

## OBSTETRICS

# Prenatal therapy with pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission of toxoplasmosis: a multicenter, randomized trial



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**BACKGROUND:** The efficacy of prophylaxis to prevent prenatal toxoplasmosis transmission is controversial, without any previous randomized clinical trial. In France, spiramycin is usually prescribed for maternal seroconversions. A more potent pyrimethamine + sulfadiazine regimen is used to treat congenital toxoplasmosis and is offered in some countries as prophylaxis.

**OBJECTIVE:** We sought to compare the efficacy and tolerance of pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission.

**STUDY DESIGN:** This was a randomized, open-label trial in 36 French centers, comparing pyrimethamine (50 mg qd) + sulfadiazine (1 g tid) with folinic acid vs spiramycin (1 g tid) following toxoplasmosis seroconversion.

**RESULTS:** In all, 143 women were randomized from November 2010 through January 2014. An amniocentesis was later performed in 131 cases, with a positive *Toxoplasma gondii* polymerase chain reaction in 7/67 (10.4%) in the pyrimethamine + sulfadiazine group vs 13/64 (20.3%) in the spiramycin group. Cerebral ultrasound anomalies appeared in 0/73 fetuses in the pyrimethamine + sulfadiazine group, vs 6/70 in the spi-

ramycin group ( $P = .01$ ). Two of these pregnancies were terminated. Transmission rates, excluding 18 children with undefined status, were 12/65 in the pyrimethamine + sulfadiazine group (18.5%), vs 18/60 in the spiramycin group (30%,  $P = .147$ ), equivalent to an odds ratio of 0.53 (95% confidence interval, 0.23–1.22) and which after adjustment tended to be stronger ( $P = .03$  for interaction) when treatment started within 3 weeks of seroconversion (95% confidence interval, 0.00–1.63). Two women had severe rashes, both with pyrimethamine + sulfadiazine.

**CONCLUSION:** There was a trend toward lower transmission with pyrimethamine + sulfadiazine, but it did not reach statistical significance, possibly for lack of statistical power because enrollment was discontinued. There were also no fetal cerebral toxoplasmosis lesions in the pyrimethamine + sulfadiazine group. These promising results encourage further research on chemoprophylaxis to prevent congenital toxoplasmosis.

**Key words:** pregnancy, prenatal diagnosis, pyrimethamine-sulfadiazine, spiramycin, tolerance, toxoplasmosis

## Introduction

In France, since 1978, there has been a policy of mandatory prenatal screening for toxoplasmosis. In case of primary infection, treatment with spiramycin (S) is generally offered,<sup>1</sup> with the aim of reducing the risk of mother-to-child transmission.<sup>2</sup> Most other countries have not adopted a systematic screening policy.<sup>3</sup> While considerable progress has been made in prenatal diagnosis and

## EDITORS' CHOICE

prognostic evaluation of congenital toxoplasmosis, the prevention program has been criticized for lack of proof from randomized trials to evaluate prophylactic treatment. A protective effect of S was suggested by an observational study in the 1960s.<sup>4</sup> However, there was a major confounding bias due to the gestational age at maternal seroconversion that was not taken into account.<sup>5</sup> Further large observational studies failed to demonstrate the efficacy of prophylactic treatment<sup>6,7</sup> and a meta-analysis of individual observational data of 1745 infected pregnant women from 26 cohorts concluded that prophylaxis was not associated with a clinically relevant effect.<sup>8</sup> The French High Authority for Health<sup>9</sup> called for randomized trials to be performed before reevaluating whether to maintain the French congenital toxoplasmosis prevention program.

In case of primary *Toxoplasma gondii* infection during pregnancy, the risk of transmission to the fetus increases sharply with gestational age at the time of infection.<sup>8,10,11</sup> Congenital toxoplasmosis may lead to fetopathy, hydrocephalus, and death. Most often, the disease is asymptomatic at birth, but may lead to chorioretinitis that can be diagnosed only later in life. The risk of brain damage is higher in case of infection in early pregnancy.<sup>4,8,12</sup> A hypothesis failed to explain that previous studies failed to demonstrate a protective effect of S may be its insufficient effect on *T gondii*. In France, S has been used for >30 years,<sup>1</sup> while in Austria and Germany, pyrimethamine-sulfadiazine (PS) is routinely used for prophylaxis >16 weeks' gestation.<sup>13,14</sup> PS is more effective than S in vitro<sup>15,16</sup> and to treat children and adults for cerebral or ocular toxoplasmosis. PS is widely used during pregnancy following a prenatal diagnosis

