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Treatments for toxoplasmosis in pregnancy (Review)

Peyron F, Wallon M, Liou C, Garner P

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[Intervention Review]

Treatments for toxoplasmosis in pregnancy

François Peyron[1], Martine Wallon[1], Christiane Liou[2], Paul Garner[3]

[1]Service de Parasitologie, Hôpital de la Croix-Rousse, 69004 Lyon, France. [2]Service de Parasitologie, Université Claude Bernard Lyon 1, 69008 Lyon, France. [3]International Health Group, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: François Peyron, Service de Parasitologie, Hôpital de la Croix-Rousse, 103 grande rue de la Croix-Rousse, 69004 Lyon, France. francois.peyron@chu-lyon.fr.

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ABSTRACT

Background

Toxoplasmosis is a widespread parasitic disease and usually causes no symptoms. However, infection of pregnant women may cause congenital infection, resulting potentially in mental retardation and blindness in the infant.

Objectives

The objective of this review was to assess whether or not treating toxoplasmosis in pregnancy reduces the risk of congenital toxoplasma infection.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (February 2006). We updated this search on 1 October 2009 and added the results to the awaiting classification section.

Selection criteria

Randomised controlled trials of antibiotic treatment versus no treatment of pregnant women with proven or likely acute Toxoplasma infection, with outcomes in the children reported. We also inspected relevant reports of less robust experimental studies in which there were (non randomly allocated) control groups, although it was not planned to include such data in the primary analysis.

Data collection and analysis

Reports of possibly eligible studies were scrutinised by two investigators.

Main results

Out of the 3332 papers identified, none met the inclusion criteria.

Authors' conclusions

Despite the large number of studies performed over the last three decades we still do not know whether antenatal treatment in women with presumed toxoplasmosis reduces the congenital transmission of Toxoplasma gondii. Screening is expensive, so we need to evaluate the effects of treatment, and the impact of screening programmes. In countries where screening or treatment is not routine, these technologies should not be introduced outside the context of a carefully controlled trial.

PLAIN LANGUAGE SUMMARY

Treatments for toxoplasmosis in pregnancy

No randomised trials identified on treatments for toxoplasmosis in pregnancy.

Toxoplasmosis is a widespread parasitic disease that usually causes no symptoms. However, infection in pregnant women may cause infection in the baby, resulting in possible mental disability and blindness. The risk to the baby is related to the gestational age at the time of infection. The greatest risk of transmission to the baby is during the third trimester, but disease is most severe when it is acquired during the first trimester. In some countries pregnant women are screened for toxoplasmosis by testing for antibodies to the parasite. Women who have no antibodies at the beginning of pregnancy but develop antibodies during pregnancy are considered to have active infection and their babies are at increased risk of toxoplasmosis. Antibiotics (spiramycin and sulphonamide) may be prescribed to try to reduce the risk of mother-to-child transmission, and to reduce the severity of infection in the baby; however these drugs have potential adverse toxic effects. Other countries feel the likelihood of success is too low and to risk the potential adverse effects of the drugs on the baby. Screening programmes will have no impact unless the interventions that are given as a result actually reduce congenital infection and improve infant outcomes. Hence this review sought evidence from randomised controlled trials on the effects of treatments on women who showed signs of toxoplasmosis infection during pregnancy. No randomised controlled trials were identified, so there is no sound evidence on which to base screening and treatment programmes; such evidence is needed and trials of adequate size should be undertaken.

BACKGROUND

'The main problem of congenital toxoplasmosis is to know how much of a problem it really is' (Fleck 1973).

Toxoplasmosis is a widespread parasitic disease and usually causes no symptoms. However, infection of pregnant women may cause congenital infection, resulting potentially in mental retardation and blindness in the infant. Risk is related to gestational age at the time of infection (Dunn 1999). Thus, the risk of transmission to the fetus is highest during the third trimester, but disease is most severe when it is acquired during the first trimester (Hohlfeld 1989). Doctors have prescribed spiramycin and sulphonamide drugs for presumed infection for the last thirty years to try to reduce the risk of mother-to-child transmission, and to reduce the severity of fetal infection.

