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Distortion product otoacoustic emissions in newborn babies with and without late-term maternal iron deficiency anaemia

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ABSTRACT

Background: Studies on animals have demonstrated that maternal iron deficiency anaemia (IDA) could result in decreased cochlear sensory hair cells and reduced amplitudes of distortion-product otoacoustic emissions (DPOAEs) of young guinea pigs. Thus, it is essential to study the functioning of cochlear hair cells using DPOAEs in human newborn babies with maternal IDA. The current study explores maternal IDA's effect on DPOAEs in newborn babies.

Method: A total of 110 newborn babies with gestational age ≥34 weeks were considered and a 'between-subjects' design was used. The participants were divided into 3 groups- "Normal" (61 babies without maternal IDA), "Mild" (28 babies with mild maternal IDA) and "Moderate" (21 babies with moderate maternal IDA). The cord blood was collected and the DPOAEs were recorded for each baby for a range of frequencies (1 k – 8 kHz) and a range of intensities (70–40 dB SPL in 10 dB steps).

Results: The analysis of both DP-gram and DP input-output (I/O) function showed that there was no significant difference ($p > 0.05$) across the normal, mild, and moderate groups in the overall presence of DPOAEs as well as the amplitude across frequencies or intensities (70–40 dB SPL). Also, the overall correlation of RBC indices with DPOAE amplitude across frequencies as well as the slope of the I/O function showed no relationship.

Conclusion: The current study concludes that there is no effect of late-term maternal IDA on the DPOAEs of newborn babies.

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1. Introduction

Anaemia has a high prevalence during pregnancy, affecting more than 40% of pregnant women globally and a haemoglobin level of less than 11 g/dL is considered 'pregnancy anaemia' (WHO, 2008, 2000). Iron deficiency (ID) is the primary cause of pregnancy anaemia and more than 50% of pregnant women in India have iron deficiency anaemia (IDA) (Kalaivani, 2009; Kaushal et al., 2022; NFHS-5, 2021). During pregnancy, a large quantity of iron is necessary to increase the red blood cell mass, expand the plasma volume and allow the growth of the foetal-placental unit (Scholl, 2005). Iron sufficiency during the prenatal period is vital for the infant to have proper brain development and sensory maturation, including the development of the auditory system (Puga et al., 2018). ID during the pregnancy affects the foetus along with the mother and the neuro-cognitive/sensory complications due to ID during this period may persist into adulthood (e.g., Sharma, 2003; Beard, 2008; Kalaivani, 2009; Sharma and Shankar, 2010; Radlowski and Johnson, 2013; Saluja et al., 2016). The greater the severity, the greater will be the effects (Cetin et al., 2004).

Iron is a crucial element for the proper development and functioning of the peripheral and central auditory systems (Jougleux et al., 2011, 2014; Yu et al., 2014). In the peripheral auditory system, iron is engaged in a variety of biochemical processes and is important for oxygen transport & delivery, growth & differentiation of cells, electro-mitochondrial transfer, and several enzymatic systems. Intra-neuronal iron participates in the synthesis and release of neuro-mediators, neurotransmitter metabolism, and synaptic transmission within the inner ear (cochlea) (Jougleux

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et al., 2014). ID can result in structural as well as functional changes in the cochlea due to the inability of blood to transport oxygen to the living tissues, and due to a compromised function of the vital enzymes (Jougleux et al., 2011, 2014; Yu et al., 2014). Animal studies have shown that ID decreases the cochlear sensory hair cells by increasing the number of apoptotic cells (Yu et al., 2014) and can cause abnormalities in the hair cells of the cochlea such as stereocilia fusion/twisting, coalescence of adjacent stereocilia, loss of stiffness of sensory hair, and loss of stereocilia (Sun et al., 1987). The cochlear hair cells are one of the highly vulnerable components of the peripheral auditory system, and their damage can result in loss of hearing along with a reduced or absent distortion product otoacoustic emission (DPOAE) (Dorn et al., 2001; Gorga et al., 2000; Liberman et al., 2004).

