

Journal of the American Academy of Audiology

In Vitro Fertilization and Hearing Impairment in Twins

Mingming Guo, Hanyao Liu, Seni Liao, Jinxia Huang, Ziruo Tan, Peixi Mo, Shunlin Ouyang, Huasong Zhang, Yanhong Chen.

Affiliations below.

DOI: 10.1055/a-2370-2695

Please cite this article as: Guo M, Liu H, Liao S et al. In Vitro Fertilization and Hearing Impairment in Twins. Journal of the American Academy of Audiology 2024. doi: 10.1055/a-2370-2695

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Medical and Health Science and Technology Plan of Longgang Shenzhen, LGKCYLWS2022019

Abstract:

Objective: This study investigates the potential correlation between in vitro fertilization (IVF) and hearing impairment in twins compared to naturally conceived twins.

Method: Analyzing data from 2416 twin infants born between 2019 and 2021. Analyze the pregnancy conditions and complications of mothers, the birth conditions of newborns, perinatal diseases, initial hearing screening results, and subsequent follow-up conditions.

Results: Our findings reveal that the incidence of hearing impairment in IVF-conceived twins is comparable to that in naturally conceived twins. Significant differences in low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia were observed between infants who passed and referred the hearing screening ($P \leq 0.05$). The IVF group exhibited a lower incidence of low birth weight ($P < 0.05$) and older maternal age ($P < 0.05$), while showing higher rates of placental abnormalities and placental abruption ($P < 0.05$). Notably, these distinctions did not translate into a significant impact on hearing impairment. Regardless of the method of conception, the following key factors contributing to hearing impairment in twins were identified: low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia.

Conclusion: IVF technology does not exert specific effects on hearing impairment in twins, with perinatal complications being the primary influencing factors.

Corresponding Author:

Dr. Huasong Zhang, The Third Affiliated Hospital of Guangzhou Medical University, Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, Guangzhou, China, 764137782@qq.com

Affiliations:

Mingming Guo, The Third Affiliated Hospital of Guangzhou Medical University, Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, Guangzhou, China

Hanyao Liu, The Third Affiliated Hospital of Guangzhou Medical University, Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, Guangzhou, China

Seni Liao, The Third Affiliated Hospital of Guangzhou Medical University, Department of Obstetrics and Gynecology, Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology; Guangdong-Hong Kong-Macao Greater Bay Area Higher Education Joint Laboratory of Maternal-Fetal Medicine, Guangzhou, China

[...]
Yanhong Chen, The Third Affiliated Hospital of Guangzhou Medical University, Department of Obstetrics and Gynecology, Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology; Guangdong-Hong Kong-Macao Greater Bay Area Higher Education Joint Laboratory of Maternal-Fetal Medicine, Guangzhou, China



This article is protected by copyright. All rights reserved.

Accepted Manuscript

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

In Vitro Fertilization and Hearing Impairment in Twins: A Comprehensive Analysis of Perinatal Factors

Mingming Guo^{a, #}, Hanyao Liu^{a, #}, Seni Liao^b, Jinxia Huang^c, Ziruo Tan^c, Peixi Mo^c,
Shunlin Ouyang^{a, *}, Huasong Zhang^{a, *}, Yanhong Chen^{b, *}

a. Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China;

b. Department of Obstetrics and Gynecology, Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology; Guangdong-Hong Kong-Macao Greater Bay Area Higher Education Joint Laboratory of Maternal-Fetal Medicine; The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China;

c. Department of Clinical Medicine, The Third Clinical School of Guangzhou Medical University, Guangzhou 511436, China.

#These authors contributed equally: Mingming Guo, Hanyao Liu

*These authors contributed equally: Shunlin Ouyang, Huasong Zhang, Yanhong Chen

ORCID:

Yanhong Chen: 0000-0002-7024-1948;

Huasong Zhang: 0000-0003-4514-6313;

Mingming Guo: 0009-0004-4218-6330.

Corresponding author:

Yanhong Chen, Prof.

Department of Obstetrics and Gynecology, Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology; Guangdong-Hong Kong-Macao Greater Bay Area Higher Education Joint Laboratory of Maternal-Fetal Medicine; The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China,
Email: 2011683122@gzhmu.edu.cn.

Huasong Zhang, Prof.

Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China,
Email: 764137782@qq.com,

Shunlin Ouyang, Prof.

Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510150, China,
Email: oysl7111@163.com.

Abstract:

Objective: This study investigates the potential correlation between in vitro fertilization (IVF) and hearing impairment in twins compared to naturally conceived twins.