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## AJOG at a Glance

**Why was this study conducted?**

The efficacy of prophylaxis for prenatal toxoplasmosis transmission is controversial, for lack of a randomized clinical trial. Spiramycin (S) is usually prescribed for maternal seroconversions. Pyrimethamine + sulfadiazine (PS) is the treatment of choice for congenital toxoplasmosis and is used in some countries as prophylaxis.

**Key findings**

The rate of placental transmission was lower with PS vs S; however, the difference fell short of statistical significance. The difference was stronger when treatment started rapidly. During prenatal follow-up, the incidence of abnormal ultrasound findings was significantly lower in the PS than in the S group.

**What does this add to what is known?**

In the first randomized trial of medications to prevent placental transmission of toxoplasmosis, PS appeared more effective than S, but a definitive conclusion would require further randomized studies.

of congenital toxoplasmosis,<sup>12,17,18</sup> based on evidence from observational cohorts suggesting that it reduced the incidence of severe cerebral signs or symptoms, when taking into account the gestational age of maternal infection.<sup>19</sup>

We hypothesized that PS would be more effective than S in reducing the risk of transplacental transmission of toxoplasmosis.

**Materials and Methods****Study design**

We performed a multicenter randomized phase-III clinical trial in 2 parallel groups, pyrimethamine (50 mg once daily orally) and sulfadiazine (1 g tid orally), with supplemental folic acid (50 mg once a week) vs S (1 g tid orally). Drugs were given open-label because more invasive follow-up was required for the PS group. A total of 36 centers in mainland France participated.

**Study population**

Inclusion criteria were: age >18 years, proven maternal seroconversion for toxoplasmosis defined as a negative serology during pregnancy followed by synthesis of specific IgG, gestational age at enrollment at least 14 weeks' gestation, and signed informed consent.

Criteria for noninclusion were: treatment with S or pyrimethamine-sulfamide for >10 days before randomization, allergy to any of the trial drugs or a history of severe skin allergy, G6PD

deficiency, liver or renal insufficiency or other serious illness in the mother, or major fetal anomaly.

**Procedures**

Treatment was to be started as soon as possible after the diagnosis of seroconversion. Follow-up was performed according to usual care. Blood cell counts and differentials were performed twice weekly in mothers during treatment with PS. In the event of severe adverse clinical or biological events possibly due to the study drugs, this was reported and treatment was discontinued immediately. An amniocentesis was offered (with the patient's consent) >18 weeks' gestation, at least 4 weeks after the estimated date of primary infection.

In cases of fetal infection, prenatal therapy with PS was offered as per usual care, and the prognosis was assessed taking into account serial ultrasound findings. In case of anomalies with poor prognosis, termination of pregnancy was considered by a multidisciplinary center for prenatal diagnosis if requested by the woman, in accordance with French law. In case of a negative polymerase chain reaction (PCR) at amniocentesis: (1) in the S group, treatment was continued until delivery according to usual procedures; and (2) in the PS group, the treatment could be stopped to reduce the risk of intolerance, when the mother received at least 4 weeks of therapy. In the absence of amniocentesis, protocol treatment was

continued for 8 weeks, and whether any further treatment was used was left up to the clinician. Ultrasound surveillance was continued monthly.

Follow-up and treatment of children with congenital toxoplasmosis was performed according to usual guidelines. In case of a negative amniocentesis or in the absence of prenatal diagnosis, children were to be followed up until definitive diagnosis.