France and Austria implemented nation-wide screening programmes during respectively 1985 and 1978 to try to detect, and treat immediately, all infections occurring during pregnancy. In these programmes, women of unknown immune status are tested during the first trimester of pregnancy. Seronegative women are advised on good hygienic measures, and are then retested monthly (France) or trimonthly (Austria) to identify any seroconversion. Women with serological evidence of recent acute infection are given spiramycin, and an ultrasound examination and amniocentesis are performed. If a positive diagnosis of fetal infection is made, sulphonamides and pyrimethamine are usually given, despite the potential risks of teratogenicity, and bone marrow toxicity to the mother and fetus (Remington 1992). Parents may also opt for pregnancy termination if there is evidence of fetal macroscopic lesions (Berrebi 1994; Wallon 1994).

In France, an estimated 44% of pregnant women are regularly checked for seroconversion at repeated intervals (Ancelle 1996) and between 5625 and 8850 women are treated with antibiotics during pregnancy every year to try to prevent congenital toxoplasmosis.

Other countries have decided against a routine, repeated screening programme in serologically negative women during pregnancy. In the USA, experts judged that such a programme was not warranted because of the low incidence of maternal infection and low chance of infection in the newborn (Bader 1997). In the UK, a working group of experts stated that "in the light of present knowledge screening for acute toxoplasmosis in pregnancy should not be offered routinely" (RCOG 1992). Because of the lack of certainty regarding the effect of treatment during pregnancy, Denmark has recently opted for screening based on the detection of infected neonates at birth rather than prenatal screening (Lebech 1999).

Opponents of routine serological toxoplasmosis screening also point out the need for improved diagnostic tests, despite the recent development of specific polymerase chain reaction (PCR) testing (Hohlfeld 1994), and the issue of cost-effectiveness (Jeannel 1990; Eskild 1996).

Ultimately, the detection of maternal, and then fetal, infection will have no impact unless the interventions that are given as a result of screening actually reduce congenital infection and improve infant outcomes. We therefore decided to review the evidence of the effects of treatment of women who seroconvert during pregnancy.

OBJECTIVES

To assess whether or not treating toxoplasmosis in pregnancy reduces the risk of congenital toxoplasma infection.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to assess all studies comparing at least two groups of pregnant women with evidence of recent toxoplasma infection, one group of which received no antibiotic treatment. We planned, however, to include only the results from randomised trials in the Analysis section of the review.

Studies comparing two different antibiotic treatments were excluded.

Types of participants

Pregnant women with Toxoplasma infection, defined by an increase in specific IgG from paired sera; or by a high level of specific IgG at the first antenatal test (Lebech 1998). Studies based on specific IgM screening were excluded. Participants may either have been included in formal screening programmes, or offered incidental testing carried out by general medical practitioners, suspecting toxoplasmosis infection.

Types of interventions

Any treatment given to reduce the risk of mother-to-child Toxoplasma transmission irrespective of the drug, dose or duration of treatment.

Types of outcome measures

The primary outcome was congenital infection, which was defined as persisting specific IgG at age one (Lebech 1998). Clinical congenital infection was defined by the additional presence of: hydrocephalus, ventricular dilatation, intra-cranial calcification or chorioretinitis.

Children with no clinical signs were considered disease free if they were seronegative at one year of age.

Clinically disease free children without a negative serology were considered as lost to follow-up. Abortion, stillbirth or infant death with no evidence of toxoplasmosis infection were also considered as lost to follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (28 February 2006). We updated this search on 1 October 2009 and added the results to Studies awaiting classification.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);

2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

See Table 1 for details of previous searches.

We did not apply any language restrictions.

