







# Auditory Pathway Maturation in Full-term Small for Gestational Age Children: A Systematic Review with Meta-analysis

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## Abstract

**Introduction** Factors of intrauterine growth restriction have been responsible for the births of full-term babies small for their gestational age (SGA). Scientific evidence points that this restriction can cause changes in the neural maturation process.

**Objectives** To analyze the absolute latencies and interpeak intervals of brainstem auditory evoked potential waves in full-term and SGA children to investigate whether there are changes of neural maturation in this population.

**Data Synthesis** The search for articles that reported the assessment of brainstem auditory evoked potential in SGA newborns compared with a control, appropriate for their gestational age, both born full-term, for the entire period available in the database research until October 31, 2021 was performed based on the MEDLINE/PubMed Central and on the Latin America and the Caribbean Health Sciences Literature and Virtual Health Library electronic databases. A total of 311 studies were found in the database research. Out of this total, 10 studies were included in the review, 5 of which were eligible for the meta-analysis, involving a total of 473 participants of both genders, with 193 participants belonging to the study group and 280 to the control group. Differences between the groups were only observed in the absolute latency of wave V (95% confidence interval [CI]: 0.02–0.15;  $p < 0.01$ ).

**Conclusion** The SGA condition is responsible for the appearance of brainstem neural conduction dysfunction measured by the brainstem auditory evoked potentials, probably by the maturation process of the auditory pathway of this population.

## Keywords

- ▶ term birth
- ▶ small for gestational age
- ▶ evoked potentials
- ▶ auditory
- ▶ brain stem

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## Introduction

The classification of fetal growth is performed through anthropometric data of the newborn compared with the reference growth curves of a specific geographical population, which relates the weight with the gestational age.<sup>1,2</sup> Newborns are considered small for the gestational age (SGA) when their weight is < 10<sup>th</sup> percentile for that specific gestational age or 2 standard deviations (SDs) lower than the established rules in the populational growth tables. On the other hand, newborns are considered adequate for the gestational age (AGA) when their weight at birth is between the 10<sup>th</sup> and the 90<sup>th</sup> percentile and with no malnutrition characteristics or growth retardation.<sup>3</sup>

Epidemiological studies have demonstrated a high global incidence of SGA newborns and have presented a gradual increase in the last years.<sup>2</sup> The current worldwide prevalence is of ~ 9.7%, with a greater prevalence recorded in South Asia (45%).<sup>4</sup>

Many risk factors are related to the birth of SGA children, including intrauterine growth restrictions (IUGRs) that have been greatly responsible for low weight and length at birth. Intrauterine growth restriction occurs due to maternal, placental, fetal, or genetic factors, and there may be a combination of any of these factors during pregnancy.<sup>2,3</sup> As a result, minimal structure damages in SGA newborns are associated with hemodynamic and metabolic deficits in the brain.<sup>4</sup> In addition, the SGA population has high rates of morbidity and mortality when compared with AGA children.<sup>5</sup>

Therefore, SGA newborns have an increased risk of neurodevelopment impairment.<sup>5-7</sup> The changes of neurodevelopment can affect the auditory pathway maturation, due to the delay in the neurological maturation.<sup>8,9</sup>

In this sense, the study of brainstem auditory evoked potentials (BAEP) has been a gold standard for investigating the maturation and integrity of the auditory pathway, from the inner ear to the brainstem.<sup>10,11</sup> Because brainstem auditory evoked potentials (BAEP) results suffer the influence of auditory maturation due to the myelination of the auditory pathway of the process fibers, which changes the appearance of waves.<sup>12,13</sup> It was demonstrated through the BAEP study that SGA newborns have significant delay for the appearance of waves III and V, and of the I-V interpeak interval, indicating auditory pathway change within the brainstem and not an impairment of the peripheral auditory system.<sup>14</sup> Later, it was shown that the significant delay of wave I and the reduction of I-V interpeak interval in the SGA population would be related to the immaturity of the basal end of the cochlea.<sup>15</sup> Recently, it was demonstrated that SGA children had an increase in the latency of waves III and V and interpeak I-III and I-V.<sup>16</sup> In line, it has been shown that prenatal factors responsible for intrauterine growth restriction (IUGR) can change the conduction time and development of brainstem or long-term nervous system development, resulting in a suboptimal outcome.<sup>12</sup> Indeed, young adults born as SGA babies have a reduction in auditory processing and in selective attention functions.<sup>17</sup>

