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Prenatal brain imaging in congenital toxoplasmosis

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Objective To describe brain imaging findings and outcomes in fetuses with confirmed congenital toxoplasmosis (CTX).

Methods Physicians from Prenatal Diagnosis Units in ten Latin American countries were contacted and asked to provide data on fetuses with ultrasound findings suggestive of intrauterine infection and a positive diagnosis of CTX. The imaging studies were reviewed, and findings were described and tabulated.

Results Intracranial findings suggestive of CTX were identified in eight patients at a median gestational age of 31.5 weeks (range, 24.4–34 weeks). Ventriculomegaly was found in seven patients [severe (3), mild (4)]. Multiple echogenic nodular foci consistent with calcifications were found in seven patients [brain parenchyma (7), periventricular zone (3) and caudothalamic zone (3)]. Diffuse periventricular echogenicity or cysts were seen in three and callosal dysgenesis in one. All six survivors have choroidoretinitis and intracranial calcifications, four suffer from developmental delay and three of these four children also suffer from seizures and blindness. Postnatal hydrocephaly was found in five children.

Conclusions Ventriculomegaly associated with multiple echo-dense nodules is characteristic of severe fetal toxoplasmosis and carries a poor prognosis. When the ventricles have normal size or are only mildly dilated, the nodules restricted to the parenchyma development may be normal. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: fetal brain; prenatal diagnosis; toxoplasmosis; fetal infections; ultrasound; MRI

INTRODUCTION

Congenital toxoplasmosis (CTX) results from transplacental infection with the protozoa *Toxoplasma gondii*. In humans, the most common source of infection is exposure to the domesticated cat or the ingestion or handling of contaminated meat. CTX is particularly prevalent in Latin American countries (Durlach *et al*., 2008; Varella *et al*., 2009).

The prenatal diagnosis of toxoplasmosis is based on routine population screening or on the ultrasonographic recognition of characteristic findings associated with intrauterine infection followed by maternal or fetal laboratory tests. In most countries, particularly in those with limited resources, prenatal screening programs do not include toxoplasmosis, and the diagnosis relies on prenatal ultrasound (US). Surprisingly, the literature on fetal imaging of toxoplasmosis is remarkably scarce (Hohlfeld *et al*., 1991; Abboud *et al*., 1995).

The purpose of this report is to present the ultrasonographic and magnetic resonance imaging (MRI) findings in a group of fetuses with confirmed CTX and to correlate between the imaging findings in these cases and prognosis.

METHODS

Fetal medicine specialists from Argentina, Chile, Uruguay, Brazil, Paraguay, Perú, Ecuador, Colombia, Venezuela, Panamá and México were contacted through the Internet or at different prenatal diagnosis courses organized during the years 2006–2009. The physicians were asked to provide images and clinical data on their cases of proven CTX.

We reviewed the files and US and magnetic resonance (MR) images of all referred fetuses. The sonograms were obtained, in all cases, using the transabdominal and/or transvaginal approach; axial views of the brain were usually obtained by the transabdominal approach and coronal and sagittal ones by the transvaginal approach (Malinger *et al*., 2006; Malinger *et al*., 2007; ISUOG guidelines, 2007).

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We reviewed the US images and video clips for signs of ventriculitis (periventricular echogenicities or irregular ventricular borders), leukomalacia, calcifications, parenchymal nodules, vasculitis (echogenic vessels) and periventricular cyst formation. The gyral pattern, corpus callosum and cerebellar morphology were also assessed. Fetal MR studies were performed using 1.5-T system standard protocols. The MR images were reviewed for the same signs as the US. Maternal blood toxoplasma-specific immunoglobulins (Ig) G, A and M; amniotic fluid polymerase chain reaction (PCR); and/or histological demonstration of toxoplasmosis during autopsy confirmed CTX infection in all cases. Other TORCH (syphilis, parvovirus B19, rubella, cytomegalovirus, herpes) infections were ruled out by maternal serology studies.

RESULTS

Eight cases were identified, and their files and imaging findings were evaluated. The mean maternal age at the time of the initial diagnosis was 26.5 years (range, 20–32 years). Five women were nulliparas, and three had a previous normal pregnancies and deliveries.

