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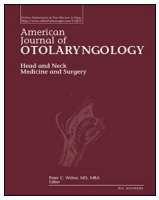

Can SARS-CoV-2 positive pregnant women affect the hearing of their newborns: A systematic review

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ABSTRACT

The 2019 coronavirus disease (COVID-19) pandemic has caused over 500 million confirmed cases (including pregnant women) worldwide. Recently, hearing status in newborns born to mothers with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has received attention. This systematic review outlines the current knowledge regarding the effects of maternal SARS-CoV-2 infection during pregnancy on newborn hearing. Intrauterine SARS-CoV-2 infection has the potential to affect the auditory system of the newborn due to intrauterine hypoxia and vertical transmission. SARS-CoV-2 might have a greater influence on hearing loss (HL) in newborns during the second and third trimesters of pregnancy. Therefore, all newborns whose mothers had COVID-19 during pregnancy should be evaluated for cochlear function, regardless of whether their mothers were symptomatic at the time of the disease. However, the understanding of this issue is not consistent and remains controversial. Since early identification and intervention of congenital HL are crucial to the language development of newborns, newborns should be provided with audiological evaluation by various approaches, including Tele-audiology, in the COVID-19 era.

1. Introduction

2019 Coronavirus disease (COVID-19) is an emerging human infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a new enclosed RNA beta coronavirus [1]. According to the WHO, as of May 13, 2022, there were over 500 million confirmed cases of COVID-19 globally, including over 6.2 million deaths [2]. Even though 11 billion vaccine doses have been administered worldwide as of May 9, 2022, the COVID-19 pandemic continues [2]. COVID-19 predominantly affects the respiratory system of the human body, but it can also cause harm to the central nervous, cardiovascular, gastrointestinal, hepatobiliary, and renal systems [3]. In addition, COVID-19 might induce otolaryngology diseases such as anosmia and sudden sensorineural hearing loss (HL) [4–6].

HL is one of the most commonly occurring major birth defects [7]. Significant bilateral HL affects 1 to 3 out of every 1000 births, and 2 to 4 out of every 100 infants in intensive care units [8]. Hearing screenings (HS) can increase the detection of newborns with HL, which is one of the world's longest-running population screening programs [9]. Early identification and intervention of congenital HL are crucial for developing speech and language [10]. However, the COVID-19 pandemic has caused delays in HS, which significantly impacts the health of both individual patients and the public [10].

Many viruses, such as rubella virus, cytomegalovirus, and herpes virus, can infect the fetus and impair its development [11]. Existing studies suggest that cytomegalovirus, herpes simplex virus, and Zika virus can cause intrauterine infections and HL in newborns after delivery [12–14]. Cytomegalovirus is the most commonly occurring viral infection during pregnancy in the United States, and it is the leading cause of non-inherited sensorineural HL [12].

SARS-CoV-2 infects human cells through the angiotensin-converting enzyme 2 (ACE2), activating transmembrane serine protease 2 (TMPRSS2), hence enhancing viral uptake [5]. The SARS-CoV-2 virus may infect both the central and peripheral nerve systems, resulting in neurological disorders [15]. According to a recent study, even mild COVID-19 can affect brain structure [16]. SARS-CoV-2 can get into the middle ear (ME) cavity and mastoid from the nasopharynx through the Eustachian tube (ET) [17]. Furthermore, an animal investigation

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verified the broad distribution of ACE2, TMPRSS2, and Furin in the ET, ME cavity, and cochlea, indicating the susceptibility of these tissues to SARS-CoV-2 [18].

Since the COVID-19 outbreak, the impact of SARS-CoV-2 on the placenta and its potential for vertical transmission has been raised concerns [19]. A recent meta-analysis published in BMJ confirmed vertical transmission of SARS-CoV-2, and the severity of maternal COVID-19 appears to correlate with infant SARS-CoV-2 positive [20]. Several previous studies have examined the hearing screening outcomes of newborns whose mothers tested positive for SARS-CoV-2 during pregnancy, revealing an increased risk of HL in these newborns [7,21]. However, the literature also reported that positive women for SARS-CoV-2 during pregnancy did not affect the HL of the delivered newborns [22]. As a result, the impact of maternal SARS-CoV-2 infection on newborn HL is unknown and controversial.

