Systematic screening and treatment of toxoplasmosis during pregnancy: is the glass half full or half empty?

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In this issue of the Journal, Mandelbrot et al[1] report findings of the first randomized clinical trial (RCT) ever performed on the treatment of acute toxoplasma infection during pregnancy. Treatment of acute toxoplasma infection during gestation is aimed at preventing mother-to-child transmission (MTCT) and to minimize clinical sequelae in already infected offspring (CSIo).[1] According to the authors, a placebo-controlled RCT was not possible because most investigators who were surveyed at the time believed that such RCT would be unacceptable, given that spiramycin has been used for this indication in France for >30 years. For this reason, the Toxogest (ClinicalTrials.gov Identifier: NCT01189448) was designed as an RCT to compare the upfront use of spiramycin vs pyrimethamine/sulfadiazine/folinic acid (PS) in women confirmed to have seroconverted during their second trimester of gestation or later. Their hypothesis was that PS would be superior to spiramycin. One hundred fifty-one women were randomly assigned to spiramycin or PS. The time of maternal infection, which is one of the most powerful factors that influences the likelihood of vertical transmission and clinical sequelae in the offspring, was estimated to have occurred between 13 and 25 weeks of gestation (WG) in their participants. The time of maternal infection was determined accurately by choosing the midpoint between the last negative and the first positive *Toxoplasma* immunoglobulin G finding in the setting of monthly screening. Women could not be enrolled in their first trimester because PS is considered unsafe for the fetus during this period; their study did not have any women enrolled past 25 WG for maternal infection, which may have been a good thing because, in the third trimester, spiramycin is known to be less effective and because the comparison would have been unfair for spiramycin. Unfortunately, Toxogest had to be terminated prematurely because of low enrollment and lack of additional funding. Given the fact that recruitment fell short of the projected sample size, did we learn anything new from Toxogest results? Fortunately, I believe the answer is an unqualified yes.

First, we learned that most French investigators who are authorities in the field would consider it unethical to design a study that includes a group in which women who acquire *Toxoplasma* infection during gestation would be given placebo and left untreated. In their experience, and as it is reflected in >30 published observational studies (including >9000 pregnant women and their offspring), treatment of acute maternal toxoplasmosis decreases MTCT and CSIo.[2] Among studies with primary data, from early[3–7] to most recent,[8–13] trends in MTCT rates and CSIo have always favored treated over untreated. Moreover, findings from these >30 studies have never concluded that the potential harm from treatment outweighs its benefits. Systematic screening and treatment for toxoplasmosis during pregnancy became controversial in the early 2000s because of articles that were published from 1999–2007[14–19] that unfortunately were biased and misleading and misunderstood the biologic impact of spiramycin on MTCT and CSIo. For instance, in these 6 studies, participants were excluded if the fetus was already affected or severely affected (this occurrence would more often fall in the untreated group). In addition, studies before 1985 were also not included in a highly quoted metanalysis because, according to the authors, immunoglobulin M was not widely available before that time.[19] Cohorts before 1985 tended to have the largest numbers of untreated women. Moreover, it was assumed erroneously that the efficacy of spiramycin could be established merely by estimating the frequency of infected vs uninfected offspring in the treated vs untreated groups. Under this assumption, an infected offspring would be tallied as a "failure" and an uninfected newborn as a "success."

However, spiramycin is unique in its capacity to concentrate in the placenta, and its effect in MTCT is far more complex.[20–22] Spiramycin partially, but not completely, diminishes MTCT and contributes to ameliorate CSIo. Spiramycin benefit can be summarized in 3 categoric effects: (1) it is successful in preventing fetal infection in some cases; (2) it is not successful in preventing infection but reduces toxoplasma burden, which results in a shift from severe to milder forms of the disease in others; and (3) it is not successful in preventing infection that results in full-blown outcomes of mild/moderate/severe congenital disease in a third group. Thus, spiramycin can avoid transmission in some pregnant women, decrease severity in others, and fail in a third group.

