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Effectiveness and Limitations of Spiramycin for Toxoplasmosis During Pregnancy: A Systematic Review

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ABSTRACT

Background: Toxoplasmosis is brought on by the protozoan parasite Toxoplasma gondii. Toxoplasmosis can be transferred from a mother to her fetus during pregnancy, resulting in congenital illness. Spiramycin is administered in the early stages as a kind of prophylaxis for the fetus and can be continued until delivery. If the fetus becomes infected, therapy is altered to a triple mixture of sulfadiazine, folinic acid, and pyrimethamine.
Objectives: This article aims to comprehensively review spiramycin as a prophylactic measure for preventing vertical transmission of infection to fetuses and its limitations, including adverse effects.
Methods: This study used a systematic review approach of publications indexed in Scopus, PubMed, ScienceDirect, and Web of Science databases from 2014 to 2024. It utilized the PRISMA flow diagram to guide the article selection process until a conclusion was reached.
Results: Based on the predetermined inclusion and exclusion criteria and in accordance with the topic of this research objective, six research articles were suitable for review. Among the six reviewed articles, spiramycin is the first-line therapy for preventing vertical transmission of Toxoplasma gondii to the fetus. The most common side effect of using spiramycin in pregnant women is paresthesia.
Conclusion: Spiramycin has an important role in preventing congenital toxoplasmosis, but it is not recommended for infected fetuses. Instead, combination therapy is superior for treating infections that have occurred in the fetus.
Keywords: Gestational; Pregnancy; Spiramycin; Toxoplasmosis

INTRODUCTION

Toxoplasma gondii, a parasitic organism, has a complex life cycle. It infects all warm-blooded vertebrates, including humans, and may cause chronic infection. Toxoplasmosis affects a wide range of hosts, with cats being the definitive host, while humans, other mammals, and birds act as intermediate hosts[1]. It is estimated that nearly one-quarter of the world's population has been exposed to this parasite[2]. The main concern in this condition is the risk of vertical transmission to the fetus. Congenital toxoplasmosis can cause permanent neurological damage, including blindness[3]. Toxoplasma gondii is one of the few pathogens capable of crossing the placenta. The risk of vertical transmission to the fetus increases with gestational age, reaching approximately 60–81% in infections acquired during the third trimester. In contrast, infection in early pregnancy is associated with more severe clinical outcomes [4]. Previous studies have shown that early congenital infection may result in hydrocephalus, chorioretinitis, intracranial calcifications, and long-term neurological impairment. Disease severity is influenced by the parasite burden and the T. gondii genotype, as well as the ability of the parasite to invade and migrate through placental tissues into the fetal circulation[5].

Spiramycin is a macrolide antibiotic with relatively low antiprotozoal activity. It is used prophylactically during pregnancy to minimize the risk of congenital toxoplasmosis, particularly in the first 16–18 weeks of gestation[6]. The risk of fetal infection varies by trimester, increasing with advancing gestational age and reaching its highest level in late pregnancy. Although transmission in early pregnancy is uncommon, infection at this stage is associated with more severe fetal consequences. In contrast, maternal infection in the third trimester often

results in asymptomatic newborns. However, if left untreated, these children may develop retinochoroiditis and neurological deficits later in childhood or early adulthood[7].

Experimental studies have shown that oral administration of spiramycin loaded onto maltodextrin nanoparticles can reduce the number of brain cysts and improve therapeutic efficacy in animal models of toxoplasmosis. These findings suggest that nanoparticle-based delivery may enhance tissue penetration, even across the blood–brain barrier. However, such results are derived from preclinical models, and their safety and effectiveness in pregnant women have not yet been directly extrapolated. Therefore, the application of nanoparticle-based spiramycin during pregnancy remains investigational and requires further clinical validation. Spiramycin is administered during pregnancy primarily for fetal prophylaxis to reduce maternal–fetal transmission of Toxoplasma gondii. Its clinical role is based on its preferential accumulation in maternal and placental tissues, with limited transplacental transfer to the fetus. As a result, spiramycin effectively lowers the risk of vertical transmission but has minimal direct therapeutic activity in established fetal infection. Spiramycin is considered suitable for preventing vertical transmission of Toxoplasma gondii because of its pharmacokinetic and safety profile during pregnancy. The drug concentrates predominantly in maternal serum and placental tissue, limiting fetal exposure while reducing the parasite burden at the maternal–fetal interface. This localization helps inhibit parasite replication before it crosses the placenta. In addition, spiramycin has a favorable safety record during pregnancy compared with other anti-toxoplasmosis agents, supporting its use as first-line prophylaxis before confirming a fetal infection. Thus, its tissue distribution and tolerability make spiramycin a rational option for preventing congenital toxoplasmosis rather than for treating established fetal disease[8].

