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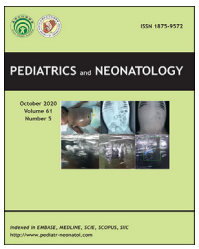

Original Article

Maturation of the auditory system in normal-hearing newborns with a very or extremely premature birth

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Background: Literature shows that lower gestational age leads to greater delays in the auditory conduction, which suggests atypical maturation of the brainstem in normal-hearing premature newborns. Our aim is to investigate if there is a difference between the extrauterine and intrauterine maturation of the auditory system in normal-hearing newborns with a very premature (28—31 weeks) or extremely premature (<28 weeks) birth.
Methods: Results of the Automated Auditory Brainstem Response Newborn Hearing Screening Program in Dutch Neonatal Intensive Care Units and diagnostic examinations were centrally registered from 1998 to 2016. Normal-hearing newborns with a gestational age of 25—31 weeks were included. Screening results at 32—45 weeks of postmenstrual age were compared between newborns born with different gestational ages. Multiple imputation was used to predict missing screening results. Small for gestational age was defined as birth weight corrected for gestational age < -1.6 standard deviation. Descriptive and (pooled) logistic regression analyses were performed.
Results: 23,964 newborns with 28,754 screening results were eligible. At the same postmenstrual age, pass rates were lower when gestational age was lower in normal-hearing newborns with a very and extremely preterm birth. Pass rates of 80% could be obtained at 34—35, 32—33, and 30—32 weeks' postmenstrual age in newborns with 25, 26—27, 28—31 weeks gestational age, respectively. Small for gestational age had an additional negative effect on pass rates.
Conclusion: Analysis of hearing screening data suggests that extrauterine maturation of the auditory system is delayed in normal-hearing newborns with a very or extremely premature birth.

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1. Introduction

Every year, approximately 15 million babies (11%) are born preterm worldwide (before 37 completed weeks of gestation).[1–3] About 85% of these births are moderate (32–33 weeks) to late preterm babies (34–36 weeks), 10% are very preterm babies (28–31 weeks) and 5% are extremely preterm babies (<28 weeks).[1] Besides cerebral palsy, intellectual disabilities and vision impairment, neonatal hearing loss (NHL) is one of the four major disabling conditions in preterm babies.

The prevalence of NHL among very and extremely premature babies is high[4–6] and consistently increases with each decreasing week of gestation (1.2%–7.5% from 31 to 24 weeks' gestational age (GA)) and decreasing birth weight (1.4%–4.8% from ≥1500 g to <750 g).[7] The period from 25 weeks' gestation up to 6 months of age is most critical to the development of the neurosensory part of the auditory system.[8] A meta-analysis of auditory brainstem maturation in normal-hearing babies born preterm showed that the duration of gestation negatively affected maturation of the auditory brainstem.[9]

An automated auditory brainstem response (AABR) hearing screening is advised for screening in the Neonatal Intensive Care Units (NICU) population [Joint Committee of Infant Hearing (JICH) position statement] from 34 weeks' postmenstrual age (PMA) onward.[10] However, a longitudinal study among 90 very and extremely preterm babies showed that AABR pass rates of >80% can already be obtained from 30 weeks' PMA.[11] Screening at a relatively low PMA may have the advantage of a low loss to follow-up, but only when the pass rate is sufficiently high. The pass rate depends on the maturation of the auditory brainstem, which may depend on the GA of the newborn.

In order to gain a better understanding of the maturation of the auditory system in the first months of life in normal-hearing newborns born very or extremely preterm, we evaluated the results from the nationwide Newborn Hearing Screening Program (NHSP) in Dutch NICUs. The aim of our study is to investigate if there is a difference between the extrauterine and intrauterine maturation of the auditory system in normal-hearing newborns with a very premature (28–31 weeks) or extremely premature (<28 weeks) birth. The results will provide information about the differences in pass rates at the same PMAs between the different GAs in very preterm and extremely preterm newborns, and the optimal age for screening given the GA of the newborn.

2. Patients and methods

2.1. Data

Before the first screening, parents of all patients were instructed about the registration of their records and the use of their records for research. Parents can refuse the registration of their screening results by informing their doctor. The Daily Board of the Medical Ethics Committee Isala Zwolle The Netherlands reviewed the research proposal of this study and concluded that the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO) did not apply to this research proposal (METC number: 180914). Therefore, this study was considered exempt from the requirement for approval.

In the Netherlands, all newborns with a gestational age (GA) < 30 weeks and most (~85%) neonates with a GA of between 30 and 32 weeks are centrally treated in one of the ten level III NICUs.

