

## Original articles

# Hearing loss in children exposed to toxoplasmosis during their gestation

## *Alterações auditivas em crianças expostas à toxoplasmose durante a gestação*

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Conflict of interest: non-existent

### ABSTRACT

**Purpose:** to verify the occurrence and the most frequent type of auditory disorders in children exposed to toxoplasmosis during pregnancy.

**Methods:** a retrospective, longitudinal study carried out in a public health institution of São Paulo. Records of children born between 2010 and 2015 were analyzed and distributed into two groups: study group, composed of 48 children born to mothers with a diagnosis of toxoplasmosis during their pregnancy; and control group, composed of 43 children without congenital infection, who were accompanied due to low birth weight. The children were evaluated two to four times during their first two years of life, by means of peripheral and central auditory function assessment.

**Results:** 47 children underwent only two evaluations and only 11 completed all the evaluations up to 24 months. In the control group, 58.1% had normal hearing, 37.2% conductive loss, 4.7% cochlear loss and absence of retrocochlear disorder. In the study group, 56.3% presented normal hearing, 20.8% conductive loss, 2.1% cochlear loss, and 20.8% retrocochlear disorder.

**Conclusion:** children exposed to toxoplasmosis during pregnancy did not differ from non-exposed children in relation to the occurrence of conductive or cochlear hearing loss. However, they showed a higher occurrence of retrocochlear disorder.

**Keywords:** Hearing; Toxoplasmosis; Spontaneous Otoacoustic Emissions; Audiometry; Hearing Loss

### RESUMO

**Objetivo:** verificar a ocorrência e o tipo mais frequente de alteração auditiva em crianças expostas a toxoplasmose durante a gestação.

**Métodos:** estudo retrospectivo longitudinal realizado em instituição pública de saúde de São Paulo. Análise de prontuários de crianças nascidas entre 2010 e 2015 distribuídos em dois grupos: grupo estudo, composto por 48 crianças de mães com diagnóstico de toxoplasmose durante a gestação; e grupo controle, composto por 43 crianças sem infecção congênita que foram acompanhadas por apresentar baixo peso ao nascimento. As crianças foram avaliadas de duas a quatro vezes durante os dois primeiros anos de vida, por meio de testes que avaliam a função auditiva periférica e central.

**Resultados:** 47 crianças fizeram apenas duas avaliações e apenas 11 completaram todas as avaliações até 24 meses. No grupo controle 58,1% apresentaram audição normal, 37,2% perda condutiva, 4,7% perda coclear e ausência de alteração retrococlear, enquanto o grupo estudo apresentou 56,3% de audição normal, 20,8% de perda condutiva, 2,1% de perda coclear e 20,8% de alteração retrococlear.

**Conclusão:** crianças expostas à toxoplasmose durante a gestação não diferiram das não expostas em relação à ocorrência de perda auditiva coclear e condutiva. Entretanto, apresentaram maior ocorrência de alteração retrococlear.

**Descritores:** Audição; Toxoplasmose; Emissões Otoacústicas Espontâneas; Audiometria; Perda Auditiva

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## INTRODUCTION

Congenital toxoplasmosis is caused by the transmission of the protozoan *Toxoplasma gondii* from the mother to the fetus. The mother is contaminated during the gestational period mainly by the ingestion of water and/or raw meats or inadequately cooked meat contaminated with sporulated oocysts. The parasite reaches the baby via placenta causing damage of different degrees of severity, which can even be responsible for fetal death. The subclinical (asymptomatic) form of the disease occurs in 70-90% of cases. However, if these are not diagnosed and treated early, 85% may suffer of infections in the eyes during childhood and adolescence and 40% can present neurological sequelae in the future. The main characteristics of congenital toxoplasmosis are: neurological and ophthalmological alterations, other symptoms of prematurity, intra-uterine growth retardation, anemia, thrombocytopenia, increased abdominal volume, enlarged lymph nodes, jaundice, sensorineural deafness, among others<sup>1-3</sup>.

