

Impact of exposure to maternal syphilis on the newborn's auditory system

Impacto da exposição à sífilis materna no sistema auditivo de recém-nascidos

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ABSTRACT

Purpose: To evaluate the audiological findings of newborns exposed to maternal syphilis, properly treated during pregnancy. **Methods:** This was a single, non-concurrent cohort study conducted in a public hospital. The sample included newborns whose mothers had positive syphilis serology and who underwent adequate treatment during pregnancy, composing the study group, and newborns without risk indicators for hearing loss, as a comparison group. **Results:** Ninety newborns participated in the study, 41 were the study group and 49 were the comparison group. In the transient evoked otoacoustic emissions test, all newborns showed a bilateral response, and when comparing the amplitudes of responses in the 3.0 kHz, 3.5 kHz and 4.0 kHz frequency bands, a smaller amplitude of response in the studied group with a statistically significant difference for the frequency of 4 kHz on the right was observed. An analysis of the response of the brainstem auditory evoked potential test showed no asymmetry of response between the ears that suggest a retrocochlear alteration, nor difference in the values of absolute latencies or interpeak intervals between groups. **Conclusion:** The electroacoustic responses were slightly lower in newborns exposed to maternal syphilis, whereas their electrophysiological responses were similar to those found in the population at low risk for hearing loss.

Keywords: Syphilis, Congenital; Syphilis; Hearing; Electrophysiology; Infant

RESUMO

Objetivo: Avaliar os achados audiológicos de recém-nascidos expostos à sífilis materna, tratada adequadamente na gestação. **Métodos:** Estudo de coorte única não concorrente, realizado em um hospital público. Fizeram parte da amostra recém-nascidos filhos de mães que apresentaram sorologia positiva para sífilis e que realizaram o tratamento adequado durante a gestação, compondo o grupo estudo, e recém-nascidos sem indicadores de risco para deficiência auditiva, grupo comparação. **Resultados:** Participaram do estudo 90 recém-nascidos, sendo 41 do grupo estudo e 49 do grupo comparação. No exame de emissões otoacústicas por estímulo transiente, todos apresentaram presença de resposta bilateralmente e, na comparação das amplitudes de respostas nas bandas de frequências de 3,0 kHz, 3,5 kHz e 4,0 kHz observou-se menor amplitude de resposta no grupo exposto, com diferença estatisticamente significativa para a frequência de 4 kHz à direita. Na análise das respostas do exame de potencial evocado auditivo de tronco encefálico, não se observou assimetria de resposta entre as orelhas que sugerisse alteração retrococlear e nem diferenças nos valores das latências absolutas ou intervalos interpicos, entre os grupos. **Conclusão:** As respostas eletroacústicas foram discretamente inferiores nos recém-nascidos exposto à sífilis materna, enquanto que as respostas eletrofisiológicas foram semelhantes às encontradas na população de baixo risco para deficiência auditiva.

Palavras-chave: Sífilis congênita; Sífilis; Audição; Eletrofisiologia; Lactente

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INTRODUCTION

The first years of life are essential to acquire and develop auditory and language skills, as this is when the maturation process takes place in both the auditory system and the neuronal plasticity of the auditory pathway. Hence, every audiological change must be early diagnosed to minimize its negative impacts on the person's life⁽¹⁾.

Exposure to neonatal syphilis is considered a risk indicator for hearing loss because it affects the inner ear and causes periostitis, atrophy of the organ of Corti, and endolymphatic hydrops in the membranous labyrinth⁽¹⁻³⁾. These changes can especially affect the spiral ganglion and fibers of the eighth cranial nerve, causing late-onset, progressive sensorineural hearing loss^(2,3).

Congenital syphilis was practically eradicated with the advent of penicillin. However, its incidence has been progressively increasing worldwide over the last 10 years^(4,5). In 2018, the detection rate of syphilis in pregnant women in Brazil was 21.4 per 1,000 live births, while the incidence of congenital syphilis was 9.0 per 1,000 live births⁽⁶⁾.

