Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Pediatric Otorhinolaryngology 146 (2021) 110754

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Hearing screening outcomes in neonates of SARS-CoV-2 positive pregnant women

Mehmet Akif Alan [a,*], Cemre Alan [b]

[a] Department of Otorhinolaryngology Head and Neck Surgery, Konya City Hospital, Konya, Turkey
[b] Department of Obstetrics and Gynecology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey

ARTICLE INFO

Keywords:
SARS-CoV-2
Hearing loss
COVID-19
Pregnancy
Neonate

ABSTRACT

Objective: The current study aimed to investigate possible association of maternal SARS-CoV-2 with newborn hearing loss. We compared hearing screening outcomes in neonates born to women with positive SARS-CoV-2 PCR test results during pregnancy with healthy controls.

Methods: Neonates born between April and December 2020 in our hospital to mothers with positive SARS-CoV-2 PCR test results during pregnancy were included in this study. Neonates with risk factors for universal newborn hearing screening (NHS) were excluded. Neonates born to mothers with positive SARS-CoV-2 PCR test results during pregnancy were compared with healthy controls in terms of newborn hearing screening results and independent variables.

Results: Neonates in the COVID-19 group were more likely to have a "refer" result in auditory brainstem responses (ABR) compared with the control group (53/118 and 28/118, respectively; $p = 0.001$). The second ABR test results did not differ significantly between the groups ($p = 0.618$). Logistic regression revealed that birth week and type of birth were not associated with the "refer" result. PCR positivity in the second trimester was more likely to produce the "refer" result in the first ABR test ($p = 0.014$).

Conclusion: SARS-CoV-2 PCR positivity in pregnancy is significantly associated with an increased risk of abnormal NHS results. Also, the timing of PCR positivity in pregnancy (trimester) may be related to abnormal NHS results.

1. Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak started as an epidemic in Wuhan, Hubei province, China, there have been more than 82,000,000 confirmed cases and more than 1,800,000 deaths worldwide as of January 1, 2021, according to the World Health Organization [1]. SARS-CoV-2 infection mainly presents symptoms such as fever, cough, sore throat, headache, nonspecific taste and smell disturbances, myalgia, diarrhea, and dyspnea [2]. Globally, population studies to date have identified several patient characteristics and reported that COVID-19 vertical transmission is highly likely, but data on pregnant patients are limited [1,3].

Hearing loss is one of the most common abnormalities present at birth. Several intrauterine infectious risk factors (toxoplasma, cytomegalovirus, herpes, syphilis, measles, mumps, rubella, varicella, and other febrile illnesses) associated with congenital sensorineural hearing loss (CSNHL) have been described [4–6]. Viruses can directly damage inner ear structures, including inner ear hair cells and the organ of Corti, or cause the induction of host immune-mediated damage [7]. Cytomegalovirus infection is the most common nongenetic cause of CSNHL, and the most common sequela of congenital rubella infection (58%) is CSNHL [8].

The coronavirus is an enveloped positive-sense single-stranded RNA virus belonging to the coronaviradae family [9]. Coronaviruses are neurotropic viruses that can reach the cranial nervous system by anterograde and retrograde transport with the help of motor proteins (kinesins and dyneins) through sensory and motor nerve endings. Also, ACE-2 receptors are expressed on glial tissues, neurons, and the brain vasculature, making the receptors a SARS-CoV-2 target [9]. Therefore, intrauterine SARS-CoV-2 infection may affect inner ear structures. To our knowledge, the possible association of SARS-CoV-2 with CSNHL has not been reported. This study aimed to compare the newborn hearing screening (NHS) outcomes of infants born to women who were SARS-CoV-2 positive during pregnancy with those of infants born to

* Corresponding author. Department of Otorhinolaryngology Head and Neck Surgery, Konya City Hospital, Konya, 42020, Turkey.
E-mail addresses: makifalannn@gmail.com (M.A. Alan), drcemrealan@gmail.com (C. Alan).

https://doi.org/10.1016/j.ijporl.2021.110754
Received 14 January 2021; Received in revised form 20 April 2021; Accepted 27 April 2021
Available online 3 May 2021

healthy women.