**Diagnosis of congenital toxoplasmosis**

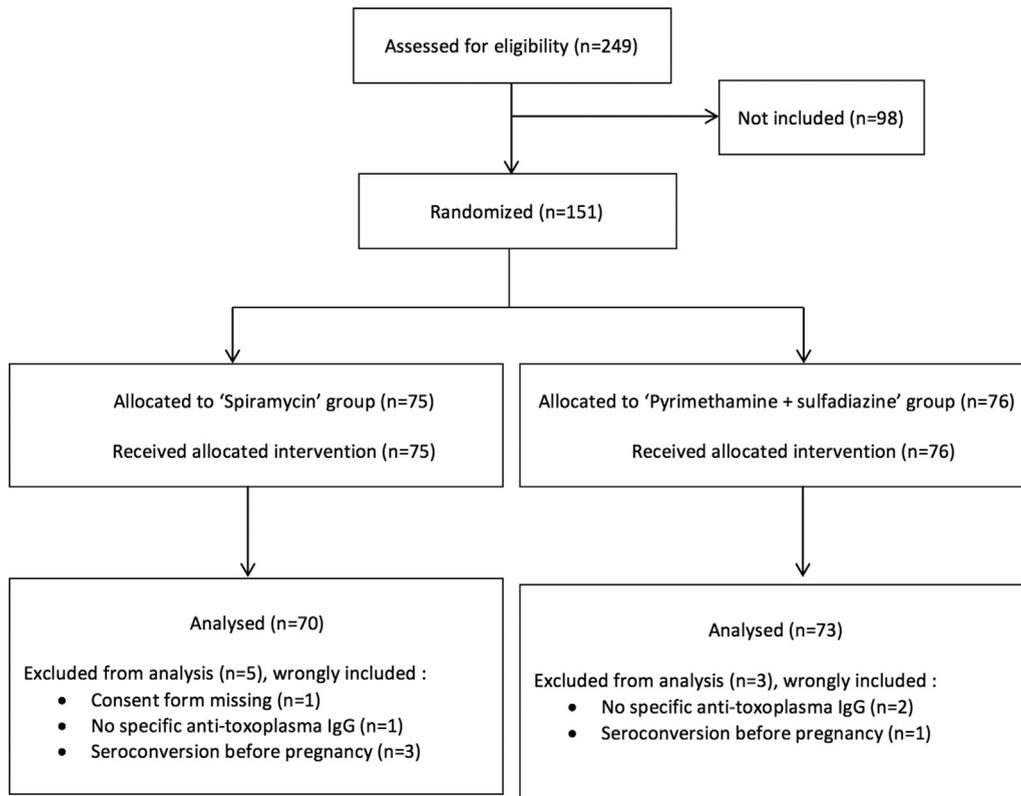
The diagnosis of congenital toxoplasmosis was defined as a positive result of PCR or mouse inoculation on amniotic fluid, PCR on cord blood, mouse inoculation of placenta, and/or the synthesis of specific antibodies (IgM and/or IgA, IgG neoantibodies by a Western blot or immunoblot) in the infant.<sup>20</sup> All amniocentesis samples were tested by real-time PCR in certified laboratories in reference centers, then retested in the coordinating National Reference Center in Reims.

The absence of transmission was definitively established by the decline until disappearance of specific IgG antibodies in the infant, in the absence of any postnatal antitoxoplasma medication in the last 2 months, confirmed on a second sample  $\geq 1$  month later to rule out serological rebound.

Secondary outcome measures were: the incidence of congenital toxoplasmosis in each group according to the time between maternal primary infection (defined as the midpoint between the last negative and the first detection of antitoxoplasmosis antibodies) and the start of antiparasitic prophylaxis and the incidence of adverse reactions in mothers and newborns in each treatment group.

**Sample size**

Based on meta-analysis data, a potential protective effect of treatment (based on the effect of treatment delay<sup>8</sup>), with an average transmission risk of 40% for second- and third-trimester seroconversions, 330 patients (165 per group) would be required to demonstrate a 40% reduction in transmission to 25% in the

**FIGURE 1**  
**Toxogest study flowchart**

Flow chart.

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PS group in the effective group using Fisher exact test with a 5% type-1 2-sided risk and a statistical power of 80%.