This systematic review seeks to improve the understanding of the audiological characteristics of newborns born to pregnant women who test positive for SARS-CoV-2 based on existing information from the literature. Furthermore, this review attempts to explain the possible underlying mechanisms by which SARS-CoV-2 causes hearing abnormalities in newborns.

2. Methods

A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [23]. No ethics approval was necessary for this review.

2.1. Search strategy

We systematically explored PubMed, Web of Science, Embase, and Scopus database. There were no restrictions on language, publication date, or publication status. The retrieval strategy was designed using a combination of medical subject headings (MeSH) terms and free words with synonyms. MeSH and free words used in the literature search included “COVID-19,” “SARS-CoV-2,” “newborn,” and “hearing.” In addition, hearing-related terms such as “hearing loss,” “cochlea,” “hearing tests,” “otoacoustic emissions, spontaneous,” “evoked potentials, auditory, brain stem,” and “hearing screening” were employed in the literature search to widen its reach. The final literature search was completed on May 11, 2022. Two reviewers (KZ and JW) independently determined the eligibility of the studies and extracted the data. Differences were resolved through discussion between the two reviewers.

2.2. Inclusion and exclusion criteria for study selection

The inclusion criteria were original human research publications written in English. The inclusion criteria for neonates were singleton pregnancies in whom the mother tested positive for SARS-CoV-2 during pregnancy. All irrelevant papers, abstracts without full text, letters to the editor, comments, review articles, and publications written in languages other than English were excluded.

2.3. Data extraction

Two reviewers (KZ and JW) extracted the data for recording using Microsoft Excel spreadsheets. The following data were included: authors, year of publication, the country in which the study was conducted, study design, study purpose, assessment period, main results, conclusions, sample size, age and gender, time of onset, side, symptoms, audiological assessment, treatments, and treatment outcome.

2.4. Assessment of risk of bias

Two reviewers (KZ and JW) independently rated the selected publications. The quality of publications included in this review was assessed using the National Institutes of Health quality assessment tool (observational cohort and cross-sectional studies) [24]. Each publication was assigned an overall quality rating of “good,” “fair,” and “poor” based on its rating. Any disagreements were addressed by discussion among the authors.

3. Results

3.1. Search outcome

A total of 66 publications were retrieved from the four databases, and 31 remained after eliminating duplicate publications. The literature was then filtered further using the titles and abstracts of the articles, removing 21 irrelevant studies and one non-English study. Next, two abstracts without full text, one placenta study, one salivary cytomegalovirus screening study, and one comment were also excluded through full-text literature identification. Ultimately, eight studies met the inclusion criteria for this systematic review. Table 1 presents an overview of the studies included in the review. The flowchart of the literature search is shown in Fig. 1.

3.2. Countries involved in relevant studies

To the best of our knowledge, relevant findings have been reported in the literature from 4 countries. Among these publications, Turkey is the major contribution, with 4 articles [7,21,26,28]. In the second place, 2 related papers were published from Italy [22,29]. Besides, there is 1 paper each from the United States and Egypt [25,27]. The distribution of countries where the study was conducted is shown in Fig. 2.

3.3. Impact on the hearing of newborns

Several case-control studies confirmed newborns delivered to pregnant mothers infected with the SARS-CoV-2 virus during pregnancy had an increased risk of developing HL [7,21,25]. Celik et al. found significant between-group differences in transient evoked otoacoustic emissions (TEOAE) results at 3 kHz and 4 kHz in newborns whose mothers were infected with COVID-19 during pregnancy versus newborns whose mothers were not infected with COVID-19 during pregnancy, while contralateral suppression of otoacoustic emissions (CLS OAE) test results revealed differences at all frequencies [21]. The researchers conclude newborns exposed to SARS-CoV-2 intrauterine have a medial olive cochlear efferent system deficit [21]. Similarly, Alan et al. revealed that newborns with COVID-19-infected mothers were more likely than the control group to have a “ refer” auditory brainstem response (ABR) (53/118 versus 28/118; $P = 0.001$) [7]. Veeranna et al. observed normal cochlear function and impaired ABR in newborns whose mothers experienced COVID-19 infection [25].

