gestational stage (about 20 weeks onward) when fetal blood can be sampled and then, if indicated, by further chemotherapy or termination. Repeated maternal serological testing is necessary because of the lack of symptoms or the non-specific nature of symptoms associated with most toxoplasma infections described above.

A wide range of tests to measure toxoplasma specific antibodies of various classes is available.[1 17] Those which measure IgM and IgG (indicative of recent and latent infection respectively) are most commonly used. The Sabin-Feldman dye test is the accepted reference test for toxoplasma infection and measures both IgG and IgM. It uses viable parasites so its use is limited to reference laboratories.

The validity of the various toxoplasma IgG assays relative to the dye test is very variable; published sensitivities range from 81% to 99% and specificities from 59% to 98%.[17] The validity of the IgM tests has been less clearly defined because series of reference sera showing dye test seroconversion are of limited availability. Furthermore, toxoplasma specific IgM can persist at low titres for many months after acute infection, so the more sensitive the test, the more likely it is that a positive result for IgM may reflect infection acquired a year or more ago. Because of this difficulty and the need in prenatal screening to date infection accurately in relation to conception assays of other toxoplasma specific antibodies, for example, IgA and IgE, and also of the avidity of IgG antibody binding, have been developed.[17 18] These have not yet been evaluated in screening; although they show promise, their usefulness may be limited by the same biological variability of the host's immune response which causes difficulty in interpreting IgM antibody results.[19]

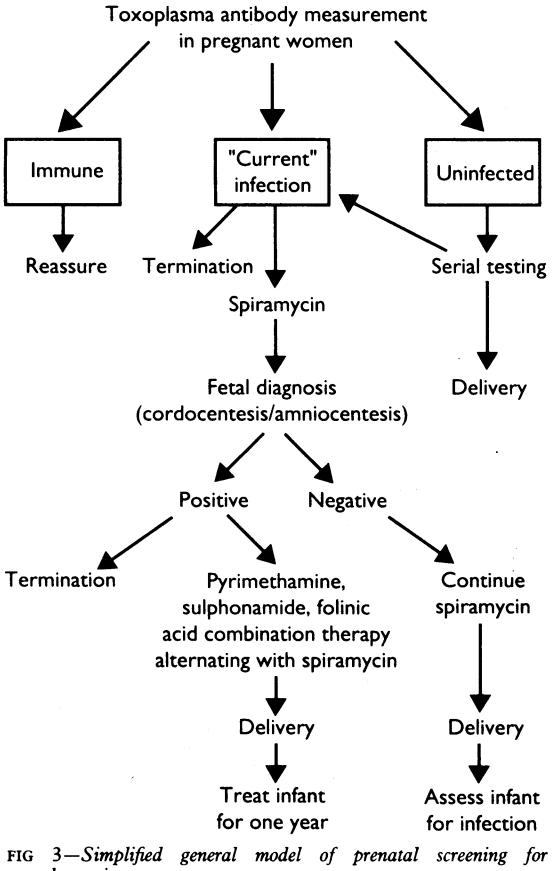


FIG 3—*Simplified general model of prenatal screening for toxoplasmosis*

GENERAL ARGUMENTS FOR AND AGAINST SCREENING

Arguments in favour of prenatal screening for toxoplasmosis are as follows. Firstly, for screen positive women intervention with chemotherapy or termination could prevent not only death and handicap caused by congenital toxoplasmosis but also the associated mental and social trauma for the patients and their families and use of resources in caring for those afflicted. Secondly, for the remainder there would be either reassurance that there is no risk to the fetus, if the woman is already immune to toxoplasma, or identification of susceptible women for primary prevention by health education. These arguments are persuasive and have been voiced by the medical profession, lay groups, and the media.[3-5 7 8 20]

Some of the arguments against prenatal screening for toxoplasmosis have been aired, but not widely, especially not in the public arena.[6 21 22] They centre on the physical and mental harms such a programme could cause to mother and fetus—both those who are infected and, equally importantly, those who are not.

