Indian J Otolaryngol Head Neck Surg (2023) 75:1847–1852
https://doi.org/10.1007/s12070-023-03786-2

ORIGINAL ARTICLE

Gestational Mild COVID-19 Infection Associated Neonatal Hearing Loss: A Case-Control Study from North India

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Received: 1 April 2023 / Accepted: 5 April 2023 / Published online: 17 April 2023

Abstract COVID-19 infection during pregnancy is potentially dangerous to neonatal hearing, as it is the period of organogenesis, and associated hyperthermia may cause vascular damage, disruption of cell migration, and death of the dividing neuroblasts. To investigate the possible association between neonatal hearing loss and gestational mild COVID-19 infection. A prospective case-control study was conducted at a tertiary healthcare centre in North India from March 2020 to Oct 2022. Cases included the neonates born to COVID-19-positive mothers were subjected to hearing screening at 1, 3 and 6 months using otoacoustic emission (OAE) and automated auditory brainstem response (AABR). Similar protocol was applied to controls, i.e., neonates borne to mothers with no gestational history of COVID infection. Results were analyzed statistically. Our study reported that the statistical difference between groups A (n = 942) and B (n = 942) for gestational COVID-19 infection and neonatal hearing loss was insignificant at 1 month (*p*-value 0.272 for OAE and *p*-value 0.634 for AABR) and also insignificant at 3 and 6 months (*p*-value 0.679 for AABR, for both). The association between gestational mild COVID-19 infection during gestation and neonatal hearing loss is statistically insignificant at initial screening as well as sequential screenings.

Keywords Mild COVID-19 Infection · Pandemic · Gestational · Neonatal hearing · Screening · Otoacoustic emission · Automated auditory brainstem response

Abbreviations

TEOAE	Transient evoked otoacoustic emission
DPOAE	Distortion product otoacoustic emission
AABR	Automated auditory brainstem response
OAE	Otoacoustic emission

Introduction

Severe acute respiratory syndrome associated with the novel Corona Virus 2 started in December 2019 in Wuhan, China, and spread to the whole world rapidly, affecting all races and ages [1]. The COVID-19 disease displayed a wide spectrum of symptoms ranging from asymptomatic carriers to severe interstitial pneumonia, and also some neurotropic symptoms such as anosmia, dysgeusia, hearing loss, tinnitus, and dizziness [2, 3].

Ministry of Health and Welfare, India has defined the mild Covid-19 disease as- the presence of symptoms of upper respiratory tract infection with or without fever, and

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without shortness of breath or hypoxia (respiratory rate ≤ 24/min without any breathlessness, SpO_2: ≥ 94% on room air) [4]. Pregnant females were considered at high risk of acquiring the infection. The vertical transmission of COVID-19 from mother to fetus is still controversial [5]. In neonatal COVID-19 cases, the common symptoms among neonates were fever, respiratory, gastrointestinal, and neurological symptoms. As the neonate cannot be separated from the mother, it is associated with late COVID-19 infection, however, breastfeeding is not [6]. Gestational mild COVID-19 infection during the first trimester is potentially dangerous to neonatal hearing, as it is the period of organogenesis, and associated hyperthermia may cause vascular damage, disruption of cell migration, and death of the dividing neuroblasts [7]. This is also the most important and sensitive period for the development of the middle and inner ear structures [8].

Gestational mild COVID-19 infection is more commonly seen during the third trimester [9]. Few studies have suggested there is a correlation between gestational insufficiency in the medial olivocochlear efferent system which was evident on TEOAE (transient evoked otoacoustic emission) test results signifying the increased risk of congenital hearing loss [10, 11].

The implications of congenital hearing loss include impaired speech, social, and emotional development. Our study aimed to investigate the possible association between neonatal hearing loss and gestational mild COVID-19 infection.

Methods

Study Design

A prospective observational case-control study was done at a tertiary healthcare centre in North India from March 2020 to October 2022.

Participants

Group A included neonates born to mothers with a history of mild COVID-19 infection during gestation. It was made sure that mothers of neonates in group A were conservatively managed with the same treatment protocol. This protocol included the administration of paracetamol (500 mg, tablet) as per need and no other drugs were administered.

Group B constituted of an equal number of neonates (as of group A) born to mothers who had an uneventful antenatal, perinatal and postnatal history as well as laboratory proven negative results for COVID-19 infection.