Method: Analyzing data from 2416 twin infants born between 2019 and 2021. Analyze the pregnancy conditions and complications of mothers, the birth conditions of newborns, perinatal diseases, initial hearing screening results, and subsequent follow-up conditions.

Results: Our findings reveal that the incidence of hearing impairment in IVF-conceived twins is comparable to that in naturally conceived twins. Significant differences in low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia were observed between infants who passed and referred the hearing screening ($P \geq 0.05$). The IVF group exhibited a lower incidence of low birth weight ($P < 0.05$) and older maternal age ($P < 0.05$), while showing higher rates of placental abnormalities and placental abruption ($P < 0.05$). Notably, these distinctions did not translate into a significant impact on hearing impairment. Regardless of the method of conception, the following key factors contributing to hearing impairment in twins were identified: low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia.

Conclusion: IVF technology does not exert specific effects on hearing impairment in twins, with perinatal complications being the primary influencing factors.

Keyword: In vitro fertilization (IVF); Hearing impairment; Twins; Perinatal complications; Respiratory distress syndrome

Hearing impairment ranks as the 4th largest global disability, affecting nearly 400-500 million individuals, exerting profound negative impacts on the lives of affected individuals^{1,2}. Moreover, a significant portion of hearing impairments is congenital, the estimated incidence of sensorineural hearing impairment (> 40 dB HL) at birth is 1.86 per 1000 newborns in developed countries³, and without timely intervention, a majority of individuals with hearing loss may progress to experience profound deafness⁴. This highlights the serious consequences of hearing impairment on daily life.

Hearing impairments in twins are closely linked to congenital factors, with age-related hearing loss in twins potentially manifesting earlier due to genetic influences⁵.

Additionally, cases of amusia in twins have been associated with deletions in the

22q11.2 chromosome region⁶. Other prenatal factors also play a significant role in the incidence of hearing impairments in twins, with Congenital Cytomegalovirus Infection being one of the most critical non-genetic factors⁷. The interplay between genetics and environmental factors is equally crucial in the occurrence of hearing impairments in twins⁸. However, the multifactorial origins of hearing impairments present at birth in twins remain unclear.

With advancements in technology, twins today include those conceived naturally as well as those born through in vitro fertilization-embryo transfer (IVF-ET). IVF-ET has become a common assisted reproductive technology (ART) procedure due to delayed childbirth, declining fertility, and infertility issues⁹. The rise in IVF-ET procedures has led to an increase in twin births, introducing uncertainties during pregnancy^{10,11}. Concerns have arisen regarding potential developmental disparities between IVF-conceived and naturally conceived infants, with studies suggesting higher rates of cardiovascular diseases and diabetes in IVF-conceived children¹². While hearing impairments in IVF newborns may be associated with premature birth¹³, a notable lack of comparison with naturally conceived twins hampers effective health management for expectant mothers. Further research is needed to assess disparities in hearing impairment incidence between the two groups.

Hearing impairment represents a major sensory deficit in humans and is the most common birth defect¹⁴. Loss of hearing in newborns has become a severe threat to the overall health of children^{15,16}. Worldwide reporting of hearing loss finds that the prevalence of moderate and severe bilateral hearing deficit (> 40 dB HL) is 1–3 per 1,000 live births in well baby nursery population^{17,18} and 2–4 in 100 infants in an intensive care population^{19,20}, affecting 6% to 8% of the world's population²¹. To investigate whether IVF-ET technology influences the incidence of hearing impairment in twin newborns, this retrospective study analyzed clinical data from twins born in our hospital between 2019 and 2021 who underwent hearing screening. The findings are presented below. This study analyzed risk factors during twin pregnancies separately to explore how these factors affect newborns' hearing based on conception methods, offering fresh clinical insights into preventing congenital deafness.

Materials and Methods

1.1 Study Population

Ethical approval was obtained from the Ethical Committee of third affiliated hospital of Guangzhou Medical University (2023-135) for this study. Clinical data from 1,208 sets of twin newborns who underwent initial hearing screening at our hospital from January 1, 2019, to December 31, 2021, were collected. All collected patients were excluded for microtia and underwent tympanometry to assess middle ear conditions,

ruling out the presence of conductive hearing disorders such as secretory otitis media. Among these, 383 sets were naturally conceived, and 825 sets were conceived through in vitro fertilization-assisted reproduction (IVF-ART). The total number of newborns was 2,416, comprising 1,314 males and 1,102 females. All participants denied a history of ototoxic drug use, familial history of congenital deafness, and any significant middle ear abnormalities in newborns.