Studies have found a prevalence of congenital toxoplasmosis between 0.6-1.3/1000 live births in different regions of Brazil<sup>4-6</sup>. It has been suggested that the chance of transmission of toxoplasmosis from mother to fetus ranges from 18.5 to 23%<sup>6,7</sup>. The risk of fetal infection is less than 15% in the first trimester, but in general, the disease is severe in the newborn. The risk of infection increases from 20 to 50% in the second trimester and from 55 to 80% in the third trimester of pregnancy, but the newborn is asymptomatic or presents a less severe<sup>8</sup>.

*Toxoplasma gondii* has been associated with auditory pathway damage since the beginning of the 1950s, with evidence of calcium deposits (similar to calcifications found in the brains of children with congenital toxoplasmosis) in the spiral ligament and cochlea<sup>9</sup>. Auditory deficit has been reported in about 20% of cases of congenital toxoplasmosis, especially in children not treated or treated for a very short period<sup>10</sup>. A study with 174 Brazilian children with toxoplasmosis diagnosed and treated early found a 3.4% cochlear loss, a 4.6% conductive loss, and a 3.4% central alteration<sup>11</sup>. The occurrence of profound deafness has been almost totally limited to cases with high clinical manifestations<sup>12</sup>, but another study reports the occurrence of unilateral or bilateral hearing loss in 26% of the

19 children with subclinical infection<sup>13</sup>. Other authors have not found an association between parasitosis and hearing loss when children are treated, and doubts persist as to the frequency with which toxoplasmosis can lead to auditory deficit<sup>12,14</sup>.

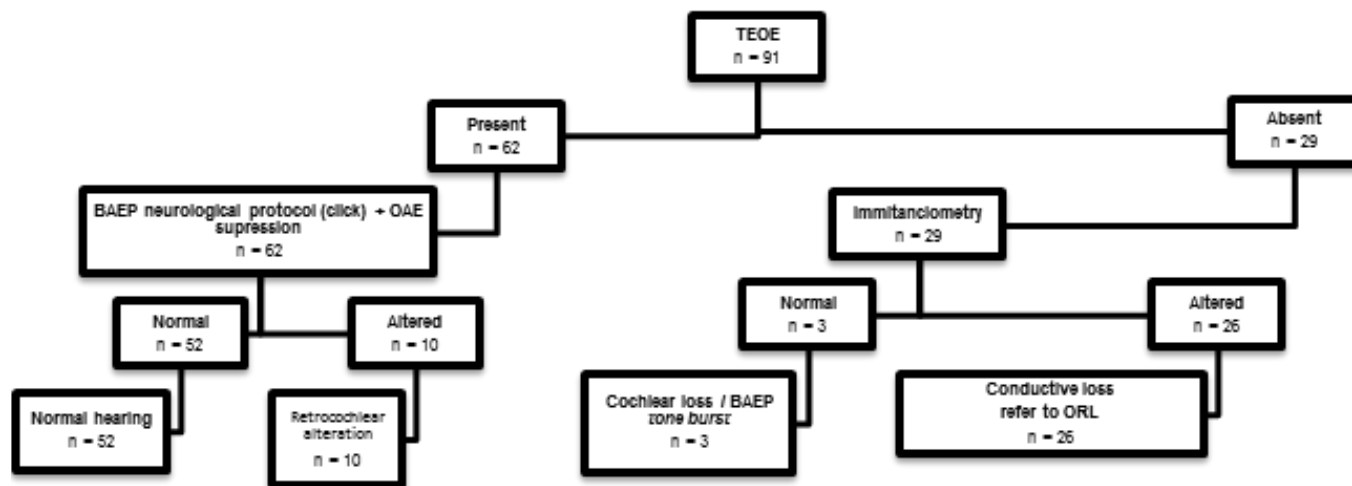
Thus, this study was carried out with the objective of verifying the occurrence and the most frequent type of auditory alteration in children exposed to toxoplasmosis during gestation.

## METHOD

The research was approved by the institution's research ethics committee under No. 0448/2015 and the written consent was obtained from the head of the outpatient clinic, co-author of the present study.