DPOAEs are the commonly used rapid pre-neural measure generated by two stimulus tones with F1 & F2 frequencies simultaneously (F_{DP} = 2F1-F2) (Zelle et al., 2017). DPOAEs have been proven to be very sensitive to the functional integrity of OHCs and the degree of reduction in the DPOAE amplitude is directly proportional to the extent of OHC damage (Dorn et al., 2001; Gorga et al., 2000; Liberman et al., 2004). They are recorded non-invasively by placing a probe in the ear canal and can be obtained easily even in newborn babies. Two studies have used DPOAEs to evaluate the effect of maternal or neonatal IDA. An animal study evaluated the effect of maternal IDA on newborn guinea pigs using DPOAEs and showed that even a mild maternal IDA can result in reduced amplitudes of DPOAEs in young guinea pigs (Yu et al., 2014). A human study measured DPOAEs at six F2 frequencies (1.5, 2, 3, 4.5, 6 & 8 kHz) in infants of 6–24 months and showed that the amplitude levels of DPOAEs are similar in the infants with and without IDA (Sundagumaran and Seethapathy, 2020). They concluded that outer hair cell functioning is not affected by the iron status in infants and suggested that fine-structure DPOAEs may help in identifying more precise changes caused due to ID.

Despite the animal study showing the structural and functional abnormalities of the cochlear hair cells in young guinea pigs with maternal ID (Yu et al., 2014), the effect of maternal ID on the peripheral auditory system is not known in human newborn babies. Though there is a study on human infants (Sundagumaran and Seethapathy, 2020), it evaluated infants above 6 months and cannot be generalized to newborn babies, as the development of the peripheral auditory system continues till 6 months of age, and the cochlear hair cells are tuned to receive specific frequency or intensity signals during this time (Graven and Browne, 2008). Therefore, it is important to study how the DPOAEs are affected by maternal IDA in newborn babies.

1.1. Aim

The current study aims to explore the maternal IDA's effect on DPOAEs in newborn babies.

2. Material and methods

The study was conducted at a rural-tribal secondary care hospital in Saragur taluk of Mysuru, a district in the southern part of Karnataka state, India. A between-subjects design was used.

2.1. Ethics

The study adhered to the "Ethical guidelines for bio-behavioural research" by All India Institute of Speech and Hearing (AIISH) (Basavaraj and Venkatesan, 2009) and guidelines of Vivekananda Memorial Hospital (VMH). The ethical clearance was obtained from AIISH ethics committee (approval no & date: WOF-174/2018–19, December 21, 2020) and institutional review board of VMH (approval no & date: IRB-10/2019–20/86, April 4, 2020).

2.2. Participants

A total of 110 newborn babies from rural-tribal areas of the Mysuru district, who were delivered at VMH, were recruited for the research. The participants were divided into three groups depending on the presence or absence of late-term maternal IDA, based on the WHO standards for haemoglobin (HGB) as a reference (WHO, 2000). "Group I (Normal)" consisted of 61 babies without maternal anaemia (HGB $\geq$11 g/dL), "Group II (Mild)" consisted of 28 babies with mild maternal IDA (HGB: 10.0–10.9 g/dL) and the "Group III (Moderate)" consisted of 21 babies with moderate maternal IDA (HGB: 7.0–9.9 g/dL). This sample size of at least 20 infants in each of anaemia groups and 60 infants in the normal group (after exclusion criteria) provided a power of 0.80 at 0.05 significance level.

2.3. Inclusion and exclusion criteria

The newborn babies with gestational age (GA) $\geq$ 34 weeks at birth (late pre-term & full-term babies) delivered at VMH during June 2021–January 2022 (8 months) who were diagnosed as "stable" by the paediatrician were included in the study. Babies admitted to the neonatal intensive care unit (NICU) for more than five days, birth weight less than 2.5 kg, family history of permanent hearing loss, hyperbilirubinemia (serum bilirubin level >20 mg/dL), and infants with a delayed birth cry, birth asphyxia, syndromes, craniofacial anomalies, in-utero infections associated with hearing loss or with any prenatal, natal and post-natal high-risk factors associated with hearing loss according to Joint Committee on Infant Hearing (2007) were excluded (JCIH, 2007). Also, babies born to mothers with sickle cell anaemia or any other complications during pregnancy were excluded from the study. Apart from maternal IDA, no other risk factors differentiated the babies in the control and anaemia groups.

