

CASE SERIES

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Treatment of ocular toxoplasmosis in pregnancy

ABSTRACT

Objectives

To describe the course of ocular toxoplasmosis during pregnancy.

Methods

This is a retrospective, noncomparative case series of four pregnant women who were treated for ocular toxoplasmosis during pregnancy.

Results

All of the participants had violent and treatment-resistant toxoplasma retinochoroiditis during pregnancy, leaving three of them with decreased visual acuity in spite of aggressive therapy. Termination of pregnancy appeared to help the recovery in two patients.

Conclusion

Pregnant state may provoke the recurrence of ocular toxoplasmosis.

Key words: *Toxoplasmosis, Retinochoroiditis, Uveitis, Pregnancy*

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The authors have no proprietary or financial interest in any product described in this study.

PHILIPP J OPHTHALMOL 2004; 29(2): 88-93.

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TOXOPLASMOSIS is the most common cause of posterior uveitis in the world, accounting for over 80% of cases in some regions.¹ It is caused by the obligate intracellular protozoan *Toxoplasma gondii*. Recurrence of congenital toxoplasmosis is still the leading cause of *Toxoplasma* retinochoroiditis, but acquired ocular disease is more common than previously suspected.²⁻⁵ More than 82% of congenitally infected individuals not treated as infants will develop retinal lesions by the time they reach adolescence.⁶

Ocular toxoplasmosis is usually a recurrent disease, and two thirds of patients present with relapses.⁷ We believe that recurrence is the result of release of *Toxoplasma gondii* trophozoites from cysts, which then actively infect the retina and release antigens stimulating an inflammatory retinochoroiditis. Some recurrences may actually be secondary to reinfection.

In this article we report four patients who had recurrences of ocular toxoplasmosis during their pregnancies, suffered from visual loss and had treatment-resistant inflammation.

METHODOLOGY

We reviewed 1,243 charts of patients followed in the Uveitis Service at the Massachusetts Eye and Ear Infirmary from November 1986 to December 2003. One hundred ninety seven patients had a diagnosis of ocular toxoplasmosis, and 4 of these patients were pregnant at the time of recurrence of their ocular disease. Clinical records of these patients were reviewed for details of clinical presentation, ophthalmic history, complications and visual outcome at final follow-up.

CASE REPORTS

Case 1

A 22 year-old Hispanic woman, an immigrant from El Salvador, presented to the Ocular Immunology and Uveitis Service of the Massachusetts Eye and Ear Infirmary with complaints of a decreased visual acuity and redness in her right eye of five days duration. The patient had an episode of intense pain in the right eye two weeks prior to the visit. The pain persisted for one week. At the time of examination the patient was 28 weeks pregnant. She was taking prenatal vitamins and did not have any allergies. Her medical history was unremarkable.

The patient's visual acuity was 20/50 (6/15) in the right eye and 20/20 (6/6) in the left eye. There were keratic precipitates on the corneal endothelium, and 3+ cells in the anterior chamber of the right eye. Dilated examination of the fundus revealed 3+ cells in the vitreous and an active focus of macula-threatening retinochoroiditis along the superotemporal arcade, and an old scar in the nasal periphery consistent with toxoplasmic lesions.

After consulting with the patient's gynecologist, the patient was begun on clindamycin 300 mg orally three times a day and atovaquone 750 mg orally twice a day. On the follow-up visit, the patient's visual acuity in the affected eye had decreased to 20/300 (6/90). The amount of cells in the anterior chamber increased to 4+ and vitreous cells were 2+. Systemic prednisone 50 mg orally daily and topical prednisolone acetate, one drop every hour in the right eye, were started. In spite of this therapy, inflammation persisted for the next three months. The patient developed posterior vitreous detachment after two months of therapy during her 33rd week of pregnancy.

Two weeks after giving birth, the patient returned for a follow-up visit. Examination revealed decreased vitreal cells to 1+ and mostly scarred toxoplasmic lesion. Visual acuity was 20/40 (6/12). Medications were discontinued.

Six weeks after delivery the patient's visual acuity was 20/25 (6/7.5) in the affected eye and there was no active inflammation. The child was healthy.

During her two-year follow-up the patient did not have recurrences of toxoplasmic retinochoroiditis.

Case 2

A 24 year-old Hispanic female with a history of panuveitis in both eyes for four years, treated with periocular steroids with little success, was referred for evaluation. The patient's medical history was remarkable for 2 caesarean deliveries. The patient reported a history of recurrence of toxoplasmosis with her second pregnancy, but this did not affect the birth of a healthy child.

