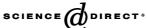


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Review

Biases in observational studies of the effect of prenatal treatment for congenital toxoplasmosis

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Abstract

The paper reviews methodological difficulties that arise when using observational studies to evaluate the effect of prenatal screening and treatment. The principle of each difficulty is described and then illustrated by a clinical example of toxoplasmosis in pregnancy and its consequences. Methods to deal with these difficulties are described. Given the limitations of existing observational studies and lack of randomised controlled trials, a systematic review of cohort studies offers the best approach for exploring potential biases.

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1. Introduction

Toxoplasma infection is due to the parasite Toxoplasma gondii and is most often a benign disease. Two populations are at risk of severe disease: (1) immunocompromised individuals, such as HIV-infected patients and (2) fetuses or children with toxoplasmosis transmitted from their mother via the placenta. Congenital toxoplasmosis may result in severe manifestations, such as intrauterine death or stillbirth, retinochoroiditis or hydrocephalus [1,2]. Prevention and clinical management of congenital toxoplasmosis varies widely among countries. Some countries, such as Austria and France, offer routine testing of pregnant women never infected by toxoplasmosis, and antibiotic treatment when seroconversion occurs during pregnancy. In other countries, screening of children is performed after birth (e.g. Denmark) or there is an explicit policy not to screen (e.g. United Kingdom). Explanations for the variation in prevention and clinical management policies include the lack of reliable information on treatment effectiveness [3-6] and variation in disease prevalence. Congenital toxoplasmosis is rare on average, at less than one case per 1000 pregnancies, and the prevalence of susceptible women is highly variable among countries. The evidence about the efficacy of prenatal treatment on mother-to-child transmission of the parasite or on clinical manifestations in infected children is based only on observational studies [7,8]. Moreover, published studies reported controversial results [1,4,5,9–14]. We hypothesized that most of the controversy in the interpretation of results could be explained by two problems: firstly, the series of events in mother-to-child transmission of toxoplasma infection is complex. Secondly, biases may be numerous in observational studies. In Fig. 1, we describe the clinical management of congenital toxoplasmosis as recommended in France with a monthly screening of pregnant women who have a first negative serology for toxoplasmosis. Women who seroconverted are most often treated by spiramycin (S). If mother to child transmission of the parasite is diagnosed (for example, by PCR analysis of amniotic fluid) then treatment is changed to pyrimethamine and a sulfonamide

(PS). After birth, a potential bias is that infected children with clinical signs are more likely to be treated and followed up compared to asymptomatic children. Other methodological pitfalls include selection of cases, lack of standardisation of outcome measures, or confounding. Examples of such biases are shown in Fig. 1 and described latter in this paper. In addition to systematic errors, small sample sizes due to the rarity of the disease yield wide uncertainty around estimations of treatment effect.

This paper provides a review of the major epidemiological issues associated with observational studies on congenital toxoplasmosis, in the absence of randomised trials. We present several biases that might alter the comparability of treated and untreated groups in observational studies and therefore alter inferences regarding the effect of prenatal treatment. We propose different solutions that should be implemented to minimise or at least to quantify these biases.

This review aims to provide a way of interpreting observational data on this topic that may also be helpful for developing experimental or observational studies in this field in the future.

2. Selection biases

2.1. Principle

The choice of a reference group is important for the validity of the estimates of treatment effect as well as for the generalisability of the results. Basically, the unexposed group should be similar to the exposed group with respect to the important predictors of disease incidence [15]. Thus, a historical control group is not relevant because other factors associated with the disease incidence and management have changed with the exposure.

In congenital toxoplasmosis studies, cohorts have often been constituted by women suspected to be contaminated by *T. gondii* and sent to a reference centre for serological diagnosis or for biological investigation. Some of these women are referred for a serological diagnosis because of

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