Aud Vest Res (2017);26(3):117-124.

REVIEW ARTICLE

The effects of preterm birth on neural development, language acquisition, and auditory system

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Received: 28 Dec 2016, Revised: 16 Mar 2017, Accepted: 24 Mar 2017, Published: 15 Jul 2017

Abstract
Background and Aim: In the last few decades, the total number of preterm newborns, with gestational age less than 35 weeks, who survived the prematurity conditions, has increased significantly. This might lead to a high prevalence of late neurocognitive and developmental abnormalities. The neurological development is closely related to the hearing and language acquisition; these factors play a crucial role in social and emotional growth. The present review emphasizes the consequences of preterm birth on neurodevelopment, speech-language, and auditory system.
Recent Findings: The relationship between the preterm birth and neural developmental indicates that prematurity could lead to a higher risk of cerebral palsy, developmental delay, and mental retardation as compared to the birth at term. The preterm newborns would be deprived of normally enriched hearing experience during the length of hospital stay, which is markedly different from that of the typical full-term newborns. This altered hearing ability might impede the early normal development of auditory neural pathways in preterm children, posing serious concerns about the acquisition of speech and language skills as compared to their normal peers.
Conclusion: Alterations in auditory and higher cortical functions in preterm children can lead to suboptimal cognition and language skills. In order to prevent and mitigate these consequences, a long-term follow-up of neurodevelopment, auditory, and linguistic abilities is proposed to fully recognize the sources of problems, and if necessary, implement the intervention programs.
Keywords: Preterm birth; auditory system; neural development; speech; language

Introduction
Preterm birth is defined as childbirth occurring before 37 completed weeks or 259 days of gestation [1]. Over the last few decades, the total number of preterm newborns with gestational age less than 35 weeks, who survived the prematurity conditions, has increased significantly [2]. This issue is apparent considering the increased prevalence of neurological disorders and learning disabilities in premature children. Follow-up studies have demonstrated that despite normal appearance during early childhood without serious neurological signs, premature children show considerable neuropsychological disorders at the school age [1,2]. In 2005, approximately 9.6% of all the births worldwide

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were preterm, and this rate was even higher in developing countries [1]. Preterm birth and its associated problems have imposed an economic burden on the governments. In 2005, according to the estimations, merely the preterm births and its associated medical and educational expenditure, and loss of productivity cost more than $26.2 billion in the USA [1].
Based on the gestational age, preterm births can be subdivided as follows: approximately 5% of preterm births occur prior to 28 weeks and are termed as "extreme prematurity", "severe prematurity" is attributed to about 15% of the preterm births that occur at 28-31 weeks, nearly 20% exhibit "moderate prematurity" and are born at 32-33 weeks, and the remaining 60%-70% are born at 34 to 36 weeks that are designated as “near term” or “late preterm” [3,4]. Approximately, 75% of the perinatal deaths and more than half of the long-term diseases are caused by preterm births. Since the last two decades, the total number of preterm births has increased considerably. For instance in the USA, the rate of preterm births rose from 9.5% in 1981 to 12.7% in 2005 [1,3]. In Africa and Asia, about 85% of births were preterm (including nearly 10.9 million childbirths) in 2005 [1]. Nowadays, preterm labor is speculated as a syndrome caused by several mechanisms, including infection or inflammation, uteroplacental ischemia, or hemorrhage, uterine overdistension, stress, and other factors [3]. Furthermore, a short interval between pregnancies, especially under six months, increases the risk of complications such as newborn death, preterm birth, and constraints on the intrauterine development [5,6].
Some studies demonstrated that the rate of neurodevelopmental impairment, cognitive deficits, learning disabilities, and issues concerning academic underachievement increase following a preterm birth [7-9]. A major part of the central nervous system (CNS) develops before reaching three years of age and continues to develop gradually over a period to attain maturity [10]. Thus, several physiological and psychosocial risk factors such as the status of the disease, medical treatments, and environment-dependent risk factors such as caregiving environments, as well as, the interaction between these parameters can negatively affect the progression of child growth and development [11]. Therefore, owing to these theories, the focus of research has recently shifted towards the early prediction of neurodevelopmental outcome and increasing awareness of the risks related to preterm births [2,11]. Although several aspects related to the effects of preterm birth have been discussed previously, and that the neurological development, hearing, speech, and language acquisition are closely related, only a few studies addressed the preterm birth with respect to these factors. Therefore, in this review, we emphasized the consequences of preterm birth neurodevelopment, speech-language, and hearing ability.
Relevant studies from 1990 to 2016 were retrieved from Science Direct, PubMed, Scopus, Google Scholar, and Scientific Information Database (SID). A total of 125 relevant articles were found using keywords such as preterm birth, auditory system, neural development, speech, and language. The assimilated data were analyzed and the related articles extracted. The selected articles included the analysis of preterm birth effects on one or more outcomes, including auditory system, neural development, and speech-language. The studies must be conducted on human subjects, such as human newborns, children, and adults with a history of preterm birth. English and Persian language articles and papers, which contained the confounding factors in addition to preterm birth, were excluded from the study. Finally, 53 articles were studied in this review.