The collected data included:

- (1) Maternal age, gestational period, mode of delivery (vaginal or cesarean section), pregnancy complications, and fetal placental conditions for both groups of mothers.
- (2) Perinatal conditions of the newborns in both groups, including gender, gestational age, preterm birth (< 37 weeks), low birth weight (< 2500g), and complications.
- (3) Results of initial and follow-up hearing screenings for both groups of newborns.

1.2 Instruments and Methods

1.2.1 Instruments

Initial Hearing Screening: Transient Evoked Otoacoustic Emission (TEOAE) instruments from the American company Natus were used for newborns in the maternity and infant room. For newborns in the Neonatal Intensive Care Unit (NICU), both TEOAE and Automated Auditory Brainstem Response (AABR) screening instruments from Natus were employed.

Follow-up Hearing Screening: Distortion Product Otoacoustic Emission (DPOAE) instruments from the Danish company Interacoustics and AABR screening instruments from Natus were used for hearing re-evaluation.

1.2.2 Methods

Newborns typically undergo initial hearing screening within 48-72 hours after birth. For critically ill infants in the NICU, screening are conducted when their condition stabilizes, but no later than before discharge. Those who do not pass the initial screening undergo a follow-up screening at 42 days after birth. If still unsuccessful, they are advised to undergo objective diagnostic audiology examinations at a specialized hearing assessment institution at 3 and 6 months of age.

Qualified medical personnel, trained in hearing testing, conducted the screenings. The newborns were tested in a quiet or naturally sleeping state, with the ambient temperature and humidity kept appropriate, and environmental noise controlled below 40 dB SPL. Results were categorized as "Pass" or "Refer" for TEOAE and DPOAE tests and as "Pass" or "Refer" for AABR tests. Any instance where hearing screening did not pass on one or both sides indicated a failed screening.

Hearing screenings and follow-ups were conducted at our hospital, and newborns who did not pass the 42-day re-evaluation were recommended to undergo a comprehensive audiological diagnostic assessment at Department of Otolaryngology and Department of Obstetrics and Gynecology of The Third Affiliated Hospital of Guangzhou Medical University. Additionally, to gain further insights into the patients' hearing impairments and their impact on their lives, we conducted telephone follow-ups.

1.3 Statistical Analysis

Data were analyzed using SPSS 25.0 statistical software. Descriptive statistics were presented as mean \pm standard deviation for continuous variables, and t-tests were used for between-group comparisons. Count data were expressed as [n(%)] and analyzed using chi-square tests. Fisher's exact test was employed if any expected cell count in a four-cell table was less than 5. A significance level of $P < 0.05$ was considered statistically significant.

2 Results

2.1 Hearing Screening and Hearing Impairment in IVF-Conceived Twins and Naturally Conceived Twins

A total of 2,416 newborns were included in the study, with 1,650 in the IVF group. Among the IVF group, 208 (12.61%) did not pass the initial hearing screening, while in the naturally conceived group of 766, 115 (15.01%) did not pass the initial screening. Of the 208 cases in the IVF group that did not pass the initial screening, 35 [2.12%] did not pass the follow-up screening. In the naturally conceived group, out of 115 cases that did not pass the initial screening, 12 [1.57%] did not pass the follow-up screening. Ultimately, there were 17 cases (1.03%) of Sensorineural Hearing Loss in the IVF group and 3 cases (0.39%) in the naturally conceived group. While the initial screening failure rate was higher in the naturally conceived group, the follow-up screening rate, as well as the incidence of hearing impairment, were higher in the IVF group. However, statistical analysis did not reveal significant differences between the two groups ($P > 0.05$), as shown in Table 1.

Table 1: Comparison of Hearing Screening and Hearing Impairment Results in Two Groups of Newborns

	Naturally Conceived Group (N = 766)	IVF Group (N = 1650)	χ^2	P
Hearing Initial Screening Failure	115 [15.01%]	208 [12.61%]	2.617	0.106
Hearing Follow-up Screening Failure	12 [1.57%]	35 [2.12%]	0.844	0.358

Sensorineural Hearing Loss	3 [0.39%]	17 [1.03%]	-	0.147
----------------------------	-----------	------------	---	-------

*Statistical analysis did not reveal significant differences between the two groups ($P > 0.05$).