Considering that full-term born children with SGA due to intrauterine changes can have neurodevelopment impairment throughout life.<sup>18,19</sup> The brainstem maturation can be affected, even with a normal hearing status, impairing the processing of auditory information.<sup>20,21</sup> Given the importance of the acquisition and development of language and auditory skills in the first 2 years of life, the first 6 months are the most important during this period. In this sense, the monitoring of SGA children deserves special attention from family members and health professionals, who can favor early and targeted auditory and linguistic stimulation to compensate for the disadvantages in neuropsychomotor development reported in the SGA population, avoiding future difficulties. Therefore, the purpose of the present systematic review with meta-analysis was to analyze the absolute latencies and interpeak intervals of waves from BAEP of full-term and SGA children to investigate if there are changes in the neural maturation in this population.

## Literature Review

### Literature Research Strategy

The search for articles was performed in October 2021 in the MEDLINE/PubMed Central (PMC), the Latin America and the Caribbean Literature in Health Sciences (LILACS), and the Scientific Electronic Library Online (SciELO) electronic databases for all the publications generated in the search, without establishing a chronological period of the searches. Given the few studies on this topic, the expansion of the search period allowed us to find as many studies as possible, contributing to greater data robustness. Manual searches of bibliographic citations of articles found in the search strategy were also performed.

The search strategy was constructed according to the PICO methodology: i) The study population included full-term, SGA newborns; ii) Auditory evaluation intervention using the auditory evoked potentials of the brainstem; iii) Comparison with the group suitable for gestational age, at term; iii) Outcome/Results auditory alterations observed in the BAEP test or normality. The descriptors of the Medical Subject Headings (MeSH) list and synonyms or variations of each descriptor were used. The search strategies were performed using the Boolean operators "OR" and "AND" with different combinations of the following descriptors in English: *Term Birth* (Mesh), *Infant, Small for Gestational Age* (Mesh), *Evoked Potentials, Auditory, Brain Stem* (Mesh), *Hearing Loss* (Mesh), and *Hearing* (Mesh) (– **Supplementary Appendix A**).

### Selection of Studies

Observational, cross-sectional, prospective, retrospective, analytical, and descriptive studies were selected according to the following inclusion criteria: (i) including SGA full-term newborns (> 37 weeks); (ii) comparing the SGA and AGA groups; (iii) having the absolute values of averages and standard deviation (SD) of wave latencies and/or BAEP interpeak intervals. Studies including high-risk newborns or with no assessment of the auditory parameter were excluded.

### Quality Assessment

The articles found through the search strategy underwent screening and eligibility assessments performed by two independent investigators who read the titles and abstracts to identify those that met the inclusion criteria or those that could not be excluded. Disagreements were resolved by consensus in team meetings. The selected studies were read in full and critically assessed to ensure they met the criteria for meta-analysis review, and data were extracted and recorded in the pretested registration form, allowing comparison between studies. Study characteristics such as author, year, title, study design, population and sampling, methods of evaluation, and main results were recorded and the study quality was assessed by the modified Newcastle Ottawa Scale (NOS), which was adapted for cross-sectional studies.<sup>22</sup> The scale has 3 evaluation parameters for which points are assigned: 1) selection (4 points); 2) comparability (2 points); and 3) outcome (3 points). In the final sum, the higher the score, the higher the quality of the study. The total scores for each study are categorized as follows: 0 to 3 points, low-quality; 4 to 6 points, adequate quality; and 7 to 9 points, high-quality. The data was reported according to the PRISMA checklist statement, and a four-phase flow diagram was produced.<sup>23</sup>

### Statistical Analysis

The meta-analysis was performed using the means of absolute latencies and interpeak intervals, SD, and number of subjects of the SGA and control AIG groups and 95% confidence interval (CI), and considering a value of  $p < 0.05$  for statistical significance, using the Review Manager software, version 5.4.1 (RevMan 5; Cochrane Organization, Oxford, United Kingdom). Heterogeneity was measured by the chi-square test (test level is  $p = 0.1$ ) and by the  $I^2$  statistic, with  $I^2 \leq 50\%$  representing low heterogeneity,  $I^2 > 50\%$  indicating moderate heterogeneity and  $I^2 > 75\%$  percentage indicating high heterogeneity.<sup>24</sup>

### Summary of Search Results

Searches in searched database brought back a total of 311 articles. Of these articles, 18 were eligible for reading, analysis, and discussion among the reviewers based on the inclusion criteria. After that, eight studies were excluded for not differentiating preterm and full-term groups at the time of data analysis. Therefore, 10 articles were included in the present review (► Fig. 1). For carrying out the meta-analysis, five articles were included as they used similar study methodologies and presented the mean and SD data in absolute values, allowing the statistical analysis to be performed.