3.4. No impact on the hearing of newborns

Several studies have shown that maternal SARS-CoV-2 virus infection does not affect newborn hearing [22,27–29]. Ghiselli et al. investigated 63 newborns whose mothers had been diagnosed with COVID-19 during pregnancy and found that 4 failed the first ABR test, but only 1 (1.6 %) had ABR alterations when they were re-examined 1 month later [22]. Mostafa et al. conducted a retrospective cohort analysis with 921 newborns, and only 1 of the 34 newborns born to COVID-19-positive mothers failed the ARB test (2.9 %) [27]. Buonsenso et al. evaluated 143 newborns whose mothers had COVID-19; 27 failed TEOAE screening, 14 of whom were normal when tested again a month later [29]. Thirty-four children were assessed with ABR between the ages of 3–6 months, and all had normal hearing thresholds [29]. Although these studies imply that maternal infection does not affect the newborn's hearing, none of them had a control group, making it impossible to compare them. Oskovi-Kaplan et al. compared the TEOAE outcomes of

Table 1
An overview of the studies included in the systematic review.

Authors, year	Country	Study design	Assessment period	Study group (n)	Control group (n)	Audiological assessment	Main results	Conclusions	Risk factor	Risk of bias
Ghiselli et al. [22] 2022	Italy	Prospective study	February 15, 2020 to February 15, 2021	63	NA	TEOAE, Acoustic Immittance, DPOAE, ABR	4 cases had altered ABR thresholds at the time of initial examination, and only 1 case eventually showed altered ABR.	No evidence of a risk factor for HL in newborns.	No	Fair
Veeranna et al. [25] 2022	USA	Retrospective study	March 2021 to March 2022	15	40	DPOAE, ABR	The two groups had similar DPOAE amplitude and I-wave absolute latency. In the SARS-CoV-2 pregnant infection group, absolute latencies III and V and I-V inter-peak intervals were significantly longer.	It may not impair the cochlear function but may affect the ABR function.	Yes	Fair
Celik et al. [21] 2021	Turkey	Cross sectional study	March 2020 to December 2020	37	36	TEOAE, DPOAE, CLS OAE	TEOAE at 3 and 4 kHz were significantly different ($p < 0.05$); CLS OAE at all frequencies was significantly different ($p < 0.05$).	Defective medial olivary efferent system in newborns with intrauterine SARS-CoV-2 infection.	Yes	Good
Alan et al. [7] 2021	Turkey	Retrospective study	April to December 2020	118	118	ABR	Newborns in the study group were more likely to have a "refer" result in the ABR than in the control group ($p = 0.001$). A SARS-CoV-2 positive in mid-pregnancy increased the likelihood of a "refer" result in the first ABR ($p = 0.014$).	SARS-CoV-2 infection increases the risk of HL in newborns, particularly during pregnancy (trimester).	Yes	Fair
Yıldız et al. [26] 2021	Turkey	Retrospective study	April 2020 to May 2021	199	NA	ABR	The first hearing test on newborns revealed unilateral HL in 21 cases (10.5 %), however, the second test 15 days later revealed normal results.	The absence of HL in the study does not rule out the possibility that SARS-CoV-2 infection causes congenital HL.	Uncertain	Poor
Mostafa et al. [27] 2021	Egypt	Retrospective study	November 2020 to April 1st, 2021	34	NA	TEOAE, ABR	Although 29 cases failed the initial hearing screening, only 1 case (2.9 %) failed when retested.	It seems no increased risk of HL in newborns.	No	Poor
Oskovi-Kaplan et al. [28] 2022	Turkey	Retrospective study	March 2020 to October,2020; before January 2020	458	339	TEOAE, ABR	The study group had a failure rate of 12.4 % in the first HS, compared to 9.4 % in the control group ($P = 0.211$); the risk of HL in the second HS was 1.3 % and 2.9 %, respectively, with no statistical difference between the two groups ($P = 0.103$).	It is not a risk factor for HL in newborns.	No	Fair
Buonsenso et al. [29] 2022	Italy	Prospective study	March 1, 2020 to April 30, 2021	143	NA	TEOAE, ABR	27 cases had abnormal TEOAE at birth, but 14 of them were normal after 1 month. ABR was tested on 34 children aged 3 to 6 months at birth, all of whom had normal hearing thresholds.	It has no effect on the hearing of newborns.	No	Fair

Notes: TEOAE: transient evoked otoacoustic emissions; DPOAE: distortion product otoacoustic emissions; ABR: auditory brainstem response; CLS OAE: contralateral suppression of otoacoustic emissions; HL: hearing loss; HS: hearing screening.