Intracranial findings suggestive of CTX were identified at a median gestational age of 31.5 weeks (range, 24.4–34 weeks); only two patients were initially referred during the second trimester. The six patients diagnosed during the third trimester were studied as part of the routine follow-up, and all of them had US examinations that were considered normal during the second trimester.

All patients were referred for evaluation following the diagnosis of abnormal sonographic findings in an outside center; these findings were severe ventriculomegaly (4), mild ventriculomegaly (3) and intracranial calcifications.

Maternal serology studies were positive for toxoplasma-specific IgG, IgA and/or IgM in all the patients; in at least one patient (case 7), seroconversion occurred after 28 weeks of pregnancy. The amniotic fluid of six patients was studied, and the PCR for *Toxoplasma* was positive in all.

The prenatal US findings observed by the referring physicians were confirmed in all the cases, but our detailed central nervous system (CNS) evaluation, performed in tertiary centers with more experience in neurosonography, demonstrated more severe and extensive brain involvement. Multiple echogenic nodular foci were found in seven patients and were located in the brain parenchyma, the periventricular zone (3), or the caudothalamic zone (3) (Figures 1–5). In one patient, the brain destruction was so severe that the parenchyma was difficult to evaluate (Figure 5). Diffuse periventricular echogenicity or periventricular cysts, similar to those observed in patients with cytomegalovirus (CMV) infection, were found in three patients (Figure 4). Other brain anomalies detected were signs of brain destruction (2) (Figure 5) and dysgenesis of the corpus callosum (Figure 2). The cerebellum was not involved in any of the patients. Non-CNS findings included hepatomegaly (2) and nonimmune hydrops fetalis (Figure 1). The placenta was thick and was apparently involved in only one patient.

Patient 7 underwent an initial MRI examination at 34 weeks following seroconversion at around 30 weeks of gestation, and a repeat examination was obtained at 37 weeks after 3 weeks of spiramycin treatment. Both examinations were quite similar and showed ventriculomegaly, abnormal cortical development with

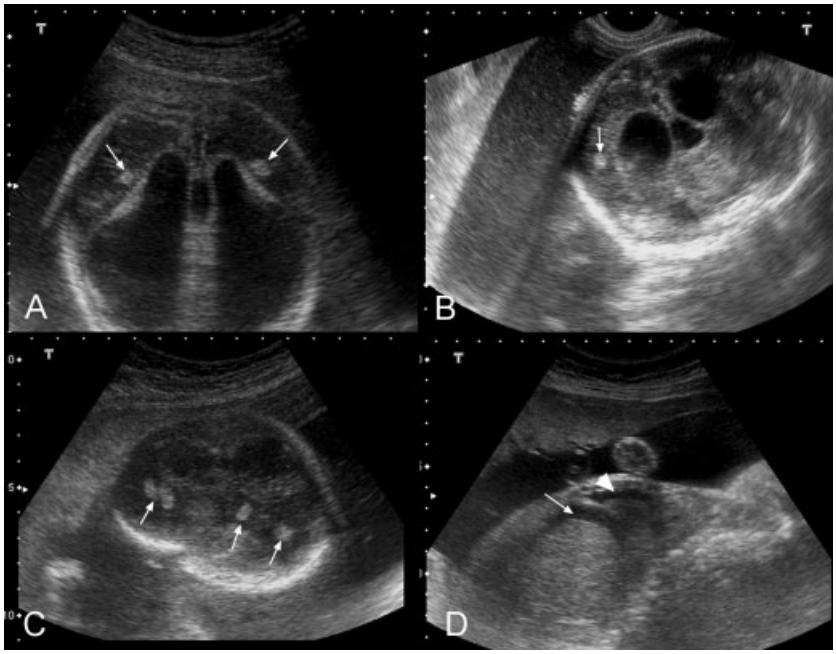

Figure 1—Patient 1. US images at 32 weeks of gestation show severe ventriculomegaly, periventricular (arrows in A) and parenchymal (arrows in B, C) nodular foci and hydrops fetalis presenting with ascites and pleural effusion (arrows in D)