It is unfortunate that the public debate has been weighted towards the advantages of prenatal screening because there is an ethical imperative to ensure certainty that the benefit to each subject of screening outweighs the harm[23] and because there is no obvious advocate for the potential subjects of this or indeed other such programmes. Screening is a powerful tool of preventive medicine because of its potential to turn a "person" into a "patient" (often wrongly) and because, although it is unlikely to be enforced in a population, it presents an offer that almost cannot be refused, especially if the subject is a pregnant woman. Tymstra calls this the "imperative nature of medical technology" and describes the response as "anticipated decision regret."[24]

The working group report is therefore timely as it subjects the available evidence on all aspects of toxoplasmosis in pregnancy to critical review in the light of the World Health Organisation criteria for screening[25] and highlights gaps in knowledge which are relevant to those criteria and require further research. These areas of uncertainty are extensive and involve some fundamental issues.

Areas of uncertainty

SIZE OF PROBLEM OF CONGENITAL TOXOPLASMOSIS

The size of the problem of congenital toxoplasmosis in the United Kingdom is unknown; this includes both numbers of new cases arising each year and the physical, emotional, and social burdens of the resulting impairment, disability, and, most importantly given the strengths of modern medical management, of handicap. If not even these basic facts are known the clinical, monetary, and other costs of a screening

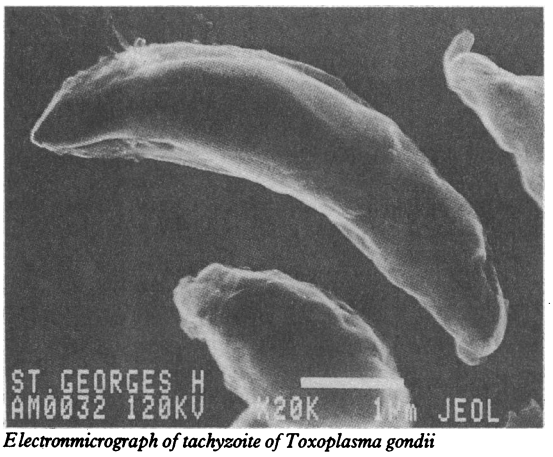
programme cannot reliably be weighed against those of disability and handicap potentially prevented.

Diagnostic suspicion of congenital infection is likely to be high among infants presenting with one or more of the signs of the classic triad, and theoretically the size of the problem of symptomatic congenital toxoplasmosis in England and Wales should be measurable with the national voluntary laboratory reporting system. The limitations of this routine data source, however, were highlighted several years ago,[26] one difficulty being that there is no single laboratory test which will identify all cases of congenital toxoplasmosis in infancy, even those in which symptoms are present.

The prevalence of symptomatic congenital toxoplasmosis at birth in the United Kingdom has therefore been estimated.[6 27] The estimates are based, firstly, on French studies conducted up to three decades ago which suggested that fetal toxoplasma infection occurs in about 40-50% of untreated maternal infections and that about 10% of infected neonates have severe disease evident at birth or in the first year of life, with involvement of the central nervous system,[1 2] and, secondly, on survey data on the incidence of gestational toxoplasmosis (about two per 1000 pregnancies) in three areas of Britain between 1970 and 1988.[1 3 5 28] A figure of about 50-70 seriously affected births a year in England and Wales can thus be derived. As these would all be babies with significant damage to the central nervous system and eye involvement the burden of disability could be considerable. This estimated figure differs substantially, however, from that (14, not all with involvement of the central nervous system) observed in 12 months during 1989-90, when paediatricians were asked to report cases of symptomatic congenital toxoplasmosis to the British Paediatric Surveillance Unit (British Paediatric Surveillance Unit, unpublished data).

A similar discrepancy between observed and expected numbers was described in Scotland,[5] and the reasons are unknown. It is too large to be explained by underdiagnosis (which is unlikely in these severe cases) and underreporting, and it reflects current ignorance of the incidence and natural history of gestational toxoplasmosis nationwide in the United Kingdom in the 1990s (in fact there is some evidence that the incidence of the infection may be declining).[29]

Even less is known about the short term and long term morbidity among the (estimated) 90% of babies with congenital toxoplasmosis who are either asymptomatic or have non-specific symptoms at birth. Authors who have argued in favour of prenatal screening suggest that there may be several hundred such children born in the United Kingdom each year who will eventually develop serious neurological damage or visual disability.[8 20 27] These estimates are based on two studies conducted in the Netherlands and the United States which together included 22 neonates with congenital toxoplasmosis who were asymptomatic or had non-specific symptoms, who were followed for up to 20 years: 17 developed retinochoroiditis, of whom six had visual impairment but none were blind; five had neurological sequelae, which was significant and persistent in only one.[30 31]