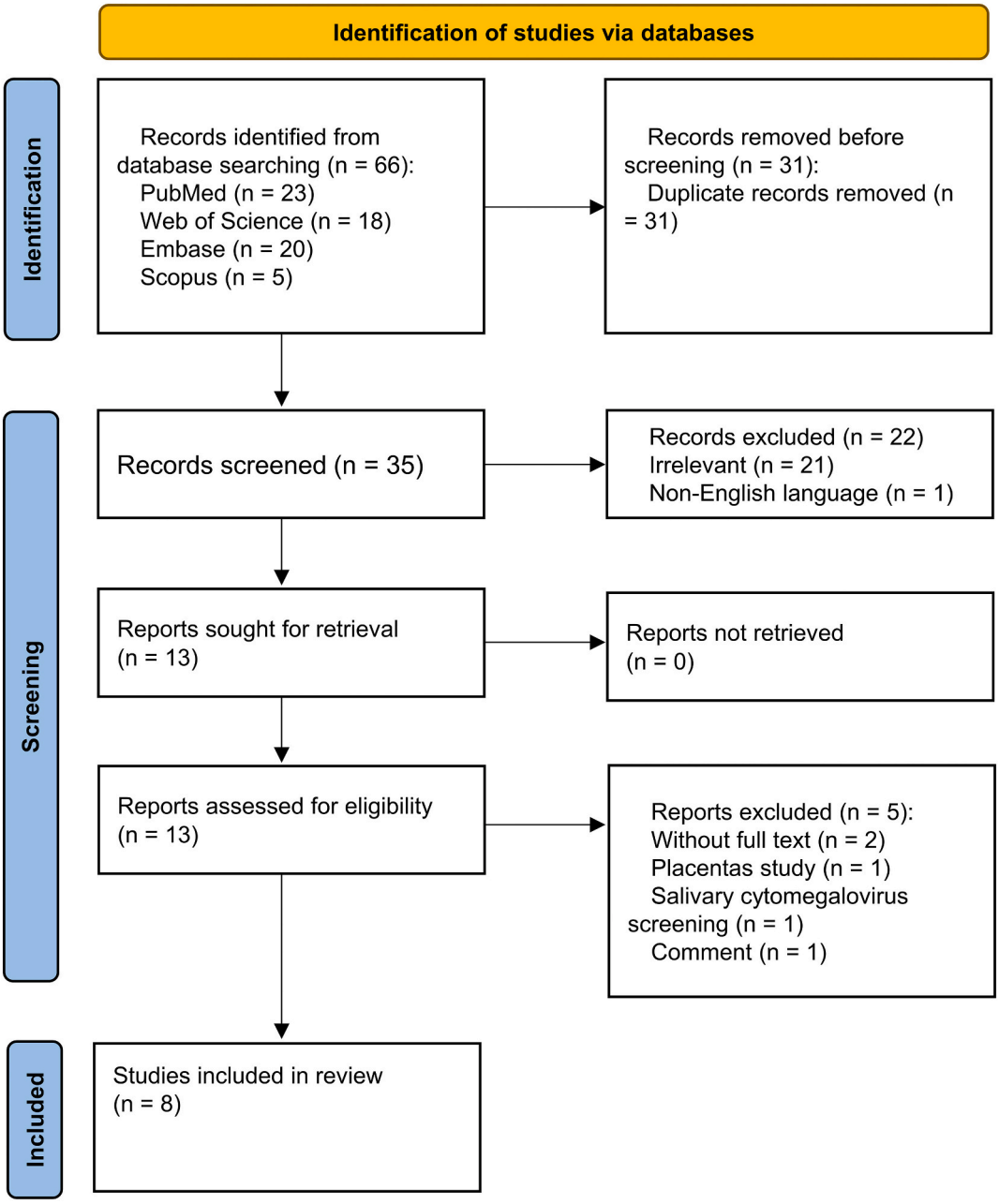

Fig. 1. Flow chart showing the process of literature screening.

458 newborns born to mothers with a history of COVID-19 infection during pregnancy to those of 339 newborns born before the COVID-19 pandemic found no statistically significant difference between the groups [28]. However, this study only evaluated the outcome of HS in newborns and lacked the findings of follow-up hearing evaluations; therefore, the incidence of HL in newborns could not be verified conclusively.

3.5. Uncertain effect on the hearing of newborns

Yldz et al. retrospectively evaluated the hearing outcomes of 199 newborns whose mothers had been infected with SARS-CoV-2 during pregnancy and showed that 21 (10.5 %) had unilateral hearing loss at the initial HS but were normal at the second hearing examination 15 days later [26]. However, the authors conclude that their study of newborns without congenital HL did not indicate that SARS-CoV-2 does not cause congenital HL; hence, a more extensive series of patients should be studied [26].