2. Materials and methods

This is a retrospective study of neonates who were born between April 2020 and December 2020 in Necmettin Erbakan University Meram Faculty of Medicine and Konya City Hospital (Konya, Turkey). The study was approved by the Necmettin Erbakan University Ethics Committee (No: 2021/3005). Women who had positive SARS-CoV-2 PCR test results during pregnancy, from the first delay of the menstrual period to delivery, and delivered between April and December 2020 were selected. Their neonates were then enrolled in the study according to the following inclusion criteria: single gestation, neonates with no risk factor for hearing loss, and neonates whose auditory brainstem response (ABR) results were available on the Turkish National Newborn Hearing Screening Database. Neonates with risk factors for hearing loss indicated by the American Academy of Pediatrics Joint Committee on Infant Hearing 2007 were excluded from the study. The risk factors are: asphyxia; a family history of hereditary childhood sensorineural hearing loss; in utero infection such as CMV, rubella, syphilis, herpes simplex, toxoplasma; craniofacial abnormalities; birth weight under 1500 g; hyperbilirubinemia that requires exchange transfusion; ototoxic medications; more than five days' stay in the neonatal intensive care unit; Apgar scores of 0–4 at the first or 0–6 at the fifth minute of birth; and stigmata or other findings associated with a syndrome [10–12].

The neonates in the control group with birth dates that matched those of the study group were randomly selected from the hospital database. NHS was performed in the first two weeks after birth using the ABR test. If a neonate did not pass the ABR test, the second ABR test (ABR refer) was performed after two weeks. The neonates were evaluated bilaterally while sleeping with no sedation. Before the ABR test, an otoscopic examination was performed by a specialist on all the neonates. Neonates who did not pass the second ABR test were referred to a secondary otolaryngology center.

As a precaution for COVID-19, NHS was performed in a well-ventilated room by an audiometrist with personal protective equipment. Disposable probs and electrodes were used for each test, while nondisposable instruments were disinfected after each use. After screening each neonate, the test room was ventilated for a minimum of 15 min. Neonates born to women who had positive SARS-CoV-2 PCR test results within 14 days before birth were observed in terms of well-being, respiratory status, and signs of illness.

The study and control groups were compared in terms of the described variables; gender, type of delivery, gestational week of PCR positivity (trimester), and ABR results were recorded as noncontinuous variables, while birth weight, maternal age, and birth week were categorized as continuous variables.

Statistical analyses were performed with SPSS 22.0 for Windows (IBM SPSS Statistics, Chicago, IL, USA). All the continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Pearson chi-square or Fisher's exact test was used to compare the patient characteristics and outcomes. An independent samples test or the Mann-Whitney *U* test was used to analyze the continuous variables. Binary logistic regression analysis was used to identify the associations of the independent variables with the ABR test results. A p-value < 0.05 was considered to indicate a statistically significant difference for all the statistical tests.

3. Results

3.1. Patient demographics

During the study period, 4663 pregnant women were screened for SARS-CoV-2 PCR positivity, and only 141 (3%) were positive. Twenty-three neonates born to these women were excluded from the study. Of these 23 neonates, 14 needed neonatal intensive care unit >5 days, 4 were multiple gestations, while 5 were <1500 g. Thus, both the control and the COVID-19 groups consist of 118 neonates. Maternal age, birth weight, and gender did not differ significantly between the groups ($p = 0.801$, $p = 0.975$, $p = 0.602$, respectively). Compared to the controls, the neonates in the COVID-19 group were more likely to be born earlier ($p = 0.004$) and cesarean section was done more often in the COVID-19 group ($p = 0.001$). Table 1 summarizes the patient demographics and clinical characteristics.

