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COVID-19 during pregnancy and its impact on the developing auditory system

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ABSTRACT

Background: This study compared distortion product otoacoustic emissions (DPOAEs) and click-evoked auditory brainstem responses (ABRs) recorded from infants whose mother had Covid-19 during pregnancy (Covid-19 group) to infants whose mother did not have Covid-19 (Control group) during pregnancy.

Methods: This study retrospectively examined records of infants in the Covid-19 group (n = 15) and control group (n = 46) who had distortion product otoacoustic emissions (DPOAEs) and click-evoked auditory brainstem responses (ABRs) recorded as part of their clinical assessment. DPOAE amplitudes, absolute latencies (I, III, and V), and I-V interpeak intervals were examined.

Results: DPOAE amplitudes were similar between the Covid-19 group and the control group. The absolute latency of wave I was similar between groups. But absolute latencies III and V and I-V interpeak intervals of the Covid-19 group were significantly prolonged compared to the control group.

Conclusion: Covid-19 infection and its complications during pregnancy may not affect the cochlear function but may affect the functioning of the auditory brainstem.

1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Covid-19 infection during pregnancy can significantly affect the development of the fetus. Pregnant women with Covid-19 infection may experience more severe symptoms compared to nonpregnant women. Studies have reported that pregnant women with covid-19 were at an increased risk of maternal morbidity [1]. Infants whose mother was Covid-19 positive during pregnancy had a higher neonatal morbidity index, severe perinatal morbidity, and higher rates of neonatal intensive care unit admission compared to newborns of women without Covid-19 diagnosis [1,2].

It is well documented in the literature that viral infection during pregnancy can significantly affect the development of the auditory system [3]. However, very little has been understood about the effect of Covid-19 infection on newborn hearing [4–6]. A recent study [6] reported that infants born to mothers diagnosed with Covid-19 during pregnancy were more likely to fail a newborn hearing screening compared to infants whose mother was not diagnosed with Covid-19

during pregnancy, indicating that Covid-19 infection during pregnancy may be a risk factor for newborn hearing screening outcomes. However, other researchers [7–10] reported contradicting findings.

The auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAEs) are two common objective measures that are used to examine the integrity of the auditory system in newborn infants. The ABR is generated due to synchronized neural discharge to acoustic stimuli such as a short duration click. Click-evoked ABR is a short latency potential that occurs between 0 and 10 ms after stimulus onset. The ABR is characterized by peaks (I to V) and valleys, generated whenever there is any synapse or sudden change of the axonal pathway in the auditory brainstem [11,12]. ABRs can be reliably recorded from all age groups.

The ABR parameters (absolute latency, interpeak intervals, and absolute amplitudes) are sensitive to maturation in the auditory brainstem [11–13]. Newborn ABR is characterized by prolonged absolute peaks and interpeak intervals and reduced peak amplitudes when compared to older children and adults [11,12,14,15]. In general, ABR parameters show systematic changes with increasing age [11–13], and it is hypothesized that these changes are due to the maturation of synapses in

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the auditory brainstem [11,12]. Desynchronized neural discharge either due to demyelination or atypical synaptic transmission can lead to abnormal ABRs characterized by prolonged absolute latency, interpeak intervals, and reduced peak amplitudes [16–18].

DPOAEs are responses generated within the cochlea when the cochlea is stimulated by two closely spaced pure-tone frequencies. DPOAEs are thought to reflect the status of the outer hair cells [19]. DPOAEs are widely used in audiology clinics to monitor hearing and identify hearing loss. Clinically, either DPOAE amplitude or DPOAE amplitude to noise ratio [or signal to noise ratio (SNR)] is compared to normative data, to determine whether an individual's outer hair cell function is normal. Normal patterns are typically associated with hearing that is within normal limits. DPOAE amplitude reflects the integrity of outer hair cells and provides no information regarding the integrity of the inner hair cells or the auditory nervous system. Damage to outer hair cells can significantly reduce DPOAEs.