2.4. Test environment

The blood samples of the mother as well as the baby were collected in a sterile environment. The DPOAEs were recorded either in the hospital or at home, in a silent area with acceptable noise limits (Hollowell, 2012).

2.5. Procedure

The test procedure started with the recruitment of pregnant women with and without IDA at the 9th month of their pregnancy and their health condition along with the treatment received throughout the pregnancy was documented. Post-delivery, their respective newborn was recruited for the study after obtaining clearance from the paediatrician and a detailed pre-natal, natal and post-natal case history was taken. The test procedures, potential risks, and benefits were explained and an informed consent for the recruitment of both mother & the baby was signed by the mother or legal caregiver, before starting the procedure.

2.5.1. Blood collection & testing

Venous blood was collected from each pregnant woman just before the delivery and the cord blood from their respective newborn baby was collected immediately after the delivery. This is a routine procedure at the hospital and was carried out by an experienced nurse under supervision. The collected samples were centrifuged immediately to separate the serum and were stored in

the refrigerator at 4 °C if the testing was delayed. Both blood samples were tested in the laboratory to obtain the RBC indices which included HGB, haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) & red blood cell (RBC) count.

2.5.2. Distortion product otoacoustic emissions (DPOAEs)

The DPOAEs were recorded for all the babies between 0 and 2 weeks after birth out of which 37% babies were tested within 48 h s after birth (23% babies tested within 24 h & 14% babies tested between 24 and 48 h after birth). The DPOAEs were recorded separately for each ear using a calibrated "SENTIERO ADVANCED" clinical otoacoustic emission analyser system (PATH MEDICAL, Germany). They were recorded when the baby was asleep or when there were minimal movements by placing the probe in the ear canal and a proper probe fit was ensured. Both DP-grams and DP I/O functions were recorded.

- DP-gram: The 2F1−F2 amplitudes were obtained at eight F2 frequencies (1 k, 1.5 k, 2 k, 3 k, 4 k, 5 k, 6 k and 8 kHz) and the F2/F1 ratio was 1.22. The DPOAEs were obtained for fixed levels of F1 (L1 = 65 dB SPL) & F2 (L2 = 55 dB SPL).
- DP I/O function: The 2F1−F2 amplitude was measured at F2 frequencies of 1 k, 2 k & 4 kHz with a fixed F2/F1 ratio of 1.22. The F2 level (L2) varied from 70 dB SPL to 40 dB SPL in 10 dB steps, and the F1 level (L1) was 10 dB more than the F2 level (L1 = L2+10 dB).

2.6. Analysis

The presence, amplitude and signal-to-noise ratio (SNR) of the DPOAE was noted for all the stimulus conditions for each subject and the data were analysed using IBM SPSS (Version 20) statistical software. For analysis and comparison of DPOAE presence across the groups, the responses with amplitude ≥5 dB SPL and SNR ≥6 dB were considered, and others were considered as "absent OAEs". But for comparison of DPOAE amplitude across the groups, all the amplitude and SNR values were considered as the DPOAEs lower than or on the order of the noise level (absent OAEs) also provide valuable information. The Kolmogorov-Smirnov (K–S) test was performed to check the normality of the overall data and Shapiro-Wilk (S–W) test was performed to check the normality of data across groups.

3. Results

The results of the K–S test for the overall data showed that 75% of the RBC were normally distributed indices ($p > 0.05$ for 9/12 observations) whereas only 50% of DP-gram (8/16 observations) and 38% of DP I/O function (9/24 observations) data had a normal distribution ($p > 0.05$). The results of the S–W test for the data across the groups showed that 75% of the RBC indices (27/36 observations), 77% of DP-gram (37/48 observations) and 76% of DP I/O function (55/72 observations) data had a normal distribution ($p > 0.05$). The percentages represent no. of observations normally distributed out of total observations in the data (e.g., 8 out of 16 DP-gram observations (50%) had a normal distribution) and the data was considered as normal distribution, if more than 75% observations were normally distributed. Thus, the *non-parametric tests* (Spearman correlation) were performed for overall data and *parametric tests* (Analysis of variance - ANOVA & repeated measures ANOVA) were performed for data across groups. The detailed statistics (along with p value) of normality tests (K–S & S–W test) are provided as supplementary material (Appendix A).

