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Toxoplasmosis during pregnancy and infancy

A new approach for Switzerland

Swiss Working Group on congenital Toxoplasmosis
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Introduction

In recent years it has become evident that screening for and treatment of acute toxoplasmosis during pregnancy may have no measurable impact on vertical transmission and neonatal morbidity and mortality. A broad lack of evidence with regard to many aspects of congenital toxoplasmosis has been recognised in a common European initiative (EUROTOXO) which reviewed several thousand published papers on the subject of toxoplasmosis during pregnancy and childhood. It was therefore clear that the strategies currently implemented in our country would, on closer inspection, no longer withstand the claim for evidence-based procedures. The arguments and call for a change of paradigm in Switzerland which follow here are the result of a national consensus-finding process involving experts from various specialities, including gynaecology/obstetrics, paediatrics/neonatology, infectiology, ophthalmology and laboratory medicine, together with representatives of the public health authorities.

The past decade

1995 hypotheses

Twelve years ago the Swiss Federal Office of Public Health established a multidisciplinary working group to review the subject of congenital toxoplasmosis (CT). This extensive effort culminated in the publication of a supplement to the Swiss Medical Weekly in 1995 [1]. At that time a seroprevalence of 46% was determined on the basis of the results of a study in 9059 women, corresponding to 11.8% of the total annual births in 23 out of 26 Swiss cantons. A risk of 1.21% seroconversion among seronegative women during pregnancy was calculated, resulting in an estimated annual figure of 548 neonates with congenital toxoplasmosis in our country. As 75% of such children can be expected to be asymptomatic at birth, the number of expected pathologies according to this calculation would have been 40 cases of chorioretinitis, possibly with impaired vision, 18 cases with cerebral lesions and 2.7 cases of perinatal death per year.

The observed burden of congenital toxoplasmosis in Switzerland since 1982

In contrast to these predictions, two local studies have found much lower numbers in recent years. A national survey conducted in 38 paediatric units of Swiss teaching hospitals between 1995 and 1998 using the Swiss Paediatric Surveillance Unit network found only 15 proven cases of symptomatic congenital toxoplasmosis, or 4 per year for this four-year period [2]. In another survey conducted in the Basel region, more than 64 000 cord blood samples, covering >90% of all neonates, were collected and studied between 1982 and 1999. Despite increasing maternal age, seroprevalence for toxoplasmosis among pregnant women steadily decreased from 53% (1982–1985) to 35% (1999). During the same period the prevalence of CT declined from 0.08% to 0.012%. A total of 28 children with congenital toxoplasmosis were identified between 1982 and 1999, and only 4 had clinical evidence of disease. This screening programme identified 1 child with congenital toxoplasmosis per 2300 live births, or 1.5 per year, far fewer than expected from previous Swiss estimates (225 : 15 000 [3] and 100 : 15 000 [4]). Clinical disease was observed in 1 of 16 250 neonates or 1 per 4.5 years [5]. A retrospective review of data gathered in the Lausanne region for 12 years between 1995 and 2006 identified a total number of 37 serologically confirmed cases of congenital toxoplasmosis, accounting for one case in 2270 live births, including one symptomatic case in infancy per 14 000 live births [6].

Strategy and cost-effectiveness

In 1995 it was believed that primary (reduction of the risk of acquiring toxoplasmosis during

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pregnancy) and secondary (treatment of acute toxoplasmosis during pregnancy) prevention were the most promising strategies. However, it was believed that general screening was not cost-effective for a low incidence country such as Switzerland. Taking into account the expected number of cases, testing on a trimestrial basis would have been the most cost-effective strategy [7]. It was left to the obstetricians' judgement to perform Toxoplasma antibody testing during pregnancy. According to health insurance (santésuisse), women are tested twice on average during pregnancy.

Prevention

Primary infection with toxoplasmosis during pregnancy may cause congenital infection and induce mental retardation and blindness in the infant [8, 9]. Primary, secondary and tertiary prevention strategies have been adopted to reduce the incidence and severity of congenital toxoplasmosis.

Primary prevention

Primary prevention strategies seek to prevent cases of congenital infection by preventing cases of maternal infection, involving pre- or early pregnancy counselling on how to avoid exposure [10].