Covid-19 infection and its complications during pregnancy may have an adverse effect on the developing auditory brainstem structures. Infants whose mother had Covid-19 during pregnancy may be at a higher risk of showing abnormal auditory function. The ABR parameters (absolute latency, interpeak intervals, and amplitudes) are sensitive to changes in the auditory brainstem structure and function [20–22]. Studies have shown that high-risk infants can show abnormal ABRs (recorded at higher intensity levels) characterized by prolonged absolute latency and interpeak intervals [20,22,23]. Thus, analyzing ABRs recorded from infants whose mother had Covid-19 during pregnancy at a higher intensity (e.g., 70 dB nHL) may help in identifying subtle

subclinical indications of changes to the auditory brainstem structures. In this study, we retrospectively analyzed ABRs obtained during routine diagnostic clinical follow-up secondary to hearing screening referrals at local hospitals. ABR parameters of infants whose mothers were Covid-19 positive during pregnancy were compared to those of infants whose mothers were not. It was hypothesized that infants whose mothers were Covid-19 positive during pregnancy may show abnormal auditory brainstem responses when compared to infants whose mothers were not Covid-19 positive during pregnancy.

2. Method

Participants included 15 infants (corrected age: 41.60 weeks; males: n = 10, females: n = 5) whose mother was Covid-19 positive during pregnancy (Covid-19 group). Pregnant women were tested positive for Covid-19 infection by an RT-PCR test between March 2021 and March 2022 in local hospitals in South Mississippi. Fig. 1 shows mothers who were Covid-19 positive and their associated symptoms and days of reported illness. In the control group, 40 infants (corrected age: 42.84 weeks; males: n = 23, females: n = 17) were included, whose mother was not Covid-19 positive during pregnancy. Infants in the control group did not have a history of risk factors such as TORCH infection or known neurological deficits. Mann-Whitney test revealed no significant differences in corrected age between control and experimental groups (U = 368, p = 0.08). Parents completed the clinical consent form. The Institutional Review Board of The University of Southern Mississippi approved the study methods.

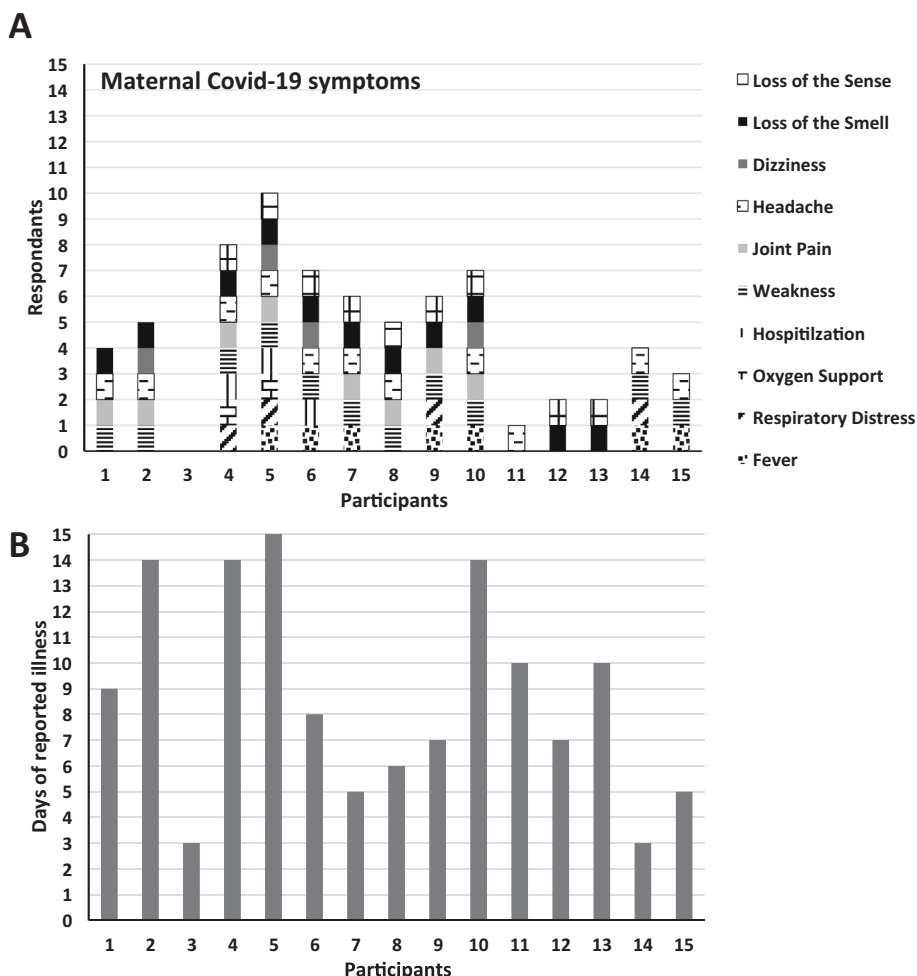


Fig. 1. Mothers who were Covid-19 positive and their associated symptoms and days of reported illness.