2.2 Comparison of Hearing Impairment Factors and Perinatal Conditions in Newborn Groups

Among the newborns, a total of 20 cases of hearing impairment were identified. Correlation analysis revealed a higher incidence of hearing impairment associated with several perinatal complications, such as low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia, all of which showed statistically significant associations ($P < 0.05$) as detailed in Table 2. This table compares various factors between newborns who passed and referred the hearing screening, indicating significant correlations with conditions like low birth weight, preterm birth, respiratory distress syndrome, respiratory pause, asphyxia, hyperbilirubinemia, and anemia in hearing-impaired newborns. In the group of newborns conceived via in vitro fertilization (IVF), consisting of 1,650 newborns, there were 917 males (55.58%) and 733 females (44.42%), with an average gestational age of 35.43 ± 17.16 weeks and an average birth weight of 2298.63 ± 533.41 g. The naturally conceived group, comprising 766 newborns, included 397 males (51.83%) and 369 females (48.17%), with an average gestational age of 35.29 ± 16.54 weeks and an average birth weight of 2167.52 ± 486.72 g. Comparison of outcomes between the two groups revealed no statistically significant differences in the incidence rates of preterm birth, respiratory distress syndrome, respiratory pause, asphyxia, hyperbilirubinemia, hypoglycemia, infection, intracranial hemorrhage, and anemia ($P > 0.05$), except for a statistically significant higher proportion of low birth weight infants in the naturally conceived group ($P < 0.001$), as shown in Table 2. This analysis underscores the importance of monitoring and managing perinatal risk factors to mitigate the risk of hearing issues in newborns.

Table 2: Comparison of Factors Related to Hearing Impairment and Perinatal

Variable	Hearing Screening			Perinatal Conditions		
	Pass	Refer	<i>P</i>	Naturally Conceived	IVF	<i>P</i>
Gender (Male/Female)	1304/109 2 (54.42%/45.58%)	10/10 (50%/50%)	0.692	397/369 (51.83%/48.17%)	917/733 (55.58%/44.42%)	0.085
Low Birth Weight	1568 (65.44%)	18 (90.00%)	0.021 *	576 (75.20%)	1010 (61.21%)	<0.001 ***
Preterm Birth	1771 (73.91%)	19 (95.00%)	0.032 *	558 (72.85%)	1232 (74.67%)	0.342
Respiratory Distress Syndrome	533 (22.25%)	9 (45.00%)	0.015 *	189 (24.67%)	353 (21.39%)	0.072
Respiratory Pause	16 (0.67%)	1 (5.00%)	0.132	4 (0.52%)	13 (0.79%)	0.605
Asphyxia	76 (3.17%)	1 (5.00%)	0.478	25 (3.26%)	52 (3.15%)	0.884
Hyperbilirubinemia	935 (39.02%)	13 (65.00%)	0.018 *	317 (41.38%)	631 (38.24%)	0.141
Hypoglycemia	354 (14.77%)	4 (20.00%)	0.523	103 (13.45%)	255 (15.45%)	0.196
Infection	524 (21.87%)	6 (30.00%)	0.382	186 (24.28%)	344 (20.85%)	0.058
Intracranial Hemorrhage	121 (5.05%)	0 (0%)	0.621	45 (5.87%)	76 (4.61%)	0.183
Anemia	637 (26.59%)	8 (40.00%)	0.177	223 (29.11%)	422 (25.58%)	0.067

Conditions in Two Groups of Newborns

*Statistical significance at $P < 0.05$.***Statistical significance at $P < 0.001$.

2.3 Comparison of Maternal Pregnancy and Delivery Conditions in Two Groups of Newborns

In the IVF group, consisting of 825 mothers, the average age was 33.23 ± 4.50 years, with a gestational period of 35.43 ± 17.16 weeks. Among them, 744 cases (90.18%) underwent cesarean section. In the naturally conceived group, the average maternal age was 30.10 ± 4.64 years, with a gestational period of 35.29 ± 16.54 weeks, and 332 cases (86.68%) underwent cesarean section. The comparison revealed that mothers in the IVF group were older ($P < 0.05$). The incidence rates of maternal complications during pregnancy were not statistically significant between the two groups for gestational hypertension, gestational diabetes, intrahepatic cholestasis of pregnancy,

anemia, premature rupture of membranes, abnormal amniotic fluid, anterior placenta, and fetal distress ($P > 0.05$). However, placental abnormalities and placental abruption had a higher incidence in the IVF group ($P < 0.05$), as shown in Table 3.