### Statistical analyses

All analyses were performed as intent-to-treat.<sup>21</sup> The main analysis was conducted including only children with definitive infection status. In the absence of definitive infection status, all the available data were used according to an algorithm analyzing the available serological follow-up, and cases with probable or possible infection were considered as infected. Children with insufficient follow-up to conclude were considered as indefinite status. The algorithm was applied blindly, ie, without knowledge of the treatment group. Robustness analyses were performed considering cases with indefinite status as: (1) missing = failure; and (2) according to maximum bias hypotheses. All univariate tests, thus including the principal comparison of transmission

rates between groups, used Fisher exact 2-sided test and all confidence intervals (CI) for dichotomous outcomes used exact binomial distribution. For adjusted estimates, we used logistic regression models, whose parameters were estimated using an integrated maximum likelihood method<sup>8,22</sup> to take into account the interval censoring of the gestational age at seroconversion and the timing of treatment initiation. We considered whether the first positive IgM test was IgG negative or IgG positive to estimate the probabilities of seroconversion at each possible date between the last negative and first positive date.<sup>22</sup> We examined whether the treatment effect was modified according to explanatory variables using the likelihood ratio test for interaction between variables. In sensitivity analyses, the results were robust to each of the functions used to estimate the gestational age at seroconversion (data not shown). All analyses

were performed with software (SAS, version 9.3; SAS Institute Inc, Cary, NC).

### Ethics

The protocol was approved by the ethics committee, the Protection des Personnes Kremlin-Bicêtre on June 10, 2010, under protocol no. 10-014 and authorized by the French Drugs Agency (Agence nationale de sécurité du médicament) on July 9, 2010. All patients gave written, informed consent.

### Results

#### Study population and follow-up

A total of 151 women were enrolled from November 2010 through January 2014 in 36 centers. Enrollment was stopped before achieving the planned recruitment because the recruitment was slower than planned and funding to prolong the study was not obtained. As shown in the flow chart (Figure 1), 70 patients were randomized to S and 73 to PS. The baseline

**TABLE 1**  
**Characteristics of study population**

Variable	Spiramycin group N = 70	Pyrimethamine + sulfadiazine group N = 73
Maternal age, y	30 (26; 33)	29 (26; 32)
Maternal weight, kg	68 (62; 78)	68 (60; 76)
Gestational age at enrollment, wk	23 (18; 28)	23 (19; 28)
Parity		
0	19 (27.1%)	24 (32.9%)
Multiparous	49 (70.1%)	46 (63.0%)
Not available	2 (2.9%)	3 (4.1%)
Allergies		
No	60 (85.7%)	65 (89.0%)
Yes	9 (12.9%)	8 (11.0%)
Not available	1 (1.4%)	
Estimated time of maternal infection, WG <sup>a</sup>	18 (13; 25)	19 (16; 24)
Time between last negative and first positive IgG serology, days	37 (22; 46)	30 (16; 45)
Time between first positive serology and start of study drug, days	11 (7; 21)	13 (6; 23)
Treatment with antiparasitic drug before enrollment	21 (30.0%)	21 (28.8%)
Amniocentesis performed	64 (91.4%)	67 (91.8%)
Ultrasound scan findings at enrollment:		
Normal	65 (92.9%)	68 (93.2%)
Abnormal <sup>b</sup>	2 (2.9%)	2 (2.7%)
Not available	3 (4.3%)	3 (4.1%)
Duration of antiparasitic treatment as randomized		
<4 weeks	6 (8.6%)	21 (28.8%)
4–8 weeks	14 (20.0%)	27 (37.0%)
≥8 weeks	43 (61.4%)	17 (23.3%)
Not available	7 (10.0%)	8 (11.1%)

Data are median (Quartile1; Quartile3) or number (percentage).

WG, weeks of gestation.

<sup>a</sup> Time of maternal infection in WG defined for description's sake as midpoint between last negative serology and first detection of antitoxoplasma antibodies; <sup>b</sup> Fetal anomalies not suggestive of congenital toxoplasmosis.

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characteristics of the study population are shown in Table 1. Ultrasound examination at enrollment showed no abnormalities relative to toxoplasmosis. An amniocentesis was later performed in 131 cases. The proportion of positive PCR for *T gondii* was 7/67 (10.4%) in the PS group vs 13/64 (20.3%,  $P = .147$ ) in the S group. The National Reference Center in Reims confirmed the results. After a positive amniocentesis, all but 1 patient