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Offspring with a lower parasitic burden, who are spared from severe disease and/or death, end up contributing to the number of "infected" children. The net effect of such intervention would be an overall decrease of severe cases and death but less than substantial effects on MTCT because some of the offspring who would have succumbed to the parasite are now born live, with milder forms, and are tallied in the "infected group." This conceptual framework appears to explain the results that were observed in the SYROCOT (Systematic Review on Congenital Toxoplasmosis) study.[19] In the SYROCOT study, severe cases were excluded to avoid "referral bias." In addition, in their analysis of clinical manifestations, 4 cohorts from outside Europe (2 in Brazil and 1 in Colombia) that contained significant numbers of severe cases, which were based mainly on neonatal screening, were also excluded. In fact, when a subgroup of SYROCOT investigators analyzed the data that included those with severe neurologic sequelae or death, prenatal treatment (spiramycin±PS) reduced the risk of severe neurologic sequelae or death.[9] The odds ratio for prenatal treatment was 0.24 (95% confidence interval [CI], 0.07−0.71). Even in the absence of placebo-controlled RTC, there is plenty of evidence that supports the treatment of acute toxoplasmosis during pregnancy, which is the reason that the Mandelbrot et al[1] study could not have a placebo arm.

Second, although statistical significance was not achieved because of the limitation in sample size brought by the unintended early termination of the trial,[1] the PS that was initiated as early as 14 WG resulted in a clear trend to lower MTCT in the PS group: 10.4% vs 20.3% as measured by positive amniotic fluid polymerase chain reaction (PCR) test results and 18.5% vs 30% as measured by observing infants up to 1 year of age, which is considered the gold standard for the diagnosis of congenital toxoplasmosis.[23] Furthermore, ultrasound manifestations of congenital toxoplasmosis were present only in the spiramycin group (8.6%) but not in the PS group (0%). What the study by Mandelbrot et al[1] has taught us is that there is a potential additional benefit in starting PS over spiramycin as the initial treatment for maternal toxoplasmosis, particularly if it is instituted as early as possible. How early during gestation PS is recommended currently for the upfront treatment of acute infection (before work up for fetal infection is undertaken) varies greatly by reference center: 32 WG,[24] 30 WG,[25] 18 WG,[26] 16 WG.[10,13] It is interesting to note that the centers with treatment regimens closer (eg, 16 WG)[10,13] in WG to the Mandelbrot et al[1] study (14 WG) have reported lower MTCT rates than other centers that initiate upfront PS later (eg, 32 WG).[24] The results of this RTC should lead to centers that recommend PS as an upfront treatment beyond 14 WG[24−26] to consider initiating PS at 14 WG.