Secondary prevention

To reduce mother-to-child transmission and morbidity from congenital toxoplasmosis, some high-incidence countries such as Austria and France have chosen a secondary prevention strategy and implemented nationwide programmes to detect and treat acute Toxoplasma infections during pregnancy [11]. In women with evidence of acute infection spiramycin is usually prescribed and amniocentesis performed. In the event of foetal infection, pyrimethamine and sulfonamides is the treatment of choice and termination is discussed if foetal abnormalities are detected on ultrasound. According to data from 603 confirmed cases of maternal toxoplasmosis detected by the French universal screening programme, the overall transplacental transmission rate was 29%. There was a direct correlation between gestational age and rate of transmission, beginning with a 2% transmission rate at 8 weeks of gestation and 6% at 12 weeks, with a sharp linear increase thereafter up to 81% transmission rate at term. An inverse relationship was found between the incidence of clinical symptoms and the gestational age at which maternal seroconversion occurs. At 13 weeks of gestation 61% of children presented with clinical symptoms, at 26 weeks the incidence was 25% and at 36 weeks 9% [12]. Thus correct identification of the gestational age at which seroconversion occurs greatly affects counselling on the risk of foetal transmission and morbidity.

While some studies have reported significantly lower transmission rates in children born to treated mothers [13–17], others have not [18–21]. In fact, after an extensive review of 2591 papers, including the nine papers which fulfilled their stringent inclusion criteria [8–15, 25], Wallon and co-workers concluded that current evidence is not sufficient to confirm that treatment of mothers who seroconvert during pregnancy prevents foetal infection and improves infant outcomes [22, 23]. There was no single randomised comparison, and control groups were mainly historical and therefore in general not directly comparable with the treatment groups. Wallon and co-workers also identified an additional problem with amniocentesis, as sensitivity and specificity of PCR diagnosis in amniotic fluid differed widely between laboratories [24, 25].

Tertiary prevention

Finally, tertiary prevention attempts to lessen the severity of disease sequelae through early detection and treatment of congenital disease. Proponents of this idea recognise that most congenital disease is subclinical at birth, but that sequelae often develop over time [26]. Tertiary prevention also involves considering termination of pregnancy for severely affected foetuses.

Eurotoxo [27]

A joint initiative

Given the growing doubts with regard to effectiveness of primary, secondary and tertiary prophylaxis of congenital toxoplasmosis, a joint initiative – called EUROTOXO – was started in 2004 by three different partners: the Institute of Child Health, London, UK, the Staten Serum Institute, Copenhagen, Denmark, and the Institute of Public Health, Epidemiology and Development, Bordeaux, France.

Stakeholders from Europe, i.e. representatives of all disciplines involved in research and care for *Toxoplasma* patients were brought together to define the implications of current scientific knowledge for a research agenda and policy decisions on how best to prevent congenital toxoplasmosis and its consequences. This initiative was launched to produce a consensus on what is currently known regarding prevention and management of congenital toxoplasmosis and its consequences, and about areas where further research is needed.

Methodology

Four panels of international experts engaged in an intensive review of thousands of published papers with a view to identifying scientifically valuable evidence on the burden of toxoplasmosis in Europe, European national prevention policies, risk factors for infection during pregnancy, effects of primary, secondary and tertiary prevention, available drugs and effectiveness of treatment, and the reliability, performance and potential risks of available laboratory and test methods.

Geographical differences

The seroprevalence of *Toxoplasma* antibodies in young women, and the incidence of congenital infection, vary from one geographical region to another. In France, for example, the reported prevalence of congenital disease is 2–3 cases per 1000 live births, a figure 20 times that in the USA, which is as low as 1:10 000 live births [25]. There is evidence that the burden of congenital toxoplasmosis is lower in Northern Europe than in the rest of the continent. In cities the prevalence of toxoplasmosis is lower than in non-metropolitan areas. It increases with age, but decreases with calendar time and varies according to geographical origin. Immigrants from Asia or Africa are at higher risk of infection due to a low seroprevalence in these populations.