Data collection and analysis

Papers that potentially met the inclusion criteria were scrutinised for a second time by two people. Information was extracted using a data extraction sheet, and this included the entry criteria, the source of the controls, and whether the authors stratified by stage of pregnancy when the infection occurred.

The quality of the studies was assessed in relation to (i) the criteria for diagnosing maternal infection, and (ii) the study design - the latter using a scale ranging from 0 to 6, based on 6 equally weighted items:
(a) randomised group allocation (b) recruitment at the same location for both groups (c) recruitment during the same period for both groups (d) analysis based on the intention to treat (e) inclusion in the analysis of patients lost to follow-up before analysis (f) no loss to follow-up or proportion < 10 % of the total sample. Each item was scored '1' for 'yes', and '0' for 'no' or 'unknown'.

Criteria for maternal infection were divided into true seroconversion, and those cases which were suspected because of a significant increase in IgG but which could not be proven because the first available sample was already positive for IgG.

RESULTS

Description of studies

Three hundred and ninety-eight studies met initial criteria for hard copy scrutiny. However, only ten of these met our pre-determined baseline criteria of the need for two comparative groups. None of the studies included comparisons between randomly allocated groups of women.

The details of the ten studies are shown in Table 2. The citations are listed under References to Excluded Trials. The reports were from France (4), Belgium (3), Germany (1), and Austria (1), and one came from a French-Danish collaboration. In eight reports, women were participating in a routine screening programme. In the other two reports, women were identified either through screening or individual testing by their physician. The number of women included in reports ranged from 11 to 689. (One report from an updated search in October 2009 has been added to Studies awaiting classification.)

Desmonts 1984 contained data previously published in 1974, so the 1974 report was excluded.

Risk of bias in included studies

No randomised trials were identified.

Effects of interventions

No randomised trials were identified.

DISCUSSION

Ideally, policies for the care of women who experience Toxoplasma infection during pregnancy should be based on research in which:

1. an intervention group and a control group of women who seroconvert during pregnancy are randomly allocated to active or expectant treatment;
2. researchers have conducted a study of sufficient power, with a large number of pregnant women;
3. there is adequate follow-up to a point at which congenital toxoplasmosis can be excluded.

From the 3332 papers published during the last 30 years on toxoplasmosis in pregnancy, we have failed to identify such a study.

Only a few studies included controls, but the controls were often not directly comparable. Thus, control groups variously comprised women who failed to comply with the antibiotic regimens, who seroconverted in late pregnancy, or who were from populations entirely unrelated to those in the intervention group. In other studies, it was simply not described where the controls came from. The timing of maternal seroconversion was only taken into account in two papers (Excler 1985; Foulon 1999).

Only six studies were based on pregnant women with proven seroconversions. In none of the studies were details available on the delay between infection and start of treatment, and details of the type of treatment were not always available.

Assessment of outcome was satisfactory in eight studies. These showed that even in the intervention groups, treatment failures are relatively common, with incidences of between one in three to one in five. Although there was a higher rate of infection described in control groups, the lack of comparability of treatment and control groups presents major difficulties with interpretation.

Thus, in our opinion, current evidence is insufficient to confirm that treating mothers who seroconvert during pregnancy prevents fetal infection. We do not exclude the possibility of benefit, but conclude that current research is inadequate to assess whether the putative benefits outweigh the potential harm of the drugs on the fetus. We believe that a randomised controlled trial is warranted to appropriately assess the effectiveness of prenatal treatment.

This review did not examine potential indirect benefits of screening. Serologic testing early in pregnancy means health professionals can target advice to seronegative women. Immune participants can be reassured, and excluded from further testing. Identifying acute infection through repeated antenatal tests means any infection can be followed up with antenatal diagnosis through PCR of amniotic

fluid, combined with ultrasound to monitor fetal development. If infection is confirmed, the parents have a choice between termination of pregnancy in the case of morphological lesions or in utero treatment with sulphonamides and pyrimethamine. Therapy and surveillance can be continued immediately after birth.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised trials were identified to guide a decision as to whether treatment of women who seroconvert during pregnancy is desirable, or not.