Consequences of preterm birth

Recently, the rate of survival of preterm infants born before 35 weeks of gestation has been shown to improve significantly [2]. This outcome might be attributed to the advancement in the medical knowledge on the intensive care procedures accompanied by the advent of drugs, such as antenatal corticosteroids and surfactants [2]. However, this rate is variable among countries as well as across different districts of a country [12]. The level of neonatal care can affect the rate of mortality; thus, cases are reported frequently from hospitals that lack the neonatal intensive care units [12,13]. Although advances in perinatal medicine have increased the rate of survival of newborns even in the most immature cases, it might lead to a high prevalence of later neurocognitive and developmental abnormalities [14,15]. Nevertheless, some critical abnormalities and their costs, discussed below, should not be neglected.

Neurodevelopmental consequences

Despite major advances in neonatal intensive care, the developmental disabilities continually demonstrate a high prevalence in preterm survivors. Neurodevelopment is one of the critical aspects of a pivotal role throughout the lifespan of the preterm survivors. About 35% of the total fetal brain and 47% of its cortical volume is gained during the final six weeks of gestation. Between 34^{th} and 41^{st} week of gestation, the volume of myelinated white matter of the CNS undergoes a 5-fold increase [11]. Due to the preterm birth before the 37^{th} week of gestation, the brain growth is accelerated postnatally outside the secure environment of the uterus [11].

Findings showed that the development of the cerebral tissue volume reduces in preterm newborns as compared to term newborns at an equivalent term age [16,17]. Reportedly, the neonatal risk factors such as gestational age, brain injury, treatment by dexamethasone, and intrauterine maturation restriction are correlated with the decrease in the cerebral tissue volume [18-21]. At the corrected age of two years in preterm newborns with more than 1250 g birth weight, working memory deficits and less hippocampal brain volume were found to be related. The relationship between working memory and hippocampal volume remained unaltered after regulating the perinatal risks, socioeconomic status, and developmental factors [22]. Investigating the relationship between preterm birth and neural developmental outcomes revealed that five to six years old children, who were born preterm, could be potentially diagnosed with cerebral palsy, developmental delay, mental retardation, and seizure disorders [23].

Some reports are also available on prolonged neurodevelopmental consequences of preterm births. For instance, in 2008, 20-36 years old adults with a history of preterm birth, presented a risk of medical and social impairments such as cerebral palsy, mental retardation, and academic underachievement that increased with an inverse proportion to the gestational age at birth [24]. However, some of the participants of the previously mentioned study were born more than three decades ago, and since then, the neonatal care has improved considerably, especially respiratory support and developmental interventions. However, although there are improvements in the standards of neonatal care, it is yet unclear that similar results would be observed in the case of current or future preterm newborns [11].

In the former preterm newborns, the memory scores and the volume of the cerebral cortex of areas responsible for memory and language decreased at the age of 12 years as revealed by magnetic resonance imaging (MRI) in comparison to the term subjects [25]. The temporal lobe is a critical area of the brain for the formation of memory and language skills. Especially, the cortical development of the temporal lobe is vulnerable in preterm newborns. Since gyrification begins during the last three months of gestation, the extrauterine environment can affect this developmental process [26].

The gyrification index of the temporal lobe is remarkably greater in preterm children than the term controls. The reading recognition score, which is a marker of language skills at eight years of age, has a negative relationship with the gyrification index of the left temporal lobe [27]. The abundant gyri in the cerebral cortex of preterm children are thin and small. Different rates of growth between the inner and outer layers of the cerebral cortex may lead to gyrification. Increased gyrification occurs when the growth in layers II and III is almost normal and significantly less than the normal growth in layers IV and V [27].