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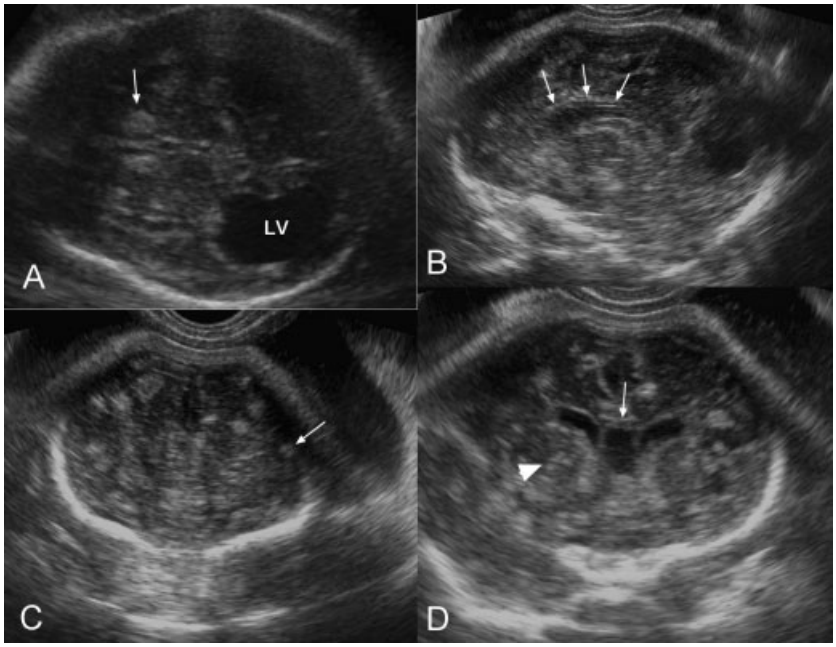

Figure 2—Patient 2. US images at 33 weeks of gestation show a large cystic dilatation of the posterior horn of the lateral ventricle (LV) in (A), caudothalamic (arrow in A, arrowhead in D) and cortical (arrow in C) nodular foci, and callosal dysgenesis (arrows in B, D)

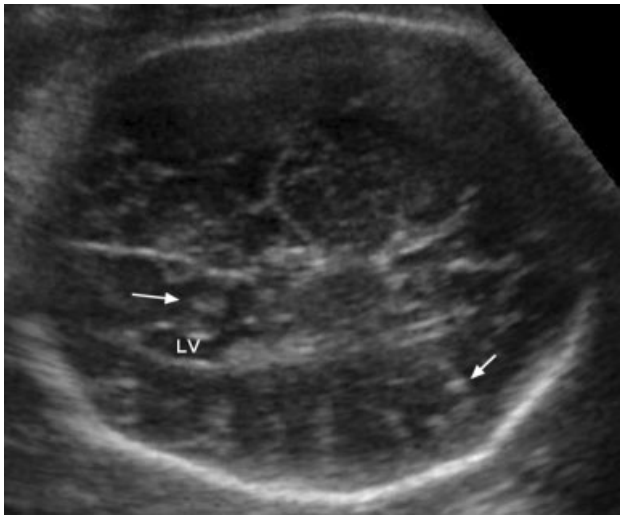

Figure 3—Patient 3. US image at 32 weeks of gestation shows normal sized lateral ventricle (LV) with minimal involvement of the brain. Only two parenchymal nodules (arrows) were identified. This child is developing normally at 4 years of age

white matter involvement and under opercularization, cysts and signs of encephalitis and brain atrophy (Figure 6).

Seven patients were treated *in utero* by spiramycin according to established protocols, but all the delivered children were affected. Patient 1 with hydrops fetalis and severe ventriculomegaly died *in utero* at 35 weeks of gestation. Seven patients were delivered, but one (patient 8) died at 48 hours. The patient that succumbed had diffuse brain involvement but only mild ventriculomegaly and no non-CNS findings. Postnatal evaluations and brain imaging were performed in the six surviving patients. All of them have signs and symptoms of CTX (Table 1). All have choroidoretinitis and intracranial calcifications, but only four suffer from developmental delay, and three of these four also suffer from seizures and blindness. Postnatal hydrocephaly secondary to brain atrophy was found in five children, and none required insertion of a ventricular peritoneal shunt.