3.2. Newborn hearing screening outcomes

Before the ABR tests, otoscopic examination showed no difference between the study group and the control group or between the right ear and the left ear. In the COVID-19 group, 37 neonates (31.4%) showed "bilateral refer" on the ABR test, 11 (9.3%) showed "right unilateral refer," 5 (4.2%) showed "left unilateral refer," while 65 (55.1%) showed "bilateral pass." In the control group, 16 neonates (13.6%) showed "bilateral refer," 4 (3.4%) "right unilateral refer," 8 (6.8%) "left unilateral refer," and 90 (76.2%) "bilateral pass" on the ABR test. The neonates in the COVID-19 group were more likely to show "bilateral refer" compared to those in the control group ($p < 0.001$).

The neonates with a "refer" result for at least one ear were compared with those with "bilateral pass" results in both the COVID-19 group and the control group. The neonates in the COVID-19 group were more likely to show "refer" compared to the control group ($p = 0.001$). "ABR refer" test results did not differ significantly between the COVID-19 and the control groups ($p = 0.618$). The health system and the National Newborn Hearing Screening Program in Turkey as well as in the whole world experienced some drawbacks due to the COVID-19 pandemic. Therefore, 20 of the 53 neonates in the COVID-19 group who failed the first ABR test did not undergo the "ABR refer" test (Table 2). "ABR refer" test results of these 20 neonates were not available in the National Newborn Hearing Screening Database.

3.3. Findings of the COVID-19 group

Ninety-three (78.8%) of the pregnant women were SARS-CoV-2 positive in their third trimester, 24 (20.4%) were positive in their second trimester, and only 1 (0.8%) woman was positive in her first trimester. Neonates whose mothers had positive PCR results in the second trimester were more likely to have a "refer" result after the first ABR test (66.6%) compared with the third trimester (38.7%, $p = 0.014$).

Table 1
Baseline characteristics of cases and controls.

Variable		Maternal Covid-19, n (%)	Control, n (%)	*p*-value	OR [95% CI] ***
Maternal Age*		27,3 ± 5,5	27,1 ± 4,7	0.801[a]	NM
Birth Weight (g)*		3260.6 ± 441.1	3258.7 ± 468.6	0.975[a]	NM
Birthweek**		38.0 (33.0–41.0)	39.0 (31.0–42.0)	**0.004**[b]	0.999 [0.809–1.235]
Gender	female	59 (50.0%)	63 (53.4%)	0.602[c]	NM
	male	59 (50.0%)	55 (46.6%)		
Type of Birth	vaginal delivery	47 (39.8%)	73 (61.9%)	**0.001**[c]	1.062 [0.590–1.914]
	caesarean section	71 (60.2%)	45 (38.1%)		

*Data are presented as mean ± SD or n (%).
**Data are presented as median (min-max) or n (%).
***Any outcomes significant at $p < 0.05$ were further assessed on logistic regression analysis in terms of ABR results.
CI = confidence interval; OR = odds ratio; NM = not modeled.
[a] P-value for independent samples test.
[b] P-value for Mann-Whitney *U* test.
[c] P-value for Pearson Chi-Square test.

Table 2
Newborn hearing screening outcomes of Covid-19 and control groups.

		Covid-19 Group, (n)	Control Group, (n)	*p*-value	OR [95% CI] *
ABR	pass	65/118	90/118	**0.001**[a]	**2.612**
	refer	53/118	28/118		**[1.461–4.670]**
ABR	pass	30/33	27/28	0.618[b]	NM
refer	refer	3/33	1/28		

*Any outcomes significant at $p < 0.05$ were further assessed on logistic regression analysis.
CI = confidence interval; OR = odds ratio; NM = not modeled.
[a] P-value for Pearson Chi-Square test.
[b] P-value for Fischer' s Exact Test.

There were 24 pregnant women who had positive SARS-CoV-2 PCR results within 14 days before birth. The neonates born to these women had no symptoms of COVID-19 and thus had no swab test.