Consequently, administering spiramycin is expected to inhibit transmission to the fetus, with verification occurring at the time of the infant's delivery. This study aims to systematically evaluate the effectiveness and limitations of spiramycin in the management of toxoplasmosis during pregnancy. Specifically, this review assesses the role of spiramycin in preventing vertical transmission of Toxoplasma gondii from mother to fetus, its impact on fetal and neonatal outcomes, and the safety profile and adverse effects of spiramycin in pregnant women compared with alternative anti-toxoplasmosis regimens.

METHOD

Study design

This systematic review was strictly conducted in accordance with the PRISMA criteria framework. Since the analysis depended solely on published studies, ethical approval or informed consent is unnecessary.

Search strategy

All literature retrieved from the database was systematically screened to fulfill the PRISMA guidelines. A systematic and comprehensive literature search was conducted in September and October 2024 across four major databases: ScienceDirect, PubMed, Scopus, and Web of Science, using the keywords toxoplasmosis AND spiramycin AND (pregnancy OR gestational). The search was restricted to English-language and full-text publications and literature.

Eligibility criteria

The inclusion criteria were limited to observational studies (cohort, case-control, or cross-sectional), involving pregnant women diagnosed with toxoplasmosis, with at least one study group receiving spiramycin treatment. Articles with identical titles or published in the same journal are considered as duplicate. Duplicate studies were identified using automated reference management screening based on titles, authors, year, and DOI, followed by manual verification of overlapping study populations and outcomes, with only the most comprehensive article retained. The outcomes of interest involved examining the effectiveness of spiramycin in preventing vertical transmission of *Toxoplasma gondii* from mother to fetus, along with evaluating the safety profile and any adverse effects associated with spiramycin use during pregnancy. The outcomes seen are the effectiveness of spiramycin in preventing vertical transmission of toxoplasmosis from infected mothers to their fetuses and the side effects of using spiramycin during pregnancy. Studies were excluded if they were in vitro or in vivo animal experiments, did not involve human subjects, lacked a control or comparison group, or did not report relevant maternal or fetal outcomes. The control group involved infected pregnant women who received no treatment or other intervention. Studies were excluded if they were conducted in vivo or in vitro, did not involve human subjects, or lacked a control or comparison group.

Data Extraction

Data from the included studies were extracted independently by six authors. Literature from each database was selected using a standardized electronic form. Once full-text eligibility was confirmed, all six authors reviewed the literature. Any disagreements during this process were resolved through collaborative discussion, ensuring a rigorous and unbiased selection process.

Data Analysis

All included studies underwent critical appraisal using the Critical Appraisal Skills Programme (CASP) checklist appropriate to their respective study designs. The authors analyzed the results from the acquired papers to delineate the efficacy and limitations of spiramycin in treating pregnant women with toxoplasmosis. The methodological quality and risk of bias were evaluated using the Newcastle-Ottawa Scale, which assigns sc from 5 to 9, with higher scores signifying greater methodological rigor.

RESULTS AND DISCUSSION

Search Result

The initial database search yielded 772 records. After removing 78 duplicate articles, 694 records remained for screening. An automated filter based on the publication period (2014–2024) excluded 535 records, leaving 159 articles for further evaluation. Title and abstract screening excluded 111 articles irrelevant to the research objectives, resulting in 48 articles eligible for full-text assessment. Out of these, only eight articles were available in full-text format. After a comprehensive full-text evaluation, two articles were excluded for not meeting the predefined methodological and relevance criteria. Ultimately, six studies were included in the final systematic review. To ensure transparency and methodological rigor, the study selection process was conducted in accordance with the PRISMA guidelines, and a corresponding flow diagram was used to illustrate each stage of study identification, screening, eligibility assessment, and inclusion (Figure 1).