Routes of infection

Few studies contribute to the evidence-based knowledge of routes of *Toxoplasma* infection in pregnant women. All findings support the notion that the oral route is probably the major source of infection, involving food preparation and consumption. Data from seven European centres in Belgium, Denmark, France, Italy, Norway, Yugoslavia and Switzerland suggest that risk factors for *Toxoplasma* infection vary according to local eating habits, food hygiene and lifestyles. Inadequately cooked or raw meat is among the main risk factors for infection consistently identified in all centres, including several kinds of meat such as beef, lamb or game. Pork has only inconsistently been reported, whereas chicken has recently been identified as a reservoir. The risk from eating cured or frozen meat remains unclear. Contact with soil contributes to a minority of infections. Owning a pet cat has been reported as a risk factor for infection in only one study, and does not play a significant role.

Effectiveness of primary prevention

A review of the effectiveness of health intervention approaches in pregnant women (primary prophylaxis) highlights the weakness of the literature in this area. Several pitfalls were identified, chiefly including unclear definition of the intervention and lack of control groups. One cohort study reported a significant reduction in seroconversion in pregnant women in Belgium, without a control group. Only two trials have been conducted and reported an increase in knowledge of routes of transmission and changed behaviour, but both lack statistical power from which to draw conclusions on the seroconversion rate. It was concluded that primary prevention had a potential effect in preventing congenital toxoplasmosis, but was still in need of improvement. At present the recommendations are based on obsolete data.

A variety of policies

In many respects the outcome of this review is somewhat sobering. There is a broad lack of knowledge, probably best reflected by the huge variety of national public health policies for the prevention of congenital toxoplasmosis in individual European countries. Five countries officially recommend mandatory prenatal screening, either by monthly testing (France, Italy) or by three-monthly testing of susceptible women (Austria, Lithuania, Slovenia). The National Institute for Clinical Excellence (NICE) reported in its guidelines for routine antenatal care that routine antenatal screening for toxoplasmosis should not be offered, because the harm from screening (unnecessary treatment, termination of pregnancies with uninfected or unaffected foetuses, distress and discomfort of repeated tests and investigations ante- and postnatally) may outweigh the potential benefits (reduction in cases of CT) [28]. Neonatal screening has been practised in the USA for a decade [25]. Denmark has officially recommended and supported a systematic newborn screening procedure, based on a pilot study [30], since 1999. However, this programme was discontinued in 2007 due to lack of evidence that treatment for toxoplasmosis was effective in preventing later attacks of ocular toxoplasmosis in children with and without ocular lesions at birth [29]. In most other European countries there is no recommendation at all or a formal recommendation not to screen. However, where routine practice is concerned, several countries conduct wild prenatal or neonatal screening procedures. The authors of the Cochrane review identified 3332 papers, none of which met the inclusion criteria for a randomised controlled trial. They concluded that we still do not know whether antenatal treatment in women with presumed toxoplasmosis reduces mother-to-child transmission, and they recommend not introducing screening in countries where treatment is not routine, outside carefully controlled trials [30].

Effectiveness of screening and diagnostic methods (Eurotoxo) [27]

Of the many studies on diagnostic methods used in congenital toxoplasmosis, only a few allow reliable assessment of the performance of the different tests involved in screening or clinical diagnosis.

Screening of seroconversion during pregnancy and prenatal diagnosis

The literature is sparse and lacks good reference tests. IgM should be the method of choice as a first-line diagnosis, with good sensitivity for all existing methods (reaching 100% with the ISAGA method) but with a high rate of false positive tests (some 6% of cases). Introduction of the *Toxoplasma*-specific IgG avidity assay with specific IgM-positive samples collected in the first half of pregnancy has improved the diagnostic routine for the detection of *T. gondii* infection in early pregnancy. The main achievement is the ability to rule out infection during pregnancy for many women who otherwise, on the basis of a positive specific IgM result and/or a high dye test titre, would have been identified as having a recent infection. The test is easy to perform in any microbiological laboratory, but there is a need for standardisation of the method and, furthermore, long-lasting low avidity is a problem in many pregnant women. In Italy, a country with routine prenatal screening for toxoplasmosis, repetition of serology and reinterpretation of the serological profile (i.e. of all previous results) in 542 mother-child pairs revealed a false-positive rate of 90% in results based on IgM-testing, and 12% based on seroconversion data [31].