We must point out that, despite the mother being infected, the fetus will not necessarily be contaminated – which explains the difference between the number of pregnant women with syphilis and the number of newborns with congenital syphilis. Such contamination depends on whether there was transplacental hematogenous dissemination of *Treponema pallidum* to the child (vertical transmission), which would then cause congenital syphilis⁽⁴⁻⁷⁾.

The global increase in cases of syphilis is mostly ascribed to the lack of condom use, indiscriminate drug use, and diversity of sexual partners. In the same perspective, we also notice an increase in the previous detection rates of syphilis in pregnant women, which points to the use of more sensitive and effective criteria to early identify maternal syphilis in prenatal care. This enables early treatment and avoids as much as possible the transplacental contamination of the fetus with *Treponema pallidum*^(8,9).

If syphilis is not treated or is inadequately treated during pregnancy, it may lead to congenital syphilis. However, the newborns may not have symptoms, and some infected newborns go through their entire lives without developing any problems⁽¹⁰⁾. In the case of symptomatic newborns, the manifestations of congenital syphilis are classified as either early- or late-onset^(3,10).

Early-onset congenital syphilis appears up to the second year of life, although more than half of these children are asymptomatic at birth^(6,11). On the other hand, newborns may have various complications, such as prematurity, low weight, jaundice, anemia, and/or hearing deficit⁽¹¹⁾.

Late-onset congenital syphilis, in its turn, appears after the second year of life, with rare clinical manifestations, usually associated with the Hutchinson's triad (malformed teeth [known as Hutchinson's teeth], interstitial keratitis, and eighth nerve lesion)⁽³⁾. However, since the advent of antibiotics, hearing loss has been the only symptom⁽²⁾.

Thus, all pregnant women diagnosed with syphilis must be treated to avoid congenital syphilis, taking benzathine penicillin in different doses, according to the phase of maternal infection^(6,11,12). Data from the Ministry of Health⁽⁶⁾ show that the adequate treatment of gestational syphilis requires the recommended medication, with titer decrease throughout the follow-up, which

is verified with nontreponemal tests. This intervention must be conducted up to 30 days before childbirth^(6,11,12).

Even with an effective maternal syphilis treatment, newborns exposed to syphilis undergo physical examinations and serum tests soon after birth^(6,12). And even with no evidence of transmission, asymptomatic newborns whose mothers had been submitted to an adequate intervention during pregnancy must be followed up until the passively acquired treponemal antibodies disappear which only occurs by the 18 months of life^(6,11,12).

From the audiological standpoint, all newborns exposed to maternal syphilis, regardless of whether the mothers had adequate treatment, must undergo audiological assessment and be monitored twice a year until they are two years old and perform treponemal tests after they are 18 months old^(6,11,12). However, we still need to find what auditory impairment may be caused by exposure to maternal syphilis, especially when the mother is adequately treated for the disease during the pregnancy^(13,14).

Hence, the objective of this study was to evaluate the audiological findings of newborns exposed to maternal syphilis.

METHOD

This study was approved by the Research Ethics Committee of the School of Medicine of Botucatu at *Universidade Estadual Paulista "Júlio de Mesquita Filho"* (São Paulo State University – UNESP) (process no. 1.759.185). The parents or legal guardians who agreed to participate in the study signed the informed consent form.

This was a nonconcurrent cohort study conducted at a public hospital from January 2017 to March 2019.

Subjects

The sample comprised newborns exposed to maternal syphilis (study group) and newborns not exposed to syphilis (comparison group). Both groups were similar regarding gestational age, birth weight, and age at post-hospital discharge hearing assessment.

The participants were classified as follows:

- Group exposed to maternal syphilis: newborns whose mothers had been diagnosed with syphilis during pregnancy. They were submitted to complete benzathine penicillin treatment, according to the stage of the disease. The nontreponemal tests revealed a decrease in titers, and the treatment ended, at the latest, 30 days before childbirth^(6,11,12). The newborns had reactive nontreponemal tests (Venereal Disease Research Laboratory – VDRL), with lower titer levels than their mothers' and non-reactive liquor VDRL;
- Comparison group: newborns with no risk indicators for hearing loss and non-reactive VDRL, whose mothers received adequate prenatal care, with no report of gestational syphilis.