None of the pregnant women who had COVID-19 was admitted into the intensive care unit: 75 (63.6%) women had no symptoms, while 43 (36.4%) had at least one symptom. In symptomatic women, the most common symptoms were cough (67.4%), myalgia (39.5%), and dyspnea (32.5%). The ABR results of the symptomatic and asymptomatic women showed no statistically significant difference ($p = 0.294$). Most of the women in the COVID-19 group ($n = 78$, 66.1%) were followed up with no medical treatment. "Hydroxychloroquine" was administered to 30 women (25.4%), "favipiravir" to 11 women (9.3%), and "lopinavir/ritonavir" to 8 women (6.7%). There was no statistically significant difference between the type of medication administered and the ABR test results ($p = 0.815$). Whether medical treatment was administered or not, ABR test results did not differ statistically significantly in the neonates ($p = 0.308$).

3.4. Binary logistic regression analysis

Binary logistic regression analysis was performed to identify the associations of the independent variables with the ABR test results (Table 1). In Table 2, logistic regression showed that SARS-CoV-2 positivity in pregnancy was statistically significantly associated with an increased incidence of "refer" on the ABR test ($p < 0.01$).

4. Discussion

Several viral infections may lead to newborn hearing loss, but it is still unknown whether COVID-19 has effects on newborn hearing. While vertical transmission and auditory manifestations of COVID-19 have been reported, the effect of maternal COVID-19 infection on newborn hearing remains understudied [1,13]. The specific aim of this study was to compare the NHS results of infants born to mothers who were SARS-CoV-2 positive with the results of infants of healthy mothers. Of note, logistic regression showed that SARS-CoV-2 PCR positivity in pregnancy is associated with an increased risk of having a "refer" result after the ABR test, suggesting that SARS-CoV-2 infection might represent a risk factor for NHS outcomes.

Conversely, recent studies have shown that vertical transmission of COVID-19 is extremely low [1,14]. Increased rates of fetal growth restriction, preterm birth, and perinatal mortality could be caused by COVID-19 infection in pregnancy [15]. Also, physiological changes due to pregnancy make women, in addition to the manifestations of an infection, more susceptible to infectious processes with the risk of adverse maternal and neonatal complications, such as premature birth, restriction of intrauterine growth, and hospitalization in an intensive care unit [16]. Delayed neuromaturation caused by fetal growth restriction, preterm birth, and perinatal mortality could increase the "refer" rate of the first ABR test in the COVID-19 group in our study. Even if it is a temporary effect, maternal COVID-19 infection could become a risk factor for hearing loss. Also, in response to viral infection, high levels of maternal inflammation can impact several aspects of fetal brain development, leading to wide-ranging neurological sequelae [17]. However, there was no statistically significant difference between the groups in terms of "ABR refer" test results. Although birth week and type of birth statistically significantly differed between the COVID-19 and the control groups, logistic regression showed that these variables were not associated with the "refer" result following the ABR test.

In the literature, possible ototoxic effects of chloroquine and hydroxychloroquine have been reported. Matz et al. reported abnormal cochleovestibular development in newborns after chloroquine treatment in pregnant women [18]. Also, hydroxychloroquine-induced ototoxicity in a child was reported first in 2002 [19]. The dose of chloroquine administered in our study was considerably higher than the usual dosage for malaria treatment; therefore, the ototoxic effects may be greater [20]. Hydroxychloroquine was administered 2×200 mg/d for five days to 30 mothers in our study, but we did not find any statistically significant difference in these neonates' ABR results in comparison with those of the controls.

Exposure to viral infections at different stages of pregnancy can trigger congenital hearing loss in several cases. However, the molecular mechanisms by which viruses induce hearing loss have not been adequately explored [21]. Several studies have shown low rates of association between COVID-19 and vertical transmission. In a study by Chen et al. no evidence of intrauterine infection caused by vertical transmission was seen in women who developed COVID-19 pneumonia in late pregnancy [22]. However, there are currently insufficient data on the perinatal outcome when the infection is acquired in the first trimester and early second trimester of pregnancy. Kotylar et al. in their systematic review, underlined that the first and third trimesters of pregnancy can be considered periods of increased inflammatory activity, whereas the second trimester is a period of overall decreased immune activity [1]. Consistent with these studies, COVID-19 in the second trimester was associated with higher rates of the "refer" result in our study. This may be attributed to decreased immune activity in the second trimester.