As soon as the cardiorespiratory condition is stable and the neonate is no longer in need of invasive ventilation or circulatory support, the neonate can be transferred in the incubator to a post-intensive care or high care department (post IC/HC) of a referral hospital after 30 weeks of gestation and at 1000 g of body weight. From 1998 to 2002 a two-stage AABR NHSP was gradually implemented in Dutch NICUs.[12] The two-stage AABR screening consists of a first AABR-test before discharge from the NICU towards a post IC/HC setting, and a second AABR-test at term age as outpatient in the NICU clinic if the newborn has failed the first AABR-test. The ALGO Portable AABR screener was used between 1998 and 2011. The Algo 3i was implemented in 2011. From 2013 it was also possible to use the AABR screener MB11 BERAphone. All newborns who failed the two-stage AABR-test were referred for further audiological diagnostic procedures. Results of the screening and first diagnostic examination at the audiologic center in the NICU graduates between October 1998 and December 2016 with one or more risk factors according to the JCIH[13] were centrally registered in an electronic registration system.[6] (Almost) all very preterm and extremely preterm newborns have at least one risk factor because "Neonatal intensive care of more than five days" is a risk factor according to the JICH. NHL was defined as impaired when a diagnostic Auditory Brainstem Response (ABR) exceeded 35 dB in one (unilateral) or two (bilateral) ears.

Birth weight and GA were also registered in the registration system. Birth weights were measured in grams by trained health professionals using calibrated digital baby scales. GA in weeks and days was determined from early ultrasound exam during pregnancy.

We extracted the results from all newborns from the electronic registration system. The data were anonymized prior to analysis. We then selected newborns with a GA from 25 to 31 weeks, who survived the admission period and who had no NHL. No NHL was defined as a bilateral pass result at the first or second stage of the AABR screening or according to diagnostic ABR results. We selected only newborns without NHL because the focus of our study is on

the maturation of the auditory system in the first months of life in normal-hearing babies.

2.2. Statistical analyses

Birth weight was categorized in two groups: Small for Gestational Age (SGA, <-1.6 SD (i.e., P5) on GA and sex-specific growth charts[14]) vs. appropriate for gestational age (AGA, ≥-1.6 SD). GA was truncated to complete weeks (e.g., from 26 weeks and 0—6 days to 26 weeks).

As the AABR results were obtained from the nationwide NHSP, the screening results were not available for each week of PMA. For example, with a refer at 35 weeks' PMA and a pass at 40 weeks' PMA, there is missing data between 36 and 39 weeks' PMA. In this example, there is no missing data before 35 weeks' PMA, because we assumed that if the newborn had a refer (in this case at 35 weeks' PMA), the screening results earlier in life (in this case <35 weeks' PMA) would have been a refer as well. Also, in this example there is no missing data after 40 weeks' PMA, because we assumed that if the newborn had a pass result (in this case at 40 weeks' PMA), the screening later in life (in this case >40 weeks' PMA) would also have been a pass. To approach the problem of missing data in the PMA between the moment of a refer and a pass, we applied multiple imputation.[15] Imputation is a statistical method that replaces missing data with substituted values based on other available information. The information that we used for the imputation was all observed pass rates for each PMA (25—46 weeks) as well as birth weight (in grams), GA (defined as (weeks + days/7)) and sex. In total, ten predictions were conducted to account for missing data uncertainty. Descriptive analyses were performed to compare the pass rates at 32—45 weeks of postmenstrual age between newborns born with different gestational ages. For each prediction, logistic regression analyses were performed and afterwards pooled to test the impact of GA (independent variable) on the pass rates (yes/no) (outcome) at a PMA of 32 weeks. The interaction between GA and sex was also investigated by adding sex and the interaction as additional variables in the model. The imputation, logistic regression analysis and the descriptive statistics were performed in R version 3.4.4 (mice, glm).

3. Results

In total, 23,964 normal-hearing newborns with a very or extremely premature birth with 28,754 AABR screening results were eligible. Of these newborns, 1472 (6.1%) were born SGA (range: 5.4—7.3%). Mean PMA for the screening results ranged from 33.1 to 35.2 weeks. Table 1 shows the sample sizes, the proportion of SGA and descriptive values for PMA by each week of GA.

Regression analyses revealed that GA had a significant ($p < 0.001$) effect on the AABR pass rates for a PMA at 32 weeks. We found no significant differences between boys and girls on the effect of GA on the AABR pass rates. Fig. 1 shows the pass rates by PMA between different GA in our sample. The imputation method predicted ten datasets to account for missing data uncertainty. Each predicted dataset is plotted with dashed lines. Large differences between the dashed lines imply more uncertainty of the predicted values. The average of the ten datasets is plotted by a bold line. This figure shows that at the same PMA, pass rates were lower when GA was lower.