At the time of the visit with us the patient's visual acuity was 20/30 (6/9) in the right eye and 20/70 (6/21) in the left eye. She was receiving one drop of prednisolone acetate hourly in the left eye. Slit-lamp examination showed posterior subcapsular cataract. Dilated fundoscopic examination revealed posterior vitreous detachment, 3+ old vitreous debris and 1+ cells in the left eye. There were bilateral choroidal lesions. Fluorescein angiography disclosed optic-disc staining of the left eye in the late frames.

The patient had undergone an evaluation, which disclosed an antitoxoplasmic IgG antibody level of 2.2 EIA units (normal range 0-0.9). Chest X-ray, gallium scan, and other laboratory tests were normal.

Because there were no vision-threatening lesions, we decided to observe the patient. Prednisolone acetate was slowly tapered. On subsequent visits the patient was found to have a progression of the cataract in her left eye and she scheduled phacoemulsification of the cataract combined with pars plana vitrectomy. Three weeks after the procedure, the patient developed a retinal detachment in the left eye and reactivation of uveitis. In that visit the patient also informed her care providers that she was 5 weeks

pregnant. The patient was referred for surgical treatment of the retinal detachment. The patient continued to have persistent inflammation in the left eye. Her condition finally stabilized with visual acuity of 20/50 (6/15) in the left eye by the third trimester of her pregnancy. The patient had a healthy baby and no reactivation of toxoplasmosis after the delivery.

Case 3

A 20 year-old Hispanic female from Brazil with a history of ocular toxoplasmosis diagnosed at 13 years of age was referred for treatment of decreased visual acuity of her right eye and pain of one-week duration. The patient was 8 weeks pregnant at the time of her initial evaluation at the Ocular Immunology and Uveitis Service. The patient

Table 1. Profile of 4 cases with recurrent ocular toxoplasmosis in pregnancy.

	Case 1	Case 2	Case 3	Case 4
Age	22	24	20	26
Affected eye	OD	OS	OD	OS
Visual acuity prior to flare-ups	20/25 (6/7.5)	20/40 (6/12)	20/50 (6/15)	20/100 (6/30)
Weeks of pregnancy at the beginning of flare-ups	28	2	7	19
Adverse events during flare-ups	Posterior vitreous detachment	Retinal detachment, cataract	Cataract	Progression of the disease to macula
Total length of inflammation	16 weeks	24 weeks	35 weeks	9 weeks
Worst visual acuity during flare-ups	20/300 (6/90)	20/200 (6/60)	Light perception with correct light projection	20/600 (2/60)
Final visual outcome	20/25 (6/7.5)	20/50 (6/15)	20/50 (6/15)	20/80 (6/24)
History of flare-ups with previous pregnancies	No previous pregnancies	Two previous pregnancies	Two previous pregnancies	One previous pregnancy

Table 2. Medications used in the treatment of ocular toxoplasmosis.

Medication	Typical dose	Safety in pregnancy
<i>Dihydrofolate reductase inhibitors</i> Pyrimethamine Trimethoprim/sulfamethoxazole ¹	100 mg loading dose 25-50 mg daily for 30-60 days 160mg/800 mg twice daily	Category C* contraindicated in the first trimester; excreted in human milk
<i>Sulfonamides</i> Sulfadiazine Sulfasoxazole Sulfadiazine/sulfamerazine/sulfamethazine ("triple sulfa") Trimethoprim/sulfamethoxazole ¹	1gm four times daily _____ _____ 160 mg/800 mg twice daily	Category C* contraindicated in third trimester and breastfeeding
<i>Tetracyclines</i> Minocycline	100 mg twice daily	Category D* contraindicated in pregnancy and childhood
<i>Prednisone</i>	1 gm/kg/day	Category C*
<i>Macrolides</i> Spiramycin Azithromycin	500 mg three times daily for 3 weeks. May repeat after 21 days 500 mg daily for 3 weeks	Category B*
<i>Antiprotozoal</i> Atovaquone	750 mg four times daily for 4-6 weeks	Category B*
<i>Lincomycin derivative</i> Clindamycin	300 mg four times daily for 30-40 days	Category B*
<i>Folinic acid</i>	5-20 mg every day during pyrimethamine therapy	Category A*

* Grading system of medications in pregnancy: **A** = safety established in human studies, **B** = presumed safety based on animal studies, **C** = uncertain safety—no human or animal studies; **D** = unsafe—evidence of risk that may be justifiable in certain clinical circumstances; **E** = highly unsafe—risk outweighs any possible benefit.