2.1. Equipment and stimuli

2.1.1. Distortion product otoacoustic emissions (DPOAE)

DPOAEs were recorded using the Eclipse-25 (Interacoustics, Middelfart, Denmark). Before data acquisition, the adequacy of probe fit was inspected. The DPOAEs to two simultaneously presented primaries (L1 = 65 dB SPL, L2 = 55 dB SPL, $f_2/f_1 = 1.22$) were recorded. DPOAE and noise levels were recorded at the DPOAE frequency of $2f_1-f_2$ in descending order of f_2 (8, 6, 5, 4, 3, and 2 kHz). Two trials were recorded for each ear. Participants were included in the study only if three out of six f_2 frequencies elicited ≥ 6 dB signal-to-noise ratio (SNR). For one infant in the Covid-19 group, DPOAEs were measured using a hand-held screener Corti (Grason-Stadler, Eden Prairie, USA) and showed SNRs of >6 dB at test frequencies (5, 4, 3, and 2 kHz).

2.1.2. Click evoked auditory brainstem responses (ABRs)

For all participants, ABRs were acquired using a two-channel Eclipse-25 system (Interacoustics, Middelfart, Denmark). A 100 μ s rarefaction click was presented at 23.5/s. Stimuli were presented monaurally via insert earphones (ER-3A, Etymotic Research, Inc.) to the right and left ears at different intensity levels (70, 40, and 20 dB nHL). Recordings were made with four surface electrodes placed at FPZ and Fz (ground) positions and referenced to the right and left mastoids. Electrode impedance was below 5k Ω . The responses were averaged over a 20 ms window, amplified (100 nV), and filtered (33-1500 Hz). Artifact rejection was set at ± 40 μ V. The signal-to-noise ratio was estimated using the Fmp technique, and the residual background noise level was estimated using a Bayesian weighting technique which is available in the Eclipse-25 system. The ABR recording was interrupted with an Fmp > 3.1 and when a clearly identifiable and replicable waveform was present. Throughout the recording, infants were on their parent's lap. All participants in both Covid-19 and control groups showed replicable ABRs at 20 dB nHL. In this study, absolute latencies (I, III, and V) and I-V interpeak intervals of ABRs recorded only at 70 dB nHL were analyzed. Waves I to V were marked by an experienced audiologist (last author) and verified by other authors.

2.2. Statistical analysis

Wilcoxon Signed-Rank test and Mann-Whitney U tests were carried out. For all analyses significance level of $p < 0.05$ was chosen. The analysis was conducted in JASP Team (2022) (Version 0.16.1).