This current study is limited by its retrospective nature and the sample size. We have missing data because of the 20 neonates who did not undergo the "ABR refer" test in the COVID-19 group. The first ABR test was performed on all the neonates shortly after birth in the hospital, but some parents probably did not bring their newborns to the hospital for a "refer" test because of the anxiety of COVID-19 infection. Therefore, we believe that NHS test participation decreased due to the COVID-19 pandemic. Also, only one woman had positive PCR test results in the first trimester. This may be related to the timing of the first wave of the virus in Konya, Turkey; it is possible that women with positive SARS-CoV-2 PCR in the first trimester have not been delivered yet.

5. Conclusion

This study suggests that SARS-CoV-2 PCR positivity in pregnancy has some temporary effects on NHS outcomes. Also, the timing of PCR positivity in pregnancy (trimester) may be associated with this effect. We suggest that COVID-19 may be considered a risk factor for hearing loss. Future studies should evaluate this association using a larger sample size.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

References

[1] A.M. Kotlyar, O. Grechukhina, A. Chen, S. Popkhadze, A. Grimshaw, O. Tal, H. S. Taylor, R. Tal, Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis, Am. J. Obstet. Gynecol. 224 (1) (2021 Jan) 35–53, https://doi.org/10.1016/j.ajog.2020.07.049, e3.

[2] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China, JAMA Neurol 77 (6) (2020 Jun 1) 683–690, https://doi.org/10.1001/jamaneurol.2020.1127.

[3] K. Narang, E.A.L. Enninga, M.D.S.K. Gunaratne, E.R. Ibirogba, A.T.A. Trad, A. Elrefaei, R.N. Theiler, R. Ruano, L.M. Szymanski, R. Chakraborty, V.D. Garovic, SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review, Mayo Clin. Proc. 95 (8) (2020 Aug) 1750–1765, https://doi.org/10.1016/j.mayocp.2020.05.011.

[4] P.E. Brookhouser, Sensorineural hearing loss in children, Pediatr. Clin. 43 (6) (1996 Dec) 1195–1216, https://doi.org/10.1016/s0031-3955(05)70514-9.

[5] S.E. Kountakis, A. Psifidis, C.J. Chang, C.M. Stiernberg, Risk factors associated with hearing loss in neonates, Am. J. Otolaryngol. 18 (2) (1997 Mar-Apr) 90–93, https://doi.org/10.1016/s0196-0709(97)90093-4.

[6] C. Meyer, J. Witte, A. Hildmann, K.H. Hennecke, K.U. Schunck, K. Maul, U. Franke, H. Fahnenstich, H. Rabe, R. Rossi, S. Hartmann, L. Gortner, Neonatal screening for hearing disorders in infants at risk: incidence, risk factors, and follow-up, Pediatrics October 104 (4) (1999) 900–904, https://doi.org/10.1542/peds.104.4.900.

[7] B.E. Cohen, A. Durstenfeld, P.C. Roehm, Viral causes of hearing loss: a review for hearing health professionals, Trends Hear 18 (2014 Jul 29), https://doi.org/10.1177/2331216514541361, 2331216514541361.

[8] A.M. Korver, R.J. Smith, G. Van Camp, M.R. Schleiss, M.A. Bitner-Glindzicz, L. R. Lustig, S.I. Usami, A.N. Boudewyns, Congenital hearing loss, Nat Rev Dis Primers 3 (2017 Jan 12) 16094, https://doi.org/10.1038/nrdp.2016.94.

[9] M.U. Ahmed, M. Hanif, M.J. Ali, M.A. Haider, D. Kherani, G.M. Memon, A. H. Karim, A. Sattar, Neurological manifestations of COVID-19 (SARS-CoV-2): a review, Front. Neurol. 11 (2020 May 22) 518, https://doi.org/10.3389/fneur.2020.00518.