Patient 3 had only parenchymal calcifications and no ventriculomegaly *in utero* (Figure 2) and is developing normally despite postnatal development of hydrocephalus. Patient 6 had mild ventriculomegaly and nodules involving only the parenchyma; this is the only child without hydrocephalus. In these patients, the number of nodules was relatively small when compared with those of the children with mental retardation.

DISCUSSION

Although there are large studies on the prenatal diagnosis of CTX(Hohlfeld *et al*., 1994; Foulon *et al*., 1999; Friedman *et al*., 1999), there are only few reports on the sonographic brain findings of affected fetuses (Blaakaer, 1986; Hohlfeld *et al*., 1991; Abboud *et al*., 1995; Pedreira *et al*., 1999; Antsaklis *et al*., 2002; Couto and Ferreira, 2006).

In the present study, ventriculomegaly was associated with multiple echo-dense nodules involving the periventricular tissue, the intermediate zone and cortex and/or the basal ganglia in six of seven patients in whom it was possible to evaluate the brain parenchyma. We believe that these findings are characteristic and when detected should prompt an evaluation for CTX.

Hohlfeld *et al*. (1991) published the only series on the prenatal imaging of CTX in 1991; 32 of 89 fetuses

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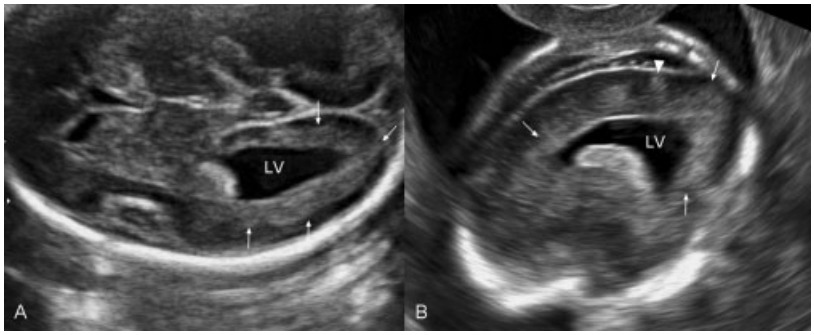

Figure 4—Patient 4. US images at 24.3 weeks of gestation show mild ventriculomegaly (LV) with increased periventricular echogenicity (arrows) similar to the echogenicites described in fetuses with congenital CMV infection. Note the presence of at least one parenchymal nodule separated from the periventricular zone (arrowhead)

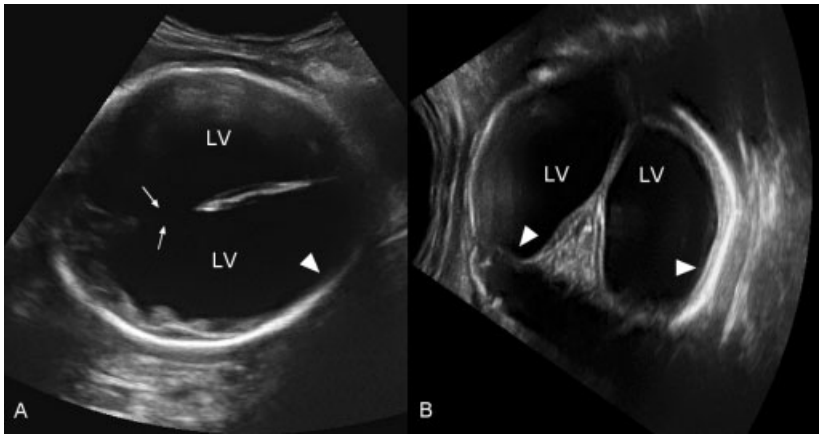

Figure 5—Patient 5. US images at 29.2 weeks of gestation. The large ventricles (LV) caused almost complete destruction of the brain parenchyma with disruption of the septi pellucidi (arrows in A). The cortical mantle has disappeared in some regions (arrowheads in A, B)

with proven *Toxoplasma* parasites in their blood or amniotic fluid developed ultrasonographic signs of infection; ventriculomegaly was present in 25 fetuses but cerebral densities only in 6. The authors did not specify their sites. In another six fetuses that were considered to have normal US examinations, postnatal brain examinations found multiple foci of brain necrosis and abscesses, sometimes involving very large areas of the brain. These false-negative results may possibly be due to the fact that the authors only used a transabdominal approach and MRI was not yet available or due to the possibility of relatively late and fast development of toxoplasma-related lesions (Friedman *et al*., 1999). The improvement in US resolution and the addition of MRI in our patients allowed a better definition of the brain findings, depiction of echo-dense nodules in most patients and the visualization of previously undescribed pathologies such as increased periventricular echogenicities, cysts and dysgenesis of the corpus callosum. In our study, we found the same non-CNS findings described by Hohlfeld *et al*. (1991): hepatomegaly, signs of hydrops and increased placental thickness. Ocular lesions, very common in children with CTX, are rarely detected *in utero* (Pedreira *et al*., 1999).