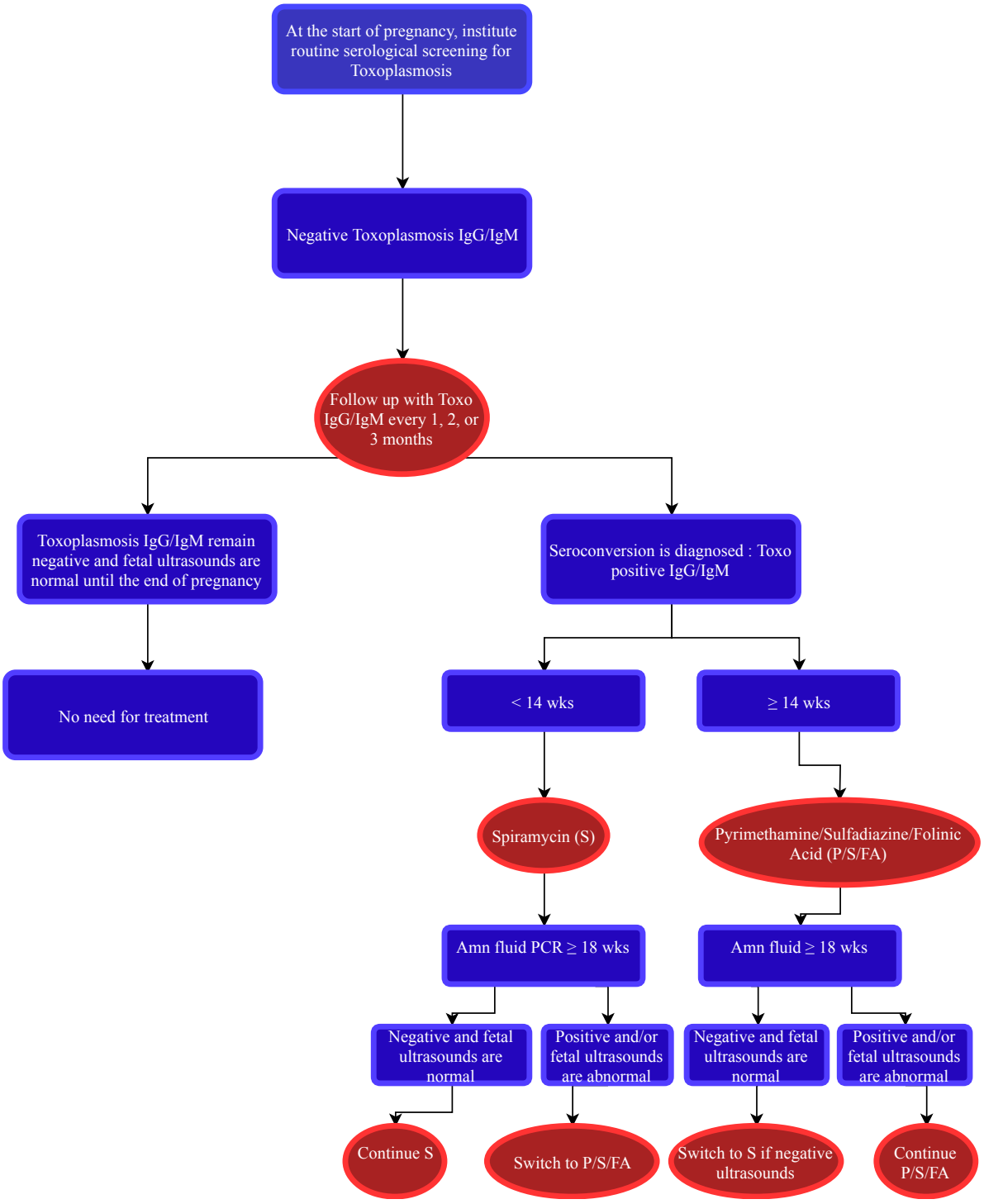
Third, timing of the initiation of treatment earlier trended toward further improved outcomes. The effect of prenatal treatment was strengthened by treatment that was initiated (eg, <3 weeks earlier). Treatment benefit varied significantly with an odds ratio for PS vs spiramycin of 1.20 (95% CI, 0.35−4.14) when initiated at >3 weeks and an odds ratio of 0.03 (95% CI, 0.00−1.63) when initiated within 3 weeks of the estimated maternal infection. Other studies have found similar trends with earlier initiation of treatment, which provides further support that prenatal treatment of maternal toxoplasmosis is effective.[11,13,19]

Fourth, the fact that a small number of infants were found subsequently to be infected in both arms, despite negative results in amniotic fluid PCR (13.3% in the spiramycin group and 25% in the PS group), supports the recommendation the observation of these babies with serial ultrasound scan results during gestation and continuing drug treatment. One reason spiramycin has been recommended in pregnant women throughout gestation, even after negative PCR and fetal ultrasound results, is the concern that the placenta may be still infected but that the infection has not reached the fetus yet.[26] In the study of Mandelbrot et al[1] study, it appears that some of the women in the PS arm had their treatment discontinued upon negative PCR test results. In patients without evidence of fetal infection by PCR and ultrasound scanning, some centers recommend continuation of therapy until the end of gestation, with either spiramycin alone or spiramycin alternated with PS on a monthly basis;[10,13] these infected children, despite prenatal therapy, rarely present with severe disease.[10,13] This fact of infected offspring in the presence of in utero treatment also further emphasizes the need to observe children for at least 1 year and ideally lifelong to evaluate fully the impact of congenital toxoplasmosis in human life. One major benefit of the initiation of treatment in utero is that, even when fetal infection occurs, it has been demonstrated that these treated children achieve a quality of life similar to those not infected.[27]

Fifth, the regimens of spiramycin and PS for maternal toxoplasmosis should be viewed as complimentary rather than binary or mutually exclusive. PS is potentially teratogenic, should not be used before 14 WG, has potential hemato-, renal-, and hepatotoxicity that requires at least weekly laboratory testing and, as reported by Mandelbrot et al[1] and others,[10,13] ideally should be used for women with acute toxoplasmosis at ≥14 WG. Spiramycin is not teratogenic, has a well-known and acceptable safety profile, and can be used any time during gestation; however, it should best be used as the initial regimen at <14 WG. In addition, spiramycin should be used throughout gestation when a work up for fetal infection by PCR and ultrasound scanning is negative.

