Screening for toxoplasmosis during pregnancy

Toxoplasma infection, when acquired in pregnancy, can cause fetal infection with potentially serious consequences for the newborn infant. It is generally held that only infants of mothers who acquire a primary infection in pregnancy are at risk and on this basis prenatal serological screening programmes have been set up in some countries, notably France. Over recent years there has been increasing pressure in the UK to follow a similar course. However, before any screening programme is introduced nationally, the benefits and risks of the programme, both clinical and financial, need to be fully assessed. As the pattern of infection and the distribution of disease may differ from country to country it is important when reviewing the information available to take this into account. What is the appropriate policy for one country may not always be appropriate for another.

A working party was recently set up by the Royal College of Obstetricians and Gynaecologists to review the available epidemiological and clinical information relating to toxoplasmosis in pregnancy and congenital toxoplasmosis and to advise on whether a prenatal screening programme should be introduced in the UK. On the basis of current evidence the group concluded that it was not appropriate at the present time to introduce a nationwide antenatal screening programme for toxoplasmosis in the UK but emphasised the need for further research in this area.

The information required to assess the benefits and risks, clinical, psychological and financial, of introducing such a programme and to determine whether the classic criteria proposed by Wilson and Jungner are satisfied includes: an understanding of the natural history of the condition, the prevalence of immunity to toxoplasmosis in women of childbearing age in the UK, the incidence of acute infection in pregnancy, the risk of transmission of infection to the fetus, and the frequency and nature of damage, both short and long term. In addition, the sensitivity and specificity, and safety, of the screening and diagnostic tests, and the efficacy of the intervention must be established.

The natural history of toxoplasma infection

Toxoplasmosis is caused by the protozoan Toxoplasma gondii and although its life cycle has been well described, the precise route of transmission to man is not well understood. It is generally assumed that the consumption of undercooked meat containing tissue cysts and the ingestion of oocysts from the faeces of infected kittens, either directly or from contaminated soil, are the major sources of infection. The relative importance of each of these routes is not known.

In most healthy individuals infection is asymptomatic or presents with mild, non-specific manifestations such as lymphadenopathy and tiredness, with or without fever. Overall about 20% of pregnant women in the UK have serological evidence of prior infection and 80% remain susceptible to a primary infection in pregnancy. A recent study has shown that the seropositivity rate in pregnant women relates to their country of birth: women born in the UK, regardless of their ethnic origin, had a significantly lower seroprevalence than those born in southern Europe or Africa.

There is a paucity of information on the incidence of infection in pregnancy in the UK but review of published studies carried out in a number of different locations in the UK suggests that this is in the order of two per 1000 pregnancies. But studies in Sweden and South Yorkshire based on stored blood samples show that seroprevalence has fallen markedly over the last 20 years. This points to a downward trend in the incidence of toxoplasmosis in the population generally suggesting a need for more current information on the seroprevalence of toxoplasmosis in women from different geographical areas.

After maternal infection the overall risk of transmission to the fetus is about 40%. This ranges from only about 15% after exposure to infection in the first trimester to about 60% after exposure in the later stage of pregnancy. On the other hand, if the fetus is infected, the earlier in pregnancy the maternal infection the greater the risk of severe disease in the fetus. This information is based on prospective studies carried out in Paris, France in the 1960s and no data are available from the UK.

Most congenitally infected infants, over 90%, are asymptomatic in the neonatal period. Presentation with the classic triad of hydrocephaly, retinochoroiditis, and intracranial calcifications is uncommon. Infected infants may present with non-specific manifestations in the neonatal period including dysmaturity, hepatosplenomegaly, jaundice, thrombocytopenia, and convulsions. Virtually all infants with symptomatic infection in the neonatal period have long term sequelae such as neurological impairment, epilepsy, or visual impairment resulting from retinochoroiditis. There is, unfortunately, little information on the long term sequelae of congenital infection in those infants who are asymptomatic at birth. Only a few prospective studies with long term follow up have been undertaken and all have suffered from small sample size, possible bias in ascertainment, and a lack of controls. It is virtually impossible to derive generalisability information from these studies. In a study in Holland of nine asymptomatic neonates followed up to 20 years, six developed retinochoroiditis, one as late as 18 years. Three of those affected had unilateral visual impairment. No neurodevelopmental defects were detected. In a study reported from the US, 13 neonates with congenital toxoplasmosis were followed up for an average of eight years. Ten were asymptomatic and three had non-specific problems at birth. In 11 children retinochoroiditis was subsequently diagnosed: three had unilateral blindness and eight normal visual function. Five of the 13 children were reported to have neurodevelopmental sequelae, one severe microcephaly, two mild and transient problems, and two minor 'cerebellar' signs.

In an attempt to estimate the incidence of symptomatic congenital infection in England and Wales, Hall reviewed the laboratory reports of possible congenital toxoplasmosis to the Public Health Laboratory Service Communicable Disease Surveillance Centre and cases of newly diagnosed congenital toxoplasmosis reported by paediatricians to the British Paediatric Surveillance Unit, an active monthly reporting scheme with 90% compliance. Based on these data there were 12 cases in the 12 month birth cohort, June 1989 to May 1990 (eight infants, one stillbirth, and three fetuses with definite or probable symptomatic infection). This is considerably lower than the number of cases that would have been predicted on the basis of the theoretical considerations. With an estimated infection rate in pregnancy of two per 1000 and about 680 000 births in England and Wales each year, 1360 acute maternal infections would be anticipated. If the transmission rate is 40% and 10% of neonates have obvious manifestations of congenital infection, there would be 544 fetal infections and 54 seriously
affected neonates both in England and Wales each year. This apparent discrepancy emphasises the need for further research.