### General Characteristics of the Studies

The articles used in the present review were published in the period from 1991 to 2020, and, regarding the classification of the study, they are cross-sectional,<sup>10,15,25,26</sup> prospective, longitudinal<sup>12,16,27</sup> prospective,<sup>28</sup> and retrospective cohort.<sup>29</sup> The main objective of the studies was to investigate the differences in the auditory pathway maturation through the study of absolute latencies and interpeak intervals of the BAEP exam among SGA newborns compared with the AGA

control group. In addition, some studies investigated differences in gender,<sup>25,29</sup> laterality,<sup>29</sup> the influence of maternal malnutrition,<sup>28</sup> and the impact of maternal hypertension.<sup>26</sup> Regarding the quality of the studies included in the meta-analysis, 1 study has low quality (3 points)<sup>29</sup> and the other 4 studies have adequate quality, scoring between 6 and 8 points. More details about the studies are summarized in ► Tables 1 and 2.

### Prevalence of Changes in BAEP Response Patterns

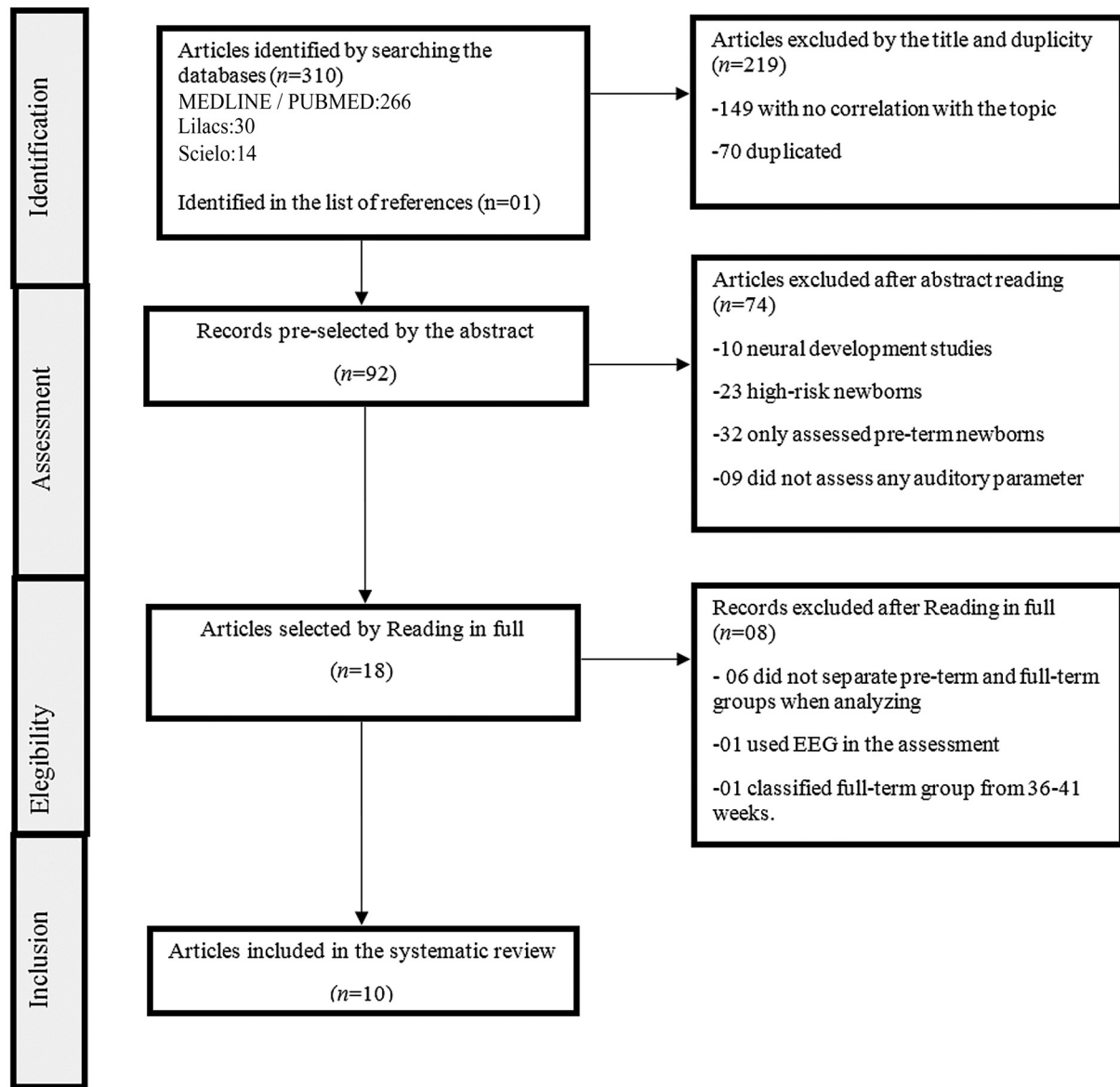
A total of 193 participants from the SGA group and 280 from the AGA group of both genders comprised the sample of studies analyzed through the meta-analysis. The gestational age varied from 37 to 45 weeks and the time of evaluation was performed in the period from 1 to 28 days of life (► Table 2). The statistical analysis revealed that there were no differences between the SGA and AGA groups in the absolute latencies of waves I ( $p = 0.19$ ), III ( $p = 0.11$ ), and intervals I-III ( $p = 0.61$ ), III-V ( $p = 0.21$ ), and I-V ( $p = 0.10$ ). The comparison of absolute latency of wave V revealed differences between the groups. ► Fig. 2 shows the forest plot chart, demonstrating that the absolute latency of wave V in SGA newborns is significantly longer than those in AGA newborns. Heterogeneity, measured by random effects, was low chi-squared  $\chi^2 = 2.78$ ;  $df = 4$  ( $p = 0.60$ ); and  $I^2 = 0\%$ , demonstrating homogeneity among studies. The CI was 95% (0.02–0.15) and the  $p$ -value was  $< 0.01$  (► Supplementary Appendix B).