Group A formed the 'case' cohort while group B formed the 'control' cohort. The neonates with low or very low birth weight, low APGAR score, maternal history of fever due to moderate to severe COVID-19 or non-COVID-19 infection, history of ototoxic drug intake during gestation, congenital anomalies, neonatal intensive care admission were excluded from the study. Written and informed consent was obtained from the parent/guardian of each participant for the publication purpose.

Hearing Evaluation

All neonates fulfilling the inclusion criteria were subjected to screening with Otoacoustic Emission (OAE) at 1 month. Those who failed screening (REFER) were retested with AABR (Automated Auditory Brainstem Response). Groups A and B were again subjected to screening by AABR at 3 and 6 months [12]. Those who failed the AABR test were deemed Fails and those who failed the OAE were deemed REFER. Neonates who failed at six months screening were referred to neuro-otologists for further intervention. Interacoustics Titan DPOAE Screening + ABRIS (Serial Number:1016596) machine was used for the above-mentioned screening. All the assessments were done in the audiology lab of the institute by a qualified audiologist.

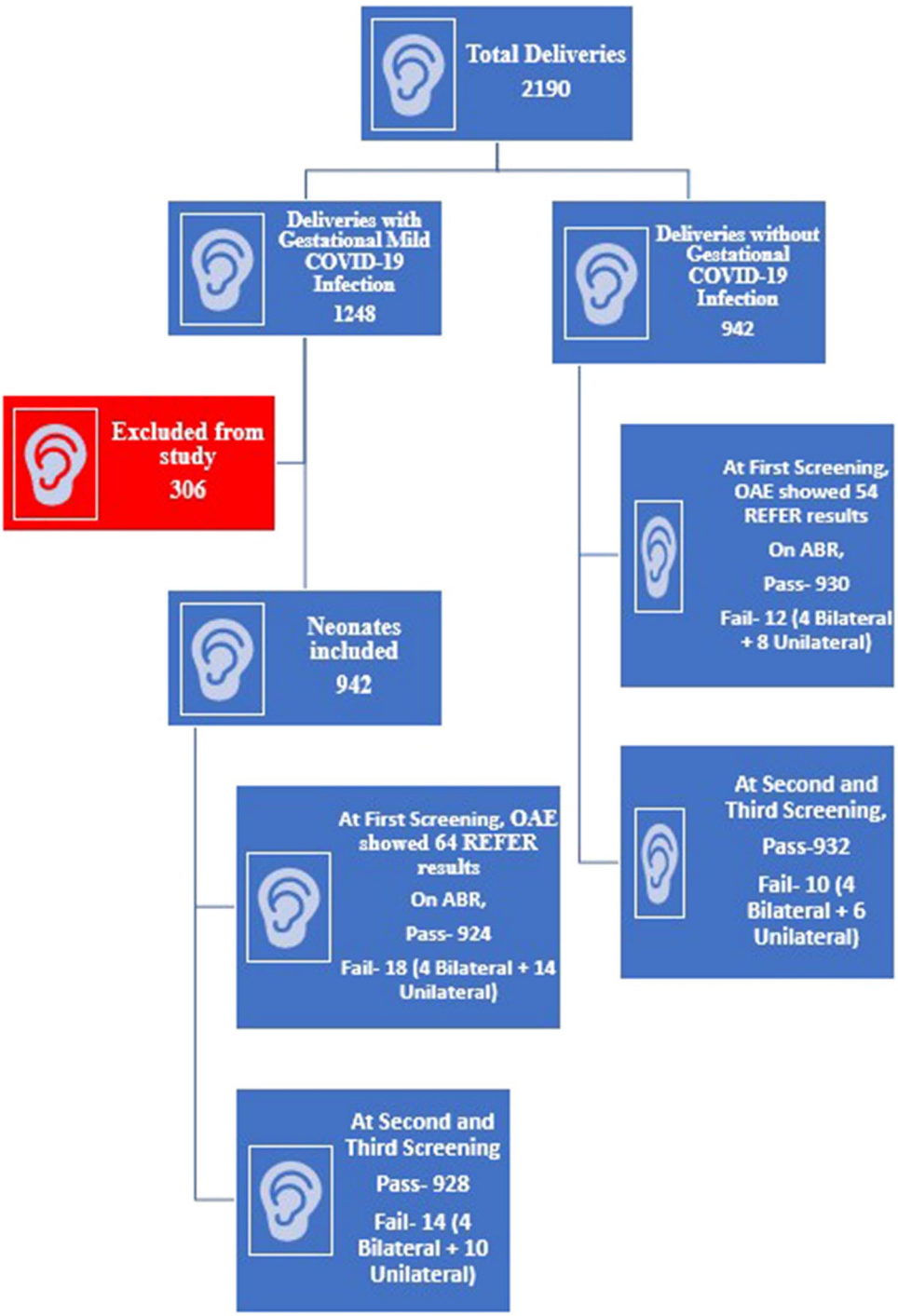
Statistics

Descriptive statistics were used to analyze the demographic and clinical variables. The categorical variables were expressed as absolute values (percentage), while the continuous variables with normal distribution were described as mean ± standard deviation (SD), and those without normal distribution as median (M) and interquartile range (IQR). The results of groups A and B at 1,3 and 6 months were statistically compared using McNemar's Chi-square test and statistical analysis was done using the SPSS (version 23) program. In all cases, the level of significance was set at a p-value < 0.05 with a confidence limit of 95%.

Results