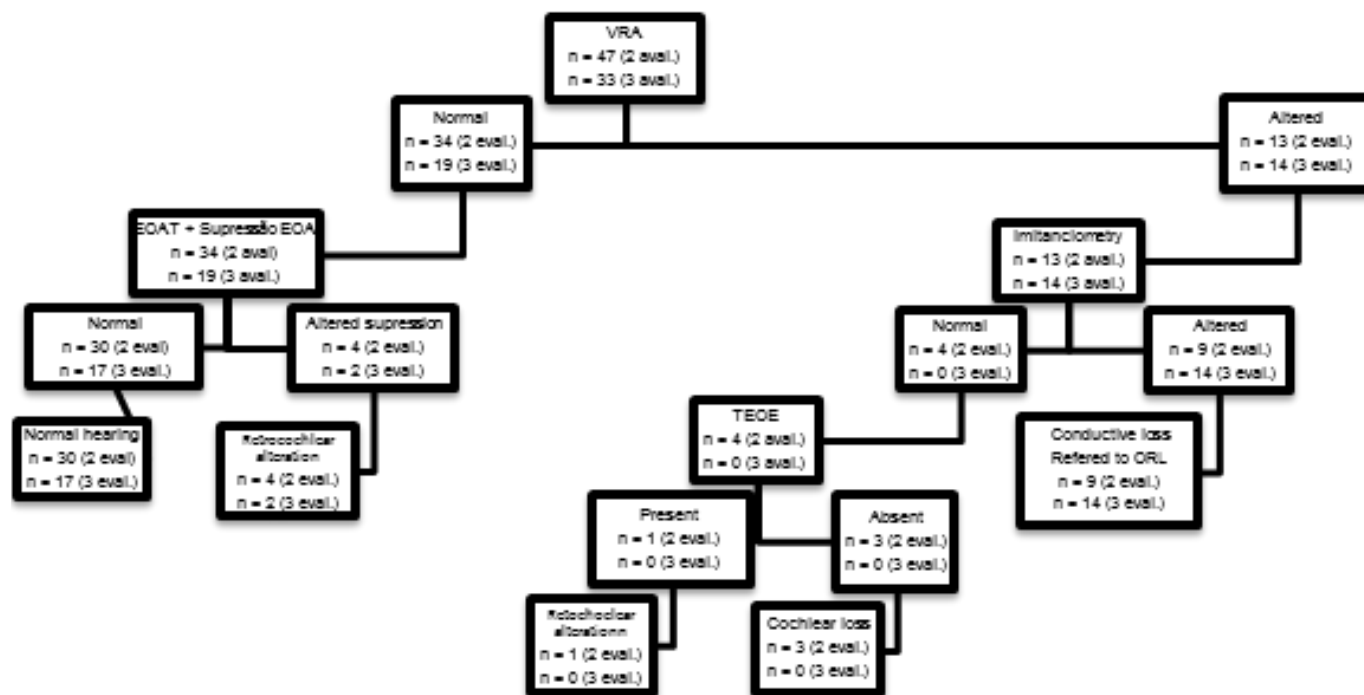
Retrospective longitudinal study with the analysis of medical records of children born between 2010 and 2015 that were attended at a public institution in the city of São Paulo. From the total of 250 medical records analyzed, 91 were selected as fitting the inclusion and exclusion criteria. For establishing the study group (SG), the children referred by the Discipline of Pediatric Infectious Disease of the institution were selected for exposure to toxoplasmosis during pregnancy without other indicators of risk for hearing loss<sup>15</sup>. For the formation of the control group (CG), we selected children who were followed up in the medical sector due to low birth weight, without any risk indicators for hearing loss<sup>15</sup>. In this way, the SG was composed of 48 children and the CG, for 43 children.