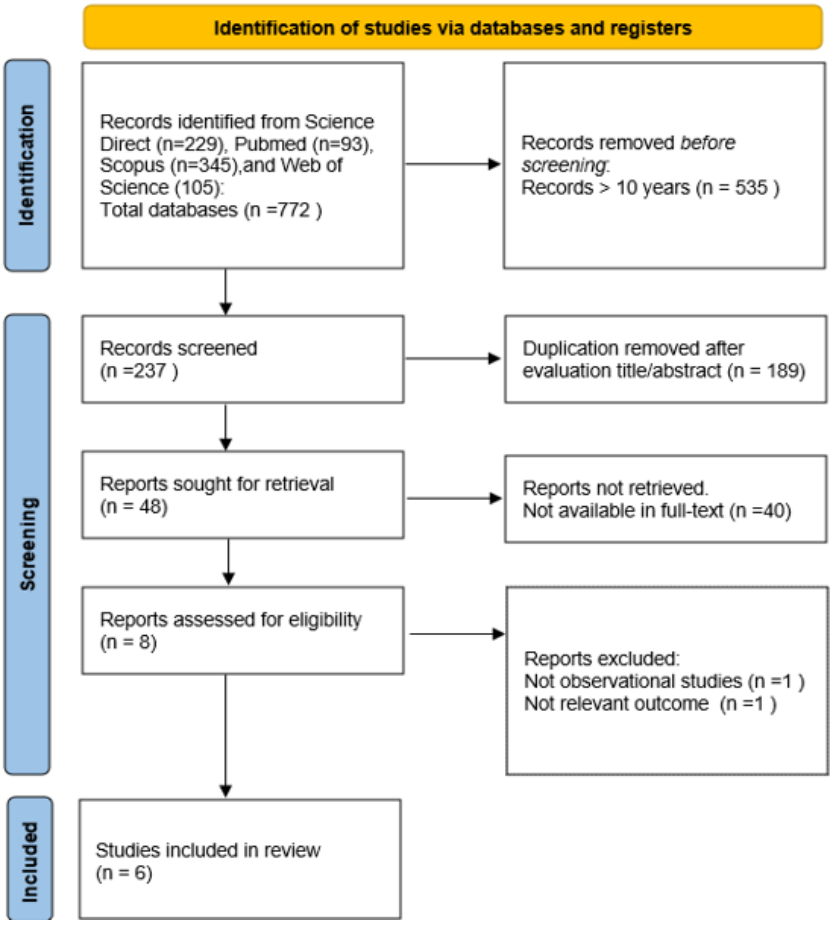

Figure 1. Search Terms and Publication Selection Process (PRISMA Flowchart)

Study Characteristics

The systematic review summarized the six studies to provide an overview of the evidence base. These studies, comprising various study designs conducted across Europe (Portugal, Italy, and the Czech Republic), Turkey, and South America (Brazil), reflected diverse clinical and epidemiological settings. The sample sizes varied considerably, ranging from 65 to 162 participants, allowing for comparison of spiramycin effectiveness across population scales. This summary highlights the heterogeneity of the included studies and provides context for interpreting the findings presented in Table I.

Table I. Characteristics of the Study

References	Drug use	Patient, population, and problem	Outcome target
Prasil, Petr et al. [5]	Spiramycin dose: 3 MIU/ 8 hours during the first trimester until 16-18 weeks of gestation. Pyrimethamine (50–100 mg per day orally), starting after 16-18 weeks of gestation) Sulfadiazine (1 g every 8 hours)	Pregnant women who tested positive for acute toxoplasmosis antibodies (IgM, IgA, and/or IgE) and received treatment	Evaluate and compare the adverse reactions of treatment spiramycin monotherapy with the dual combination P/S
Çakırca, Tuba Damar,et al.[9]	Spiramycin (dosage is not stated)	Pregnant women diagnosed with acute toxoplasmosis infection (ATI)	Evaluate the prevalence of toxoplasmosis through clinical and laboratory findings, focusing on pregnancy and fetal outcomes, to compare the effects of spiramycin versus placebo
Valentini, P et al.[10]	Spiramycin: 3 × 10^6 IU (equivalent to 870 mg) four times daily until delivery. Cotrimoxazole: 960 mg twice daily Folinic acid: 4 mg per day Pyrimethamine: 25 mg per day Sulfadiazine 0.75 g per day	Pregnant women and their newborns who were suspected of being infected with toxoplasmosis	Compare the effectiveness of spiramycin/cotrimoxazole (Spy/C) versus pyrimethamine/sulfonamide (P/S) and spiramycin alone (Spy) in preventing mother-to-child transmission of toxoplasmosis during pregnancy.
Diesel, Amanda Andrade, et al.[11]	Sulfadiazine 1 g every 6 hours Pyrimethamine 50-75 mg once daily for 1-2 days, followed by 25-50 mg once daily Folinic acid 10-25 mg per day) versus Spiramycin 3 MIU every 8 hours Azithromycin (in cases where spiramycin 3 MIU every 8 hours is not used).	Pregnant women confirmed to have acute toxoplasmosis.	This study aims to describe a population of pregnant women at risk for transplacental transmission of toxoplasmosis, identify the incidence of the congenital form of the disease, determine placental transmission through PCR analysis of amniotic fluid, and detail the treatments administered, maternal adverse effects, and complications observed in fetuses and children.
Losa, A., Carvalho, I., Sousa, B et al.[12]	Pyrimethamine: 2 mg/kg/day for the first 2 days, then reduced to 1 mg/kg/day for maintenance Sulfadiazine is often administered at a dose of 50 mg/kg twice daily Folinic acid is administered at 10-15 mg every three days Spiramycin:3 million IU every 8 hours	Pregnant women with seroconversion of *Toxoplasma gondii* during pregnancy and their newborns at risk of congenital toxoplasmosis. The main clinical problem is vertical transmission, which may lead to severe fetal or neonatal morbidity and long-term complications.	Spiramycin: To prevent vertical transmission from infected pregnant women to the fetus. P+S+FA: To treat newborns with confirmed congenital toxoplasmosis to prevent long-term complications like chorioretinitis or developmental delays.
Avelino, Mariza M[13]	Spiramicyn was administered at a dose of 3 g/day since diagnosis until delivery, irrespective of whether the fetal infection had been	Pregnant women with positive serology and their newborns at risk for congenital toxoplasmosis.	evaluate whether treating pregnant women with spiramycin, in the absence of monitoring for toxoplasmosis seroconversion,