Table 1 Sample sizes, the proportion of small for gestational age and descriptive values for postmenstrual age by each week of gestation.

GA	n	% SGA	PMA mean (sd), min/max (in weeks)
25	856	7.3%	35.2 (4.2), 25—46
26	1738	6.6%	34.7 (4.3), 26—46
27	2438	8.2%	34.2 (43), 27—46
28	3254	6.5%	33.6 (4.4), 28—46
29	4139	5.4%	33.2 (4.2), 29—46
30	5417	5.5%	33.1 (3.8), 30—46
31	6122	6.0%	33.3 (3.3), 31—46

GA: gestational age, SGA: small for gestational age (<1.6 SD), PMA: postmenstrual age, sd = standard deviation.

Fig. 2 shows the pass rates for the SGA newborns. The ten predicted datasets are plotted with dashed lines and the average by a bold line. This figure shows that SGA newborns had lower pass rates compared to the total group of newborns.

Table 2 shows the PMAs by GA at fixed pass rates of 80% and 90% in the total and SGA sample of newborns, respectively. Pass rates of 80% and 90% could be obtained between 30-35 and 32—37 weeks' PMA, respectively, depending on GA. Newborns who were SGA had lower pass rates. Pass rates of 80% and 90% in SGA newborns could be obtained between 31—37 and 33—41 weeks' PMA, respectively, depending on GA. The pass rates for AGA newborns were similar to the pass rates of the total group of newborns.

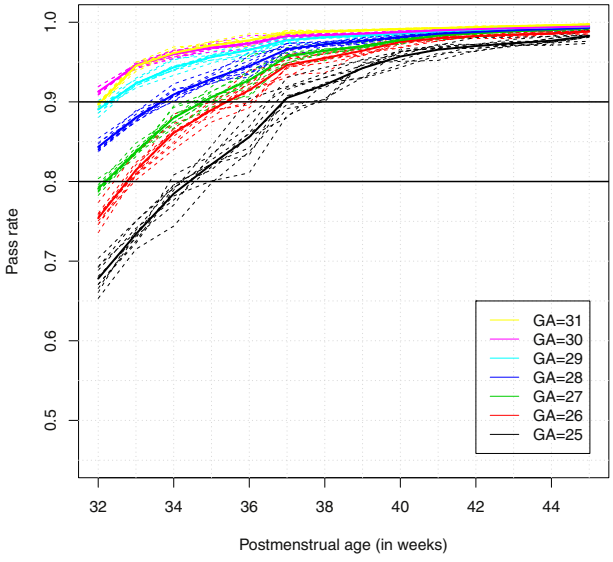

Figure 1 Pass rates by postmenstrual age in weeks between newborns born with different gestational ages in the ten predicted (dashed lines) and averaged (bold lines) datasets.

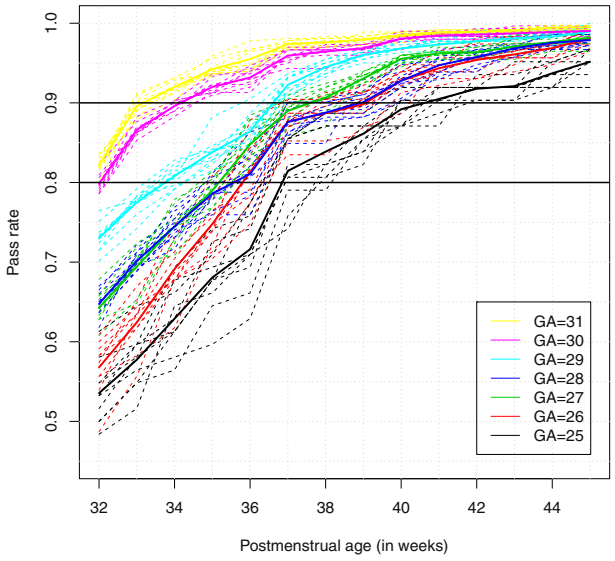

Figure 2 Pass rates by postmenstrual age in weeks between small for gestational age newborns born with different gestational ages in the ten predicted (dashed lines) and averaged (bold lines) datasets.

Table 2 Postmenstrual age by gestational age at fixed pass rates of 80% and 90% in the total and small for gestational sample of newborns.

GA	Total group (n = 23,964)		SGA group (n = 1472)	
	PMA 80% pass	PMA 90% pass	PMA 80% pass	PMA 90% pass
25	34—35	37	37	41
26	33	36	36	39
27	32—33	35	35—36	38
28	31—32	34	35—36	39
29	30—31	32—33	34	36—37
30	30—31	32	32	34
31	31—32	32	31—32	33

PMA: postmenstrual age, GA: gestational age, SGA: small for gestational age (<1.6 SD).