The children of both groups were followed for a period of two years with periodic hearing evaluations performed by the audiology team, composed by the authors of the study. The evaluations were performed at birth (1<sup>st</sup> evaluation), between 6 and 9 months (2<sup>nd</sup> evaluation), between 9 and 24 months (3<sup>rd</sup> evaluation), and at 24 months (4<sup>th</sup> evaluation). The audiological evaluation consisted of: Transient evoked otoacoustic emissions (TEOE), suppression of otoacoustic emissions, visual reinforcement audiometry (performed from six months of age) and CPA (performed from two years of age), Acoustic immittance and brainstem auditory evoked potential (BAEP) by click stimuli and tone burst. The procedures used varied according to the age group and were performed in both ears in all cases (Figures 1 to 3).



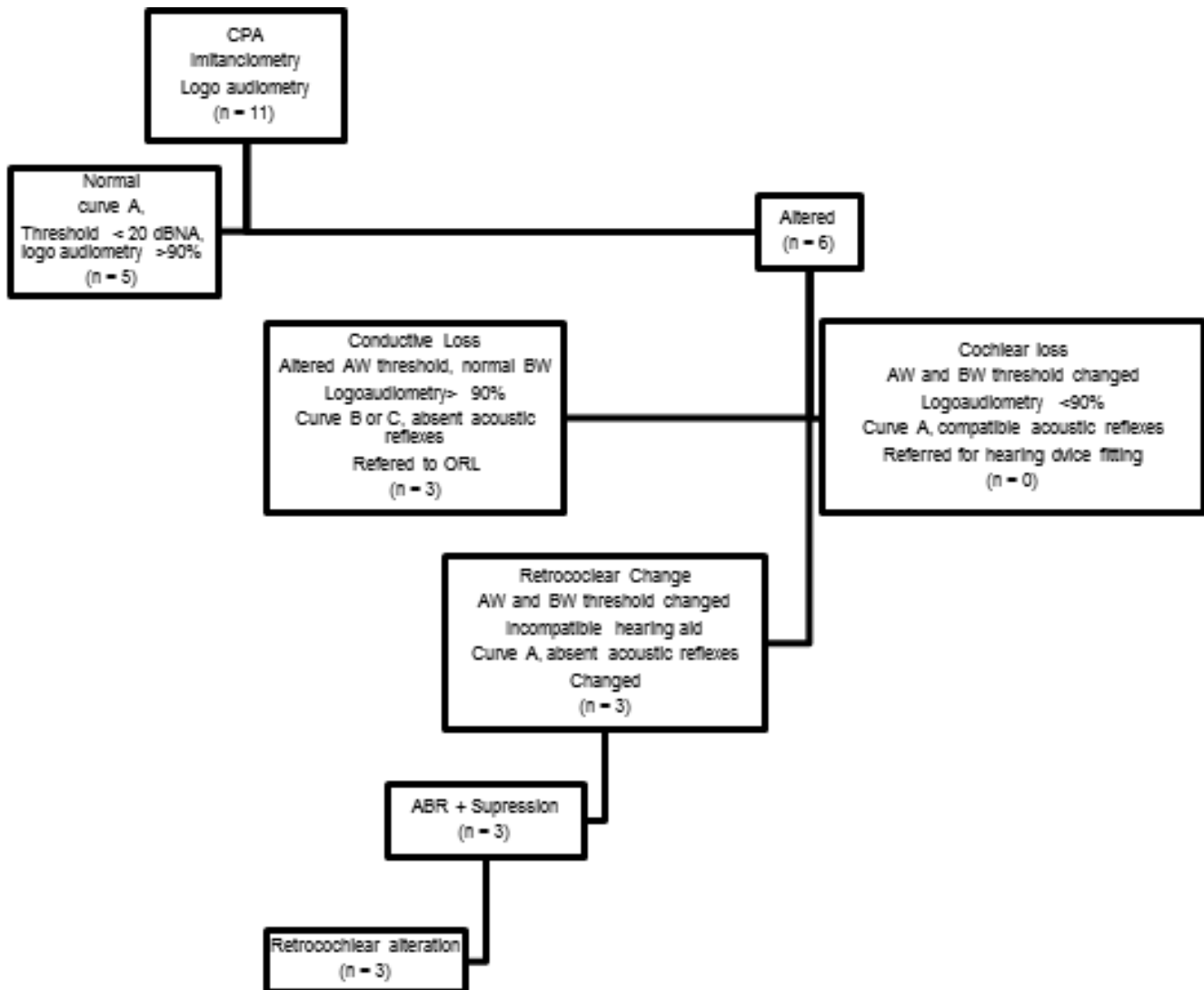
ORL –Otolaryngologist

Figure 1. Flowchart of the first evaluation protocol (at birth)