The inclusion criteria for both groups were as follows: having been born at the study site and undergone, in a single session, examination of both the transient evoked otoacoustic emissions (TEOAE) and brainstem auditory evoked potentials (BAEP) with click stimulus (neurodiagnostic protocol).

The exclusion criteria for both groups were as follows: prematurity, mothers using drugs during pregnancy, and presence of any other risk indicator for hearing loss, according to the Joint Committee on Infant Hearing (2019)⁽¹⁾.

Order of the assessments

Technical specifications of the otoacoustic emissions

We recorded the responses of both ears in the TEOAE examination, while the newborn was naturally sleeping in a silent room. If the newborn woke up during the examination, the parent/guardian was asked to put them back to sleep. The equipment we used in all the assessments was the OtoRead/Interacoustics, whose probe, with a microphone attached, was introduced into the external acoustic meatus. The pass parameter was established as an analysis criterion with a standardized protocol, using click stimulus at 83 dB SPL, assessing six frequency bands between 1.5 kHz and 4.0 kHz. For the equipment to automatically consider the exam as pass, the following criteria had to be met: 6 dB or more response amplitude in relation to noise amplitude in at least three frequency bands.

Thus, after printing the recordings, we assessed the response amplitudes at 3.0 kHz, 3.5 kHz, and 4.0 kHz, as they were the most frequent ones. Also, the pass criteria used in the service give priority to response present in three consecutive frequency bands, including 4.0 kHz⁽¹⁵⁾.

Technical specifications of neurodiagnostic click-BAEP

The equipment used for the click-BAEP was the ICS Charter (GN Otometrics/Denmark). After cleaning the skin with an abrasive substance (Nuprep[®]), the surface electrodes, brand Neuroline[®], were positioned at specific sites. The active electrode was fixed on the forehead (Fz), the reference electrodes were fixed in the mastoid region (M1 and M2), and the ground electrode was fixed on the forehead. The stimulus was presented via ER 3A insert earphones, with monoaural filtered clicks (band-pass filter, high-pass at 100 Hz and low-pass at 3000 Hz), lasting 100 μ s, with rarefaction polarity. We presented 2,048 clicks in 15 ms analysis time, repeated to confirm wave reproducibility. Electrode impedance was kept below 3 kOhms. The stimulus repetition rate was set at 21.1 clicks per second (c/s) in each ear, at 80 dB nHL. The main parameters assessed in neurodiagnostic

click-BAEP were the absolute latencies of waves I, III, and V and the latencies of the interpeak intervals I-III, III-V, and I-V for both ears, as well as the interaural difference.

A speech-language-hearing pathologist specialized in audiology and experienced in electrophysiological assessments in children marked the waves and analyzed the recordings.

Statistics

We compared the TEOAE response amplitudes and the click-BAEP latencies between newborns with and without exposure to maternal syphilis by fitting multiple linear regression models, considering the effects of sex, gestational age, and birth weight. The associations were considered statistically significant when $p < 0.05$. The analysis was made in the SPSS software, v 21.0.

RESULTS

A total of 90 newborns participated in the study: 41 in the group exposed to maternal syphilis and 49 in the comparison group. All of them underwent the TEOAE and click-BAEP examinations when they were between zero and one month old. The sample characterization data regarding sex, gestational age, and birth weight are shown in Table 1.

In the TEOAE examination, all the newborns in both groups reached the pass result, which indicates the bilateral presence of response. Hence, we compared both groups' response amplitudes at 3.0 kHz, 3.5 kHz, and 4.0 kHz and observed an increase in response amplitude in both ears in the comparison group, with a statistically significant difference at 4.0 kHz in the right ear ($p < 0.028$) (Table 2).