Implications for research

Further studies are needed to evaluate the benefits of maternal treatment schedules. They should use standardised interventions and outcome measures and should be based on a proper randomisation.

Countries, which do not currently perform widespread screening, should carefully conduct appropriate research before introducing screening in any form. A large study could randomise health care clinics to 'no screening' (existing practice in these countries) or 'screening, with follow up of seronegative women and treatment if they seroconvert'. Only then will it be possible to know whether the package of care is effective in preventing congenital toxoplasmosis.

In countries where screening is already routine, research will be more difficult because of the belief in screening of health professionals and the public. Congenital infection remains a problem despite intervention, as has been described in this review, so a randomised study could compare different treatments. Thus, all women would be offered routine screening, but treatment after seroconversion would be randomised e.g. to the following groups: spiramycin, with sulphonamides and pyrimethamine if fetal infection was identified at amniocentesis; spiramycin alone; sulfadoxine-pyrimethamine alone; and sulfadiazine with pyrimethamine.

France and Austria have been expected by many other countries to produce evidence on the benefits of their national screening programmes. Ironically, it now seems that now these two 'leaders' will have to depend on other countries to demonstrate whether or not such programmes are efficient and cost-effective.

ACKNOWLEDGEMENTS

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Douche C, Benabdesselam A, Mokhtari F, Le Mer Y. Value of prevention of congenital toxoplasmosis. *Journal Francais de Optalmologie* 1996;**19**:330-4.

Excler 1985 *{published data only}*

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Desmonts 1984	Not randomised.
Douche 1996	Not randomised.
Excler 1985	Not randomised.
Foulon 1999	Not randomised.
Knerer 1995	Not randomised.
Kraubig 1966	Not randomised.
Lambotte 1976	Not randomised.
Roux 1976	Not randomised.
Thoumsin 1992	Not randomised.

Study	Reason for exclusion
Wallon 1997	Not randomised.

Characteristics of ongoing studies *[ordered by study ID]*

EMSCOT study

Trial name or title	European Multicenter Study on Congenital Toxoplasmosis.
Methods	
Participants	14 centers in 11 European centers.
Interventions	None.
Outcomes	Comparison of practice (maternal screening versus no screening or screening at birth), treatment regimen measured outcomes: risk of fetal infection, severity of infection, performances of diagnostic tests.
Starting date	1997
Contact information	Pr Eskild Petersen SerumstatenInstiut Copenhagen.
Notes	

ADDITIONAL TABLES

Table 1. Details of previous searches

October 2001
In addition, an electronic search was performed using the key words 'congenital and toxoplasmosis' on 6 databases: MEDLINE (1966-09/2001), EMBASE (1989-03/2001), Pascal (French) (1990-2000), Biological Abstracts (1990-2001), Pharmaceutical Abstracts (1970-2000), Current Contents (1998-2000). References of the papers were scanned for additional potentially interesting studies. Members of the European Research Network on Congenital Toxoplasmosis and other experts were asked for relevant published or unpublished data. The abstracts and titles of each of the 3332 papers thus identified were individually checked by two people independently and all papers dealing with animal models, biological aspects of the disease, congenitally infected children without data on pregnancy, and isolated case reports were excluded. This provided a list of studies that potentially met the inclusion criteria, and these were obtained as hard copies.