References	Drug use	Patient, population, and problem	Outcome target
	confirmed		impacts the prognosis of the patients.

Table II. The Outcome of the Use of Spiramycin with Other Anti-Toxoplasmosis Drugs for Pregnant Women

References	Variable	Spiramycin alone	P/S or not receive treatment	(Spy/C) or Sul+Py+AF	Result or P value
Prasil, Petr et al. [5]	All adverse reactions 36.6% (n = 41)	38.9% (n = 30)	31.4% (n = 11)		p=0.003
	Toxic allergic reactions 8.9% of cases (n = 10)				
	Cranial paraesthesia, a neurotoxic side effect	9.1% (n = 7)	8.6% (n = 3)		NS
	Additional adverse effects, including nephrotoxicity, vaginal discomfort, and gastrointestinal distress	19.5% (n = 15)	(-)		
Çakırca, Tuba Damar,et al.[9]	Congenital toxoplasmosis (CT)	1 child (1.1%),	4 newborns (30.8%)		(p = 0.001)
Valentini, P et al.[14]	Preventing mother-to-child transmission of toxoplasmosis during pregnancy.	43 mothers (35%)	10 mothers (8.1%)	70 mothers (56.9%)	(P = 0.014) showed a significant trend toward reduced toxoplasmosis transmission • Specifically, compared to Spy/C, Spy was associated with a higher likelihood of congenital infection (odds ratio [OR] 4.368; 95% CI: 1.253 to 15.219). • Spy/C was compared with Pyr/Sul, no significant reduction was observed (OR 1.83; 95% CI: 0.184 to 18.274).
Diesel, Amanda Andrade, et al.[11]	Positive PCR = 6/40 (15%) Negative PCR = 34 Non-PCR = 25 Total of toxoplasmosis gestational cases n=65	-	-	-	• 1 died (first 54 hours); 4 continued therapy for 10 months; 1 without therapy (maternal rejection) • 9 (26.5%) IgG negative; 24 (70.6%) IgG positive without IgM; 1 (2.9%) had a congenital abnormality and received triple therapy • 2 neonates required congenital toxoplasmosis therapy • 6 children (9.2%) were diagnosed with congenital toxoplasmosis; 2 mothers experienced severe side effects from triple therapy
Losa, A., Carvalho, I., Sousa, B et al.[12]	Pregnant women with seroconversion Neonates with confirmed CT	83.1% (59/71) of pregnant women	-	No exact number stated (part of 71)	• Vertical transmission rate was 3%. No serious side effects in the mother were reported. • Effective therapy for neutropenia in 17.5% of cases (treated with increased folinic acid dose)
Avelino, Mariza M[13]	Prognosis igM and igA	n= 120 pregnant women	n= 115	-	• A total of 40.7% (66/162) of neonates were delivered with serious infections. Vertical transmission due to reactivation during pregnancy affected 5.5% (9/162) of neonates, with one presenting with a severe systemic infection • In cases where infected pregnant women did not receive adequate treatment, the chance of severe illness (neuro-optical) in neonates increased significantly.

References	Variable	Spiramycin alone	P/S or not receive treatment	(Spy/C) or Sul+Py+AF	Result or P value
					• Fetal IgM was found to cause ocular impairment in 48.0% (12/25) of fetuses • Neonatal IgA was linked to neuro-ophthalmologic and systemic aspects of the disease

Table III. Recommendation Guidelines for the Use of Spiramycin Oral Toxoplasmosis in Pregnancy