Electronmicrograph of tachyzoite of Toxoplasma gondii

The dangers of extrapolating from such a small sample are obvious, but, paradoxically, there are problems in studying this aspect of congenital toxoplasmosis. Most important is the difficulty of prospectively identifying sufficient numbers of asymptomatically infected neonates for follow up and the need to follow such cases for many decades. The alternative is retrospective measurement of the burden of visual disability caused by congenital toxoplasmosis by recruiting patients with visual symptoms. However, this approach is complicated by appreciable difficulties in conclusively diagnosing toxoplasmic retinochoroiditis in otherwise healthy children and adults.[32] Nevertheless, even if several hundred subclinically infected infants are born each year in the United Kingdom, would the substantial financial and clinical costs of a national screening programme be justified to prevent visual impairment which may remain uniocular and which may not appear until adulthood, even old age?

SUITABILITY OF SCREENING TESTS

The burden of physical and emotional harm which would be caused by screening is as unquantifiable as that due to congenital toxoplasmosis, but concerns may be identified, which mainly centre on the testing and diagnostic procedures. Contrary to expectations raised in the public debate, there is no one simple test which will correctly identify infection after conception, much less tell a woman what she really wants to know, which is whether her *baby* is infected and damaged.

Screening programme algorithms which have been proposed for the United Kingdom[5 27] entail measuring toxoplasma specific IgM at booking and at least once or twice more during pregnancy. Although this has the advantage of cheapness compared with the French system (see below), it has three disadvantages. Firstly, there is the difficulty, described above, of interpreting a "positive" result in terms of timing when infection occurred relative to conception. Secondly, even a high test specificity, such as 94% quoted for one "in house" IgM ELISA,[5] would generate many false positive results. If an incidence of maternal toxoplasmosis in England and Wales of two per 1000 births and a test sensitivity of 100% are assumed 97% of positive screening test results would be false. It can further be calculated that over 35 000 pregnant women a year in England and Wales would have a first abnormal result at each screening encounter. Although the specificity of the diagnosis would be increased among women who are screen test positive by undertaking a battery of confirmatory tests,[5 27] this would usually entail a delay of up to two weeks and would represent a substantial burden of anxiety, which is likely to persist in some women after the supposedly reassuring negative confirmatory tests.[33] Even then there will be no definitive answer as to whether or not the baby is infected. Thirdly, there would be the likelihood of a lower efficacy of chemotherapy compared with that in published results (see below)[16]: a poor outcome in the Paris programme (in which testing was monthly) was associated with delay between maternal infection and institution of treatment.

Recognising the difficulties with the use of IgM as an initial screen, the Paris programme adopted a different test procedure.[15] Toxoplasma IgG is measured at

booking and the test repeated monthly among women found to be susceptible to detect seroconversion. This is a more specific method of identifying infection after conception, especially if the standard of the toxoplasma dye test is used.

This approach, however, would be extremely costly in Britain; unlike France (where the reverse is true) about 80% of women of childbearing age may be susceptible and therefore eligible for follow up. Furthermore, the acceptability of frequent testing may be low, as suggested by a recent pilot study of prenatal screening for toxoplasmosis in the Netherlands.[34] Despite the optimum conditions of an enthusiastic research project 30% of women did not complete the screening algorithm; moreover, 33 out of 77 seroconversions turned out to be false positive results—either because of the limitations of the test or because of administrative problems with the programme.

The Dutch study was the first to describe in detail not only the results but also the practical problems of a national prenatal screening programme for toxoplasmosis; this is in contrast to the results from the highly experienced, enthusiastic French centre of excellence.[15 16] Detailed descriptions of the French programme outside Paris or of the Austrian programme, including an evaluation of compliance, false positive and false negative findings, and other adverse effects described below, have not been published; nor is there any published evidence that the incidence of congenital toxoplasmosis in these countries as a whole has declined as a result of their screening programmes.[2]

EFFICACY OF INTERVENTION AFTER PRENATAL SCREENING VERSUS UNWANTED EFFECTS

Women who entered a toxoplasmosis prenatal screening programme modelled on that in figure 3 who had a "positive" result on screening and confirmatory testing would have to face some difficult decisions about choosing termination versus chemotherapy. Detailed pretest counselling would be necessary to enable these decisions to be as informed as possible within the limits of existing knowledge.