3.1. RBC indices

Out of 110 mothers and their respective babies, the maternal HGB was available for all the babies and the neonatal RBC indices were available for 108 babies as the cord blood samples of 2 babies which were haemolyzed, were discarded. The RBC indices other than HGB (HCT, MCV, MCH, MCHC & RBC count) were available only for 70 mothers as they are not tested routinely for all mothers. One-way ANOVA was performed to compare the RBC indices of mothers just before delivery (maternal) as well as the newborn babies (neonatal) across the groups and the results along with the descriptive statistics are provided as supplementary material (Appendix B). The results revealed that there was a significant difference ($p < 0.005$) for all the maternal RBC indices across the groups. The post-hoc tests (Bonferroni) showed a significant difference between all the pairs (normal-mild, normal-moderate & mild-moderate groups) for HGB & HCT, between normal-mild, normal-moderate groups for MCV & MCH and between normal-moderate groups for MCHC & RBC count. Despite the maternal RBC indices being significantly different across the groups, the results for the neonatal RBC indices did not show any significant difference across the groups. The higher-order tests were not performed as there were missing values.

3.2. DP-gram

The presence of DPOAEs at individual frequencies was analysed for all 110 babies and the overall presence was analysed for 105 babies as the data of 5 babies had missing values at few frequencies. The results showed that 48 out of 60 (81%) babies in the normal group, 21 out of 25 (84%) babies in the mild group and 13 out of 20 (70%) babies in the moderate group had an overall presence of DPOAEs (at 3 or more frequencies) in both ears. The DPOAE presence at each frequency across normal, mild, and moderate groups for each ear has been provided in Table 1. The equality of population proportions test was used to compare the overall presence of DPOAE as well as the presence of DPOAE at different frequencies among the 3 groups. The results showed that, the overall presence of DPOAEs did not show any significant difference across the groups. The comparison at each frequency showed that, the normal group had a significantly better presence of DPOAEs at 4 kHz in the right ear when compared to the moderate group ($Z = 2.255$, $p = 0.024$) and a significantly poor presence at 6 kHz in the left ear when compared to the mild group ($Z = -2.242$, $p = 0.025$). This could be due to chance factor.

The descriptive statistics (mean & standard deviation) obtained for the DPOAE amplitude at different frequencies (1 k, 1.5 k, 2 k, 3 k, 4 k, 5 k, 6 k and 8 kHz) across groups for each ear are provided in Fig. 1.

Repeated measures ANOVA and ANOVA were carried out to compare the DPOAE amplitude at different frequencies of both ears across the groups. The results did not show any significant difference across the groups ($F(2,100) = 1.160$, $p = 0.318$), but there was a significant main effect of frequency on the DPOAE amplitude ($F(7,100) = 92.651$, $p < 0.001$). The mid frequencies showed a better amplitude than the low or high frequencies. Also, there was a significant interaction effect ($F(14,100) = 1.732$, $p = 0.045$) between ear, frequency, and groups.

Furthermore, the Spearman correlation coefficient was obtained for the overall data (all babies) to check the correlation of RBC indices (maternal & neonatal) with the DPOAE amplitude across different frequencies (1 k, 1.5 k, 2 k, 3 k, 4 k, 5 k, 6 k and 8 kHz). Only the maternal HB out of 13 RBC indices showed a significant positive correlation with DPOAE amplitude at 4 kHz in the right ear and 2 kHz in the left ear. This could be due to the chance factor as there

Table 1
The average percentage of overall presence and presence of DPOAE at different frequencies (1 k, 1.5 k, 2 k, 3 k, 4 k, 5 k, 6 k and 8 kHz) in normal, mild, and moderate groups are provided for both ears.