Institution	Recommendations
The Society of Obstetricians and Gynaecologists of Canada [15]	− Pregnant women suspected of having an acute infection should undergo repeat testing within 2-3 weeks. Then, instead of waiting for the repeat test result, spiramycin medication is started immediately (II-2B)*. − If maternal infection is confirmed but the fetus is not affected, spiramycin should be administered for fetal prophylaxis to prevent the transfer of organisms across the placenta from mother to fetus (I-B)**. − If a positive amniotic fluid polymerase chain reaction confirms or strongly suggests fetal infection, women should be treated with pyrimethamine, sulfadiazine, and folinic acid (I-B)**.
South Australian Perinatal Practice Guidelines [16]	− If infection occurs within the first 12 weeks of pregnancy, provide spiramycin. Mild to moderate infection: 6,000,000 to 9,000,000 in total, split into doses. Severe infections: 12,000,000 to 15,000,000 total units in two divided doses. If the amniocentesis PCR is positive, counsel the (pregnant) woman or partner about termination. − Infection between 13 and 43 weeks: Give Spiramycin. Mild to moderate infection: 6,000,000 to 9,000,000 in divided doses. Severe infection: 12,000,000 to 15,000,000 international units in two divided doses. OR, if unavailable, give Atovaquone 750 mg twice a day (or 1,500 mg once a day if necessary) with food for 21 days. Azithromycin 500 mg daily for three days, followed by weekly treatment for four weeks, may also be used. If the ultrasound is abnormal, consult with the woman or her partner.
Australian Pregnancy Care Guidelines[17]	Spiramycin and sulfonamide medications have been used to treat toxoplasmosis in order to reduce mother-to-child transmission and the severity of fetal illness.
BNF for Children [18]	Spiramycin may minimize the risk of maternal infection affecting the fetus. If there is evidence of placental or fetal infection, pyrimethamine, sulfadiazine, and folinic acid may be administered beyond the first trimester.
Canadian Family Physician [6]	If primary T gondii infection is detected during pregnancy, therapy is done for fetal protection or to reduce disease severity. To prevent vertical transmission in maternal infections without fetal infections, spiramycin is the preferred medication. Spiramycin is a macrolide antibiotic that cannot pass the placenta but is concentrated within it. If the amniotic fluid polymerase chain reaction analysis findings are negative for T.gondii, 1 g orally every 8 hours for the rest of the pregnancy is given.

*Ranking of the Canadian Task Force on Preventive Health Care (II-2B): Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group - There is fair evidence to recommend the clinical preventive action

** Ranking of the Canadian Task Force on Preventive Health Care (I-B): Evidence obtained from at least one properly randomized controlled trial - There is fair evidence to recommend the clinical preventive action.

Among the studies listed in Table II, spiramycin—either used as monotherapy or in combination with other anti-toxoplasmosis agents—demonstrated heterogeneous clinical outcomes in pregnant women with toxoplasmosis and their newborns. Several studies consistently reported that spiramycin-based regimens were

associated with a lower risk of maternal–fetal transmission compared with no treatment, particularly when the therapy was initiated early after maternal infection. Combination therapies, including spiramycin with pyrimethamine–sulfadiazine or triple regimens, were generally administered in higher-risk pregnancies or cases with confirmed fetal infection and showed variable effectiveness. While some studies suggested a potential reduction in congenital toxoplasmosis rates with combination therapy, others did not demonstrate a significant advantage over spiramycin monotherapy. Notably, combination regimens were more frequently associated with maternal adverse effects, occasionally necessitating treatment adjustment or discontinuation. Overall, these findings indicate that spiramycin is consistently associated with reduced vertical transmission, whereas combination therapy may provide additional benefit in certain cases but may lead to increased toxicity, underscoring variability across studies and treatment strategies.

Guidelines for Toxoplasmosis in Pregnancy

According to multiple guidelines, spiramycin has been determined to be non-teratogenic and may significantly reduce the danger of maternal-to-fetal transmission of *Toxoplasma gondii*. Spiramycin treatment is initiated immediately upon the maternal diagnosis of toxoplasmosis, provided that fetal infection has not been confirmed. In cases where fetal infection is detected, spiramycin is discontinued and replaced with alternative treatments, such as sulfonamides, pyrimethamine, or folinic acid. As outlined in the South Australian Perinatal Practice Guidelines[16], if spiramycin is unavailable, it can be substituted with atovaquone or azithromycin, with dosage recommendations provided. The guidelines recommend a spiramycin dosage of 1 to 3 grams per day, equivalent to 6,000,000 to 9,000,000 international units, administered in divided doses. While spiramycin is commonly prescribed for pregnant women diagnosed with toxoplasmosis, the evidence regarding its efficacy in managing toxoplasmosis during pregnancy remains limited, particularly in Asian populations. To address this gap, we present an overview of several cohort studies investigating the use of spiramycin to prevent maternal-fetal transmission.

DISCUSSION

Effectiveness of Spiramycin

Spiramycin is effective in preventing the transmission of Toxoplasma gondii from mother to fetus and in reducing the risk of congenital infection, especially when used in combination with other drugs. Prompt initiation and adherence to treatment are critical for optimal outcomes.