¹Trimethoprim/sulfamethoxazole is a combination of a dihydrofolate reductase inhibitor and a sulfonamide.

did not have any significant medical history or allergies, and was not taking any systemic medications. She was using topical prednisolone acetate hourly and scopolamine twice daily in her right eye. Her visual acuity was 20/400 (3/60) in the right eye and 20/20 (6/6) in the left eye. Slit-lamp examination revealed keratic precipitates on the corneal endothelium, 3+ cells in the anterior chamber, and pigment deposits on the anterior capsule of the lens of the right eye. Dilated fundus examination showed an active toxoplasmic lesion adjacent to an old scar in the right eye, and 3+ vitreous cells. The left eye had an old chorioretinal scar, but there were no signs of active inflammation.

The patient was begun on atovaquone 750 mg orally twice daily and clindamycin 300 mg orally four times daily. Her follow-up visit in 10 days revealed worsening visual acuity in the affected eye: light perception with correct light projection, 3+ cells in anterior chamber and increased vitreous cells (4+). Systemic prednisone was added to the regimen at a dose of 60 mg orally daily. In spite of this therapy, inflammation persisted for the remaining 7 months of the patient's pregnancy.

On her follow-up visit 3 weeks post-delivery the patient's visual acuity remained at 20/400 (3/60). There was active inflammation with 3+ cells in the anterior chamber and extensive posterior synechiae obstructing the view of the fundus, along with posterior subcapsular cataract. Atovaquone was substituted with pyrimethamine 25 mg orally twice daily, folic acid 5 mg orally twice weekly and sulfadiazine 1000 mg four times daily. The patient was continued on clindamycin. Control of inflammation was achieved within five weeks after delivery, with resulting visual acuity of 20/80 (6/24) in the right eye.

Case 4

A 26-year-old Hispanic female with a history of ocular toxoplasmosis and glaucoma was referred for further evaluation and treatment. The patient was 22 weeks pregnant with her second child. She reported a history of recurrence of toxoplasmosis during her first pregnancy, leaving her with vision of 20/100 (6/30) in the left eye. The patient complained of loss of vision in her left eye for three weeks. She was started on therapy by the physician who saw her at that time. She was taking clindamycin 300 mg orally four times daily, sulfadiazine 500 mg orally twice daily, timolol maleate (Timoptic 0.5%, Merck Sharpe & Dohme, PA, USA) 1 drop and brimonidine (Alphagan Allergan, CA, USA) 1 drop twice a day in the left eye, as well as prednisolone acetate 1 drop four times daily in the left eye. Visual acuity was 20/25 (6/7.5) in the right eye and 20/600 in the left eye. Intraocular pressure was 15 mm Hg in the right and 21 mm Hg in the left eye. Slit-lamp examination showed 2+ cells in the anterior chamber of the left eye. The dilated fundus examination was

significant for an active inflammatory lesion in the macula and 2+ vitreal cells. Cup-to-disc ratio was 0.5 in the right and 0.6 in the left.

An infectious disease specialist recommended increasing the dose of clindamycin to 450 mg orally four times daily, and increasing sulfadiazine to 1 g orally four times daily. Three weeks later the patient returned with resolution of the anterior chamber inflammation, but 2+ vitreous cells persisted. Control of inflammation was achieved in three more weeks of continued therapy. Visual acuity in the left eye remained 20/800 (1.5/60).

RESULTS

We have described four patients with recurrent ocular toxoplasmosis during their pregnancy. The clinical features are summarized in Table 1.

Two patients had recurrence of toxoplasmic retinochoroiditis early in pregnancy, at 2 and 7 weeks, and the other two patients had recurrences at 28 and 19 weeks of pregnancy. All participants had a violent course of inflammation. Three patients had a prolonged course. Three of the four patients had permanent decrease in their best corrected visual acuity. Two developed cataracts and one developed retinal detachment. One patient had a decrease in visual acuity from 20/100 (6/30) to 20/800 (1.5/60) in the affected eye due to macular involvement in spite of aggressive therapy and a short duration of inflammation. Interestingly, two participants provided history of recurrences of ocular toxoplasmosis during their previous pregnancies. The details were unavailable for those incidents. Natural termination of pregnancy appeared to help the resolution of inflammation in two patients.

