

The Relationship Between the Presence of Severe Acute Respiratory Syndrome-Coronavirus-2 during Pregnancy and Neonatal Hearing Loss

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ABSTRACT

Introduction: In this study, we investigated the maternal severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection's effect on newborn hearing loss.

Methods: Thirty-nine newborns whose mother's SARS-CoV-2 real time-polymerase chain reaction test was positive at the time of parturition were included in this study. Another 39 newborns who were born from healthy pregnancies were selected as the control group. Neonates with risk factors for hearing loss determined by the American Academy of Pediatrics Joint Committee on Infant Hearing 2007 and those with ear pathology were excluded. The newborn hearing screening was done with auditory brainstem response (ABR) test. Second ABR test (ABR-2) was performed on newborns who failed the 1st test (ABR-1). The third ABR test (ABR-3) was performed on newborns who failed the second ABR test (ABR-2). The screening results were analyzed statistically.

Results: In the control group, a total of 6 (15.4%) newborns failed ABR-1, five newborns in one ear (3 right, 2 left), and one newborn in both ears. In the study group, a total of 14 (35.9%) newborns failed ABR-1, 11 newborns from both ears and 3 (2 right, 1 left) newborns from one ear. ABR-1 results were significantly worse in the study group's neonates ($p=0.038$). In addition, the rate of involvement of both ears was higher in the study group ($p=0.018$; $p<0.05$). 1 (16.7%) newborn in the control group and 2 (14.3%) newborns in the study group failed the ABR-2 in both ears. There was no statistically significant difference according to the ABR-2 test ($p=0.681$; $p>0.05$). All babies passed the ABR-3.

Conclusion: There was a significant relationship between neonatal hearing loss and maternal SARS-CoV-2 infection. This hearing loss is usually bilateral and temporary.

Keywords: SARS-CoV-2, hearing loss, maternal-fetal relations, neonatal screening*, auditory brainstem response

Introduction

Coronavirus disease-2019 (COVID-19), emerged in the Wuhan district of China in December 2019, was declared as a pandemic by the World Health Organization (WHO) (1). As of 26 July 2021, 194,835,316 approved cases and 4,175,129 deaths related to COVID-19 have been reported (2). COVID-19 is caused by a new member of the Coronaviridae family identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is a single-stranded RNA virus which affects the entire population and pregnant women (3,4).

Angiotensin-converting enzyme (ACE) plays a crucial role in the renin-angiotensin system. ACE-2 is a transmembrane peptidase that is a homologue of ACE and presents in the heart, lungs, kidney, intestine, and other organs (5,6). ACE-2 also functions as an intracellular inlet point for SARS-CoV and SARS-CoV-2 (7).

Previous studies reported that, ACE-2 production increases in the kidneys, uterus and placenta during pregnancy, also this enzyme presents in the fetal lung and brain tissue (8). Although pregnancy is not an increased risk of contracting SARS-CoV-2 infection, it has been reported that SARS-CoV-2 infection is more severe in pregnant women. The need for intensive care and invasive ventilation and mortality rates were higher in pregnant women (9,10). A study conducted on mice showed that the virus involves the uterus and placenta during pregnancy (11). Studies that investigated the transmission of SARS-CoV-2 from pregnant mothers to their newborn reported different results. However, Wang et al. (12) reported a SARS-CoV-2 infected neonate whose COVID-19 positivity was confirmed by pharyngeal swab PCR-36 hours after birth, born from a COVID-19-positive pregnant.



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It is known that intrauterine infections can cause congenital or acquired, acute or late-onset, unilateral or bilateral, conductive or sensorineural, permanent or temporary types of hearing loss. Various pathogens such as toxoplasma, rubella, cytomegalovirus (CMV), herpes, and syphilis can cause congenital sensorineural hearing loss (SHL) after intrauterine infection (13). Viruses, the most common cause of non-genetic congenital hearing loss, can damage hearing cells, auditory organs, auditory pathways, and auditory centers by direct or host-mediated immune reactions (14).

The auditory brainstem response (ABR) test is an essential diagnostic tool for detecting audiometric thresholds in infants and other patients for whose hearing thresholds are difficult or impossible to determine. The ABR test can be performed with various stimuli. While ABR with click stimulus is the gold standard method in newborn hearing screenings, tone burst ABR has become the gold standard for estimating frequency-specific hearing thresholds in infants under five to six months (15,16).

There are limited studies in the literature about congenital hearing loss associated with SARS-CoV-2, which is shown to be transmitted vertically, is neuroinvasive and neurodegenerative, and has a relationship with SHL in adults (17,18). In this study, we investigated the presence and features of SHL in newborns of COVID-19 infected pregnant.