Risks associated with prenatal diagnosis

In 2005 a prospective randomised trial documented risks associated with amniocentesis compared with controls [32]. This trial, conducted in 1986, reported a procedure-related rate of foetal loss of 1.0% (95% CI, 0.3–1.5) for amniocentesis as compared with a control group. Evidence from available controlled studies suggests that the excess pregnancy loss associated with mid-trimester amniocentesis with concurrent ultrasound guidance is 0.6% (95% CI, 0.3–0.9). Other complications related to amniocentesis include vaginal bleeding, leakage of amniotic fluid, infection, and foetal injury. Some studies have also reported associations between amniocentesis and neonatal complications, including neonatal respiratory distress syndrome and orthopaedic complications. The latter, however, have usually been associated with early amniocentesis. In addition, recent studies have shown conflicting results regarding an association between amniocentesis and risk of preterm delivery. The available evidence suggests no increased risk of preeclampsia, abortion, placenta praevia, dysfunctional labour or late foetal or infant death associated with amniocentesis. It has also been suggested that the number of additional foetal losses significantly exceeds the number of prevented cases of congenital toxoplasmosis [33].

Psychological consequences of prenatal screening

Potential psychological consequences of prenatal screening and diagnosis of congenital toxoplasmosis include parental anxiety due to false positive results and uncertainties about the prognosis of children with a positive prenatal diagnosis. Due to a larger number of false positive results, parental anxiety may be particularly important in screening strategies that include more frequent serological testing. A positive screening result, particularly early in pregnancy, may represent maternal infection prior to conception, in which case the foetus would be at very low risk for congenital toxoplasmosis. Hence the outcome of prenatal screening and diagnosis of congenital toxoplasmosis is inherently uncertain and may entail substantial, and at times unnecessary, anxiety or other negative psychological reactions for the affected women and their families [32].

Prenatal diagnosis

Only 5 of the 13 studies assessing performance of foetal diagnostic tests are of good methodological quality. PCR technique has increased the accuracy of foetal diagnosis, but its sensitivity remains below 83%. The specificity of PCR is almost 100% in reference laboratories, but much lower rates have been reported in some laboratories. Recent studies reported that PCR diagnosis combined with isolation of the parasite from amniotic fluid in reference laboratories allows accurate diagnosis attaining sensitivity of 91% and specificity of 99%, but takes up to six weeks.

Postnatal diagnosis in children

Postnatal diagnosis in children born to seroconverting mothers is based on IgM and IgA detection with low performances before one year of age. The sensitivity of tests for IgM or IgA in early infancy is limited, ranging from 52% to 66%. The best performances are observed using ISAGA (IgM) and ELISA (IgA). Alternative strategies have combined these methods with tests for specific antibody bands using the ELIFA technique or immunoblot. Increased sensitivity of up to 96% within the first three months of life are reported for combinations of these tests.

Neonatal screening

Only two studies conducted in Denmark and Switzerland allow appropriate assessment of tests. Neonatal screening is based on IgM or IgA tests: the sensitivity of IgM alone is low; combined IgM

and IgA testing is the most accurate, with sensitivity of 94% and specificity of 99.9% [5, 34]. As shown by Gilbert et al., the detection rate is highest until week 2 after birth, but declines thereafter. According to recently published EMSCOT data, performance of IgM and IgA was poor if the mother seroconverted in early pregnancy [35].

Conclusion regarding diagnostic tests

In conclusion, tests used in both screening and diagnosis strategies perform inadequately and lack standardisation and thus reliability. Another important aspect of secondary prevention relates to associated risks, the most important being foetal loss associated with amniocentesis.

Effectiveness of prenatal treatment

Concerning antiparasitic treatment it must be stated that there are no pharmacokinetic or pharmacodynamic studies in children and pregnant women. Data on serum concentrations of spiramycin suggest that the levels attained are below the minimal inhibitory concentration for *Toxoplasma gondii*. There are no randomised controlled trials of prenatal treatment, and there is no clear evidence that prenatal treatment has a clinically important effect on the risk of transmission. Moreover, the variation in the observed effect of prenatal treatment on the occurrence of clinical disease can be explained by biases.