[10] E.N. Appelbaum, J.B. Howell, D. Chapman, A. Pandya, K.M. Dodson, Analysis of risk factors associated with unilateral hearing loss in children who initially passed newborn hearing screening, Int. J. Pediatr. Otorhinolaryngol. 106 (2018 Mar) 100–104, https://doi.org/10.1016/j.ijporl.2018.01.024.

[11] Joint Committee on Infant Hearing, Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs, 2007.

[12] J.A. Lee, C.H. Mehta, S.A. Nguyen, T.A. Meyer, Hearing outcomes in children of diabetic pregnancies, Int. J. Pediatr. Otorhinolaryngol. 132 (2020 May) 109925, https://doi.org/10.1016/j.ijporl.2020.109925.

[13] I. Almufarrij, K. Uus, K.J. Munro, Does coronavirus affect the audio-vestibular system? A rapid systematic review, Int. J. Audiol. 59 (7) (2020 Jul) 487–491, https://doi.org/10.1080/14992027.2020.1776406.

[14] S.C. Moreno, J. To, H. Chun, I.M. Ngai, Vertical transmission of COVID-19 to the neonate, Infect. Dis. Obstet. Gynecol. (2020 Nov 12;2020) 8460672, https://doi.org/10.1155/2020/8460672.

[15] E.A.N. Wastnedge, R.M. Reynolds, S.R. van Boeckel, S.J. Stock, F.C. Denison, J. A. Maybin, H.O.D. Critchley, Pregnancy and COVID-19, Physiol. Rev. 101 (1) (2021 Jan 1) 303–318, https://doi.org/10.1152/physrev.00024.2020.

[16] Á.F. Lopes de Sousa, H.E.F. Carvalho, L.B. Oliveira, G. Schneider, E.L.S. Camargo, E. Watanabe, D. de Andrade, A.F.C. Fernandes, I.A.C. Mendes, I. Fronteira, Effects of COVID-19 infection during pregnancy and neonatal prognosis: what is the evidence? Int. J. Environ. Res. Publ. Health 17 (11) (2020 Jun 11) 4176, https://doi.org/10.3390/ijerph17114176.

[17] H. Liu, L.L. Wang, S.J. Zhao, J. Kwak-Kim, G. Mor, A.H. Liao, Why are pregnant women susceptible to COVID-19? An immunological viewpoint, J. Reprod. Immunol. 139 (2020 Jun) 103122, https://doi.org/10.1016/j.jri.2020.103122.

[18] G.J. Matz, R.F. Naunton, Ototoxicity of chloroquine, Arch. Otolaryngol. 88 (1968) 370–372, https://doi.org/10.1001/archotol.1968.00770010372008.

[19] M.B. Coutinho, I. Duarte, Hydroxychloroquine ototoxicity in a child with idiopathic pulmonary haemosiderosis, Int. J. Pediatr. Otorhinolaryngol. 62 (1) (2002 Jan 11) 53–57, https://doi.org/10.1016/s0165-5876(01)00592-4.

[20] P. Prayuenyong, A.V. Kasbekar, D.M. Baguley, Clinical implications of chloroquine and hydroxychloroquine ototoxicity for COVID-19 treatment: a mini-review, Front Public Health 8 (2020 May 29) 252, https://doi.org/10.3389/fpubh.2020.00252.

[21] M. Karimi-Boroujeni, A. Zahedi-Amiri, K.M. Coombs, Embryonic origins of virus-induced hearing loss: overview of molecular etiology, Viruses 13 (1) (2021 Jan 6) 71, https://doi.org/10.3390/v13010071.

[22] H. Chen, J. Guo, C. Wang, F. Luo, X. Yu, W. Zhang, J. Li, D. Zhao, D. Xu, Q. Gong, J. Liao, H. Yang, W. Hou, Y. Zhang, Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records, Lancet 395 (10226) (2020 Mar 7) 809–815, https://doi.org/10.1016/S0140-6736(20)30360-3.