### Discussion

The present meta-analysis showed that, compared with AGA newborns, SGA full-term newborns presented a delay in the conduction of auditory information from the 8<sup>th</sup> cranial nerve to the brainstem, evidenced by the prolongation of the time of wave V conduction measured by investigating the BAEPs.

The prolongation of wave V latency can have different meanings, such as the maturation process of central auditory pathways or by peripheral conductive alteration, for instance.<sup>30</sup> All studies used in our review only included in their investigations full-term participants with normal hearing, who presented the bilateral presence of otoacoustic emissions and a type A tympanometry curve<sup>10,16,25,27,31</sup> and were free of risk factors, known for affecting hearing function.<sup>15,26,28,29</sup> Therefore, the risk factor studied that could affect hearing function was the SGA factor. This offers a great opportunity to investigate the functioning of the central nervous system (CNS) and the development of neuro-sensorial hearing function in this population.<sup>32</sup>

It was a consensus in the analyzed studies that the main causes of SGA status are due to factors of intrauterine growth, which impairs the growth potential of the fetus. Several factors are known as being responsible for IUGR, such as severe diabetes, uteroplacental insufficiency, maternal smoking or drugs, low socioeconomic class, or multiple pregnancies.<sup>26</sup> Thus, it has been proposed that prenatal factors are responsible for changes in the initial development of the neural function of nonasphyxiated SGA babies.



**Fig. 1** Flowchart of identification and selection of articles for the systematic review. *N*: number.

**Table 1** General characteristics of studies included in the systematic review ( $n = 5$ )

Study (author, year)	Gestational age (weeks)	<i>n</i> SGA	<i>n</i> AGA	Period of assessment	BAEP			
					Clicks (sec)	Intensity dB	Waves	Interpeak
Jiang et al. (1991) <sup>12</sup>	37–42	24	178	1 month	NR	70	NR	I-III, III-V, I-V
Sarda et al. (1992) <sup>26</sup>	38–40	13	26	Neonatal	20	80	NR	I-V
Soares et al. (1998) <sup>15</sup>	38–43	25	25	Neonatal	100	60–80	I, III, V	I-V
Angrisani et al. (2015) <sup>31</sup>	37–41	35	35	Neonatal	27.7	80	I, III, V	I-III, III-V, I-V
Angrisani et al. (2020) <sup>16</sup>	37–41	4	4	Neonatal	27.7	80	I, III, V	I-III, III-V, I-V

**Abbreviations:** AGA adequate for gestational age; dB, decibel; *n*, number; Neonatal, 0–28 days of life; NR, not related; SEC, seconds; SGA, small for gestational age.