ORL –Otolaryngologist; VRA - Visual reinforcement audiometry

Figure 2. Flowchart of the protocol of the second and third evaluation (6 to 9 months and 9 to 24 months) with the distribution of the individuals who performed 2 and 3 evaluations



AW – air way; BW – bone way; ORL - Otolaryngologist

**Figure 3.** Flowchart of the protocol of the fourth evaluation (24 months) with the distribution of the individuals who performed 4 evaluations

The TEOAE screening and TEOAE suppression were performed with a ILO V6 device. For the TEOAE study, the non-linear click type stimulus was used between 75 and 85 dBpeNPS. TEOAEs were considered present when the signal-to-noise ratio was higher than 3 dB in the 1 kHz band and 6 dB in the 2, 3 and 4 kHz bands, with reproducibility higher than 50% and probe stability greater than 70%. The TEOAE suppression was performed using two probes, one in each ear, with alternating presentation of two seconds of linear clicks at 65 dBpeNPS without noise and two seconds of clicks with contralateral noise at 60 dBNPS. At the end of 260 series of clicks, suppression was considered when there was a minimum decrease of 0.2 dB in the general response<sup>16</sup>.

Acoustic immittance measurements were performed with the *Interacoustics* brand imitanciometry screener T235 recording the tympanometric curve and the contralateral acoustic reflex search in the frequencies from 0.5 to 4 kHz. Normal type A tympanometric curve with acoustic reflexes present between 70 and 90 dB above the auditory threshold was considered in the frequency studied<sup>17</sup>.

The audiometry with visual reinforcement was performed in children from six months in acoustic booth with supra-aural earphones model TDH39 and Maico brand audiometer MA41, using complex visual reinforcement (toy with movement and light). Thresholds of up to 15 dBHL were considered normal and the mean was of 0.5 to 4 kHz. Bone scan was

performed with a bone vibrator positioned on the mastoid and contralateral masking was used when necessary<sup>18</sup>.

The CPA was performed in children aged two years or more with the same equipment. The child was conditioned to associate the detected sound with a motor act (insert piece into the toy). The investigation of the speech recognition threshold (SRT) was performed with the identification of requested figures with a gradual decrease in the sound pressure level of the stimulus up to 50% of the child's correct answers were obtained. The percentage of speech recognition index (PSRI) was performed with the identification of figures at 40 dBNS in relation to the average of the thresholds of the frequencies of 0.5, 1 and 2 kHz<sup>18</sup>.

The BAEP was performed with the *Intelligent Hearing Systems Smart-EP* equipment with insertion earplugs and surface electrodes positioned at points C<sub>z</sub>, F<sub>z</sub>, A<sub>1</sub> and A<sub>2</sub>. The click stimulus was presented at 80 dBNA. Waves I, III and V and interpeak intervals I-III, III-V and I-V were recorded. The analysis of the absolute and interpeak latencies was performed using the criterion proposed by Gorga<sup>19</sup>. Electrophysiological threshold research was performed with a burst tone of 0.5 to 4 kHz by airway (AW) and by bone (BW) in children with suspected cochlear loss<sup>20</sup>.

For airway threshold research, at least 2000 stimuli were presented. The sound pressure level of the tone burst stimulus decreased by 20 dB from 80 dBnNA until the V wave was no longer visualized. Then, the intensity was increased 10 by 10 dB until the lowest intensity was obtained, in which the V wave appeared in a smaller amplitude, being considered the electrophysiological threshold. A normal threshold of 30 dBnNA was considered for each frequency, corresponding to 20 dBNA<sup>20</sup>.