4. Discussion

The main finding of this study is that, at the same PMA, pass rates in AABR hearing screening were lower when GA was lower for normal-hearing newborns with a very or extremely premature birth. This is even more obvious in SGA very and extremely preterm newborns. This suggests that extrauterine maturation of the auditory system is delayed in these newborns. Because the maturation of the auditory system extrauterine seems to be slower at a lower GA, we recommend adjusting the screening age such that at least 80% pass. Pass rates of 80% in very and extremely preterm newborns could be obtained between 30 and 35 weeks' PMA depending on GA.

The auditory system of the fetus becomes functional at around 25 weeks' gestation.[8] The period from 25 weeks' gestation up to 6 months of age is most critical to the development of the neurosensory part of the auditory system.[8] Monson et al. showed that changes in the cortical microstructure that accompany cortical maturation of the primary auditory cortex had mainly taken place before the PMA of 28 weeks.[16] In addition, rapid changes were taking place in the nonprimary auditory cortex between 26 and 42 weeks' PMA.[16] The environment and care practices for the fetus intrauterine or the neonate in the NICU are also critical factors in the development of the auditory system.[8] Acoustic pollution was more intensely investigated in different neonatal intensive care settings. Attempts to indicate which source of noise (monitor, incubators, ventilatory circuits, conversations) is most harmful to the hearing is complicated because of co-occurrence.[17—19] These results suggest that the maturation of the auditory system is sensitive to the GA of the newborn, which is in agreement with our study.

Literature suggests that screening is recommended from 34 weeks' PMA onward.[10] This is in line with our results for AGA newborns with a GA of 25 weeks because pass rates of nearly 80% (77%) could be attained at 34 weeks' PMA. However, our study also shows that pass rates of 80% could already be achieved at 32—33 and 31—32 weeks' PMA in AGA newborns with a GA of 26—28 weeks and all newborns with a GA of 29—31 weeks, respectively. This is a clinically relevant finding because screening of these newborns at an early PMA within the NICU period ensures that only a minority of the newborns with a referral have to return for a second test as an outpatient. This may reduce the loss to follow-up rate. When focusing on SGA newborns with a GA <29 weeks, we found that these newborns needed two to three more weeks to attain the 80% pass rate. This finding is also confirmed by the results of Jiang's study that showed increased latencies in ABR in very preterm newborns (<30 weeks) with SGA compared to age matched very preterm AGA newborns.[20]

A strength in our study is the large sample size from an unselected nationwide cohort of very and extremely preterm newborns, which enables us to provide accurate information on the impact of GA on the pass rates. Furthermore, the NHSP in Dutch NICUs is highly effective with a low loss to follow-up due, among other reasons, to the electronic registration system that facilitates screening, tracking and follow-up after abnormal screening results.[6] Another strength is the use of GA-specific reference charts for birth weight, which enables us to study the additional effect of SGA adjusted for GA. A limitation of our study is that we did not investigate the impact of the type of AABR screener (ALGO Portable AABR screener, Algo 3i, MB11 BERAphone.) on the results. Another limitation is that we did not screen the neonate weekly between 32 and 36 weeks PMA. Although screening results were available for all PMAs starting from the week they were born, in many cases the first screening was obtained during admission to the NICU as soon as the newborn was stable and nearly ready for referral. Sometimes, a second screening after a referral took place the night before discharge from the NICU towards a post IC/HC setting. Therefore, the age of screening may have depended on the clinical condition of the newborn, which may also reflect the maturation of the newborn. This could have introduced potential bias in the

direction of slightly higher pass rates in all GA groups because of the imputation methodology used. Therefore, besides our recommendations for the timing of screening for the different GA's, a stable cardiorespiratory clinical condition of the newborn is also important to take into account. In cases with poor clinical outcome (e.g., Bronchopulmonary dysplasia), screening may be delayed by several weeks to reach an equivalent maturation of the auditory system. Another limitation is that we did not investigate all newborns' characteristics and specialized procedures that may delay obtaining a pass at the screening. Very preterm and extremely preterm newborns have compromised systems that make them more vulnerable to otologic conditions. More research is needed to investigate the effect of the clinical outcomes of the newborn on his or her screening results.

In our study, we only selected very and extremely preterm newborns without hearing loss because the focus of our study was on the maturation of the auditory system in the first months of life in normal hearing babies. In this large sample of 23,964 very and extremely preterm newborns with 28,754 screening results, we showed that at the same PMA, pass rates were lower when GA was lower with an additional negative effect in those with SGA. In other words, maturation of the extrauterine auditory system seems to be delayed. Our results underline the difficulty to create similar favorable extrauterine conditions as in intrauterine ones. However, more research is needed to validate our results.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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