The analysis of the click-BAEP examination did not reveal response asymmetry between the ears in either group suggestive of retrocochlear change. Also, the comparison of the parameters assessed in this examination between the groups did not show a difference in the absolute latency values of waves I, III, and V and interpeak intervals I-III, III-V, and I-V for both ears (Tables 3 and 4).

DISCUSSION

The objective of this study was to verify the audiological findings in newborns exposed to gestational syphilis, whose mothers had undergone complete treatment for the disease.

Table 1. Sample characterization regarding sex, gestational age, and birth weight

Groups/Variables	Comparison group (n=49) n (%)	Syphilis group (n=41) n (%)	Total 90
Females	28 (57)	19 (46)	47
Males	21 (43)	22 (54)	43
Gestational age ^a	39 s (min. 37s; max. 41s)	39s (min. 37s; max. 41s)	
Birth weight ^a	3,267 kg (min. 2,165; max. 4,585)	3,275 kg (min. 1,800; max. 4,265)	

^asummary in median, minimum (min.) and maximum (max.) values of gestational age and birth weight, in weeks (s) and kilograms (kg)

Subtitle: n = number of subjects; % = percentage

Table 2. Comparison between the groups regarding the amplitudes of the transient evoked otoacoustic emissions

Frequencies	Comparison group		Syphilis group	p-value
	Mean (SD)		Mean (SD)	
RE 3.0 kHz	14.9 dB (± 6.1)		13.0 dB (± 5.8)	0.139
RE 3.5 kHz	16.0 dB (± 6.0)		15.3 dB (± 5.5)	0.519
RE 4.0 kHz	14.9 dB (± 6.0)		12.3 dB (± 4.9)	0.028
LE 3.0 kHz	13.7 dB (± 6.0)		13.1 dB (± 5.3)	0.628
LE 3.5 kHz	16.0 dB (± 5.8)		14.1 dB (± 6.1)	0.166
LE 4.0 kHz	14.5 dB (± 5.8)		13.4 dB (± 5.3)	0.473

p-value regarding the comparison between the groups ($p < 0.05$; multiple linear regression models)

Subtitle: RE = right ear; LE = left ear; SD = standard deviation

Table 3. Comparison of the latencies of the brainstem auditory evoked potentials between the groups

	BAEP	Comparison group		Syphilis group	p-value
		Mean (SD)		Mean (SD)	
Right ear	I	1.6 ms (± 0.1)		1.6 ms (± 0.1)	0.264
	III	4.4 ms (± 0.2)		4.4 ms (± 0.2)	0.852
	V	6.6 ms (± 0.3)		6.7 ms (± 0.3)	0.405
	I-III	2.8 ms (± 0.2)		2.8 ms (± 0.2)	0.406
	III-V	2.2 ms (± 0.2)		2.3 ms (± 0.2)	0.069
	I-V	5.1 ms (± 0.5)		5.1 ms (± 0.3)	0.637

p-value regarding the comparison between the groups ($p < 0.05$; multiple linear regression models)

Subtitle: BAEP = brainstem auditory evoked potential; SD = standard deviation; ms = milliseconds; I, III, and V = absolute latencies of the waves; I-III, III-V, and I-V = interpeak intervals

Table 4. Comparison of the latencies of the brainstem auditory evoked potential between the groups

	BAEP	Comparison group		Syphilis group	p-value
		Mean (SD)		Mean (SD)	
Left ear	I	1.6 ms (± 0.1)		1.6 ms (± 0.1)	0.286
	III	4.4 ms (± 0.2)		4.4 ms (± 0.2)	0.954
	V	6.6 ms (± 0.2)		6.7 ms (± 0.3)	0.364
	I-III	2.8 ms (± 0.2)		2.8 ms (± 0.2)	0.562
	III-V	2.2 ms (± 0.2)		2.3 ms (± 0.2)	0.084
	I-V	5.1 ms (± 0.4)		5.1 ms (± 0.3)	0.946

p-value regarding the comparison between the groups ($p < 0.05$; multiple linear regression models)

Subtitle: BAEP = brainstem auditory evoked potential; SD = standard deviation; ms = milliseconds; I, III, and V = absolute latency of the waves; I-III, III-V, and I-V = interpeak intervals

Even when the mother is adequately treated for syphilis during pregnancy, the protocols recommend that these newborns be submitted to electroacoustic and electrophysiological examinations soon after birth, as well as long-term follow-up of the auditory pathway development^(6,11,12,15).