In the BAEP record by bone way, a bone vibrator was placed in the mastoids and an alternating stimulus was presented at 50 dBNA, decreasing by 10 in 10 dB. As an electrophysiological threshold, the lowest intensity at which the V wave was identified and replicated by the examiner was considered. An electrophysiological threshold  $\leq 20$  dBnNA was considered normal<sup>20</sup>.

From the results obtained in the exams, children were classified in relation to hearing as: normal hearing, conductive loss, cochlear loss, and retrocochlear alteration.

- Normal hearing: presence of TEOAE and suppression of TEOAE and BA-EP normal neurological protocol (1<sup>st</sup> evaluation); Behavioral auditory thresholds  $\leq 15$  dBHL, type A tympanometric curve, presence of contralateral acoustic reflexes bilaterally, presence of TEOAE (2<sup>nd</sup> and 3<sup>rd</sup> evaluations); Previously mentioned results, plus LRF  $<20$  dBNA and IPRF  $> 90\%$  (4<sup>th</sup> evaluation);
- Conductive loss: absence of TEOAE, tympanometric type B or C, absence of bilaterally contralateral acoustic reflexes, BAEP with high electrophysiological thresholds by AW and normal by BW (1<sup>st</sup> evaluation); Behavioral auditory thresholds  $\geq 20$  dBNA per AW and  $\leq 15$  dBNA per VO, type B or C tympanometric curve, absence of bilaterally contralateral acoustic reflexes, absence of TEOAE (2<sup>nd</sup> and 3<sup>rd</sup> evaluations); Previously reported, plus RLI equal to or 10 dB above the mean of 0.5, 1 and 2 kHz and IPRF  $> 90\%$  (4<sup>th</sup> evaluation);
- Cochlear loss: absence of TEOAE, type A tympanometric curve, elevated electrophysiological auditory thresholds by AW and BW in the BAEP with a burst tone of 0.5 to 4 kHz (1<sup>st</sup> evaluation); Auditory behavioral thresholds  $\geq 20$  dBNA per AW and BW, tympanometric curve type A, absence of TEOAE (2<sup>nd</sup> and 3<sup>rd</sup> evaluations); Previously cited results, plus LRF equal to or 10 dB above the mean of 0.5, 1 and 2 kHz and IPRF  $<90\%$  (4<sup>th</sup> evaluation);
- Retrocochlear alteration: presence of TEOAE, altered BAEP with absence of waves (auditory neuropathy spectrum) or central alteration (increased interpeaks I-III, III-V or I-V); Absence of suppression of TEOAEs, tympanometric curve type A (1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> evaluations); Results, plus lower than expected RFI in relation to auditory behavioral thresholds (4<sup>th</sup> evaluation).

Statistical analysis was performed using the IBM SPSS Statistics program (version 23.0) and sought a difference between groups regarding the occurrence of auditory alterations using Pearson's chi-square test and Fisher's exact test. The level of significance was set at 5% ( $p < 0.05$ ).

## RESULTS

The presence of children in the 2<sup>nd</sup> (6 to 9 months), 3<sup>rd</sup> (9 to 24 months) and 4<sup>th</sup> (24 months) evaluations in each group is presented in Table 1. There was no statistically significant difference regarding the presence of children in the evaluations, indicating that both groups were monitored in a similar way.

**Table 1.** Quantity of audiological evaluations per child in each group

Group	Number of evaluations			p-value
	2	3	4	
	n (%)	n (%)	n (%)	
SG	24 (51,1)	18 (54,5)	6 (54,5)	0,956
CG	23 (48,9)	15 (45,5)	5 (45,5)	
Total	47 (100)	33 (100)	11 (100)	

Pearson's chi-square test

SG: study group

CG: control group

The comparisons between the groups in relation to the results of the auditory evaluations obtained from the children who attended two, three and four evaluations are presented in Tables 2, 3 and 4, respectively.