Spiramycin has both effectiveness and limitations that can be explained by pharmacokinetics and pharmacodynamics. Spiramycin exhibits a high ionization rate in the acidic environment of the stomach, with a pKa of 7.9. This condition indicates slow absorption and results in absorption at points further down the digestive tract. However, spiramycin is stable in the stomach. Spiramycin is widely distributed into tissues, with a volume of distribution of approximately 383 L at steady state. In fallopian tube tissue, concentrations range from 4.4 to 33 mg/kg, while concentrations in the ovaries, myometrium, and vaginal mucosa exceed plasma concentrations[20]. Spiramycin concentrations in the placenta are 3-5 times higher than maternal serum concentrations. However, despite high placental concentrations, local accumulation occurs in the placenta and does not penetrate optimally into the fetal circulation, resulting in very low spiramycin concentrations in fetal blood. Furthermore, spiramycin is a lipophilic macrolide, making it effective in preventing transmission to the fetus and thus non-teratogenic[21].

From a pharmacodynamic perspective, spiramycin is a macrolide antibiotic that inhibits protein synthesis by binding to the 50S ribosomal subunit; therefore, it is bacteriostatic, with effectiveness being strongly influenced by drug concentration at the site of infection. Spiramycin has the ability to achieve tissue and intracellular concentrations significantly higher than serum levels, including in the respiratory tract and alveolar macrophages (up to 10–20 times serum levels), ensuring that concentrations at the site of infection generally exceed the MIC of the target pathogen. In addition, spiramycin exhibits a significant and longer post-antibiotic effect (PAE) (24 hours), longer than that of erythromycin. It also has a very high inhibitory quotient in tissues (indicating effective exposure to bacteria) and reduces the adhesion of Gram-positive bacteria to epithelial cells. These abilities, together with its clinical effectiveness, especially in tissue infections and infections by intracellular pathogens, including toxoplasmosis, allow bacterial growth to be controlled even though the drug concentration in plasma has decreased [20].

Several studies have been conducted on the use of spiramycin in pregnant women. None of the mothers who received spiramycin prophylaxis had a positive Toxoplasma PCR in amniotic fluid, whereas all mothers who

refused prophylaxis had positive results ($p < 0.01$) (Avci, 2016). Another study reported a vertical transmission rate of 3.4% in women treated immediately with spiramycin-cotrimoxazole, compared to 71.4% in untreated cases[22]. Spiramycin alone was less effective compared to combination therapies. For instance, spiramycin combined with cotrimoxazole showed a significant reduction in transmission rates compared to spiramycin alone (odds ratio 4.368)[14]**.** Additionally, spiramycin combined with trimethoprim-sulfamethoxazole was more effective than spiramycin alone (OR 2.78)[23].

Infants born to mothers treated with spiramycin generally showed fewer signs of congenital infection. In one study, only 2.6% of infants were infected, and none showed symptoms of congenital infection[24]**.** Another study found that all infected newborns of mothers treated adequately with spiramycin-cotrimoxazole were asymptomatic, while 28.5% of inadequately treated cases had postnatal sequelae[22]. The timing and adherence to spiramycin therapy are crucial. Delayed or poor compliance with treatment increased the risk of congenital infection and neonatal morbidity[13,22]. Spiramycin's effectiveness is somewhat limited by its poor placental penetration, which may affect its ability to treat the fetus directly[25]. However, it remains a first-line treatment due to its safety profile and effectiveness in reducing transmission rates.

Among the included studies, the primary outcomes evaluated were fetal seroconversion, reduction in parasitemia as reflected by decreased vertical transmission rates, and the impact of treatment timing on maternal–fetal outcomes. Overall, spiramycin was associated with a reduction in congenital transmission compared to no treatment, as demonstrated by Cakirca et al. (2023) who reported that treated mothers had significantly lower transmission rates than untreated women, and by Avelino et al. (2014) who found that spiramycin reduced both vertical transmission and severity of congenital toxoplasmosis. Similarly, Diesel et al. (2019) reported that spiramycin was effective in preventing fetal infection in cases with negative PCR results, whereas confirmed fetal infections required escalation to combination therapy. However, variability across studies was observed. Valentini et al. (2015) found that spiramycin monotherapy was associated with a higher risk of congenital infection compared to combination regimens, suggesting that monotherapy may be less effective in certain clinical contexts. Losa et al. (2024). reported a low incidence of congenital toxoplasmosis, likely influenced by early antenatal screening and timely initiation of therapy.

Several factors appeared to influence treatment effectiveness. Gestational age at therapy initiation was critical, as earlier treatment following maternal seroconversion was generally associated with lower transmission rates, while delayed diagnosis during critical periods of pregnancy may reduce spiramycin efficacy. Duration and continuity of therapy also played a role, with sustained treatment contributing to improved outcomes. Patient adherence was another important factor, although it was not consistently assessed; potential non-compliance might have contributed to persistent transmission in some cohorts. Differences in parasite strain, maternal–fetal health status, and study design further contributed to heterogeneity in findings. Collectively, these results suggest that spiramycin is most effective when initiated early, administered consistently, and monitored adequately throughout pregnancy.