Ear	Group	Total N	Overall Presence (%)	DP-gram (Frequency)							
				1 kHz	1.5 kHz	2 kHz	3 kHz	4 kHz	5 kHz	6 kHz	8 kHz
Right	**Normal**	61	82%	70%	88%	95%	84%	**93%**	85%	57%	21%
	Mild	28	84%	63%	78%	83%	86%	83%	80%	71%	40%
	Moderate	21	65%	91%	89%	95%	89%	**74%**	71%	80%	20%
Left	**Normal**	61	81%	66%	87%	90%	72%	88%	71%	**52%**	23%
	Mild	28	88%	64%	73%	91%	71%	88%	88%	**81%**	19%
	Moderate	21	70%	73%	88%	100%	83%	95%	89%	53%	15%

‡ The significantly different values ($p < 0.05$) are in bold.

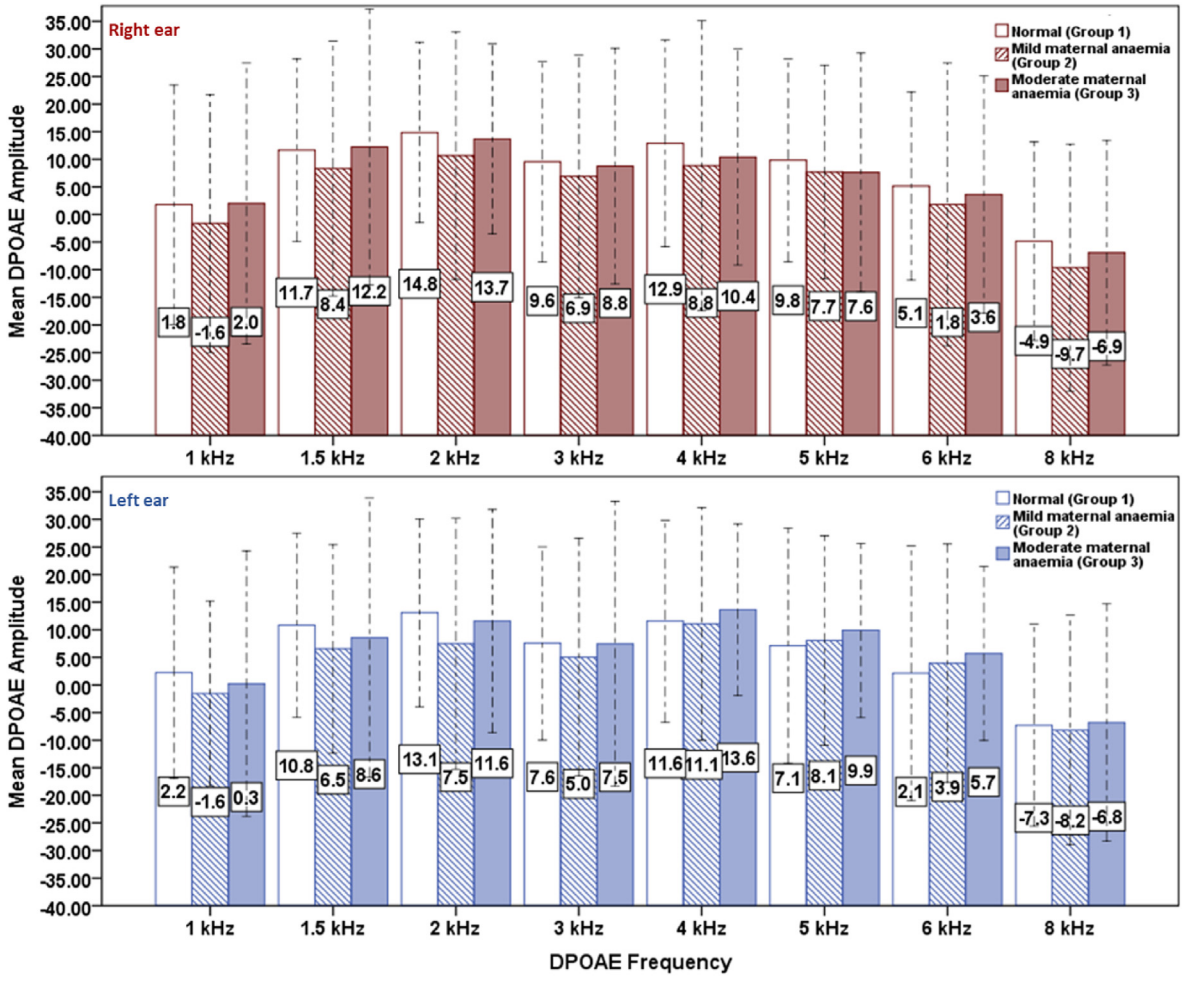

Fig. 1. Mean and standard deviation of DPOAE amplitude at different frequencies (1 k, 1.5 k, 2 k, 3 k, 4 k, 5 k, 6 k and 8 kHz) across normal, mild, and moderate groups for both ears.

were multiple correlations. The details of Spearman correlation for the amplitude values of DP-gram with RBC indices are provided in Table 2.

3.3. DP I/O function

For the DP I/O function, the DPOAE presence, amplitude and slope were analysed for 106 babies out of 110 babies as the data of 4 babies had missing values at 2 or more intensity levels. The presence of DPOAEs at 1 k, 2 k, & 4 kHz for different intensities (70, 60, 50 & 40 dB SPL) across the normal, mild, and moderate groups for both ears are provided in Table 3. The equality of proportions test showed a significantly better presence of DPOAEs at 1 & 2 kHz (60 dB) in the left ear for the normal group when compared to the mild group. There was no significant difference between normal & moderate as well as mild & moderate groups.

The descriptive statistics (mean & standard deviation) were obtained for the DPOAE amplitude at different intensities and frequencies across groups for both ears (Fig. 2) and the slope of the DPOAE amplitude across intensities was calculated at 1 k, 2 k and 4 k Hz using the Microsoft Excel "SLOPE" function. One-way ANOVA was carried out to compare the DPOAE amplitude as well as the slope at different levels & frequencies in both ears across the groups. The results of ANOVA showed no significant difference in