One area of uncertainty would be the risk of transplacental transmission having already occurred at the time of diagnosis with serious damage to the fetus, compared with the risk of terminating a pregnancy with either a normal uninfected fetus or an infected fetus destined to be an asymptomatic infant. The risk of fetal infection is directly related to duration of gestation at which maternal toxoplasmosis occurs, but that of severity of its effect is inversely related.[1 2] Thus it is impossible to give a precise estimate of the risk of an affected baby to women who are positive on testing. Some women will therefore inevitably choose termination at the earliest opportunity rather than risk a badly damaged baby. It was because of this, often unnecessary, fetal wastage that the Paris programme adopted the algorithm of offering chemotherapy with spiramycin followed by fetal blood sampling, as figure 3 shows.[15 16]

The decision to undergo fetal diagnosis is also difficult because cordocentesis itself carries an intrinsic fetal loss rate of 1-2% even in the best hands; the tragic and unnecessary loss of a normal pregnancy in which maternal toxoplasmosis was suspected was recently described in detail by the mother involved.[35] Although no such complications were described by the experienced investigators in the French series, seven of their 42 subjects had to undergo repeat fetal blood sampling.[15]

Other significant harms to the screened women would include the complications of the drug treatment (spiramycin is relatively safe, but pyrimethamine and sulphonamides can have serious unwanted effects) and the psychological and physical sequelae of late second trimester abortion. That may be preferable to the birth of a baby severely damaged by congenital toxoplasmosis, but the difficulty of predicting severity of the condition makes the balance a fine one; the Paris programme encouraged termination only if there was *both* fetal infection *and* either evidence that maternal infection occurred in early pregnancy or ultrasonographic evidence (which may take some time to develop) of the severe manifestations of congenital toxoplasmosis.[16]

Against this background screened women should also know that, although the published results of the Paris programme were encouraging, a successful outcome could not be unreservedly guaranteed: the risk of transplacental transmission of the organism was reduced by *prompt* chemotherapy with spiramycin by about 60%.[16] The efficacy of treatment in reducing the severity of the condition among fetuses in whom infection had not been prevented was not clear because this was not evaluated with concurrent matched controls. Moreover, the sensitivity of fetal diagnosis was only 83%. There were no false positive fetal diagnoses, but one such case was recently described in Britain.[36]

In summary, harms caused by a mass prenatal screening programme for toxoplasmosis would include, firstly, wastage of uninfected fetuses or infected but undamaged fetuses and, secondly, grief and disappointment over the birth of an infected damaged baby in spite of compliance with the diagnostic and treatment programme. Of course such an event might have occurred without screening (or it might not if treatment simply ameliorated what might have ended as a spontaneous abortion), but expectations about prevention and having a normal baby inevitably would have been raised and only the most careful and detailed counselling before screening would temper those expectations and prevent expression of grief through litigation. Thirdly, there would be maternal anxiety about the screening and the diagnostic and decision taking processes, which would be prolonged in some cases, and which may themselves have an adverse effect on the outcome of pregnancy.[37] Fourthly, there would be the physical complications of chemotherapy and of termination of pregnancy. Of course these harms should be weighed against those due to congenital toxoplasmosis, which would have been prevented; the crucial question is whether they balance, and the answer is unknown.

CONCERNS ABOUT THE NATURAL HISTORY OF GESTATIONAL TOXOPLASMOSIS

A controversial issue, raised briefly in the working group report, centres on questioning an established belief about the natural history of toxoplasmosis. The underlying principle of the French and Austrian programmes is that congenital toxoplasmosis can result only from infection first acquired in pregnancy, that latent maternal toxoplasmosis does not pose a threat to the fetus. This principle is based on the observation that (until recently) two or more recognised cases of congenital toxoplasmosis among siblings had not been reported.