Table 3: Comparison of Maternal Pregnancy and Delivery Conditions in Two Groups of Newborns

	Naturally Conceived Group (N = 383)	IVF Group (N = 825)	t/ χ^2	P
Maternal Age (years)	30.10±4.64	33.23±4.50	11.120	<0.001***
Gestational Weeks	35.29±16.54	35.43±17.16	1.123	0.262
Cesarean Section	332 [86.68%]	744 [90.18%]	3.288	0.070
Gestational Hypertension	38 [9.92%]	101 [12.24%]	1.384	0.240
Gestational Diabetes	93 [24.28%]	243 [29.45%]	3.486	0.062
Intrahepatic Cholestasis	13 [3.39%]	23 [2.79%]	0.333	0.564
Anemia	100 [26.11%]	254 [30.79%]	2.763	0.096
Premature Rupture of Membranes	52 [13.58%]	137 [16.60%]	1.818	0.178
Abnormal Amniotic Fluid	26 [6.79%]	62 [7.52%]	0.204	0.651
Placental Abnormalities	32 [8.36%]	101 [12.24%]	4.034	0.045*
Anterior Placenta	7 [1.83%]	29 [3.52%]	2.576	0.108
Placental Abruption	4 [1.04%]	24 [2.91%]	4.017	0.045*
Fetal Distress	21 [5.48%]	34 [4.12%]	1.116	0.291

*Statistical significance at $P < 0.05$, ***Statistical significance at $P < 0.001$.

2.4 Analysis of the Stimulating Effect of IVF on Other Risk Factors

To investigate whether IVF may stimulate the impact of previously analyzed risk factors, we conducted a separate analysis of infants who passed and referred the hearing screening. Despite the limited number of infants with hearing impairment in our dataset, hindering statistical comparisons, we still observe significant differences in the occurrence of certain factors. Non-IVF infants have a higher incidence of hyperbilirubinemia (100% vs. 58.82%) and hypoglycemia (66.67% vs. 11.76%) compared to IVF infants. In contrast, IVF infants with hearing impairment more frequently experienced respiratory distress syndrome (0% vs. 52.94%), infections (0% vs. 35.29%), and anemia (3.33% vs. 41.18%) compared to naturally conceived infants.

Table 4: Comparison of Factors in Infants with Hearing Impairment in Non-IVF and IVF Groups

	Pass (N = 763) - Non-IVF	Pass (N = 1633) - IVF	Refer (N = 3) - Non-IVF	Refer (N = 17) - IVF
Gender (Male/Female)	397/366 (52.0%/48.0%)	907/726 (55.5%/44.5%)	0/3 □0%/100%□	10/7 (58.8%/41.2%)
Low Birth Weight Infants	573/763 □75.10% □	995/1633 □60.93% □	3/3 □100%□	15/17 □88.24%□
Premature Birth	555/763 □72.74% □	1216/1633 □ 74.46 %□	3/3 □100%□	16/17 □94.12%□
Respiratory Distress Syndrome	189/763 □23.85% □	344/1633 □20.45% □	0/3 □0%□	9/17 □52.94%□
Respiratory Pause	4/763 □0.52%□	12/1633 □0.73%□	0/3 □0%□	1/17 □5.88%□
Asphyxia	25/763 □3.28%□	51/1633 □3.12%□	0/3 □0.0%□	1/17 □5.88%□
Hyperbilirubinemi a	314/763 □41.15% □	621/1633 □38.03% □	3/3 □100%□	10/17 □58.82%□
Hypoglycemia	101/763 □13.24% □	235/1633 □14.39% □	2/3 □66.67%□	2/17 □11.76%□
Infections	186/763 □24.38% □	338/1633 □20.70% □	0/3 □0%□	6/17 □35.29%□
Intracranial Hemorrhage	45/763 □5.90%□	76/1633 □4.65%□	0/3 □0%□	0/17 □0%□
Anemia	222/763 □29.10% □	415/1633 □25.41% □	1/3 □3.33%□	7/17 □41.18%□

Note: Percentages are based on the total number of infants in each group.

3 Discussion

The key findings of this study can be summarized as follows: (1) Premature birth, combined with respiratory distress syndrome and hyperbilirubinemia, are independently associated with an increased risk of referring the hearing screening in twins; (2) Among the factors affecting twins are not linked to “Refer” results or other prenatal diseases, except for placental abnormalities; and (3) Among infants with “Refer” results, those conceived through IVF face a higher risk of respiratory distress syndrome, infection, and anemia leading to “Refer”. In contrast, infants conceived

naturally are more susceptible to the impact of hyperbilirubinemia and hypoglycemia. These findings suggest that IVF-conceived twin infants are more prone to the influence of respiratory distress syndrome, contributing to the pathogenesis of referring the hearing screening.