Table 2
Spearman correlation coefficient values obtained by correlating the amplitude values of DP-gram with maternal and neo-natal RBC indices.

RBC indices	Ear	1 kHz	1.5 kHz	2 kHz	3 kHz	4 kHz	5 kHz	6 kHz	8 kHz
Maternal									
HGB	**Right**	0.065	0.010	0.150	0.146	**0.234***	0.178	0.127	0.132
	Left	0.141	0.1566	**0.202***	0.1763	0.05	0.0578	−0.002	0.025
HCT	**Right**	0.030	−0.078	0.158	0.128	0.196	0.109	0.054	−0.017
	Left	0.165	0.186	**0.275***	0.174	0.065	0.049	−0.066	0.041
Neo-natal									
HGB	**Right**	0.031	−0.059	0.026	0.019	0.061	0.020	0.076	−0.070
	Left	0.027	−0.0111	0.054	0.0549	0.0195	0.0065	−0.006	−0.084
HCT	**Right**	−0.003	−0.073	0.034	0.023	0.064	0.024	0.065	−0.088
	Left	0.022	−0.033	0.056	0.059	0.008	0.001	−0.032	−0.076

*$p < 0.05$.

Table 3
The average percentage of presence of DPOAE at 70, 60, 50 & 40 dB SPL in normal, mild, and moderate groups are provided for both ears at 1 k, 2 k, & 4 kHz.

Freq	N	Group	Right				Left			
			70 dB	60 dB	50 dB	40 dB	70 dB	60 dB	50 dB	40 dB
1 kHz	59	**Normal**	49%	31%	7%	0%	47%	**40%**	7%	0%
		Mild	48%	35%	4%	0%	31%	**15%**	4%	0%
		Moderate	47%	26%	16%	0%	40%	20%	5%	0%
2 kHz	26	**Normal**	91%	83%	48%	7%	91%	**82%**	34%	2%
		Mild	87%	70%	43%	13%	83%	**54%**	33%	4%
		Moderate	88%	82%	41%	6%	79%	63%	42%	5%
4 kHz	21	**Normal**	85%	75%	27%	5%	78%	62%	19%	3%
		Mild	79%	54%	33%	0%	88%	72%	28%	8%
		Moderate	80%	75%	40%	10%	76%	67%	29%	5%

Note: The significantly different values are in bold.

the amplitude of DPOAE across the normal, mild, and moderate groups at different frequencies as well as intensities. Multivariate tests were not performed because of the missing values at lower intensities (50 & 40 dB SPL).