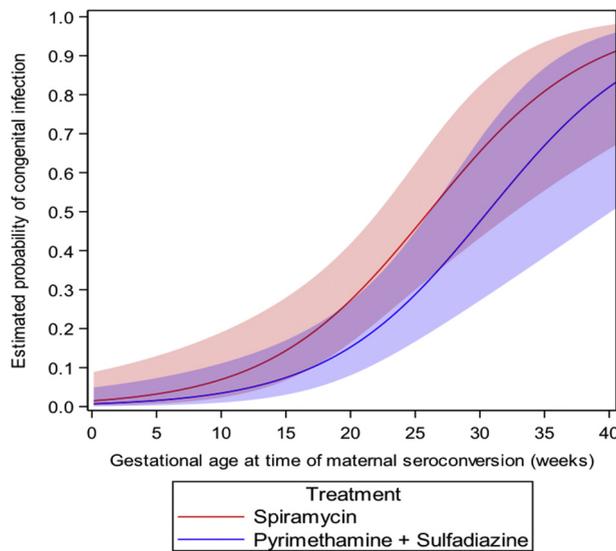
received pyrimethamine and a sulfonamide. Following negative amniocenteses, patients in the S group continued the same treatment, whereas patients in the PS group had a shorter duration of treatment with PS.

### Congenital toxoplasmosis

The diagnosis of congenital toxoplasmosis was established in 30 children (29 certain, 1 probable), excluded in 95 children (75

certain and 20 probable), and remained undefined in 18 children. There were 6 children who had congenital toxoplasmosis although the amniocentesis result was a negative PCR, 2/15 (13.3%; 95% CI, 1.7–40) in the S group and 4/16 (25%; 95% CI, 7.3–52) in the PS group. The median time between maternal seroconversion and amniocentesis in these cases was 48.8 days (range 29–67). The diagnosis of congenital toxoplasmosis was

**FIGURE 2**  
Transmission rate according to treatment and gestational age



Predicted risk of mother-to-child transmission of *Toxoplasma gondii* by gestational age at maternal seroconversion, for each treatment group.

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made at birth except for 1 child in the PS group with a delayed diagnosis at 5 months despite regular follow-up.

As expected, the mother-to-child transmission rate increased significantly with the gestational age at seroconversion (odds ratio [OR], 1.17 for each additional week higher; 95% CI, 1.08–1.27) (Figure 2).

The transmission rate was 12/65 in the PS group (18.5%; 95% CI, 9.9–30.0), vs 18/60 in the S group (30%; 95% CI, 18.8–43.2) but this difference did not reach statistical significance ( $P = .147$ ). The effect of prenatal treatment did not differ after adjustment for gestational age at seroconversion: unadjusted OR, 0.53 (corresponding to the difference above) and adjusted OR, 0.47 ( $P = .12$ ), respectively. The effect of prenatal treatment was modified according to the timing of initiation ( $P$  for interaction = .03). It varied significantly with an OR for PS vs S of 1.20 (95% CI, 0.35–4.14) when initiated >3 weeks and an OR of 0.03 (95% CI, 0.00–1.63) when initiated within 3 weeks of the estimated maternal infection.

During follow-up, abnormal ultrasound findings appeared in 6 of 70 fetuses

in the S group (8.6%), vs none in the PS group ( $P = .012$ ). These abnormal findings were associated with severe congenital toxoplasmosis leading to termination of pregnancy in 2 cases and were cerebral hyperchogenic foci in 4 cases.

### Tolerance

A total of 26 severe adverse events (SAE) were reported, 12 in the S group and 14 in the PS group. They were analyzed blindly by the scientific committee. Two were the terminations of pregnancy for fetal toxoplasmosis. Twenty SAEs were unrelated to the study drugs or toxoplasmosis. Two women in the PS group developed maculopapular rashes, 1 associated with liver function abnormalities, which resolved after discontinuation. A third case declared as SAE was actually moderate; the patient had nausea and vomiting, which transiently improved with metoclopramide, then reappeared, again improved for 10 days when treatment was fractioned, and finally switched to S; although the nausea improved, the patient had to continue metoclopramide. Finally, another case of rash, associated with fever, disappeared spontaneously without changing the study drug.

Perinatal outcomes were unremarkable, except for the 2 cases of terminations of pregnancy (Table 2). The median gestational age was 40.1 weeks and birthweight 3375 g, with no difference between the 2 treatment groups.