Comparison with Combination Therapy

Spiramycin is primarily used to prevent the transplacental transmission of Toxoplasma gondii from a mother to her fetus. This is particularly important in the early stages of pregnancy. Studies have shown that Spiramycin can significantly reduce the rate of vertical transmission when administered promptly after maternal infection[22,26,27]. For instance, the vertical transmission rate was 3.4% among women treated immediately with Spiramycin-Cotrimoxazole, compared to 71.4% in untreated cases[22].

Combination therapy is used when fetal infection is confirmed, either through polymerase chain reaction (PCR) testing of amniotic fluid or ultrasound indications of severe symptoms such as hydrocephalus. Combination therapy has been shown to effectively reduce the severity of clinical manifestations in newborns. For example, administering Pyrimethamine, Sulfadiazine, and Folinic Acid after the 16th week of pregnancy has been associated with lower rates of clinical manifestations in newborns[14,26,27].

Across the included studies, comparison with combination therapy revealed that spiramycin monotherapy is generally effective in reducing vertical transmission when fetal infection has not yet been confirmed. However, it may be less effective than combination regimens in high-risk or confirmed cases. Cakirca et al. (2024) demonstrated significantly lower transmission rates among mothers treated with spiramycin compared to untreated mothers, supporting its preventive role. Similarly, Avelino et al. (2014) reported that spiramycin reduced both vertical transmission and severity of congenital toxoplasmosis compared with no treatment, although infections still occurred, potentially influenced by timing of diagnosis, parasite strain, or unassessed treatment adherence. In contrast, Diesel et al. showed that when fetal infection was confirmed by

positive PCR, escalation to triple therapy (pyrimethamine, sulfadiazine, and folinic acid) was necessary, while spiramycin remained effective in PCR-negative cases. Valentini (2015) further highlighted that spiramycin monotherapy was associated with a higher risk of congenital infection compared to combination therapy with spiramycin, cotrimoxazole, and folinic acid (OR 4.368; 95% CI: 1.253–15.219), with no significant difference between the combination regimens. Losa et al. reported a low incidence of congenital toxoplasmosis in a cohort primarily treated with spiramycin, likely reflecting early screening and timely intervention. Overall, the evidence suggests that spiramycin is appropriate as first-line prophylaxis before confirmed fetal infection, whereas combination therapy appears more effective in reducing the risk of transmission once infection is established. However, heterogeneity in study design, sample size, and diagnostic protocols limits direct comparison and underscores the need for prospective controlled trials.

Safety Adverse Effect

Spiramycin, a macrolide antibiotic, has been used in clinical practice for about 70 years and is known for its effectiveness against a variety of pathogens, including Toxoplasma gondii[28,29]. It is particularly valued for its low incidence of resistance and minimal side effects, which enhance patient compliance[30]. This is because spiramycin has a steady-state volume of distribution (Vss) of approximately 383 L, far exceeding total body water. As a result, the fraction of the drug in the systemic circulation is relatively small, limiting potentially toxic plasma exposure. Distribution studies also indicate that although spiramycin accumulates in certain tissues such as the lung and placenta, fetal blood concentrations remain low, with a fetal-to-maternal concentration ratio of less than 0.5, indicating limited systemic transfer to the fetus[31]. In addition, from a pharmacodynamic perspective, spiramycin works by bacteriostatic. This mechanism does not cause direct membrane damage or bacterial cell lysis; therefore, the inflammatory response due to the release of bacterial cell components can be minimized[20].

Spiramycin is generally well tolerated, with studies showing no significant treatment-emergent adverse events in healthy subjects[28]. Common side effects, when they do occur, include gastrointestinal disturbances, such as nausea, abdominal pain, and diarrhea. Due to this safety profile, spiramicyn is a reliable choice for treating various infections, including during pregnancy. Its minimal side effects and low resistance rates contribute to its continued use in clinical practice[28–30]. However, as with any antibiotic, careful consideration of individual patient risk factors and adherence to prescribed treatment regimens are essential to minimize adverse effects and ensure effective outcomes[30,32].

Clinical Guideline Consistency

The findings of this review are largely consistent with current international clinical guidelines regarding the management of toxoplasmosis during pregnancy. Several institutions recommend spiramycin as the first-line therapy for maternal infection when fetal involvement is confirmed. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommend immediate initiation of spiramycin when acute maternal infection is suspected, even before confirmatory repeat testing, to reduce the risk of vertical transmission (II-2B). Similarly, if maternal infection is confirmed but fetal infection is not detected, spiramycin is advised for fetal prophylaxis (I-B).