There are additional reports of the imaging findings in CTX. Couto and Ferreira (2006) describe ventriculomegaly and multiple large periventricular echogenic nodules in a patient diagnosed in the second trimester. Cuillier and Avignon (2006) describe the neurosonographic and MRI findings in a 30-week fetus. Transvaginal sonography demonstrated ventriculomegaly, increased periventricular echogenicity with multiple intraparenchymal echogenic nodules and brain abscess formation, and MRI confirmed the findings and also showed partial left cerebellar hypoplasia. Garel demonstrates a good correlation between US and MRI in diagnosing brain abnormalities in fetal toxoplasmosis at 31 weeks (Garel, 2004).

Interestingly, in our patients as well as in those reported by other authors, the US signs are usually unidentified during the second trimester, indicating either that it takes a prolonged time for the insult to develop (Gay-Andrieu *et al*., 2003) (it develops following the US examination usually performed at 18–22 weeks of gestation) or that the third trimester infection is more frequent than that previously reported. In only one of our patients, we have accurate documentation that late infection resulted in severe fetal brain involvement. Friedman *et al*. reported an affected fetus without ultrasonographic findings at 27 weeks that developed ventriculomegaly with echo-dense nodules at 31 weeks despite antitoxoplasmosis treatment (Friedman *et al*., 1999).

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Table 1—Clinical and imaging findings of eight patients with proven prenatally diagnosed CTX

Patient number	1	2	3	4	5	6	7	8
Gestational age at diagnosis, years	32	33	31	24.3	29.2	33	34	26.6
Time of seroconversion	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	28–30	6–20
US/MRI findings								
Ventriculomegaly	Severe	Severe	No	Mild	Severe	Mild	Severe	Mild
Periventricular nodular foci	Yes	Yes	No	No	No	No	Yes	Yes
Parenchymal nodular foci	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Caudothalamic nodular foci	No	Yes	No	No	No	No	Yes	Yes
Periventricular echogenicity/cysts	No	No	No	Yes	No	No	Yes	Yes
Dysgenesis del CC	No	Yes	No	No	No	No	No	No
Cerebellar findings	No	No	No	No	No	No	No	No
Brain destruction	No	No	No	No	Yes	No	Yes	No
Non-CNS involvement	NIHF	H	No	No	H	No	No	No
Placental involvement	No	Yes	No	No	No	No	No	No
Postnatal imaging								
Technique	NR	CT	US	CT	CT	CT	US-MRI	NR
Hydrocephalus	NR	Yes	Yes	Yes	Yes	No	Yes	NR
Multiple calcifications	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR
	IUFD	Alive	Alive	Alive	Alive	Alive	Alive	Neonatal death
Neonatal follow-up								
Age (years)	NR	4	4	1.8	2	1	0.6	NR
Neurodevelopmental delay	NR	Yes	No	Yes	Yes	No	Yes	NR
Seizures	NR	Yes	No	Yes	Yes	No	No	NR
Blindness	NR	Yes	No	Yes	Yes	No	No	NR
Choroidoretinitis	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR

NIHF, nonimmune hydrops fetalis; H, hepatomegaly; CT, computerized tomography; IUFD, intrauterine fetal death; NR, not relevant.