The groups did not differ in relation to the occurrence of conductive and cochlear losses when compared to children with the same number of hearing evaluations in each group. There was a tendency of the GE to present a higher occurrence of retrocochlear alterations in the children who attended two evaluations.

**Table 2.** Occurrence of hearing changes in children present to two evaluations

Result of audiological evaluation	Group		p-value
	CG	GE	
	n (%)	n (%)	
Normal	15 (65,2)	15 (62,5)	-
Conductive	6 (26,1)	3 (12,5)	0,464
Cochlear	2 (8,7)	1 (4,2)	> 0,999
Retrocochlear	0 (0,0)	5 (20,8)	0,057#
Total	23 (100)	24 (100)	

Fisher's exact test.

SG: study group

CG: control group

# - Value with a tendency to statistical significance at 5% ( $p < 0,05$ )

**Table 3.** Occurrence of hearing changes in children present to three evaluations

Result of audiological evaluation	Group		p-value
	CG	SG	
	n (%)	n (%)	
Normal	7 (46,7)	10 (55,6)	-
Conductive	8 (53,3)	6 (33,3)	0,479 <sup>a</sup>
Cochlear	0 (0,0)	0 (0,0)	IC
Retrocochlear	0 (0,0)	2 (11,1)	0,509 <sup>b</sup>
Total	15 (100)	18 (100)	

Pearson's chi-square test (<sup>a</sup>) and Fisher's exact test (<sup>b</sup>)

SG: study group

CG: control group

IC - Incalculable

**Table 4.** Occurrence of hearing changes in children present to four evaluations

Result of audiological evaluation	Group		p-value
	CG	SG	
	n (%)	n (%)	
Normal	3 (60,0)	2 (33,3)	-
Conductive	2 (40,0)	1 (16,7)	> 0,999
Cochlear	0 (0,0)	0 (0,0)	NC
Retrocochlear	0 (0,0)	3 (50,0)	0,196
Total	5 (100)	6 (100)	

Fisher's exact test  
 SG: study group  
 CG: control group  
 IC – Incalculable

The final audiological diagnosis considering all the evaluations performed in each child in both groups is presented in table 5. There was a difference between the auditory evaluation distributions of the two groups ( $p$ -value = 0.004), with a higher occurrence of retrocochlear alteration in the SG. From the 10 children

diagnosed with retrocochlear alteration, seven presented no TEOAE suppression, two presented an increase of the I-III interpeak in the BAEP, characterizing a low brain stem change, and one presented alteration in both suppression and BAEP. There were no cases of spectrum of auditory neuropathy.

**Table 5.** Occurrence of hearing changes in the total sample

Result of audiological evaluation	Group		p-value
	CG	SG	
	n (%)	n (%)	
Normal	25 (58,1)	27 (56,3)	-
Conductive	16 (37,2)	10 (20,8)	0,338 <sup>a</sup>
Cochlear	2 (4,7)	1 (2,1)	0,611 <sup>b</sup>
Retrocochlear	0 (0,0)	10 (20,8)	0,004 <sup>*b</sup>
Total	43 (100)	48 (100)	

Pearson's chi-square test (<sup>a</sup>) and Fisher's exact test (<sup>b</sup>)  
 \* - Statistically significant value at the level of 5% ( $p < 0,05$ )  
 SG: study group  
 CG: control group

## DISCUSSION

Congenital toxoplasmosis is a potential risk indicator for sensorineural hearing loss<sup>15</sup>. The infection can be detected in the prenatal period by performing the maternal serology and medicated early. All SG children were followed up at the Pediatric Infectology outpatient clinic and were treated for one year with sulfadiazine, pyrimethamine and folinic acid and were referred for audiological evaluation and follow-up in the sector of Children's Audiology.

There was a decrease in the sample number inversely proportional to the number of auditory evaluations, indicating the children's evasion along

the audiological follow-up. This was expected, since evasion is a trend observed in longitudinal studies<sup>11</sup>.