Thus, this study sought to analyze the findings of the TEOAE and click-BAEP examinations between newborns exposed to maternal syphilis and newborns without risk indicators, comparing them and verifying possible early audiological changes in the group exposed to this condition.

Since all the newborns had a pass result (i.e., presence of bilateral response in the TEOAE examination), we analyzed the TEOAE response amplitudes to obtain additional information on the functioning of the cochlear outer hair cells⁽¹⁶⁾. The result revealed that the group exposed to maternal syphilis generally had lower response amplitude, though with a statistically significant difference only at 4.0 kHz in the right ear. This shows an inferior performance in this population, which can be confirmed in studies with larger samples and a cohort design.

Moreover, further investigation using distortion-product otoacoustic evoked emissions to verify the performance of the cochlear outer hair cells can provide additional information for the analysis of frequencies higher than 4.0 kHz and up to 10 kHz, concentrated on the basal region of the cochlea.

In this study, we only analyzed the TEOAE amplitude per frequency band. However, future studies with complementary analyses of other parameters intrinsic to this final result, such as analysis of noise and response amplitude, can contribute to a better knowledge of the difference we observed.

The TEOAE amplitude analysis was approached in various pieces of research, showing that it is influenced by other risk indicators, including hyperbilirubinemia, ototoxic medication, and perinatal asphyxia⁽¹⁷⁻¹⁹⁾.

Response amplitude verification makes it possible to refine the criteria for normality used when interpreting TEOAE results. Hence, lower response amplitudes in this examination can reflect a pathological cochlear finding. However, the clinical relevance of this finding is not yet clear⁽¹⁶⁾. Consequently, further

investigation is needed to explain the phenomenon found in the newborn exposed to maternal syphilis.

Regarding the neurodiagnostic click-BAEP investigation, we did not find differences in the latencies of waves I, III, and V or interpeak intervals I-III, III-V, and I-V. Therefore, we can state that there were no differences between the groups in the sample studied. Even though wave amplitude is not a parameter analyzed in clinical routine, its measure can provide additional information to compare with the control group in future research. These data agree with a study conducted by Gleich et al. in 1994⁽¹³⁾, who likewise did not find in newborns a causal relationship between serologic evidence of syphilis and BAEP change.

Therefore, the neural synchrony of the brainstem auditory structures was not affected in the short run by exposure to maternal syphilis when they had been adequately treated^(20,21).

We must highlight that congenital syphilis is often seen in generalist terms – i.e., all newborns whose mothers had syphilis are considered disease carriers. Consequently, they are not careful to identify the newborns actually susceptible to having congenital syphilis and do not differ the form of treating this condition in prenatal care or the gestational phase when the contamination took place.

Therefore, professionals who work in programs for the early identification of hearing loss in children must assess, together with the medical team, the treatment conditions throughout the pregnancy. They must also assess the serum tests of both the mother and her asymptomatic baby at the moment of the audiological assessment to better interpret the results of the audiological tests throughout their follow-up.

This study presented unprecedented results regarding the electroacoustic and electrophysiological findings, suggesting that, in these people, the cochlea was more fragile due to the condition. This was shown with the inferior, though discrete performance in the TEOAE response amplitude. As for the neural activity, assessed with the click-BAEP, we did not find any differences between the groups. Thus, we emphasize the need for auditory development follow-up to identify whether there are long-term audiological changes. We also highlight the importance of research with the same topic, using a larger sample and data from their auditory follow-up.

CONCLUSION

The TEOAE response amplitude of newborns exposed to maternal syphilis, whose mothers had been adequately treated during pregnancy, was lower, especially at 4.0 kHz, in the right ear. On the other hand, the electrophysiological responses with click-BAEP were similar to those found in the population at low risk of hearing loss.

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