Table 2. Treatment in pregnant women diagnosed with toxoplasmosis

Study	Trimester	Inclusion criteria	Controls selection	Quality score	Regimen	Infected	Not infected	Lost to follow-up	% Infected children
Desmonts 1984	all	seroconversion ; "significant increase in IgG"; "clinical signs and high levels of IgG"	unknown; historical controls (seroconversions prior to screening)	3	spiramycin (2-3 g/d) for at least one month : 388	88	297	3	22 (95% CI 18, 27)
					no treatment : 154	85	60	9	52 (95% CI 44, 60)
Douche 1996	all	seroconversion	late seroconversions inadequate follow-up	4	spiramycin (2g/d) : 64	9	60	0	13 (95% CI 6, 24)
					spiramycin + PS after positive antenatal diagnosis : 5				
					no treatment : 29	29	0	0	100 (95% CI 63, 100)
Excler 1985	first	seroconversion or increase in IgG	unknown	2	spiramycin (3g/d) : 31	2	29	0	6 (95% CI 1, 23)
					no treatment : 4	0	4	0	0 (95% CI 0, 60)
	second				spiramycin : 55	15	40	0	27 (95% CI 16, 41)
					no treatment : 13	5	8	0	38 (95% CI 15, 68)
	third				spiramycin: 18				
					no treatment : 13	26	99	0	21 (95% CI 14, 29)
	all				spiramycin : 104	22	82	0	21 (95% CI 14, 30)
					no treatment : 30	26	99	0	21 (95% CI 14, 29)

Table 2. Treatment in pregnant women diagnosed with toxoplasmosis *(Continued)*

Knerer 1995	14-29 week	seroconversion	untreated patients or non-compliers	4	spiramycin (3 g/d) : 9	0	9	0	0 (95% CI 0, 37)
					no treatment : 2	2	0	0	100 (95% CI 20, 100)
Kraubig 1966	all	seroconversion (18) ; increase (x2) dye test ; dye test > 1000	unknown	4	P + Su : 59	3	56	0	5 (95% CI 1, 15)
					no treatment : 84	14	70	0	17 (95% CI 10, 27)
Lambotte 1976	all	seroconversion	untreated patients or non-compliers	4	spiramycin + S (3g/d each, 4 weeks/6) : 28	0	28	0	0 (95% CI 0, 15)
					no treatment : 101	10	91	0	10 (95% CI 5, 18)
Roux 1976	all	seroconversion (10) ; evolutive infection* (18) ; high IgG levels (25)	late seroconversions (5) inadequate follow-up (1)	3	spiramycin (3 g/d) : 47	2	43	2	4 (95% CI 0.7-15)
					no treatment : 6	5	1	0	83 (95% CI 36, 99)
Thoumsin 1992	all	seroconversion	unknown	2	spiramycin + PS (dose unknown) : 99	10	89	0	10 (95% CI 5-, 8)
					no treatment : 101	10	91	0	10 (95% CI 5, 20)
Wallon 1997	all	seroconversion	Lyon : - Copenhagen : screening at delivery	4	spiramycin (3 g/d) ± PS : 564	141	381	42	24 (95% CI 20, 27)
					no treatment : 125	26	99	0	21 (95% CI 14, 29)
Foulon 1999	all	seroconversion	unknown	2	spiramycin ± PS or Az: 119	46	69	4	39 (95% CI 30-48)

Table 2. Treatment in pregnant women diagnosed with toxoplasmosis *(Continued)*

	no treatment: 25	18	7	0	72 (95% CI 50-87)

WHAT'S NEW

Date	Event	Description
1 October 2009	Amended	Search updated. One report added to Studies awaiting classification (Garcia 1995).

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 3, 1999

Date	Event	Description
20 September 2008	Amended	Converted to new review format.
28 February 2006	New search has been performed	Search updated but no new trials identified.

CONTRIBUTIONS OF AUTHORS

François Peyron and Paul Garner were responsible for the conception of the study and the original protocol draft. Martine Wallon, Christiane Liou and François Peyron were responsible for identifying the papers, extracting the date and writing the first draft. All authors took part in its revision and approved the final version. Martine Wallon was responsible for updating the review in October 2001.

François Peyron is the study guarantor.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- European Union Directorate General XII, Belgium.
- Cochrane Infectious Diseases Group, Liverpool, UK.
- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Pregnancy Complications, Infectious [*prevention & control]; Toxoplasmosis [*prevention & control]

MeSH check words

Female; Humans; Pregnancy