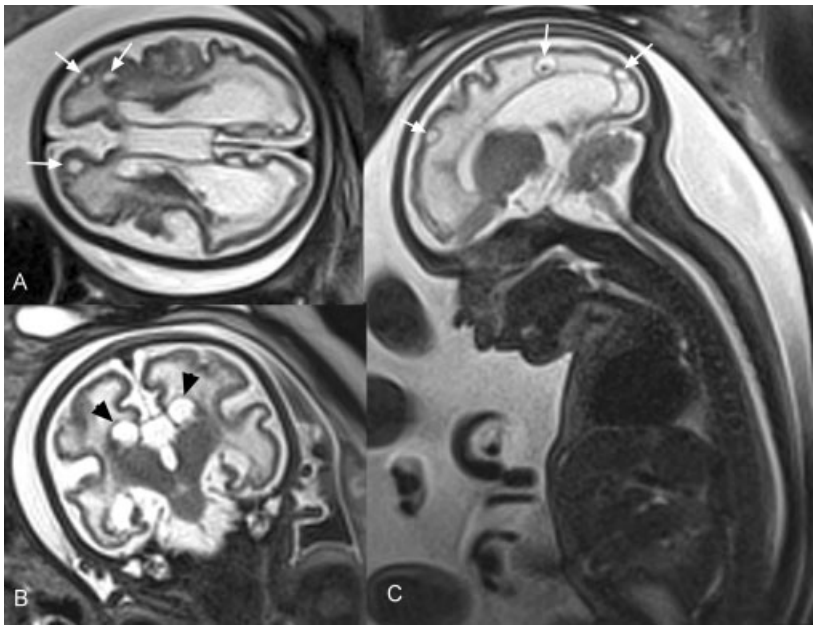

Figure 6—Patient 7. MRI images at 34 weeks of gestation. Axial (A), coronal (B) and sagittal (C) T2-weighted images demonstrate multiple annular lesions of varying sizes, with heterogeneous signal, predominantly hyperintense (arrows). Note diffusely distributed edema throughout the parenchyma, supratentorial ventricular dilatation and bilateral periventricular pseudocysts (black arrowheads)

The differential diagnosis of these brain abnormalities includes other TORCH infections, particularly CMV, metabolic or hemorrhagic insults and tuberous sclerosis.

Unlike CMV infection, which has a predilection for the periventricular zone (Becker, 1992; Fitz, 1992), the intracranial echogenic nodules of fetal toxoplasmosis can occur in multiple brain areas. Periventricular cysts and intraventricular adhesions, characteristic of CMV infections, appear to be uncommon in fetuses with CTX. Unlike CMV infection, CTX is not associated

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with fetal microcephaly probably due to the prominent ventriculomegaly.

Non-CNS involvement (thickened placenta, with hyperechoic areas, liver echogenicities, hepatomegaly, ascites and pericardial or pleural effusions) is frequent but not pathognomonic of CTX and when isolated adds little to the differential diagnosis (Blaakaer, 1986; Hohlfeld *et al*., 1991; Friedman *et al*., 1999; Couto and Ferreira, 2006).

In severe cases, CTX may produce brain abscesses with cystic formation resembling metabolic or posthemorrhagic insults.

Tuberous sclerosis may also demonstrate a similar echogenic nodular pattern, but the nodules are usually less echogenic, ventriculomegaly is not common and cardiac rhabdomyomata are easily identified (Malinger *et al*., 2007).

In our relatively small study, there appeared to be a correlation between the extent of brain and non-CNS involvement and outcome. Although in two of our patients normal ventricular size or mild stable ventriculomegaly with few brain nodules was compatible with normal development, it should be mentioned that Hohlfeld *et al*. failed to find a correlation between absence of ventricular enlargement and good prognosis (Hohlfeld *et al*., 1991). Diffuse brain involvement resulted in our group in early death or mental retardation.

Although spiramycin treatment of primary infection during gestation reduces the frequency of congenital infection, maternal antitoxoplasma treatment in patients with well-established fetal brain involvement will not prevent sequelae in the fetus (McAuley *et al*., 1994; McLeod *et al*., 2006). We could not appreciate the effect of treatment in our patients because all were treated; however, it seems that it has a role only in patients with minimal disease.

CONCLUSIONS

CTX may manifest *in utero* with CNS abnormalities including multiple echogenic, nodular foci located in the brain parenchyma, periventricular or caudothalamic zones; brain destruction; diffuse periventricular echogenicity and periventricular cysts; and dysgenesis of the corpus callosum as well as non-CNS findings. In our patients, the prognosis seems to be correlated to the extent of brain involvement.

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