In recent years, however, with the advent of pregnancies among transplant recipients and AIDS patients, it is now well documented that reactivation with severe fetal infection can occur in immunocompromised women.[2 38] It seems rash to suppose that this never occurs among immunocompetent women, and such cases have indeed been reported.[2 39-41] Furthermore, toxoplasmic retinochoroiditis among siblings has been described by several authors.[2 42] As this condition is believed to be nearly always due to congenital rather than acquired infection (indeed this is one of the arguments for screening) then, clearly, symptomatic congenital toxoplasmosis *can* occur as a

result of reactivation (or possibly prolonged parasitaemia after an infection shortly before conception). It is probably uncommon, but it deserves further research because a screening programme based on detecting only new maternal infections might contribute only partly to preventing congenital infection.

Tertiary prevention

Recognising the resource implications of adopting a prenatal screening programme modelled on the Paris algorithm and also that such a programme had failed in one state in the 1970s, the Massachusetts Department of Public Health has adopted a strategy for tertiary prevention of congenital toxoplasmosis.[43] The premise is that early diagnosis and treatment of infected neonates would prevent or minimise the risk of adverse sequelae. The same blood sample collected from newborn babies on to filter paper to test for metabolic disorders is used to measure toxoplasma specific IgM. "Positive" babies are treated with pyrimethamine, sulphonamides, and folinic acid for the first year of life.

This is an ingenious approach which is still under evaluation. There are, however, two major problems. The first is that, though the efficacy of early neonatal treatment in preventing the sequelae of congenital toxoplasmosis is unknown on the one hand (and can only be assessed in such a programme, with prolonged follow up of recruited subjects), on the other, several asymptomatic infected babies are likely to suffer the serious side effects from chemotherapy. The second problem is the unreliability of neonatal toxoplasma IgM as a predictor of congenital toxoplasmosis. The Massachusetts programme cites a figure of 90% sensitivity. However, other authors quote a lower figure of 70% for equally sensitive tests.[17] To overcome this problem it has been suggested that neonatal toxoplasma IgA may be a better indicator of congenital toxoplasmosis than IgM; this approach, however, has not yet been evaluated.[17]

Conclusions

The multidisciplinary working group report concluded that a national prenatal screening programme for toxoplasmosis should not at present be introduced in the United Kingdom, mainly because of a lack of evidence that the benefits would outweigh the risks.[9] This is an additional observation to societal concerns about prenatal screening in general.[44,45]

The report also outlined a research agenda to address some of the gaps in knowledge about prevention, diagnosis, and management of toxoplasmosis which are highlighted in this review. It emphasised that decisions about screening will need regular review in the light of knowledge gained. Meanwhile, the main thrust towards preventing congenital toxoplasmosis will be health education focusing on avoiding consuming undercooked meat and raw goat's milk and on washing hands after contact with raw meat, garden soil, and cats' litter trays. Information about toxoplasmosis and how to avoid it should now be generally available to pregnant women in the United Kingdom through both central[46] and local initiatives, although ideally it should also be targeted at women planning to become pregnant or girls still at school.

If advocates of screening are not influenced by the arguments of the working group then pressure to introduce a programme is likely to continue. Unfortunately, public campaigns may create demand without the appropriate health service infrastructure being in place to deal effectively with it (for example, medical education; validated test algorithms; fetal diagnostic expertise; counselling; and laboratory, obstetric, and paediatric resources). Currently, women have the worst of both worlds: anxiety about toxoplasmosis and the possible need to be screened on the one hand and an unclear health service response on the other. Though people have a right to be fully informed about health issues, the ethics of raising expectations which cannot be met are questionable.[47]

In the mean time, general practitioners and obstetricians must deal appropriately with patients who request "the toxoplasma test": there are two possible scenarios.

Firstly, there are the women who have not yet conceived, who are influenced by messages in the media[48] and wish to know whether they are immune or susceptible. For them an IgG test with a high specificity is needed. Most local laboratories use the toxoplasma latex agglutination test as an IgG "screen," which has a specificity of about 80%.[17] Moreover, there is evidence of considerable variation between laboratories in the way that this assay is performed and read.[49] In a population with a prevalence of toxoplasma antibody of about 20% (such as that of British women of childbearing age) over 40% of "positive" latex agglutination tests will be false, and these women would be incorrectly reassured that they were immune. If they subsequently acquired gestational toxoplasmosis and delivered a damaged infant there could be medicolegal implications, quite apart from the personal tragedy. This scenario illustrates the need for a well informed medical response to clinical demands generated from outside the health service; the clinician should consult the local microbiologist for information on the test and if necessary consult further with one of the toxoplasma reference laboratories.