There were conductive losses in all evaluations, with no statistically significant difference between the groups. In the final diagnosis, about 1/3 of the children presented conductive loss, similar to that obtained in the literature<sup>21</sup>. Conductive loss, although transitory, causes fluctuation in hearing resulting from recurrent otitis media, and may cause language/learning problems due to inconsistent auditory input during the critical auditory developmental period.

The groups studied did not differ in relation to the occurrence of cochlear loss. Considering the total sample, cochlear loss occurred in two children (4.7%)

of the group without risk of hearing loss and one child (2.1%) of the study group, diagnosed in the first two evaluations and referred for hearing aid adaptation and speech therapy. The incidence of hearing loss is 1 to 3: 1000 in the general population<sup>15</sup>. The greater occurrence of cochlear loss in the CG of the present study was not expected and may be justified by the reduced number of the sample or by the fact that 50% of the cochlear hearing losses are of genetic origin<sup>22</sup>. The occurrence of cochlear loss in the SG (2.1%) is similar to the result of a study with treated children with congenital toxoplasmosis, which obtained 3.8% of cochlear losses<sup>11</sup>. These results are in contrast to studies conducted in Europe and the United States which, with the same drug therapy used in the present study, observed a reduction of auditory sequelae with early detection and treatment of congenital toxoplasmosis<sup>14,23</sup>.

The main finding of the present study was the high occurrence of retrocochlear alterations in children exposed to toxoplasmosis during pregnancy (20.8%), differing statistically from the control group (0%).

The presence of retrocochlear alterations makes the child with congenital toxoplasmosis, even when treated, at risk for alterations in auditory processing and language. In fact, 29.6% of language alterations were found in children with congenital toxoplasmosis treated early and followed up to three years of age<sup>11</sup>. Thus, the child with congenital toxoplasmosis, even when treated early, needs to be accompanied by a multidisciplinary team throughout its development, in order to detect early changes in auditory processing and language, which may negatively affect school learning.

The retrocochlear alteration in congenital toxoplasmosis could be related to the postnatal inflammatory response of the internal acoustic meatus to the presence of *T. gondii*. Such an immunological reaction would damage the vestibulocochlear nerve, which is found in the internal acoustic meatus, and would justify the greater occurrence of retrocochlear alterations in the SG<sup>24</sup>.

The occurrence of retrocochlear auditory disorders in 20.8% of the SG children in the present study is similar to that found in the literature, between 21.1 and 35.5%<sup>4,11,25</sup>. However, it differed from other studies in which the prevalence found was significantly lower or even zero<sup>14,23,26,27</sup>. This difference is due to the fact that many studies only perform the evaluation of the peripheral auditory system, without including BAEP and suppression of TEOAE. In the present study, the medial

olivocochlear efferent system presented alteration in eight of the 10 children with retrocochlear alterations. Such a system acts on the speech comprehension in the noise, in the selective attention that implies in future alterations of the auditory processing, which would justify to include the evaluation of this structure by means of the suppression of the TEOAE.

In addition, the literature points out the methodological differences between the studies, mainly in relation to the selection of the audiological evaluation tests, diagnosis and early treatment; and periodicity of the treatment performed as the cause of the discrepancies between the results of the studies<sup>28</sup>. The main differences also occur in relation to audiological monitoring: many studies do not follow the cases periodically. A study conducted in Brazil followed 174 children with toxoplasmosis for up to 36 months, obtaining results similar to those described in the present study<sup>11</sup>.

The occurrence of retrocochlear alterations in children exposed to toxoplasmosis during pregnancy indicates the need to evaluate the peripheral and central auditory system in this population as well as monitoring the development of hearing and language skills.

A limitation of this study due to its clinical and retrospective nature was the lack of application of all procedures in all children, considering the service flow chart of the service in which the study was performed (Figures 1 to 3). Another limitation of this study was the difficulty of keeping track of all children up to two years of age due to circumvention.

## CONCLUSION

Children exposed to toxoplasmosis during gestation did not differ from those not exposed in relation to cochlear and conductive hearing loss. However, they had a higher occurrence of retrocochlear alterations.

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