### Comment

This is the first randomized controlled trial to be performed regarding the prevention of congenital toxoplasmosis following maternal seroconversion. The transmission rate was 2-fold lower when using PS, vs S. The difference was in line with our initial hypotheses, but did not reach statistical significance, probably for lack of statistical power. Our results are consistent with some observational data. In a retrospective study that accounted partially for gestational age, Prusa et al<sup>23</sup> reported a lower transmission rate when the PS-based “Austrian treatment scheme” was used, in comparison with the small minority of pregnancies in which other regimens or no therapy were used. Hotop et al<sup>13</sup> reported that the rate of vertical transmission in Germany using intermittent PS prophylaxis >16 weeks’ gestation was lower than expected when taking into account gestational age, although there was no reference group. In a retrospective study, Valentini et al<sup>24</sup> compared transmission rates from mothers with primary *Toxoplasma* infection according to whether they received S/cotrimoxazole, PS, or S alone; S alone appeared least effective to prevent transmission. The Syrocot study<sup>8</sup> showed no difference in transmission according to whether S or PS were used, but prescriptions differed according to gestational age.

In our study, the efficacy of PS vs S tended to be stronger when therapy was started within 3 weeks of seroconversion, and although this did not attain statistical significance, the interaction term was significant. This is indirect evidence that there is a window of opportunity to prevent fetal infection after maternal infection, before the tachyzoites cross the placenta, although the time between primary infection and fetal infection may be variable. Experimental data show that placental infection by *T gondii* precedes the passage of the parasite to the

**TABLE 2**  
**Perinatal outcomes**

	Spiramycin group		Pyrimethamine + sulfadiazine group	
	N	%	N	%
<b>Pregnancy outcome</b>				
Liveborn	68	97.1%	73	100.0%
TOP	2	2.9%		
<b>Infant sex<sup>a</sup></b>				
Male	32	47.1%	37	50.7%
Female	35	51.5%	36	49.3%
Not available	1	1.5%		
<b>Birthweight, g<sup>a</sup></b>				
n (dm)	62 (8)		67 (6)	
Median (IQR)	3460 (3180; 3720)		3340 (3060; 3630)	
<b>Length, cm<sup>a</sup></b>				
n (dm)	48 (22)		54 (19)	
Median (IQR)	50 (48; 52)		50 (49; 51)	
<b>Head circumference, cm<sup>a</sup></b>				
n (dm)	48 (22)		47 (26)	
Median (IQR)	34.8 (33.8; 35.5)		34.8 (33.5; 35.0)	
<b>Gestational age at delivery<sup>a</sup></b>				
n (dm)	48 (22)		47 (26)	
Median (IQR)	40.1 (38.9; 41.0)		40.3 (39.3; 41.1)	

dm, data missing; IQR, interquartile range (Quartile 1; Quartile 3); TOP, terminations of pregnancy.

<sup>a</sup> Not including TOP.

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fetus,<sup>25</sup> and clinical cases have been reported of placental infection without fetal infection.<sup>16</sup> In large observational studies, shorter intervals between maternal infection and the initiation of antiparasitic therapy were associated with significantly lower transmission.<sup>8,26</sup> Delayed transmission may explain cases of congenital toxoplasmosis despite a negative PCR at the time of amniocentesis. Since the sensitivity of current PCR techniques is high, these cases are likely to be due to transmission in the weeks or months following the amniocentesis.

We also observed that the incidence of prenatal cerebral signs of toxoplasmosis following prophylactic therapy was significantly lower in the PS than in the S group, in fact all of the cerebral signs appeared in the S group. This suggests that

starting PS very early may be beneficial for fetuses with congenital toxoplasmosis, as has been reported from retrospective cohort data.<sup>19,27</sup> There has not yet been a randomized controlled trial to evaluate prenatal toxoplasmosis therapy. To confirm whether antenatal therapy with PS is effective, long-term follow-up for the infants would be required, which was not available in our trial.