Further, the Spearman correlation coefficient was obtained for overall data (all babies) to check the correlation between the RBC indices (Maternal & Neonatal) and the slope of the DP I/O function. None of the maternal or neonatal RBC indices showed a correlation with the slope.

4. Discussion

Maternal IDA has been proven to have effects on the mother as well as the infant and its effect is higher when the severity is more. In the current study, the neonatal RBC indices did not show any difference across the groups, despite the maternal RBC indices being significantly different across normal, mild, and moderate groups. Also, none of the neonatal RBC indices correlated with maternal haemoglobin. Hence, in this study, the neonatal RBC indices were not affected by maternal anaemia. This could be because the current study considers only the late-term HGB (value just before delivery) as many of the rural pregnant women visited the hospital during the third trimester and the values of earlier trimesters were not available. The maternal HGB varies widely during pregnancy and the HGB in the earlier trimesters can also have an effect. It is suggested to consider all the trimesters of pregnancy in future studies for assessing the effect of the maternal iron status on the infant.

4.1. DPOAEs

DPOAEs are very sensitive to the functional integrity of OHCs and the magnitude of damage to the OHCs is directly proportional to the amount of drop in the amplitude levels of DPOAEs (Gorga et al., 2000). In the current study, the DPOAE average amplitude of all the newborn babies varied across the frequencies (1–8 kHz) and was higher when compared to adults which is on par with the earlier research studies (Blankenship et al., 2018; Gorga et al., 2000; Sundagumaran and Seethapathy, 2020). But the overall DPOAE presence observed in the normal group (81%) of the current study was on the lower side when compared to the earlier findings which are about 90–100% (e.g., Sundagumaran and Seethapathy, 2020; Vybhavi and Srinivas, 2021). This could be attributed to the difference in the day of testing. The earlier studies tested the babies after 24 or 48 h of birth and the current study could not avoid testing of the babies before 48 h of birth as most of the babies were discharged before 48 h. There could be an effect of the debris and vernix on DPOAEs despite the cleaning of the ear canal of babies soon after birth.

Both DP-gram and DP I/O functions showed a similar presence, amplitude and slope (only in the I/O function) of DPOAE across the groups at almost all frequencies. The difference between the groups in the DPOAE presence at some frequencies cannot be considered a significant result as this could be due to the chance factor. Also, the correlation between RBC indices and DPOAE amplitude/slope showed no significant relationship.

Though animal studies have shown that there is an effect of maternal IDA on the peripheral auditory system of young guinea pigs resulting in decreased cochlear sensory hair cells and reduced amplitudes of DPOAEs (Yu et al., 2014), the current study demonstrates no effect of the maternal IDA on the peripheral auditory system of human newborn babies. This agrees with the previous study on human infants (6–24 months) with and without anaemia which has also shown that there is no effect of iron status on OHC functioning in infants (Sundagumaran and Seethapathy, 2020).

There is a disagreement between animal and human studies regarding the effect of ID on the auditory system and further research is required to explore more on this. This could be partly due to the difference in the way the studies are conducted. Animal studies are conducted by controlling the maternal iron status