The preterm birth increases the risk of injury to brain gray and white matter. In addition to volumetric differences, several studies exhibit transformed microstructure and connections in the brain of preterm newborns [27,28]. Surprisingly, in the absence of injury, significant alterations can occur in the structure and microstructure of the brain that modify the development. These alterations are linked to neurodevelopmental impairments, and the cortical centers for language development in the temporal lobe and the adjacent areas are vulnerable to these alterations, as described previously [29,30]. Early detection can lead to early interventions. In the case of preterm birth, early interventions could be valuable because the plasticity of network connections in preterm children is hypothesized to provide an opportunity for enhancing the basic language skills with increasing age [31]. Contraindications to prevent this plasticity are absent and would not enhance other neurodevelopmental aspects, such as working memory deficits and abnormal cerebral tissue structure [32,33]. Thus, additional studies are essential to explore the role of special learning programs or treatments in the enhancement of neural plasticity and reduction of negative outcomes of preterm birth.

Speech and language outcomes

For most individuals, language in its oral/aural mode is the primary tool for communication [34]. Early development of speech and language plays a major role in communication as well as socio-emotional dependency. Both socio-emotional dependency and language acquisition depend on experience and sensitive or critical periods that end early in life. Previous studies indicate that several components of the speech signals are available to the fetus, and auditory signals for speech perception and socio-emotional attachment may be present during the fetal stage [34]. However, whether auditory experience during the fetal and perinatal period is essential for the development of spoken language and the effects of unusual perinatal auditory stimulation on peripheral and central auditory system of preterm newborns are yet to be elucidated [34].

Prematurity and extremely low birth weight (<1000 g) place the children at a high-risk of mental and language problems, which might be specific or indicate general cognitive difficulties [35]. Specific educational aid and or need for repeating a grade in school are likely to occur in such children as compared to their normal-weight peers [36]. The reported "Bayley language scores" for preterm newborns with gestational age under 32 weeks showed a declined performance on language and cognitive measures in extremely low birth-weight preterm newborns than the controls [37]. Furthermore, the preterm newborns did not differ in stress patterns at the corrected age of four or six months [38]. Extremely preterm children use age-appropriate speech sounds less than their peer group, thereby displaying that the general cognitive impairment exerts a major role in the development of language issues, such as speech production deficits, grammatical errors, and phonetic inaccuracy [35].

The assessment of children born before 26 weeks of gestation revealed that the risk of speech, language, and educational problems is higher at the age of six years in extremely preterm children. In addition, the likelihood of such problems was 2-fold in very preterm boys than girls [35]. Therefore, the preterm children are delayed in the development of speech and language capabilities as compared to the term children. For instance, a meta-analysis performed on children aged 3-12 years with a history of preterm birth showed significantly lower scores on language tests than those of term peers irrespective of the difficulty level of the test; the problems of preterm children with complex language increases with age [39]. These problems can continue to adulthood. Although the receptive vocabulary of very preterm adolescents advances significantly by the age of 16 years; the problems in sophisticated language skills and general cognition persist continually [40].

Using fMRI, the assessment of the neural activity responsible for auditory comprehension of sentences in teenagers with a history of preterm birth demonstrated that activation in the middle frontal gyri of both hemispheres increases significantly by increasing the syntactic difficulty [41]. Such results showed that prematurity can modify the neural response during auditory comprehension tasks, especially complex tasks such as increased syntactic difficulty.

Thus, optimal lifestyle and learning environment may prove beneficial. Beforehand, it has been reported that in the absence of neurosensory impairments, preterm children, with educated mothers and living under the supervision of both parents were successful in their lives [42]. Health and support organizations should educate the parents and help in providing better conditions for premature newborns and children, to reduce the potential consequences of premature birth.

Preterm birth and auditory system

Preterm hospitalized newborns cannot have rich hearing experience during their early development. The early stages of development in these newborns take place in medical environments where excessive sound levels are supposed to be controlled according to the guidelines [43]. Notably, the mother’s abdominal and uterine tissue acts like a low-pass filter with a cut-off frequency of approximately 500 Hz [34]. These different auditory stimulations along with extra uterine development can lead to adverse functions of the auditory system [44]. Changes in these functions can occur in the peripheral sensory organ, auditory nerve, and or central pathways, some of which are discussed below.

Peripheral auditory system

Some researchers have determined that the human fetus can hear the sounds beginning at three months before birth [34]. An ultrasound-based study showed that at 27th week, 96% of the fetuses reacted by movement to extremely loud low-frequency pure tones presented to them [45]. Therefore, the cochlea of the newborns might exhibit maximum sensitivity at low frequencies, mainly <1000 Hz, with thresholds that are higher than those for adults [45]. Since, as a result of premature birth, the final stages of fetal development occur outside the mother's body, such newborns are deprived of the sensory redundancy of mother's speech and other associated sounds. These auditory stimulations are speculated to play a vital role in the development of cochlear innervations [34,45].