3. Results

3.1. DPOAEs

Fig. 2 shows the DPOAE amplitudes as a function of frequency for

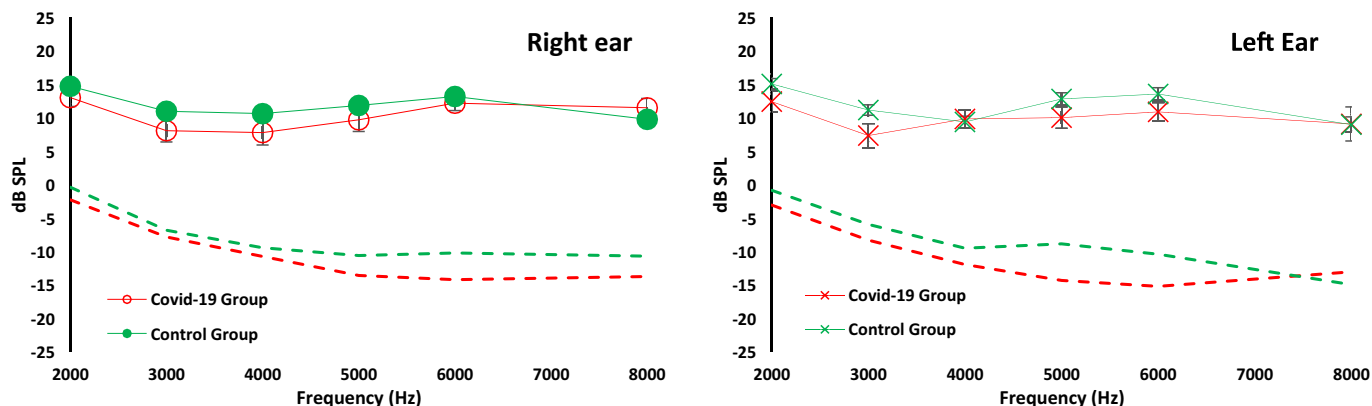


Fig. 2. DPOAE amplitudes are plotted as a function of test frequency for the right and left ear for both groups. Error bars around the mean represents standard error.

Covid-19 and control groups. Wilcoxon Signed-Rank test revealed no significant differences in DPOAE amplitude between ears in both the groups ($p > 0.05$) for all test frequencies, hence right and left ear DPOAE amplitudes were grouped. Mann-Whitney U test showed no significant differences in DPOAE amplitude between groups [2 kHz ($U = 275$, $p = 0.97$); 3 kHz ($U = 276$, $p = 0.96$); 4 kHz ($U = 289$, $p = 0.75$); 5 kHz ($U = 301$, $p = 0.57$); 6 kHz ($U = 303.5$, $p = 0.54$); 8 kHz ($U = 249$, $p = 0.63$)] suggesting bilateral normal outer hair cell function in all participants.

3.2. ABRs

3.2.1. Absolute latencies

Fig. 3 shows absolute latencies for the right and left ear for both groups. Wilcoxon Signed-Rank test revealed no significant differences in absolute latencies (I, III, and V) between ears in both the groups ($p > 0.05$), hence right and left ear latencies were grouped. Mann-Whitney U test revealed no significant group differences in wave I latency ($U = 1115.5$, $p = 0.56$). However, the absolute latencies of wave III ($U = 788.50$, $p = 0.005$) and V ($U = 688.50$, $p < 0.001$) of infants in the Covid-19 group were significantly prolonged when compared to control groups.

3.2.2. Interpeak intervals

Fig. 4 shows interpeak intervals for the right and left ear for both groups. Wilcoxon Signed-Rank test revealed no significant differences in I-V interpeak interval between ears in both the groups ($p > 0.05$), hence right and left ear interpeak intervals were grouped. Mann-Whitney U test revealed that the I-V interpeak intervals were significantly prolonged ($U = 680.5$, $p < 0.001$) in the Covid-19 group compared to the control group.

4. Discussion

In this study, DPOAEs and ABRs recorded from infants whose mothers had Covid-19 during pregnancy were compared to those of infants whose mothers were not. In newborn infants, the cochlear function is assessed by recording DPOAEs. Infants with healthy cochlea demonstrate DPOAEs with large amplitudes. DPOAEs of infants whose mother had Covid-19 during pregnancy were similar to those of infants whose mother was not diagnosed with Covid-19 during pregnancy suggesting that these infants have a normal cochlear function.

The auditory brainstem function is assessed by recording ABRs. ABRs contain five major peaks but clinically, peaks I, III, and V are examined. Peak I is generated from the distal portion of the auditory nerve and reported to be matured in full-term infants [11,12,24]. Whereas peaks III and V are generated by higher auditory centers and are not matured in full-term infants [11,12,24] possibly due to poor synaptic efficacy [11,12].