Following adjustments for confounding factors like parental characteristics, prenatal anomalies, and infant health, our study reveals no notable link between neonatal Newborn Hearing Screening (NHS) and hearing impairment, irrespective of natural conception or IVF. This aligns with previous research¹³, challenging earlier suggestions that In Vitro Fertilization Assisted Reproductive Technology (IVF-ART) may increase the risk of hearing impairment. Our study emphasizes that there is no differential impact on hearing development between natural conception and IVF.

In a comprehensive comparison between infants with hearing impairment and those with “Pass”, we observed that hearing impairment is independently associated with the risks of low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia in twins. Perinatal infections are a significant cause of hearing impairments in twins^{22,23}, yet children with such infections were not included in this study, suggests that the families involved place a high value on the well-being of their infants. Infantile hearing impairments may be preventable through immunization, early prenatal diagnosis, proper treatment of infections, and avoiding the prescription of ototoxic drugs²⁴, underscoring the significance of infections in infantile hearing impairments. Apart from infections, genetic non-syndromic, asphyxia, and prematurity are more common in infantile hearing impairments²⁵, and this study also focuses on non-infectious factors. Preterm birth has long been considered a significant risk factor for hearing impairment, as it represents a crucial negative factor for the development of the nervous system^{20,26}. Notably, the association of respiratory distress syndrome and hyperbilirubinemia with hearing impairment in twins is reported for the first time in this study. While previous studies highlighted increased risks associated with IVF in adverse perinatal outcomes, our findings provide novel insights into the specific factors contributing to hearing impairment in twins.

The acute detrimental effects of respiratory distress syndrome on the nervous system have been recognized in early studies²⁷⁻²⁹, much like the well-established adverse effects of hyperbilirubinemia³⁰, although previous studies were focused on singleton infants³¹. However, our study unveils a novel revelation regarding the impact of these conditions on neonatal hearing impairment in twins. Given the prevalence of respiratory distress syndrome and hyperbilirubinemia, this information holds paramount importance for twins pregnant women³², emphasizing the critical need for prompt delivery when confronted with these conditions to avert the onset of hearing impairment in fetuses. Moreover, the incidence of placental abnormalities in IVF infants surpasses that in naturally conceived infants^{33,34}, and IVF infants face issues such as hearing impairment, hypoxia, and respiratory distress syndrome. It is evident that respiratory distress syndrome resulting from placental abnormalities is a major

contributor to hearing impairment in IVF infants. Therefore, during routine prenatal check-ups, particular attention should be paid to the status of the placenta in IVF fetuses, especially when there are indications of placental abnormalities or early detachment. Proactive measures should be taken to prevent respiratory distress syndrome in fetuses in such cases.

We conducted a comprehensive comparison of perinatal conditions and maternal pregnancy characteristics between the IVF and non-IVF groups. Our findings unveiled a correlation between low birth weight and maternal age at childbirth, aligning with previous research. This study further corroborates the influential role of fetal low birth weight and advanced maternal age in the manifestation of hearing impairment.

When differentiating infants who passed the hearing screening from those with hearing impairment into the IVF and non-IVF groups, we scrutinized potential risk factors. A higher incidence of hyperbilirubinemia was observed in non-IVF infants compared to IVF infants. Meanwhile, infants with hearing impairment in the IVF group exhibited a greater likelihood of experiencing respiratory distress syndrome compared to naturally conceived infants. Although explicit statistical differences were not discerned, proportional variations were evident.

This section of the analysis underscores the heightened risk of hyperbilirubinemia in naturally conceived infants. For mothers with natural conception, adopting a proactive monitoring and prevention approach toward hyperbilirubinemia is recommended to better safeguard infant hearing. Conversely, for IVF-conceived infants, the increased incidence of respiratory distress syndrome, potentially associated with the impact of IVF on the placenta, emphasizes the necessity for enhanced prevention measures against respiratory distress syndrome in IVF pregnancies. This is particularly significant for protecting infant hearing in IVF pregnancies.

This study is subject to limitations such as a relatively small sample size, discrepancies in case numbers between the naturally-conceived and IVF-conceived groups, and potential selection bias due to sourcing subjects solely from a single hospital. To address these limitations, we plan to increase the sample size, conduct multicenter studies, and further explore the incidence of hearing impairment in comparison to existing literature.

Conclusion

Given the higher incidence of twin births facilitated by IVF-ET technology, our study sought to examine the potential impact of IVF on hearing impairment in twins compared to naturally conceived twins. However, our analysis did not reveal any discernible influence. The primary factors associated with the occurrence of hearing impairment in twins were identified as low birth weight, preterm birth, respiratory distress syndrome, and hyperbilirubinemia—common perinatal complications.