Methods

This prospective controlled study was conducted at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Obstetrics and Gynecology between January 2021-July 2021 on pregnant women and their newborns with the approval of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02-67990, date: 07/04/2021).

Populations, Inclusion and Exclusion Criteria

All pregnant women who were included in this study, were applied İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Obstetrics and Gynecology for delivery. As an institutional rule, all patients were tested for SARS-CoV-2 with PCR before hospital administration. Pregnant women whose naso/oropharyngeal swab PCR results during the hospitalization procedure were positive for COVID-19 and their newborns were included in the study as the study group. Healthy pregnant women and their newborns were randomly chosen as the control group.

Pregnant women who have a chronic disease, multiple pregnancies, gestational diabetes, pregnancy-related disease such as preeclampsia, symptoms of COVID-19 (such as anosmia, myalgia, cough, dyspnea), previous history of COVID-19, received COVID-19 treatment, did not accept cesarean delivery and had insufficient mental capacity was excluded from the study. In addition, neonates who have risk factors for hearing loss as specified by the American Academy of Pediatrics Joint Committee on Infant Hearing 2007; such as hypoxia, a family history of hereditary SHL, prenatal infection such as rubella, craniofacial abnormalities, parturition weight under 1500 g, hyperbilirubinemia that requires exchange transfusion, ototoxic treatments, intensive care unit stay more than five days; APGAR scores of 0-4 at the 1st or 0-6 at

the 5th minute of parturition and stigmata or other findings associated with a congenital syndrome and neonates with ear pathologies were excluded (19).

Sample Size and Sampling Technique

The minimal subject size was calculated according to the study by Celik et al. (18). The minimal subject size was 78 with 80% confidence interval and 5% tolerable error assumptions. All COVID-19-positive pregnant women (study group) who met the study criteria during the study period were included in this study. An informed consent form was obtained from all subjects.

Procedures and Data Collection

Study Design

Day 0 (birth): Combined naso/oropharyngeal swabs were collected from pregnant women before delivery by the same physician. To reduce the risk of transmission, COVID-19 PCR-positive pregnant women's delivery were performed by cesarean section within the first 24 hours after their admission. Pregnant women whose COVID-19 PCR tests were negative and delivered by cesarean section were included as a control group to ensure the standardization.

Day 1 (initial hearing evaluation): Neonates that included in this study were taken for ontological examination 24 hours after birth to the same institution's otorhinolaryngology department and audiology department. Automates Auditory Brainstem Response (AABR) screening test results of neonates with normal ear examination and tympanogram (type A) were included in the study. Newborns who passed the AABR test (ABR-1) considered having normal hearing. Newborns who failed their AABR test (ABR-1) were called 10 days later for the second evaluation.

Day 10 (second hearing evaluation): AABR test (ABR-2) was performed by the same specialist audiologist. Newborns who passed the AABR test (ABR-2) considered having normal hearing. Newborns who failed their AABR test (ABR-2) were called 20 days later for a third evaluation.

Day 30 (third hearing evaluation): AABR test (ABR-3) was performed by the same specialist audiologist. Newborns who passed the AABR test (ABR-3) considered having normal hearing.

Collection of Swab Samples and PCR Tests

The swabs were taken from the oropharynx and nasopharynx, respectively, with the same stick by an expert otorhinolaryngologist. RT-qPCR kit (Bio Speedy, Turkey) targeting the RNA-dependent RNA polymerase (RdRp) gene was used to detect SARS-CoV-2.

Hearing Screening Test

Hearing screening tests were performed using AABR (Madsen Accuscreen Pro, GN Otometrics, Denmark) device after birth in the institution's audiology department by the same, 10 years experienced, audiologist. According to the Republic of Turkey Ministry of Health's Neonatal Hearing Screening Protocol, the first hearing screening test must be performed within the first 72 hours after birth before discharge from hospital. The second ABR test was performed within 7-15 days after delivery, and the third ABR test was completed within 15-30 days (before

the 30th day). All tests were carried out in a soundproof room with a noise value not exceeding 35 dbA (20). The neonates with normal type A tympanogram and acoustic reflex test who failed the AABR tests were considered to have SHL and referred for further evaluation.

Statistical Analysis

The minimal subject size was estimated using the G* Power program version 3.1 (21). The statistical analysis was performed with SPSS 22 (IBM SPSS Statistics, USA). Normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov and Levene's tests, respectively. The comparisons of two independent groups were performed using the Mann-Whitney U test and chi-square test or Fisher's exact test. Hearing screening results were compared with the chi-square test between the neonates whose mothers' COVID-19 PCR was positive and neonates whose mothers' COVID-19 PCR was negative. The statistical significance level was set as $p < 0.05$.