Effectiveness of postnatal treatment

There is also a lack of evidence on the effect of postnatal treatment in children, especially for pyrimethamine/sulfonamides, which account for a high frequency of adverse events in children. One single randomised controlled trial from Brazil shows an effect of cotrimoxazole vs. no treatment on the recurrence of retinochoroiditis [36].

Implications of the Eurotoxo findings for the Swiss approach

Old perceptions and habits

In Switzerland wild early pregnancy screening is performed, an estimated 90% of women being tested for *Toxoplasma*-specific antibodies at some time during pregnancy. Leaflets with primary prevention messages have been distributed in some regions, but their contents are based on old perceptions rather than evidence regarding most important transmission routes. Furthermore, there is no nationwide consensus and the leaflets in question are not uniform. Diagnosis of acute toxoplasmosis during pregnancy has been based on seroconversion, on IgM and IgG testing, and more recently on IgG avidity testing. In many cases, i.e. based on the presence of IgM and IgG antibodies, acute toxoplasmosis was a suspected rather than a proven diagnosis, and many women were treated on the basis of a questionable interpretation of the screening results. Treatment of pregnant women differed between centres, with low dose pyrimethamine/sulfadoxine treatment more prominent in the German-speaking regions and spiramycin treatment followed by prenatal diagnosis more often performed in the French-speaking regions of the country. Neonates have been evaluated serologically and clinically at birth. Clinical evaluation included eye examination and cerebral ultrasound, and in some centres, in the case of proven neonatal toxoplasmosis, also testing of cerebrospinal fluid. Treatment of infants with proven or suspected congenital toxoplasmosis also differed between centres. In some clinics children with suspected or asymptomatic congenital toxoplasmosis were prescribed low-dose prophylactic pyrimethamine/sulfadoxine (Fansidar®), while symptomatic infected children were usually treated with four-week cycles of alternate spiramycine or pyrimethamine/sulfadiazine and folinic acid. Treatment was usually given for one year or until disappearance of passively acquired maternal antibodies. Infected children usually undergo annual eye examinations until adolescence/adulthood.

An accurate estimation of the burden of CT

Switzerland has approximately 73 000 live births per year. Taking the data from the cord blood screening in the Basel region into account, a total of 32 cases of congenital toxoplasmosis (Basel: 1/2300 live births) and of 4.5 symptomatic neonates/infants (Basel: 1/16 250 live births) per year would be expected for the whole country, the latter figure being exactly the same as observed in the 1995–98 SPSU survey [2]. Among 39 622 pregnancies between January 1991 and December 1999, the Basel group identified 71 women with proven or suspected acute toxoplasmosis during pregnancy [5]. These figures correspond to those observed in the Lausanne region [6]. Thus, it can be anticipated that among 73 000 pregnancies 130 women at most will have acute toxoplasmosis during pregnancy each year in Switzerland.

Risks versus benefits

Given these low numbers, unsystematic screening during pregnancy and the limited performance of tests to identify acute toxoplasmosis during pregnancy with certainty, it seems very likely that a significant number of women will either be missed or treated for a presumed rather than a real acute infection during pregnancy. Further, due to the fact that taking all available information into account it is not possible to demonstrate any effect of treatment during preg-

nancy on transmission rates or on foetal/neonatal morbidity, it is extremely unlikely that screening as presently performed in Switzerland would be of any benefit. In contrast, such screening is very likely to be associated with a significant burden of anxiety and distress among women with suspected acute toxoplasmosis during pregnancy. Given the low morbidity and the vertical transmission rate observed in Switzerland in recent years, the risk associated with invasive prenatal diagnosis is especially likely to outweigh any benefit that may be expected.

Still a minor benefit …

Nevertheless, the lack of evidence that treatment during pregnancy would decrease transmission rates and foetal/neonatal morbidity and mortality also means that a minor benefit cannot be ruled out with certainty. Hence it is important to have a surveillance system in order not to miss major changes when adapting the old strategy.