Notably, there were no significant differences in maternal pregnancy complications and neonatal perinatal complications between IVF-conceived pregnancies and naturally conceived pregnancies, except for a higher maternal age, increased incidence of placental abruption, and higher newborn weight in the IVF group. In summary, IVF technology does not demonstrate specific effects on hearing impairment in twins. The influencing factors primarily stem from perinatal complications in newborns, emphasizing that this technology does not lead to long-term harm.

Declarations

This manuscript contains the following sections: Ethics, consent and permissions, Data availability statement, Competing interests, Consent to publish, Authors' contributions, Acknowledgments and Funding.

Ethics, consent and permissions

This study was approved by the Sun Yat-sen Memorial hospital, Sun Yat-sen University ethics committee, and informed consents were obtained from all studied participants.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

We have no conflicts of interests to declare.

Consent to publish

We have obtained consent to publish from the participant to report individual patient data.

Authors' contributions

Mingming Guo, Hanyao Liu and Huasong Zhang analyzed the data and wrote the manuscript. Mingming Guo, Hanyao Liu, Jinxia Huang, Ziruo Tan, Peixi Mo, Huasong Zhang and Yanhong Chen identified and collected patients. Mingming Guo, Hanyao Liu and Huasong Zhang advised on data analysis. Mingming Guo, Hanyao Liu and Huasong Zhang wrote the manuscript. All authors have read and approved the final manuscript.

Acknowledgments and Funding

The work was funded by the Medical and Health Science and Technology Plan of Longgang Shenzhen (No. LGKCYLWS2022019).

Abbreviations and Full Terms Table

Abbreviation	Full Term
IVF	In Vitro Fertilization
IVF-ET	In Vitro Fertilization-embryo Transfer
ART	Assisted Reproductive Technology
IVF-ART	In Vitro Fertilization-assisted Reproduction
TEOAE	Transient Evoked Otoacoustic Emission
NICU	Neonatal Intensive Care Unit
AABR	Automated Auditory Brainstem Response
DPOAE	Distortion Product Otoacoustic Emission
NHS	Newborn Hearing Screening

References:

- ¹ Brown, C. S., Emmett, S. D., Robler, S. K. & Tucci, D. L., Global Hearing Loss Prevention. *OTOLARYNG CLIN NAM* **51** 575 (2018).
- ² Haile, L. M. *et al.*, Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. *The Lancet* **397** 996 (2021).
- ³ Nance, W. E., Lim, B. G. & Dodson, K. M., Importance of congenital cytomegalovirus infections as a cause for pre-lingual hearing loss. *J CLIN VIROL* **35** 221 (2006).
- ⁴ L Bubbico, A Rosano & Spagnolo, A., Prevalence of prelingual deafness in Italy. *ACTA OTORHINOLARYNGO* **1** 17 (2007).
- ⁵ Duan, H. *et al.*, A Genome-Wide Association Study of Age-Related Hearing Impairment in Middle- and Old-Aged Chinese Twins. *BIOMED RES INT* **2021** 1 (2021).
- ⁶ Szyfter, K. & Wigowska-Sowińska, J., Congenital amusia—pathology of musical disorder. *J APPL GENET* **63** 127 (2022).
- ⁷ Cordray, H., Liu-Lam, O., Tey, C. S. & Alfonso, K., Congenital Cytomegalovirus Infection and Hearing Outcomes in Twins: A Systematic Review of Reported Cases. *OTOL NEUROTOL* **44** e53 (2023).
- ⁸ Momi, S. K., Wolber, L. E., Fabiane, S. M., MacGregor, A. J. & Williams, F. M. K., Genetic and Environmental Factors in Age-Related Hearing Impairment. *TWIN RES HUM GENET* **18** 383 (2015).
- ⁹ Lv, P. *et al.*, Altered thyroid hormone profile in offspring after exposure to high estradiol environment during the first trimester of pregnancy: a cross-sectional study. *BMC MED* **12** (2014).
- ¹⁰ Yoder, N., Tal, R. & Martin, J. R., Abdominal ectopic pregnancy after in vitro

fertilization and single embryo transfer: a case report and systematic review. *REPROD BIOL ENDOCRIN* **14** (2016).

¹¹ Erenus, M. *et al.*, The effect of embryo quality on subsequent pregnancy rates after in vitro fertilization. *FERTIL STERIL* **56** 707 (1991).

¹² Aljahdali, A. *et al.*, The duration of embryo culture after mouse IVF differentially affects cardiovascular and metabolic health in male offspring. *HUM REPROD* **35** 2497 (2020).