Sixth, most of the pregnant women in France who seroconvert during gestation and who benefit from prenatal antitoxoplasma are asymptomatic and do not have identifiable risk factors for toxoplasma infection.[28,29] This means that, if the criteria to enter into the study would have been presence of symptoms, most women who seroconverted and were qualified for the trial would have not been enrolled. That women usually do not have symptoms during gestation and/or identifiable risk factors is also a reality in the United States; it has been

FIGURE
Proposed algorithm



Proposed algorithm for serologic screening and follow up of pregnant women who were identified to be at risk for seroconversion during gestation (negative for *Toxoplasma* immunoglobulin G and M).

Amn, amniotic; *FA*, folinic acid; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *P*, pyrimethamine; *PCR*, polymerase chain reaction; S, spiramycin; *Toxo*, toxoplasmosis.

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well-demonstrated by the toxoplasmosis Chicago group.[30] Thus, the only approach that guarantees the provision of benefit of prenatal treatment to each of the 200,000,000 women who become pregnant each year worldwide is by systematic serologic screening. The global annual incidence of congenital toxoplasmosis has been estimated to be 190,100 cases (95% CI, 179,300−206,300), corresponding to a burden of 1.20 million disability-adjusted life years (95% CI, 0.76−1.90).[31] Yet, only few countries (eg, France, Austria, Germany, Uruguay, Lithuania, Argentina) protect their fetuses by universal serologic screening during gestation, followed by treatment of women who seroconvert.[32] Surprisingly and unfortunately, this is not the case in the United States (and other countries) where toxoplasmosis screening during pregnancy is not universally recommended.[32,33]

In countries, which includes the United States, where systematic serologic screening is not recommended, severe disease alarmingly is still seen.[34] However, it is common for clinicians in the United States to express their surprise to reports of severe disease because they rarely see congenital toxoplasmosis in their daily practices. Two major reasons may explain the reason that congenital toxoplasmosis is not seen more frequently in clinical practices but only in reference centers such as the Palo Alto Medical Foundation *Toxoplasma* Serology Laboratory (http://www.pamf.org/Serology/). *Toxoplasma* seroprevalence (as an indirect evidence of the parasite circulating in a region) has been declining over decades,[35] which make it more difficult for individual practitioners to see the still existing burden of the disease. Moreover, the placenta does a much better job than we think and better than any medical intervention to safeguard the fetal brain from *Toxoplasma gondii*[36] and, for that matter, from any other infection.[37,38] Thanks to the placenta "fortress," even in those women who seroconvert, transmission does not occur in a significant group of them.[38]

Based on the published literature, starting with the first observations by Desmonts and Couvreur[3] in the 1970s to the most recent ones,[1,13] systematic screening for toxoplasmosis, as we do for other rare diseases such as Rubella (https://www.acog.org/Patients/FAQs/Routine-Tests-During-Pregnancy#why), should be performed for every pregnant woman where *Toxoplasma* infection is known to occur because congenital toxoplasmosis can result in devastating neurologic and ocular consequences and death and because congenital toxoplasmosis is preventable and treatable in utero. The Figure provides a proposed algorithm of such a program. An important additional concern is cost, which will have to be addressed by each country. In the United States, Stillwaggon et al[39] has shown that routine serologic screening during pregnancy, as it is performed monthly in France, is feasible and cost-saving, with the assumption that the cost of serologic screening is contained. Novel developments in serologic testing that include less expensive point-of-care technology[40] and plasmonic-based diagnostic platforms[41] could meet the technologic and cost challenges that are associated with massive screening. The question should not be anymore, to treat or not to treat, but what to treat with. The glass is sufficiently full in the areas of epidemiology, biology of the parasite and infection, efficacy of drugs, and laboratory science to implement systematic screening for toxoplasmosis, even if the glass will remain half empty because of the lack of placebo-controlled RCTs. Same as for penicillin or ceftriaxone for pneumococcal pneumonia, no ethical clinician or investigator will ever call for a placebo arm in the treatment of pneumococcal pneumonia because placebo-controlled clinical trials were never performed. It is time to not leave anymore pregnant women who silently seroconvert for toxoplasmosis during gestation in the equivalence of a placebo arm.

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