A new approach

As shown by studies from Switzerland and Denmark, combined IgM and IgA screening at birth serves to identify the vast majority of infected neonates, given 94% sensitivity and 99.9% specificity [5, 27]. Denmark, with a birth prevalence for toxoplasmosis of 2.1 in 10 000 liveborn neonates, has already published the results of a nationwide neonatal two-step screening programme for congenital toxoplasmosis. In 55 out of 262 912 newborns (=1/4780) congenital toxoplasmosis was confirmed by specific IgG, IgM and IgA antibodies. Twelve of 47 newborns examined (=1/21 909) showed clinical signs of infection such as retinochoroidal lesions or intracranial calcifications. One child had hydrocephalus, intracranial calcifications and retinochoroidal lesions. Retinochoroiditis with macular involvement was diagnosed in 9.6% of the eyes at birth and in 15.6% at one year of age [37]. Thus, newborn screening in Denmark between 1999 and 2007 did not show that identification and treatment of infected children had any impact on ocular morbidity, and this led to discontinuation of this campaign in Denmark in 2007 [29]. In fact only a single study shows a treatment effect of cotrimoxazole on recurrence of retinochoroiditis [37]. Similarly to treatment during pregnancy, no evidence is available of any benefit from treating children with congenital toxoplasmosis. Nevertheless, not to treat a symptomatic infection at birth, for which potentially effective drugs are available, will probably not be acceptable for caregivers and paediatricians. Clinical evidence, however, strongly suggests that symptomatic children will be identified even without any pregnancy or neonatal antibody screening due to clinical symptoms identified before or after birth.

Change of paradigm is reasonable

In the absence of evidence

Lack of available evidence does not mean that no intervention or treatment has any effect at all, and hence it appears very difficult to propose straightforward recommendations. On the other hand, there are sufficient arguments to put in question the wild screening system currently practised in Switzerland and to propose a change of paradigm regarding congenital toxoplasmosis.

Step 1

Given the low incidence and even lower morbidity of congenital toxoplasmosis, together with the the fact that any intervention during pregnancy presumably has little or no impact but involves significant risks, on the basis of published evidence it appears that secondary prophylaxis can in no way be recommended and testing during pregnancy should therefore be discouraged.

Step 2

Primary prevention should be strengthened, by providing women with evidence-based information on major sources of toxoplasmosis and transmission routes of importance.

Step 3

Finally, to ensure that any possible impact of a change of paradigm is not overlooked, the surveillance system requires adaptation.

As a general screening system in neonates using Guthrie cards appears to be inefficient in the light of experience in Denmark, the Swiss Working Group on congenital Toxoplasmosis proposes to maintain the ongoing surveillance programmes in the Basel and Lausanne regions.

Symptomatic children diagnosed with congenital toxoplasmosis should still be treated, however, with a strong recommendation to enroll them in international studies comparing different potentially effective drug regimens.

Symptomatic congenital toxoplasmosis should again be included in the SPSU surveillance system.

Recommendations

- Publish a consensus/position paper (paediatricians, obstetricians, biologists, public health)
- Develop a common national leaflet with recommendations on how best to prevent acquisition of toxoplasmosis during pregnancy, and distribute it to all obstetricians and women pregnant or planning pregnancy
- Cease testing for *Toxoplasma* antibodies before and during pregnancy – this requires forceful and intensive promotion of the change in paradigm among physicians following pregnancies or responsible for medical laboratories
- Maintain and evaluate the ongoing surveillance systems
- Reactivate SPSU surveillance of symptomatic congenital toxoplasmosis
- Treat children with symptomatic congenital toxoplasmosis – enroll virtually all of these children in upcoming international treatment studies

Thoughts on the practical implementation of this new approach

Clearly, a change in paradigm of this kind cannot be implemented from one day to the next. On the day when these new recommendations are published, many seronegative pregnant women will be scheduled for follow-up tests. Other pregnant women will have started antiparasitic treatment for suspected or proven acute toxoplasmosis during pregnancy. These women should obviously not be caused added confusion, and it is certainly reasonable not to change the approach discussed and defined earlier. It will also take time to adapt existing local guidelines to the new recommendations. The Swiss Working Group on congenital Toxoplasmosis therefore assumes that nationwide implementation of the new strategy will take one or two years until completion.

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