¹³ Yin, J. *et al.*, Association between in vitro fertilization-embryo transfer and hearing loss: risk factors for hearing loss among twin infants in a cohort study. *EUR J PEDIATR* **182** 1289 (2023).

¹⁴ Cushing, S. & Papsin, B., Cochlear Implants and Children with Vestibular Impairments. *Seminars in Hearing* **39** 305 (2018).

¹⁵ Purcell, P. L. *et al.*, Cochlear Implantation in Infants: Why and How. *TRENDS HEAR* **25** 582781971 (2021).

¹⁶ McGregor, S. & Goldman, R. D., Language outcomes after cochlear implant. *CAN FAM PHYSICIAN* **68** 737 (2022).

¹⁷ A, E., J, L., C, S., D, T. & P, Z., Newborn and Infant Hearing Loss: Detection and Intervention. *PEDIATRICS* **103** 527 (1999).

¹⁸ Mehl, A. L. & Thomson, V., Newborn Hearing Screening: The Great Omission. *PEDIATRICS* **101** e4 (1998).

¹⁹ Yoon, P. J., Price, M., Gallagher, K., Fleisher, B. E. & Messner, A. H., The need for long-term audiologic follow-up of neonatal intensive care unit (NICU) graduates. *INT J PEDIATR OTORHI* **67** 353 (2003).

²⁰ Wang, C. *et al.*, Prevalence and independent risk factors for hearing impairment among very low birth weight infants. *INT J PEDIATR OTORHI* **93** 123 (2017).

²¹ Wilson, B. S., Tucci, D. L., Merson, M. H. & O'Donoghue, G. M., Global hearing health care: new findings and perspectives. *The Lancet* **390** 2503 (2017).

²² Angueyra, C., Abou Hatab, H. & Pathak, A., Congenital Cytomegalovirus and Zika Infections. *The Indian Journal of Pediatrics* **87** 840 (2020).

²³ Rawlinson, W. D. *et al.*, Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *The Lancet Infectious Diseases* **17** e177 (2017).

²⁴ Jiang, F., Kuper, H., Bright, T. & Qin, W., Etiology of Childhood Bilateral Sensorineural Hearing Loss in Shandong Province, China. *AM J AUDIOL* **29** 236 (2020).

²⁵ Morzaria, S., Westerberg, B. D. & Kozak, F. K., Systematic review of the etiology of bilateral sensorineural hearing loss in children. *INT J PEDIATR OTORHI* **68** 1193 (2004).

²⁶ Chung, E. H., Chou, J. & Brown, K. A., Neurodevelopmental outcomes of preterm infants: a recent literature review. *Translational Pediatrics* **9** S3 (2020).

²⁷ Lo-Cao, E., Hall, S., Parsell, R., Dandie, G. & Fahlström, A., Neurogenic pulmonary edema. *The American Journal of Emergency Medicine* **45** 673 (2021).

²⁸ Quasney, M. W., López-Fernández, Y. M., Santschi, M. & Watson, R. S., The Outcomes of Children With Pediatric Acute Respiratory Distress Syndrome.

PEDIATR CRIT CARE ME **16** S118 (2015).

²⁹ Vermillion, S. T., Soper, D. E., Bland, M. L. & Newman, R. B., Effectiveness of antenatal corticosteroid administration after preterm premature rupture of the membranes. *AM J OBSTET GYNECOL* **183** 925 (2000).

³⁰ Hansen, T. W. R., Wong, R. J. & Stevenson, D. K., Molecular Physiology and Pathophysiology of Bilirubin Handling by the Blood, Liver, Intestine, and Brain in the Newborn. *PHYSIOL REV* **100** 1291 (2020).

³¹ Ebbesen, F., Ehrenstein, V., Traeger, M. & Nielsen, G. L., Neonatal non-hemolytic hyperbilirubinemia: a prevalence study of adult neuropsychiatric disability and cognitive function in 463 male Danish conscripts. *ARCH DIS CHILD* **95** 583 (2010).

³² Zhu, X. *et al.*, Perinatal Outcomes and Related Risk Factors of Single vs Twin Pregnancy Complicated by Gestational Diabetes Mellitus: Meta-Analysis. *COMPUT MATH METHOD M* **2022** 1 (2022).

³³ Jauniaux, E., Moffett, A. & Burton, G. J., Placental Implantation Disorders. *OBSTET GYN CLIN N AM* **47** 117 (2020).

³⁴ Rifouna, M. S. *et al.*, First trimester trophoblast and placental bed vascular volume measurements in IVF or IVF/ICSI pregnancies. *HUM REPROD* **29** 2644 (2014).