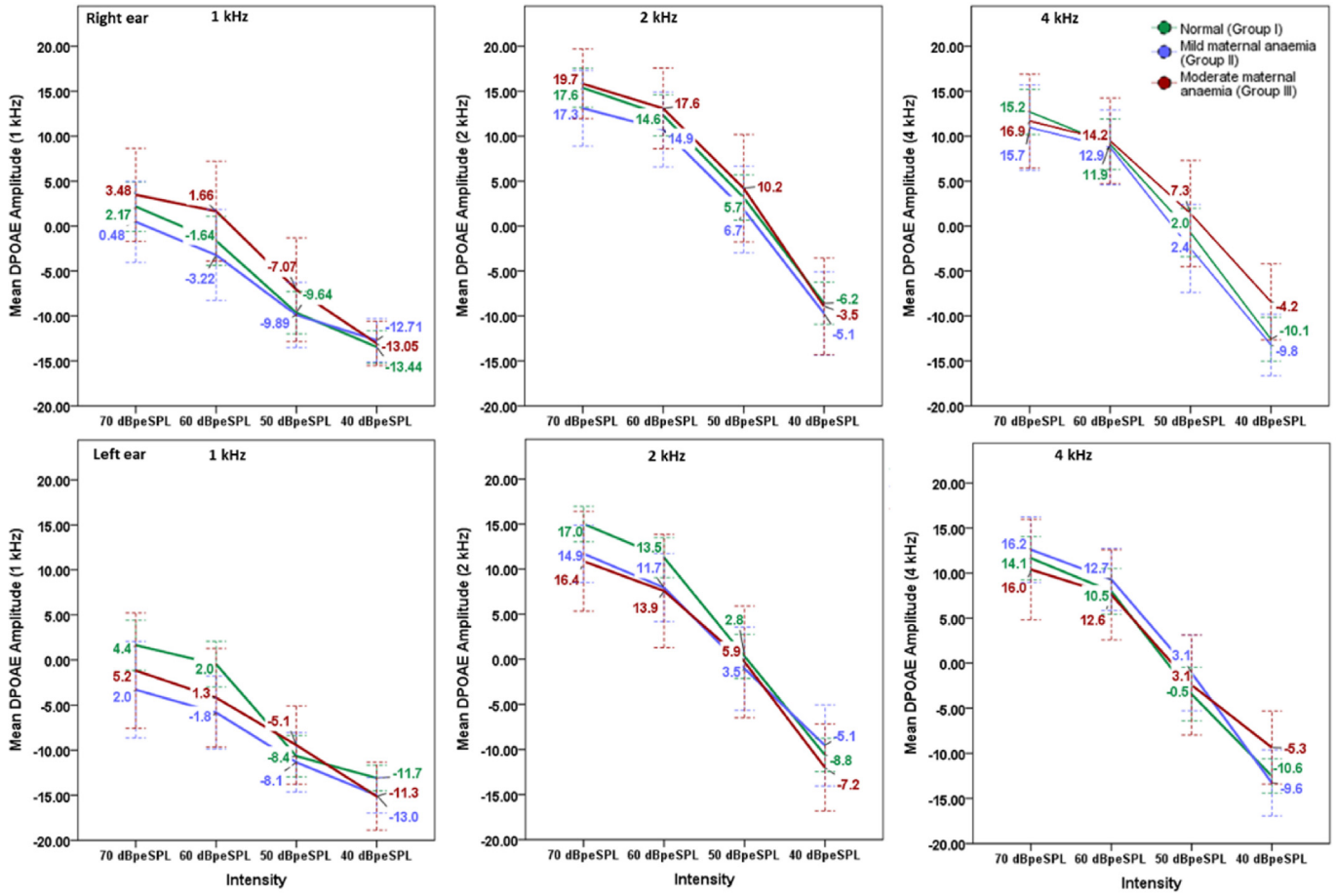

Fig. 2. Mean and standard deviation of DPOAE amplitude for different intensities (70, 60, 50 & 40 dB SPL across the normal, mild, and moderate groups for both ears at 1 k, 2 k, & 4 k Hz frequencies. The upper panel shows the right ear amplitude values and the lower panel shows the left ear amplitude values of the DP I/O function.

strictly with a regulated diet in a controlled environment. On the other hand, iron status varies a lot in humans, especially during pregnancy due to differences in the factors affecting iron status such as diet, intervention, adherence to iron supplementation etc and it is practically not possible to control all the variables affecting the iron status in the human studies. Future studies.

4.2. Conclusion

The current study concludes that the functional integrity of cochlear hair cells of human newborn babies is not affected by the late-term maternal iron status as well as neonatal iron status, which was shown using DPOAEs. Further longitudinal studies with subsequent follow-ups are required to conclude the course of the relationship.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joto.2023.05.005.

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