3.6. Effects of different trimesters on the hearing of newborns

The impact of maternal SARS-CoV-2 infection on newborns' hearing might vary depending on the stage of pregnancy. Oskovi-Kaplan et al. reported that newborns of mothers infected with COVID-19 throughout mid- and late pregnancy had a significantly greater probability of failure in their first HS than controls ($p = 0.031$) [28]. In the study conducted by Celik et al., 67.6 % of mothers had COVID-19 in late pregnancy and 32.4 % in mid-pregnancy [21].

4. Discussion

In this review, we investigated the effects of maternal SARS-CoV-2 infection during pregnancy on the hearing of the newborn population using the existing literature. Of the 8 studies included in this review, 3

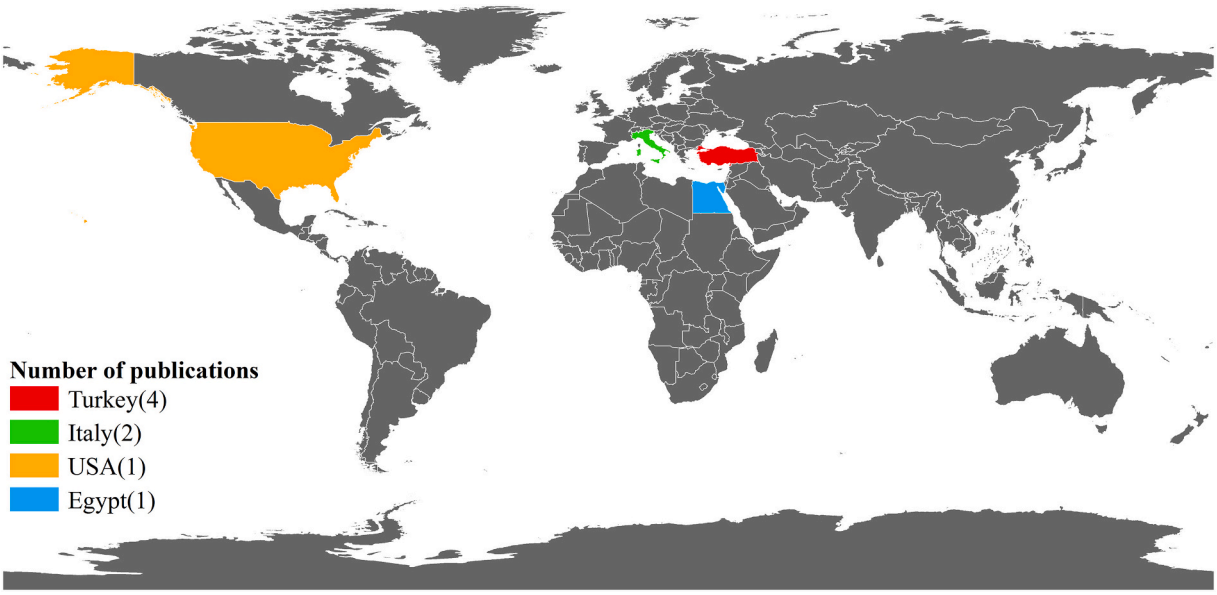

Fig. 2. Figure showing the distribution of countries of studies included in the systematic review.

studies concluded that there was an effect on hearing in newborns, 4 studies concluded that there was no effect, and 1 study concluded that it could not be determined. However, it is important to note that the 3 studies that were considered influencing hearing in newborns were case-control studies. Most of the remaining studies did not have a control group to allow for comparison.