Secondly, there are the women who are already pregnant and are either "worried well" or have a recent or current history of symptoms compatible with acute acquired toxoplasmosis. This is of course a diagnostic not a screening situation. It should, however, be clear from this review that careful counselling of the patient and her partner about the implications of a "positive" test result is still essential *before* the investigations begin.

The mainstay of diagnosis of acute acquired toxoplasmosis, in pregnant or non-pregnant subjects, is specific antibody measurement as already described, although identification of the organism or antigen may be necessary in immunocompromised patients.[1,17] The response of most local laboratories to a request for diagnosis of suspected acute toxoplasmosis would be to perform a toxoplasma IgG screen and then to refer "positive" serum samples to a reference laboratory for further investigation; however, the option exists for some laboratories to offer diagnosis themselves, using ELISA "kits" for measuring specific IgG and IgM. Practitioners should be wary of this approach because of the varying reliability of such kits referred to earlier in this review.

The investigation of symptomatic pregnant (or non-pregnant) patients should reflect the differential diagnosis of toxoplasmosis, which might include other causes of "glandular fever," lymphadenopathy, or uveitis. Patients who present with isolated lymphadenopathy may come to biopsy: the histological picture of toxoplasmic lymphadenopathy is said to be characteristic, although the organisms or tissue cysts are only rarely seen.[1,2,17] Those who present with uveitis should be seen by an ophthalmologist and should also be investigated serologically by a reference laboratory because clinical diagnosis is not always reliable.[32] The most difficult cases will be in pregnant women with vague, non-specific symptoms with an uncertain date of onset: consultation with the local microbiologist and, if necessary, the reference laboratory microbiologist is essential and is an integral part of management.

Arguments about the pros and cons of screening

often become polarised; 15 years ago Sackett and Holland described the protagonists as "evangelists" and "snails."[50] Up to now the evangelists have held the limelight over the issues of prenatal screening for toxoplasmosis. This review has attempted to redress the balance by taking account of the snails' view of the subject and by outlining alternative approaches to preventing the damage which toxoplasma can cause.

The illustrations of the toxoplasma tachyzoite and the tissue cyst were kindly provided by Dr Richard Holliman, consultant medical microbiologist at the Toxoplasma Reference Laboratory, St George's Hospital, London.

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ANY QUESTIONS

What are the risks of cardiovascular complications in a patient receiving weekly intravenous injections of 10 ml of 15% magnesium sulphate?

Ten millilitres of 15% magnesium sulphate contains 6 mmol of magnesium (1·5 g). The dose administered as an intravenous bolus to control cardiac arrhythmia is 4-12 mmol. A bolus of 8 mmol of magnesium sulphate results in a doubling of the serum concentration, which returns to the normal range (0·7-1·1 mmol/l) within 20 minutes by a combination of renal clearance and redistribution.[1] Cardiac toxicity has not been reported after boluses of 4-12 mmol of intravenous magnesium for cardiac arrhythmia, even when followed by an intravenous infusion of 60 mmol over 24 hours (serum magnesium concentration 1·6-2·0 mmol/l at the end of the infusion).

All patients report a feeling of cutaneous warmth during rapid bolus administration of magnesium, akin to that after injection of radiological contrast; a transient small fall in mean blood pressure results. Slow intravenous injection does not result in any haemodynamic sequelae. Cardiac toxicity is evident only when the serum magnesium concentration rises in excess of 4 mmol/l, at which time sinus bradycardia and increasing atrioventricular block are seen.[2] Coma and death from respiratory depression supervene at serum concentrations of 6 mmol/l.

Iatrogenic magnesium toxicity is largely confined to children treated with frequent magnesium sulphate enemas and is rarely seen. The symptoms are predominantly neurological with drowsiness, irritability, coma, and muscle weakness; electrocardiographic changes or cardiac toxicity, or both, are not reported.

The average oral intake of magnesium is 5-12 mmol/day, roughly a third of which is absorbed in the small bowel under the influence of vitamin D. Urinary excretion is 3-5 mmol/day in magnesium balance.[3] Unless renal function is impaired a weekly dose of 6 mmol is unlikely to result in an appreciable accumulation of magnesium.—TERI MILLANE, *clinical research fellow in cardiology, London*

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