Between March 2020 and October 2022, a total of 1248 neonates were delivered by mothers with a history of COVID-19 infection during gestation. Out of these, 942 neonates were included in Group A as per inclusion criteria while 306 neonates were excluded from the studies as per exclusion criteria. After the first screening at the age of one month, 64 neonates failed screening by OAE in group A and 54 in group B. On AABR at 1 month, 924 neonates passed while 18 failed among group A, whereas 930 passed and 12 failed among group B. However, on AABR, at 3 and 6 months, both, 928 neonates passed while 14 failed among group A, whereas 932 passed and 10 failed among group B. No change in results was noted at 3 and 6 months (Fig. 1).

Fig. 1 Scheme of the study



We observed that the mean age for mothers at the time of delivery was 28.76 ± 4.2 years (with an IQR of 24–33 years). 168 (17.83%) mothers acquired COVID-19 infection during the first trimester, 260 (27.60%) during the second, and 514 (54.56%) during the last trimester. (Fig. 2) Male neonates were 1004 and females were 880 with male to female ratio of 1.14:1. The mean weights for groups A and B were 2938.5 g and 2868.7 g. The mean gestational age for groups A and B were 38.4 and 39.2 weeks, respectively (Table 1).

At first screening, unilateral hearing loss was seen among 14 neonates of group A and 8 neonates of group B on AABR, while at 3 as well as 6 months, 10 infants from group A and 6 from group B failed AABR test. Bilateral hearing loss was seen among 4 neonates of groups A and B, each, at 1 month of age and also at 3 and 6 months of age. Statistical analysis of our results showed that there was no significant statistical difference between case (group A) and controls (group B) concerning neonatal hearing loss (Table 2).

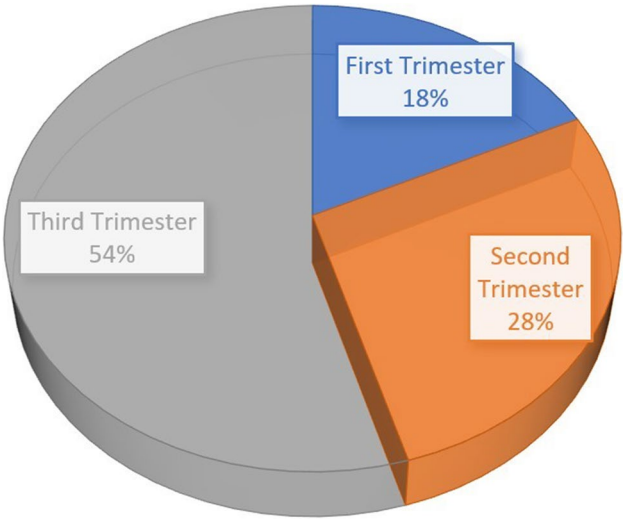


Fig. 2 Distribution of gestational mild COVID-19 infection as per trimesters

Discussion

Congenital hearing loss has a significant impact on the social and psychological development of an infant. Congenital hearing loss can be caused by environmental as well as genetic factors. Environmental factors include infections, ototoxicity, prematurity, and asphyxia [13]. Especially viral infections, congenital or acquired, such as cytomegalovirus, rubella virus, etc. can cause permanent or temporary hearing loss [14].