Results

Thirty-nine SARS-CoV-2 PCR-positive pregnant women and 39 healthy pregnant women were included in the study. No deaths were observed in the pregnant women and their babies included in the study. The mean age of the COVID-19-negative pregnant women (group 1) included in the study was 27.77 ± 3.55 (minimum: 22; maximum: 34) years, while the mean age of the COVID-19-positive group (group 2) was 28.53 ± 3.68 (minimum: 22; maximum: 36) years. The mean weeks of delivery were 38.43 ± 1.14 (minimum: 28; maximum: 41) and 37.77 ± 2.61 (minimum: 36; maximum: 41), respectively. The birth weights of the newborns were 3407.56 ± 610.98 gr (minimum: 2650 gr; maximum: 4610 gr) and 3504.36 ± 408.6 gr (minimum: 2225 gr; maximum: 3900 gr), respectively. The pregnant women included in the study and newborns of these pregnant women were statistically similar according to their demographic characteristics ($p < 0.05$) (Table 1).

In the control group, 6 of 39 (15.4%) newborns; five newborns in one ear (3 right, 2 left) and one newborn in both ears failed the first ABR test (ABR-1). In the study group, 14 of 39 (35.9%) newborns; 11 newborns from both ears and 3 (2 right, 1 left) newborns from one ear, failed ABR-1. According to the ABR-1, the number of newborns who failed the test in the study group was statistically significantly higher ($p = 0.038$; $p < 0.05$) (Table 2). In addition, the number of newborns who failed the ABR-1 test in both ears was significantly higher in the study group ($p = 0.018$; $p < 0.05$) (Table 3).

In the second ABR test (ABR-2) performed on newborns who could not pass the first ABR-1 after 10 days. One newborn (16.7%) in the control

group and 2 newborns (14.3%) in the study group could not pass the test in both ears. According to the ABR-2, no statistically significant difference was found between the groups ($p = 0.681$; $p > 0.05$). The third ABR test (ABR-3) was performed on babies who could not pass the second ABR test 20 days later and all babies passed ABR-3.

Discussion

In this study, the rate of failing the ABR-1 test was found to be statistically significantly higher in newborns of pregnant women with COVID-19 compared to newborns of healthy pregnant women. In addition, the rate of failing the ABR-1 test bilaterally was statistically significantly higher in newborns of pregnant women with COVID-19 compared with newborns of healthy pregnant women. However, it was found that this difference disappeared in the second and third control ABR tests performed on those who did not pass the test. The data obtained in our study showed that temporary SHL developed in newborns of pregnant women with COVID-19.

Viral infections, which have a definite relationship with congenital SHL, are (toxoplasmosis, rubella, CMV, herpes, and syphilis) infections, especially CMV (22-25). It is known that the vertical transmission of SARS-CoV-2 infection, which was declared a pandemic by the WHO in 2019, is low in pregnant women (26,27). There has been no study in the literature aimed at isolating the virus in the ear of the fetus. However, the locations where the virus is isolated in adults were the cerebrospinal fluid, middle ear, and mastoid bone, which were anatomically close to the inner ear and auditory tract (28-30). In addition, there are findings of extensive brain involvement in autopsy studies in COVID-19 patients (31,32). This situation led to the hypothesize that the inner ear may be affected by COVID-19 and that this virus, which can affect the inner ear, may develop SHL in newborns of pregnant women with COVID-19.

There are two studies in the literature examining the presence of SHL in babies of pregnant women with COVID-19 (17,18). In a retrospective study by Alan and Alan (17), babies of healthy pregnant women and babies of 236 pregnant women infected with SARS-CoV-2 were evaluated with the ABR test, and the rate of SHL in the first ABR was statistically significantly higher in the babies of pregnant women who had COVID-19. However, this difference disappeared in the second ABR test performed on newborns (17). The rate of failing in the first ABR was found to be statistically significantly higher in pregnant women who had COVID-19 in the second trimester compared in those who had it in the third trimester (66.6% and 38.7%, respectively; $p = 0.014$). In their study, the period of infection and the symptoms of the disease of mothers who had COVID-19 infection differ. In addition, there is no

Table 1. Examination of the characteristics of the subjects

Parameter		COVID-19 (-) pregnant (control group)	COVID-19 (+) pregnant (study group)	p
Maternal age		27.77 ± 3.55 (28)	28.53 ± 3.68 (28)	0.399*
Birth week		38.43 ± 1.14 (38)	37.77 ± 2.61 (38)	0.413*
Birth weight		3407.56 ± 610.98 (3420)	3504.36 ± 408.62 (3500)	0.384*
Gender	Male	24 (61.5%)	22 (56.4%)	0.645**
	Female	15 (38.5%)	17 (43.6%)	