This change in neural development may be important to determine the subsequent neurological performance.<sup>33</sup> This justifies the fact that SGA newborns have a heterogeneous population, as they present different patterns of develop-

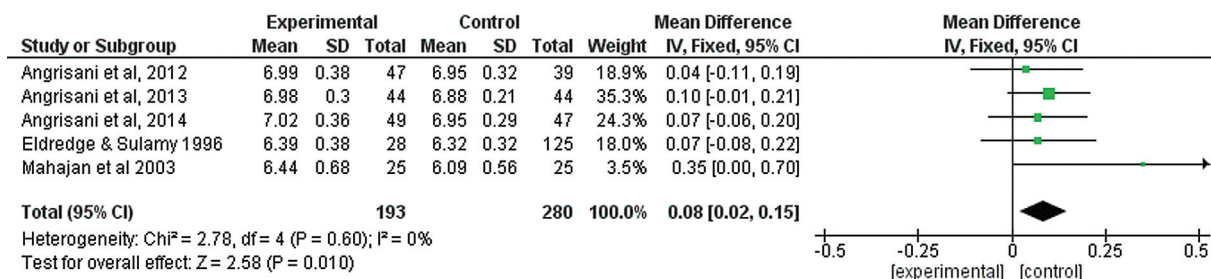
ment in the face of aggression suffered during intrauterine life.<sup>31</sup>

This heterogeneity of clinical manifestations is observed in the results of the studies included in the present

**Table 2** General characteristics of the studies included in the meta-analysis ( $n = 5$ )

Study (author, year)	Modified NOS score	Gestational Age (weeks)	n SGA	n AGA	Period of assessment	BAEP			
						Clicks (sec)	Intensity dB	Waves	Interpeak
Eldredge et al. (1996) <sup>29</sup>	3	38–45	28	125	Neonatal	NR	60	I, III, V	I-III, III-V, I-V
Mahajan et al. (2003) <sup>28</sup>	8	38–41	25	25	Neonatal	NR	70	I, III, V	I-III, III-V, I-V
Angrisani et al. (2012) <sup>10</sup>	8	37–41	47	39	Neonatal	27.7	80	I, III, V	I-III, III-V, I-V
Angrisani et al. (2013) <sup>25</sup>	8	37–41	44	44	Neonatal	27.7	80	I, III, V	I-III, III-V, I-V
Angrisani et al. (2014) <sup>27</sup>	6	37–41	49	47	Neonatal	27.7	80	I, III, V	I-III, III-V, I-V

**Abbreviations:** AGA, adequate for gestational age; dB, decibel; NR, not related; n, number; NOS, Newcastle-Ottawa Scale; Neonatal, 0–28 days of life; SEC, seconds; SGA, small for gestational age.

**Fig. 2** Forest plot of studies demonstrating differences of means and 95% confidence intervals between SGA and AGA newborns for absolute wave V latency in milliseconds.

systematic review. So, five studies concluded with their investigations that there are changes in neural development in the SGA population influencing the maturation process of the auditory pathway, resulting in abnormalities in the BAEP test.<sup>10,12,16,26,31</sup> On the other hand, five studies<sup>15,25,27–29</sup> did not evidence differences between the SGA and AGA groups. These disparities among the results can be justified by some peculiarities among the studies, such as the population studied, differences of methodologies, the type of study used, and the small number of participants in some of the studies.<sup>16,26</sup>

Seeking a better understanding of the influence of body proportionality in the process of auditory maturation in SGA newborns, two study groups were analyzed in the first six months of life, one classified as asymmetric and the other as a symmetric group. In the first days of life, there was an alteration in the BAEP in more than 30% in SGA groups, both symmetric and asymmetric, suggesting transitory retro cochlear alterations. Since at 6 months, only 3.39% continued with retro cochlear alterations, indicating a permanent neural disfunction. These alterations are discussed in terms of inadequate brain development, influenced by the lack of fundamental nutritional elements for the normal development of the fetus, caused by IUGR.<sup>31</sup>