Pregnant women became infected with COVID-19 in large numbers during each wave of the pandemic. It is still unclear whether vertical transmission of COVID-19 from the infected mother to the fetus is possible [5]. A systemic review investigated the possibility of vertical transmission among neonates of COVID-19-infected mothers using nasopharyngeal swabs and IgM positivity in cord blood reported no positivity [15]. Another systemic review reported 8 COVID-19-positive neonates among 179 infected mothers [16]. The role of SARS-CoV-2 in congenital hearing loss is still debatable. The possible mechanism for maternal viral infection associated congenital hearing loss can be due to direct damage to the organ of Corti, stria vascularis, or neurons, damage to host immune response to viral antigen, indirectly decreasing the immunity and causing secondary infections, and unknown mechanisms [14].

Most of the mothers showed COVID-19 positivity in the third trimester (54.56%) in our study. A study by Yildiz et al. [17] also showed maximum COVID-19 positivity among mothers during the third trimester (47%). Ghiselli et al. [18]

Table 1 Perinatal case history information

	Group A		Group B	
Birth weight (g)	Mean 2938.5 (range 2530–3960)		Mean 2868.7 (range 2750–3675)	
Gestational Age (weeks)	Mean 38.4 (Range 35–42)		Mean 39.2 (Range 36–42)	
Gender	Male	502	Male	486
	Female	440	Female	456
Apgar Score	1’	9.3 (range 6–10)	1’	9.5 (range 6–10)
	5’	9.8 (range 6–10)	5’	9.8 (range 6–10)

Table 2 Statistical analysis of neonatal hearing screening at various ages

Stage of neonatal hearing screening	Type of hearing test	Type of result		Results		*p*-value (χ^2 value)
				Group A (Cases)	Group B (Controls)	
At 1 month	OAE	Pass		878	888	0.272 (1.21)
		REFER	Unilateral	50	48	
			Bilateral	14	6	
	AABR	Pass		924	930	0.634 (0.23)
		Fail	Unilateral	14	8	
			Bilateral	4	4	
At 3 months	AABR	Pass		928	932	0.679 (0.17)
		Fail	Unilateral	10	6	
			Bilateral	4	4	
At 6 months	AABR	Pass		928	932	0.679 (0.17)
		Fail	Unilateral	10	6	
			Bilateral	4	4	

also reported maximum COVID-19 positivity among mothers in the third trimester (63.5%). Conversely, another study by Alan et al. [11] observed maximum COVID-19 positivity among mothers in the first trimester (78.8%). Our study reported an insignificant relationship between gestational COVID-19 infection and neonatal hearing loss at 1 month (p-value 0.272 for OAE and p-value 0.634 for AABR) and 3 and 6 months (p-value 0.679 for AABR, for both). Our study showed bilateral REFER results in 14 patients (1.4%) and 50 (5.30%) unilateral REFER results for group A, while REFER results for group B were 6 bilateral (0.63%) and 48 unilateral (5.09%), at 1 month. Alan et al. [11] reported that 31.4% of COVID-19 group infants had bilateral REFER results. However, AABR results were statistically not significant for these infants. Mostafa et al. [19] recently reported that 18% of neonates failed at 1 month and 2.9% on AABR. They observed higher failure rates only during primary screening. Kaplan et al. [20] found that 12.4% of neonates failed the first screening and 1.3% failed the second screening. They observed no statistically significant difference between cases and controls. Kosmidou et al. [21] reported that 21.87% of neonates failed the first screening while all these neonates cleared the second screening. A study by Tanyeri Toker et al. reported no significant association between COVID-19 infection during different trimesters and congenital hearing loss. Furthermore, similar to our study they have suggested that gestational COVID-19 infection is not associated with permanent congenital hearing loss [22].

Our study was monocentric. This serves as a limitation as our study's results may not apply to a different population. Thus, we propose that the further studies should be multicentric. Also, the lack of prolonged follow-up was another limitation.

Conclusion

We found that the statistical difference between groups A and B concerning neonatal hearing loss was insignificant at 1, 3 and 6 months. This implicated that there is no significant association between gestational COVID-19 and neonatal hearing loss. Thus, we propose multicentric studies with long-term follow-up to detect the late effects of gestational mild COVID-19 infection on neonatal hearing.

Author Contributions LBR: Design, Conduct, Analysis, Presentation of Research. SR: Design, Conduct, Analysis, Presentation of Research. RB: Design, Conduct, Analysis, Presentation of Research. ST: Design, Conduct, Analysis. HCB: Design, Conduct, Analysis, Presentation of Research. RR: Conduct, Analysis, Presentation of Research. AS: Conduct, Analysis, Presentation of Research. OSC: Conduct, Analysis, Presentation of Research.

Funding Not applicable.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical Approval The authors assert that all the procedures contributing to the present work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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