*: Mann-Whitney U test ($p > 0.05$), **: Pearson chi-square ($p > 0.05$). COVID-19: Coronavirus disease-2019

Table 2. Evaluation of first ABR test results

First ABR test	COVID-19 (-)	COVID-19 (+)	p
ABR pass	33 (84.6%)	25 (64.1%)	0.038*
ABR refer	6 (15.4%)	14 (35.9%)	

*Pearson chi-square test, value: 4.303; p<0.05. COVID-19: Coronavirus disease-2019, ABR: Auditory brainstem response

Table 3. Evaluation of affected ear laterality of newborns who did not pass the test

Affected ear	COVID-19 (-)	COVID-19 (+)	p
Unilateral	3 (21.4%)	5 (83.3%)	0.018*
Bilateral	11 (78.6%)	1 (16.7%)	

*Fisher's exact test (p<0.05), Coronavirus disease-2019

standardization in the treatment of pregnant women with COVID-19, and 25.4% of the pregnant women included in their study were given hydroxychloroquine, which was reported to be ototoxic and may cause malformation in newborns when used during pregnancy (33,34). In a cross-sectional study by Celik et al. (18), the Transient Evoked Otoacoustic Emissions (TEOAE) test was performed on the babies of 73 healthy and COVID-19-infected pregnant women who passed the bilateral ABR test before and hidden SHL was investigated. As a result of the study, SHL at high frequencies (3-4 kHz) was found in the babies of pregnant women with COVID-19. It has been found that when the contralateral ear is suppressed, SHL in babies with COVID-19 becomes more pronounced and all frequencies are affected. High-frequency SHL in these infants has been associated with the efferent system involvement. However, there was no correlation between the SHL detected in these babies and pregnancy trimesters. In accordance with the study of Alan and Alan (17), this study also differs in terms of the duration of COVID-19 infection and the patients' symptoms (18). When both studies are evaluated together, the SHL caused by COVID-19 infection is temporary, according to the ABR test. This SHL is especially high frequencies according to the TEOAE test results.

Unlike these studies mentioned, the standardization of this study is unique. The pregnant women who were asymptomatic at the time of admission and had a positive COVID-19 PCR test were included in our prospective study for standardization since the severity of the COVID-19 infection is closely related to the symptoms. In addition, no COVID-19 treatment was given to the pregnant women before delivery, and all pregnant women in the study and control groups were delivered by cesarean section to prevent the newborns from being affected by the delivery method and to minimize the risk of transmission to healthcare personnel.

The mechanism of development of SHL after viral infection is still in the theoretical phase. Prominent among these hypotheses are virus-induced degeneration in inner ear structures, apoptosis of the cells of the auditory tract, microcirculation disorders, and immune response-mediated SHL (35). The cytokines responsible for this immune response that causes SHL due to viruses are interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (36,37). In the immune response seen in COVID-19, an increase in IL-1, IL-6, and IL-10 is observed, and drugs that suppress these cytokines, which also have prognostic features, are used to treat

the disease (38). This similarity in primary cytokines shows that the microcirculation disorder caused by the virus and the immune response may be responsible for SHL seen in newborns of pregnant women with COVID-19. Transient activation in the cochlear immune response results in spontaneous recovery in SHL (39,40). The temporary nature of SHL in newborns in this study may be explained by the transient nature of microcirculation disorder and immunity seen in COVID-19 and the fact that the infection occurred in mothers at the latest stage of the pregnancy, right before delivery.

Study Limitations

Although this study has outstanding aspects compared to the studies in the literature, it has some limitations. The hearing test data of our research are nominal, the diagnostic ABR for determining the thresholds, and the additional OtoAcoustic Emissions tests were not used in our study, which causes us not to obtain numerical data, thus limiting this study. Secondly, only the common conditions were excluded that may lead to conductive hearing loss, so all of the hearing loss detected in this study was accepted as SHL. Another limitation is that only asymptomatic pregnant women with positive SARS-CoV-2 PCR tests were included in this study to optimize the standardization. For this reason, the possible effects of the virus at the earlier stages of pregnancy or symptomatic COVID-19 infection's effect on newborn hearing during pregnancy could not be investigated.

Conclusion

The COVID-19 pandemic is affecting the entire population and the healthcare system at all stages. It is an unavoidable fact that this pandemic can also affect pregnant women. Babies of pregnant women with COVID-19 may develop pathologies related to the characteristics of the virus and disease. In this study, we examined the newborns of pregnant women with COVID-19 in terms of SHL. We demonstrated the presence of a temporary SHL in these babies with an objective methodology with optimal standardization. However, studies with larger sample size are needed to be performed order to determine this relationship further.

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02-67990, 07/04/2021).

Informed Consent: An informed consent form was obtained from all subjects.

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