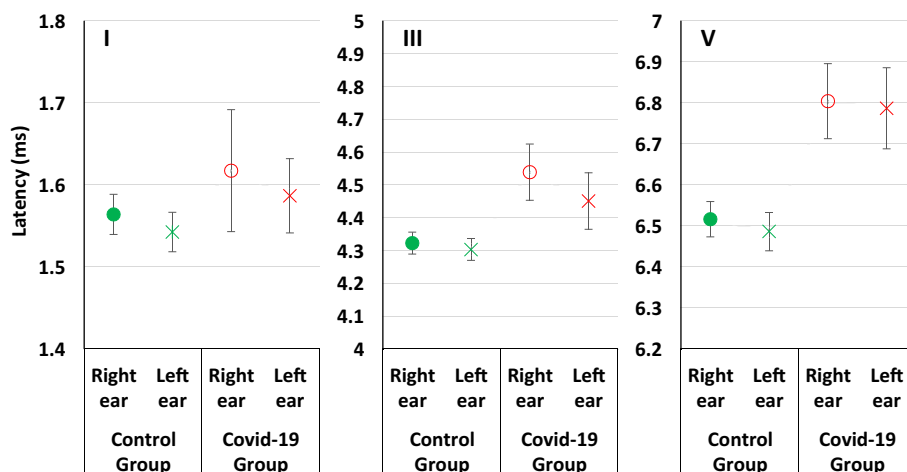


Fig. 3. Absolute latencies are plotted for the right and left ear for both groups. Error bars around the mean represents standard error.

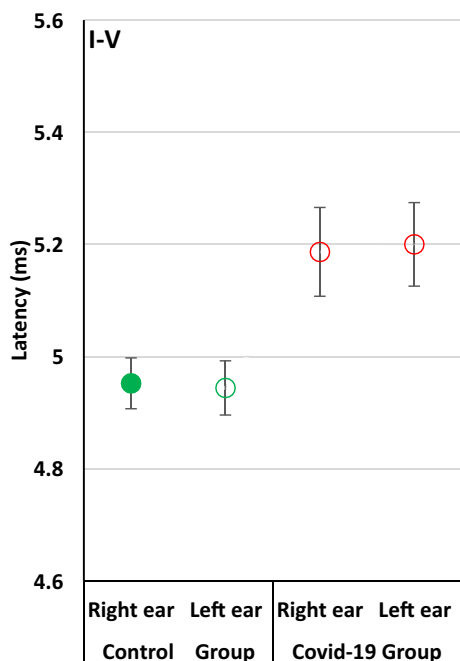


Fig. 4. I-V interpeak interval plotted for right and left ear for both groups. Error bars around the mean represents standard error.

Previous studies have consistently reported that high-risk infants may demonstrate abnormal ABRs [20,22,23]. ABRs of high-risk infants are characterized by significantly prolonged absolute latencies and interpeak intervals. Covid-19 infection and its complication during pregnancy may put the developing fetus at high risk for hearing loss. In this study, both the Covid-19 group, and the control group showed the presence of click ABR thresholds at a typical response level (20 dB nHL) and normal DPOAEs in both ears. However, analysis of ABRs recorded at a higher intensity (70 dB nHL) revealed significantly prolonged absolute latencies (III, and V) and I-V interpeak in the Covid-19 group compared to the control group, suggesting abnormal auditory brainstem function. Findings from this study suggest that COVID-19 during pregnancy may not be a risk factor for hearing loss, consistent with more recent findings [7–9]. However, infants whose mothers had Covid-19 during pregnancy may show immature auditory brainstem responses when compared to those infants whose mothers did not have Covid-19 during pregnancy. It is possible that Covid-19 infection and its complications during

pregnancy may affect axonal and or synaptic function in the auditory brainstem. In the event detection thresholds are within normal limits prolonged absolute latencies and interpeak intervals may not garner appropriate attention.

To the best of the author's knowledge, this is the first study on infants reporting abnormal ABR findings in infants whose mother had Covid-19 during pregnancy. Subtle delay at birth in the maturation of the auditory brainstem may show greater developmental differences in the maturation of higher auditory centers. Some researchers have proposed that infants with prolonged ABR interpeak intervals at an early stage may experience prolonged developmental problems later in life [25,26]. Hence, longitudinal studies are warranted to examine the maturation of the auditory system in infants whose mothers had Covid-19 during pregnancy.

Currently, Covid-19 infection during pregnancy and its impact on the developing auditory system is not well understood. More research on auditory processing in infants is warranted. One of the limitations of this study is the small sample size in the experimental group. Future studies should be carried out with a large sample size.

5. Conclusion

Covid-19 infection and its complications during pregnancy can have a negative impact on the still-developing auditory system. Infants whose mothers had Covid-19 during pregnancy may have a normal cochlear function but may show significantly prolonged neural timing for acoustic stimuli at the level of the auditory brainstem. These neural delays could be due to atypical axonal and synaptic functions. Future studies are required to examine auditory system maturation in these infants.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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