The evaluation of contralateral suppression of Otoacoustic Emissions (OAEs) showed abnormalities in efferent olivocochlear bundle pathways based on the determination of decreased inhibitory effects of contralateral noise on OAEs response [44]. Since efferent pathways are involved in the processing of auditory stimuli and that the preterm newborns encounter intense higher frequencies, longitudinal studies would allow an in-depth understanding of the impact of such reduced inhibitory effects on the development of the auditory system and communication.

Auditory nerve and central auditory system

During structural and functional maturation of the auditory system, synaptogenesis occurs in synchronization with the growth of dendrites, axons, and myelination [46]. Acoustic experience is a substantial part of the development of the cellular structure of the auditory system. It can also affect the formation or integration of neural connections in the auditory brainstem [47]; for example, abnormal brainstem evokes a response at the corrected term date in babies born at 23-27 weeks of gestation [48]. In preterm infants and children, the gestational age at birth is proposed as one of the main factors explicating the functions of brain [2].

MRI studies have shown that abnormalities in the cerebral structure are frequent in preterm newborns. Inadequate long-term neurodevelopment has been shown to be related to the magnitude and location of these abnormalities [46].

Electrophysiological assessments can reveal rather subtle effects of prematurity on neural processes. Auditory brainstem response (ABR) assessment is a proven method to examine the maturation and development of the auditory system. Acceleration in the maturation of the auditory system is reported between 32 and 34 weeks post-conception. In addition, the continual myelination in the auditory cortex might lead to continued development up to late childhood [49].

The transmission of nerve impulses in the auditory brainstem impairs the central regions in high-risk preterm newborns. The evaluation of the neural conduction time in the auditory brainstem shows that in high-risk very preterm newborns, the latency of wave V, III-V, and I-V intervals is considerably longer than that of normal term newborns. The impairment is primarily related to the associated perinatal problems (for example, apnea, sepsis, hypotension, and hyperbilirubinemia) and some extent to very preterm birth [50]. In preterm infants with normal hearing and term corrected age, a recent meta-analysis reported prolonged I-V and III-V latencies [51]. Therefore, the preterm birth, its consequences, and associated perinatal problems exert a negative effect on the conduction time of auditory signals in the eighth cranial nerve and brainstem [50,51]. These effects may be long-lasting. Considerable differences were reported in the auditory brainstem response (ABR) test results with respect to I-III and III-V inter-peak intervals and wave III absolute latency in previously preterm children at four to six years of age [10].

A longitudinal study on the effects of early and late preterm birth on brainstem auditory system evoked responses in children with normal neurodevelopment reported that late preterm newborns have significantly long mean absolute and inter-peak latencies at five years of age [52]. Some of these findings regarding the preterm birth have been related to the adverse effects on neural synchronization in response to transient auditory stimuli [53]. However, addressing the mechanisms underlying the maturation of auditory system could provide a deep insight; such mechanisms include maturation of cochlea and hair cells, myelination of axons, dendritic growth, and increased efficiency of synapses.

A large amount of axonal myelination and other aspects of neurodevelopment occur in the last weeks of pregnancy and the first few weeks after birth. Similarly, a major part of myelination of the auditory pathways in the brainstem occurs in the last weeks of pregnancy earlier and faster as compared to other senses. Thus, it can be hypothesized that a great degree of prematurity would increase the effects of the factors involved in the development of the auditory nervous system. Therefore, early preterm newborns and children show fewer abnormal results as compared to late peers [52].

Conclusion

In conclusion, early detection can lead to early interventions. Accumulating evidence indicates that by early detection of hearing problems and performing timely interventions, language skills of preterm newborns and children will develop and improve with increasing age. Therefore, the preterm birth or early exposure to extrauterine sound environments could lead to some potentially undesired effects on the development of the neural system. Thus, a large number of premature newborns face a higher risk of adverse neural and developmental outcomes and changes in auditory functions. Neonatal diseases and prematurity can affect the low- and high-order auditory processing. The altered auditory stimuli-encodings and changes in the cortical functions can lead to suboptimal language skills. In order to prevent and mitigate the aforementioned consequences, the long-term follow-up of auditory and linguistic abilities is proposed for preterm newborns to fully recognize the sources of issues and implement intervention programs.

Conflict of Interest

The authors declared no conflicts of interest.

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