The American Academy of Pediatrics (AAP), the Canadian Family Physician, and the BNF for Children also support the use of spiramycin in early pregnancy, particularly before 18 weeks of gestation, emphasizing its safety profile and non-teratogenicity. The recommended dosage is generally 1 g (3 million IU) orally three times daily (total 9 million IU/day), continued until delivery in cases where amniotic fluid PCR remains negative, and there is no ultrasound evidence of fetal infection. These recommendations align with the evidence summarized in this review, which shows that spiramycin effectively reduces vertical transmission when administered promptly after maternal seroconversion.

Guidelines consistently recommend escalation to combination therapy—typically pyrimethamine, sulfadiazine, and folinic acid—when fetal infection is confirmed by positive amniotic fluid PCR or suggestive ultrasound findings. This is in accordance with the evidence discussed in the comparison section, which found that spiramycin monotherapy was less effective than combination regimens in cases of confirmed fetal infection. Therefore, the transition from spiramycin prophylaxis to combination therapy reflects an evidence-based, risk-adapted approach.

There are no official government guidelines in Indonesia regarding toxoplasmosis. However, there is an article on toxoplasmosis during pregnancy. In accordance with external guidelines, this article states that first-line therapy for toxoplasmosis during pregnancy is spiramycin. Spiramycin administered during pregnancy can reduce the frequency of vertical transmission of T. gondii, especially in the first trimester. For pregnant women

with acute toxoplasma infection, it is recommended to be administered until delivery, even if the PCR test is negative, to anticipate the possibility of fetal infection. Spiramycin should not be administered to patients who are hypersensitive to macrolides[33].

Overall, the concordance between the reviewed studies and established guidelines strengthens the clinical validity of spiramycin as first-line prophylaxis for maternal toxoplasmosis without confirmed fetal infection and supports combination therapy as the preferred strategy in confirmed or high-risk fetal cases. However, variations in national recommendations regarding dosing regimens and alternative agents (e.g., atovaquone or azithromycin in certain settings) highlight the need for standardized protocols supported by high-quality comparative trials.

The use of spiramycin as a first-line treatment to prevent vertical transmission of *Toxoplasma gondii* to the fetus is widely adopted across several countries. A study by Valentini et al. (2015) suggests that the combination of spiramycin and cotrimoxazole may be more effective in preventing vertical transmission. Among the six reviewed articles, some fetuses remained infected despite the administration of spiramycin, although the infection rate was lower compared to those treated with medications other than spiramycin. The side effects associated with the use of spiramycin in pregnant women include paresthesia, toxic allergic reactions, gastrointestinal disorders, vaginal discomfort, and laboratory abnormalities.

This systematic review has several important limitations that should be considered when interpreting the findings. At the study level, the majority of included studies were observational in design (cohort or retrospective analyses), which are inherently subject to selection bias, confounding factors, and incomplete outcome reporting. Sample sizes were relatively small, ranging from 65 to 162 participants, thereby limiting statistical power and reducing the robustness of effect estimates. Additionally, variability in treatment regimens, timing of spiramycin initiation, diagnostic criteria (including PCR use), and outcome definitions contributed to methodological heterogeneity across studies. At the review level, only six studies met the inclusion criteria despite comprehensive database searches, which restricts the breadth of available evidence and limits the ability to perform quantitative synthesis. The geographic representation of the included studies was also limited, predominantly involving European and South American populations, thereby potentially reducing generalizability to other regions, particularly Asian settings where epidemiological patterns may differ. Furthermore, as this review included only English-language publications from selected databases, publication and language bias cannot be fully excluded.

The major strength of this study was following the PRISMA checklist using multiple databases, which was in line with the PICO questions as our baseline. Our population in this study consists of pregnant women diagnosed with toxoplasmosis with the intervention of Spiramycin, while the control groups involved the ones who used other toxoplasmosis treatments, and the outcome possibilities were pregnant women's health status, side effects, and the possibility of its vertical transmission to the fetus. All articles have been subjected to critical appraisal using the Critical Appraisal Skills Program (CASP) for cohort[34] and cross-sectional[35] studies. However, this study has some limitations, like any heterogeneity of studies, using an observational study type instead of an experimental one, inconsistencies in control groups, and variability in sample sizes. It is suggested that further research be conducted on more subjects using experimental methods.

CONCLUSION

Spiramycin plays an important role in reducing the risk of maternal-to-fetal transmission of *Toxoplasma gondii* when fetal infection has not yet been confirmed. However, once fetal infection is established, spiramycin is no longer recommended, and combination therapy has been shown to be more effective in these circumstances. Further high-quality prospective studies are warranted to strengthen the current evidence base and to better define optimal treatment strategies.

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CONFLICTS TO INTEREST

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