The potential causes of newborn HL caused by maternal SARS-CoV-2 infection remain elusive. It might involve multiple underlying mechanisms. First, SARS-CoV-2 infection in pregnant women might cause respiratory distress and hypoxia [30]. Thus, since a pregnant woman is a particular entity with a fetus in the uterus, SARS-CoV-2 infection affects not only the pregnant woman herself but also the fetus [30]. Second, SARS-CoV-2 infection in pregnant mothers can cause placental dysfunction, resulting in intrauterine hypoxia [31]. This infection can cause localized placental hypoxia through direct damage to the placental villi [32]. And yet, perinatal hypoxia is one cause of transitory or permanent HL in newborns [33]. Third, SARS-CoV-2 affects newborns after being transmitted vertically through the placenta. The placenta serves as a physiological and immunological barrier between the mother and the fetus, preventing viral transmission [34]. However, SARS-CoV-2 can invade placental tissue and cause infection and inflammation in placental cells [35]. A prospective, multicenter investigation found that infection occurred in 5.1 % of newborns born to mothers infected with SARS-CoV-2 during pregnancy, implying that SARS-CoV-2 can be transmitted intrauterine [36]. Strong evidence from another study revealed that 12 % of SARS-CoV-2-positive pregnant women transmit the virus intrauterine, and that intrauterine transmission may even occur in asymptomatic individuals [37]. Therefore, SARS-CoV-2 has the potential to affect the auditory system of newborns [6]. All newborns whose mothers with COVID-19 should be evaluated for cochlear function, even if their mothers were asymptomatic during pregnancy [21].

In humans, the cochlea forms 2.5 coils at 10 weeks of gestation, when the Colti organ and hair cells develop [38]. During embryonic development, certain viral infections might disrupt the development of the cochlea and the production of hairs and supporting cells [39]. Therefore, SARS-CoV-2 might affect the development of auditory organs more in mid-and late pregnancy than in early pregnancy. Screening the latest omics studies on the SARS-CoV-2 pathogenesis may provide valuable information for matching postnatal HL markers and major genes involved in the primary stages of auditory system development with virus-induced host changes [39].

SARS-CoV-2 testing in newborns should be emphasized. According to a study, single oral or rectal swabs failed to detect SARS-CoV-2 in 40–60 % of infected infants, whereas dual oral and rectal swabs considerably enhanced the detection rate of SARS-CoV-2 [37].

The COVID-19 pandemic has posed a significant challenge to health care systems worldwide, severely impacting the delivery of routine otolaryngology care [40]. Telemedicine plays an essential role in providing medical services and avoiding human cross-contamination [41,42]. Over the last decade, Tele-audiology (including remote HL) has grown significantly as the technological landscape has altered [43]. Ameyaw et al. reported that using distortion product otoacoustic emissions to screen newborn hearing over the Internet was comparable to the traditional face-to-face on-site HS approach [44]. The ongoing omicron pandemic has had a tremendous impact on society because of its incredible spread and intrinsic severity [45]. According to current predictions, the COVID-19 pandemic is expected to continue until November 2023 [46]. Therefore, Tele-audiology screening for newborns will be a valuable option for a more extended period in the future.

This systematic review has some limitations. First, the absence of high-quality case-control studies prevents the conduct of additional meta-analyses. Second, studies in this area were conducted in only five countries, lacking international data representation. Therefore, multi-ethnic, prospective, international, and multicenter research is needed in the future. Third, the presently available studies have a relatively short follow-up period for newborns. Nevertheless, the virus-caused HL may take some time to become noticeable [26]. A recent meta-analysis found a link between fetal Zika virus exposure and HL in children's first years of life [47]. As a result, the monitoring period for newborns with HL should be extended to detect probable late-onset hearing impairments caused by SARS-CoV-2 infection during pregnancy [27]. Fourth, the omicron variant differs from the prior SARS-CoV-2 characteristic; however, no studies on the effect of omicron on newborn hearing have been conducted.

5. Conclusions

In conclusion, whether SARS-CoV-2 positive pregnant women will affect the hearing of their newborns remains unclear, based on the current evidence in the literature. After maternal SARS-CoV-2 infection, the auditory system of the newborn may be affected due to intrauterine hypoxia and vertical transmission. In mid-and late pregnancy, SARS-

CoV-2 might have a more significant effect on HL in newborns. However, the HL in newborns caused by maternal SARS-CoV-2 infection is still not fully understood. Therefore, prospective, multicenter, large-scale clinical studies need to be conducted in the future. In addition, some basic studies (e.g. omics studies) are also warranted.

Abbreviations

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
HL hearing loss
HS hearing screening
ACE2 angiotensin converting enzyme 2
TMPRSS2 triggers transmembrane serine protease 2
ME middle ear
ET Eustachian tube

CRediT authorship contribution statement

Xiangming Meng: Conceptualization, Methodology, Writing - review & editing;
Kangxu Zhu: Investigation, Data Curation, Formal analysis;
Jing Wang: Investigation, Data Curation, Software;
Pan Liu: Investigation, Data Curation, Formal analysis.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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