### Safety

We observed 2 rashes requiring hospitalization related to PS, 1 associated with liver enzyme elevation. We observed no hematologic toxicity in the 72 patients, all of whom received folinic acid. In a literature review of studies mostly in nonpregnant patients, a high rate of treatment discontinuation was reported.<sup>28</sup> However,

observational studies using PS in pregnancy showed few adverse events. Hotop et al<sup>13</sup> reported no hematological adverse event and only 1 allergic reaction in 119 pregnancies (0.8%), however, nausea and/or vomiting were frequent. Prusa et al<sup>29</sup> reported a single case of allergic reaction with shortness of breath and swollen tongue after taking PS. Of note, the PS regimens differed from the Toxogest trial. Tolerance is generally good in the fetus and neonate,<sup>13,18,30,31</sup> with rare exceptions.<sup>32</sup> It is recommended to avoid exposure during the first 2 months of gestation if possible. Pyrimethamine is a dihydrofolate reductase inhibitor, leading to bone-marrow toxicity, thus requiring administration of folinic acid and weekly blood cell counts. Among the other molecules of the same class, only trimethoprim is effective and without significant hematological toxicity, but its antiparasitic activity is 10–100 times lower than that of pyrimethamine. Sulfonamides are contraindicated in case of allergies to sulfonamides or G6PD deficiency. In case of oliguria and low urinary pH, sulfadiazine can precipitate in the urine and lead to crystalluria.<sup>33</sup>

Regarding S, its tolerance is usually excellent, and there was no SAE in the S group that could be drug-related. Other options may be considered for further studies, but lack pregnancy data.<sup>34,35</sup> Macrolides or related molecules such as azithromycin, roxithromycin, and clarithromycin have a comparable mode of action, and atovaquone could have the advantage of being effective (experimentally) on cysts, but has poor bioavailability.

Another important issue in using PS for prophylaxis is the risk of reducing the sensitivity of prenatal diagnosis. In our experience, 6 cases with a negative amniocentesis turned out to have congenital toxoplasmosis, including 1 with delayed diagnosis until 5 months after birth. The proportion tended to be higher after PS (4 cases) than S (2 cases), although the difference did not reach statistical significance due to small numbers. The sensitivity of PCR for prenatal diagnosis on amniotic fluid has been reported to be as high as 95%,<sup>36,37</sup> due to technical improvements that are not routinely available worldwide<sup>38</sup>; however,

in a nationwide survey in France the sensitivity in clinical practice in 2016 was 88% Centre National de Référence Toxoplasmose (CNR, unpublished data). There are several possible explanations for the discordance between negative PCR on amniotic fluid and an infant with congenital toxoplasmosis. This may be due to delayed transmission from the placenta after the amniocentesis and in some cases after prophylaxis was stopped. It may also be due to a large reduction in parasite load following more effective antiparasitic treatment.

The main limit of our study was lack of power because the trial was prematurely interrupted before reaching the targeted sample size due to slow recruitment and lack of funding to prolong the trial. Also, transmission in the S group was lower than expected, presumably because there were fewer third-trimester infections than anticipated. Such a trial is difficult to conduct because the incidence of maternal seroconversion is low<sup>39</sup> and because cases are dispersed outside of reference centers. Furthermore, while infants with a diagnosis of congenital toxoplasmosis were followed up by specialists, those presumed uninfected were referred to local pediatricians or general practitioners, who did not always pursue follow-up<sup>20</sup> until documenting a negative serology.

We did not conduct a placebo-controlled trial, because a survey showed that most investigators were convinced that this would be unacceptable for patients and for clinicians in the French context, where the use of S has been common practice for 30 years. We chose not to double-blind to facilitate rapid management in the event of serious adverse reactions and to limit costs.

### Implications for clinical practice

Our findings add evidence in favor of using PS for the prevention of placental transmission of toxoplasmosis beyond the first trimester of pregnancy. We suggest that guidelines might offer women with toxoplasmosis seroconversion an informed choice. The French screening program is thought to account for the striking improvement in clinical patterns of congenital toxoplasmosis seen in

France over the last 40 years<sup>27</sup> and also as compared to the United States where screening and treatment is not offered.<sup>1,30</sup>

### Conclusion

The difference in the incidence of congenital toxoplasmosis between PS and S was in agreement with the expected difference, but did not reach statistical significance, possibly because the trial was interrupted without reaching the planned sample size. Furthermore, there was a significant interaction with time to treatment initiation, where the difference between PS and S was larger when started within 3 weeks of seroconversion. These promising findings call for further research. The lessons learned with this first randomized clinical trial should help to design a new international study, possibly involving alternative potent antiparasitic regimens to optimize tolerance, to give a definitive answer to the question of the prevention of the congenital toxoplasmosis. ■

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