DISCUSSION

Many women are diagnosed with or experience recurrence of ocular toxoplasmosis during pregnancy. Newly diagnosed ocular toxoplasmosis in pregnant women is much less common than recurrence of toxoplasma retinochoroiditis. Pregnancy creates an interesting immunologic state in which strong immune responses are suppressed in order to prevent rejection of a fetus by the mother, and pregnancy-associated immunomodulation is thought to cause an ameliorating effect on some of the autoimmune diseases, such as multiple sclerosis,⁸⁻¹¹ rheumatoid arthritis,^{12,13} juvenile idiopathic arthritis¹⁴ and sarcoidosis¹⁵. The effect of pregnancy on the eye has not been studied well. Pregnancy associated immunomodulation may have a deleterious effect in patients with infectious ocular disorders.

It is well known that immunocompromised patients are at increased risk for developing acute toxoplasmosis, which has a poor prognosis and may be rapidly fatal if left untreated. Ocular toxoplasmosis may follow a severe

course in patients with AIDS, having atypical features, such as large areas of retinal necrosis,¹⁶ lesions arising perivascularly and not from old scars,¹⁷ bilateral inflammation, and inflammation extending into the orbit and causing cellulitis and panophthalmitis.¹⁸ Ocular toxoplasmosis may be more severe in elderly patients due to age-related waning of host immune defenses.^{19,20}

Certain timidity exists, even in specialty-trained uveitis specialists when treating pregnant patients with ocular toxoplasmosis. In one survey the majority of physicians stated that they would treat only severe vision-threatening acute toxoplasmosis in pregnant women.²¹ Adverse effects which medications may cause to the fetus limit treatment options for pregnant women with toxoplasmic retinochoroiditis.

In Table 2 we review the safety of medications used in treatment of ocular toxoplasmosis.

Combination clindamycin and atovaquone may provide a safe approach to treatment of acute ocular toxoplasmosis in pregnant patients. The optimal duration of specific therapy must be adjusted according to therapeutic response. We define a positive response to treatment as a sharpening of the borders of retinochoroidal lesions and decrease of vitreal cells. We continue therapy in immunocompetent patients at least for 30-60 days. Addition of oral corticosteroids may be started within 48 hours after initiation of antimicrobial therapy for intense ($\geq 3+$) vitreal cellular response.

A macrolide, such as clindamycin or azithromycin, combined with atovaquone may provide an excellent treatment option for pregnant patients. Sulfonamides should be avoided in the third trimester, because they compete with bilirubin for serum proteins, causing kernicterus. Pyrimethamine is potentially teratogenic and should be avoided, especially in the first trimester.

Comanagement with an infectious disease specialist is advised, as is consultation with an obstetrician. Some agree that there is a lack of evidence to support routine employment of antibiotic treatment for acute toxoplasmic retinochoroiditis in the general population.²² But it may be especially important to treat medically pregnant women with ocular toxoplasmosis, since antibiotic therapy prescribed to mothers who have toxoplasmic retinochoroiditis during pregnancy decreases the percentage of children developing retinochoroidal toxoplasmic lesions during the first and second years of life.^{23, 24, 25, 26}

Pars plana vitrectomy may be useful in the care of selected patients with toxoplasma retinochoroiditis for removal of antigenic proteins, inflammatory cells, and persistent vitreous opacities. Intravitreal/intraocular antibiotic injections may be an option for treating pregnant patients with ocular toxoplasmosis,²⁷ thereby avoiding systemic toxicity, side effects, and possible

teratogenicity. Martinez and colleagues²⁷ reported a case series of pregnant women with active toxoplasmic retinochoroiditis, who were treated with a combination of intraocular clindamycin and dexamethasone with good visual outcomes. We have successfully treated several cases of ocular toxoplasmosis unresponsive to conventional therapy with intravitreal injections of clindamycin.²⁸ Patients in our series were not pregnant. They had intolerance to systemic therapy. The resolution of inflammation in these patients and improvement in visual acuity make us believe that penetration of systemic medications may be inadequate in treatment of ocular toxoplasmosis and is responsible for the poor visual outcomes in the pregnant women described in this article.

The host immune system plays a critical role in response to ocular toxoplasmosis. It has been postulated that pregnancy may be a triggering factor in the recurrence of ocular toxoplasmosis.^{29,31} Friedman and Knox³⁰ reported active toxoplasmic retinochoroiditis during five pregnancies of four patients, and Bosch-Driessen et al.³¹ described seven women with ocular toxoplasmosis who had recurrences during pregnancy. Four of those women had reactivation of toxoplasmic lesions with each subsequent pregnancy. We believe that pregnancy not only predisposes a patient for recurrence of ocular toxoplasmosis, but may also present favorable conditions for a more aggressive form of this disease. Large cohort studies may lead to a better understanding of toxoplasmosis in pregnancy.

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