**Screening for toxoplasma infection in pregnancy**
The aim of the screening test is to identify maternal infection by detecting seroconversions among women who are seronegative for toxoplasma IgG antibody and by identifying those women who have toxoplasma IgM in the initial serum taken on booking. Numerous methods are available but there is a wide variation in the reported performance of these assays. The accepted reference test is the Sabin Feldman dye test, which measure both IgG and IgM antibodies but as this requires live, viable parasites it is difficult to perform outside a reference laboratory.

Tests based on the detection of IgM in sera may be difficult to interpret because of the difficulty in distinguishing recent gestational infection from prepregnancy toxoplasmosis because of the persistence of IgM. There are large individual variations in IgM response to toxoplasma infection and the use of a sensitive test may detect very low concentrations of IgM persisting from infection months or even years before conception.13

Testing for seroconversion requires repeated samples in all women seronegative at booking. In the UK this would necessitate the retesting of 80% of women at intervals during pregnancy in contrast to France where only 20% of pregnant women are susceptible and require repeat testing. Because of the cost implications it has been suggested that in the UK only one or two repeat samples might be sufficient. This would have disadvantages as delay in treatment after the onset of maternal infection is likely to decrease its efficacy.

The sensitivity and specificity of the screening test in predicting fetal infection is critical to the performance of a screening programme. Even highly specific tests generate large numbers of false positive results when the condition being screened for is uncommon. If one assumes an incidence of two per 1000 and a screening test with a 99% sensitivity and a 99% specificity, of every 100 women testing positive 17 would be 'truly' infected and 83 would not be infected. For the 17 women infected, assuming postconception infection, seven would transmit the infection to the fetus and the most likely outcome would be asymptomatic infection.

**Confirmation of the diagnosis**
After the initial positive screening test a further blood sample is required to confirm or refute the diagnosis of infection in the mother. This would have considerable cost implications and would increase the work load of the reference laboratories of which there are three in England and Wales, one in Scotland, and one in Northern Ireland.

To avoid unnecessary termination of uninfected fetuses facilities for fetal blood sampling would be required to establish whether fetal infection had occurred. Cordocentesis, which can only be undertaken after 18 weeks, carries a risk of fetal loss of 1–2% even in experienced hands.14 This is currently available in only six centres in the UK, which would be inadequate if a national screening programme was introduced. At present fetal diagnosis depends on the isolation of the parasite from fetal blood or amniotic fluid which can only be carried out in specialist centres and may take up to 45 days. The use of new methods such as the polymerase chain reaction to detect toxoplasma DNA are under investigation.

**Treatment**
After the confirmation of maternal infection, if the parents elect to continue the pregnancy, the antibiotic spiramycin, which is not currently licensed in the UK, is given at a dose of 3 g a day, to reduce the risk of fetal infection.15 The efficacy of the drug remains uncertain as estimates are based on comparison with historical controls in whom fetal infection had occurred at a time when fetal diagnostic techniques had not yet been established.16 It has not been evaluated in a randomised control trial and such a trial would not now be considered ethical. After the confirmation of fetal infection by cordocentesis alternating courses of spiramycin and a combination of sulphadiazine, pyrimethamine, and folinic acid are given. These drugs are contraindicated in early pregnancy because of their toxicity and possible teratogenic effects. For children with proved congenital infection a course of treatment with spiramycin alternating with sulphadiazine, pyrimethamine, and folinic acid is usually recommended after birth, although the efficacy of this regimen has not been evaluated in a controlled trial. Treatment is given for 12 months on the assumption that it will limit tissue damage, not as a curative step. After this time it is unlikely to be beneficial unless active eye lesions are present. Treatment needs to be closely monitored with frequent blood samples to detect any adverse effect on the marrow. All infants born to mothers with proved infection will require continued follow up until congenital infection can be excluded or, for those infected, to identify problems that may arise.

**Potential adverse consequences of screening**
The possible adverse psychological effects of antenatal screening include the anxiety created by the initial test to identify a possible cause of fetal abnormality, the waiting for the results, and the consequences of a positive test. False positive results lead to further investigations and false negative results may lead to inappropriate reassurance. After the confirmation of maternal infection some women may elect to have their pregnancy terminated rather than wait for a diagnosis of fetal infection in late pregnancy when termination is more problematic. The psychological consequences of antenatal screening must not be underestimated and adequate facilities for counselling must be available.17

**Conclusion**
Antenatal screening for congenital toxoplasmosis fails to fulfil the criteria for the introduction of a screening programme in the UK. Present evidence does not suggest that there is a large public health problem: symptomatic congenital toxoplasmosis appears to be rare and evidence that most infants with asymptomatic infection go on to have serious sequelae is lacking. No suitable screening test is currently available and, although probably beneficial, treatment has not been fully evaluated. At present the balance between potential risk and benefits of such a programme do not favour its introduction. It seems reasonable in the light
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of present evidence to concentrate on giving advice to pregnant women on how they may reduce their risk of contracting toxoplasma infection. The effectiveness of this approach to prevention has not been evaluated but the potential for harm is considerably less than with universal antenatal screening.

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Arch Dis Child 1993 68: 3-5
doi: 10.1136/adc.68.1_Spec_No.3

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