Other cross-sectional studies monitored the central auditory system in SGA children, who were assessed in 3 different periods: at birth, at 6 months old, and at 3 years old. The authors concluded that SGA children had an increase in the latency of waves III and V, and of interpeak I-III and I-V, in all moments of evaluation. Due to probable intrauterine nutritional restriction of essential nutrients, resulting in changes

in the formation and number of synapses.<sup>16</sup> In fact, it has been described that nutritional damages during pregnancy interfere with dendritic arborization, impairing the number of synaptic connectivity and the process of myelination of nerve fibers.<sup>32</sup> These factors, either isolated or together, interfere with the quality of the sound stimulus transmission. Therefore, when using the dichotic listening technique to evaluate the auditory perception and language asymmetry, as well as the changes in the auditory attention in young adults who were born SGA, a reduction in the auditory processing and damaged functions of selective attention were observed.<sup>17</sup>

When considering the relationship between maternal hypertension and the presence of brainstem conduction time abnormalities in SGA children, BAEP was investigated. The researchers describe that SGA babies with maternal hypertension have an acceleration of brainstem conduction time, compared with other SGA and AGA babies. This shortening of conduction time is likely caused by a change in the development of neurotransmitters and of the catecholaminergic systems.<sup>26</sup> To better investigate this conduction acceleration, it was hypothesized that the shortening observed in the IV interval in SGA newborns could be due to a cochlear functional immaturity, causing a delay in wave I and a consequent reduction in the IV interval, which could be investigated by studying latency lengthening with intensity reduction. The authors concluded that there was no difference between the AGA and SGA groups.<sup>15</sup>

In order to investigate more specifically which brainstem region could be affected in SGA newborns by IUGR factors, the ratio of the interpeak intervals III-V and I-III was used as

an investigation factor, representing, respectively, the conduction time of the upper and lower brainstem. Small for the gestational age children even have I-V, I-III, and III-V intervals similar to those of AGA children. When comparing the ratios of the intervals, SGA children differed from the AGA ones, showing a decrease in this interval up to the age of 2 years old, with the III-V interval relatively shorter. Therefore, this suggests that prenatal factors responsible for IUGR may alter the higher brainstem or the long-term development of the nervous system, resulting in a suboptimal outcome.<sup>12</sup>

Research aimed at investigating maternal nutritional health conditions analyzed the BAEP responses in SGA newborns born to malnourished mothers, compared with an AGA control group, children of healthy mothers, and no significant differences were found between the groups. However, the study shows that, although within the normal range, the absolute latencies of waves V and I-V interpeak were found at the upper limit of normality in the study group compared with the control group.<sup>28</sup>

All these findings confirm that SGA babies represent a heterogeneous population and that IUGR factors can alter the normal development of the fetus, which, can have different consequences on brain development. In addition, the present review showed that there is a scarcity of studies what investigate the impact of the SGA age on auditory function, the few studies are conflictin. Demonstrating that it is still a challenge to be overcome and better investigated, as observed in the limitation of the number of articles in this review. Through the meta-analysis, we were able to alleviate some gaps between the studies, mainly on the number of participants and, therefore, it was possible to observe that SGA newborns, when compared with an AGA group, present disadvantages in the neural development of the auditory pathway, demonstrated by the prolongation of the V wave.

Therefore, we must consider that this systematic review and meta-analysis also has some limitations, such as the small number of studies found, of which only five were eligible for meta-analysis and three are from the same research group, which studied the specific population of a region, further limiting the findings. Thus, more studies with different methodological designs are needed, with different age groups of studies and different regions, and that include in their investigations more tests and exams for a better understanding of the repercussions of the SGA status on the maturation process of the auditory pathways and on the development of auditory skills.

## Final Comments

The present review demonstrates that SGA newborns at full-term have a heterogeneous group of manifestations. The review results, together with the meta-analysis performed, agree that the SGA condition is responsible for dysfunction manifestations in the neural conduction of the brainstem, and possibly the factors of IUGR are responsible. Therefore, this population should be considered at risk for alterations in the development of auditory skills. Follow-up studies of this

population for long periods are necessary to verify the continuity of these alterations and offer specific treatments.

## Conflict of Interests

The authors have no conflict of interests to declare.

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