

INTRODUCTION AND RATIONALE

Hearing is a key sense to develop communication which is the basis of learning and education. The child who can't communicate can't learn. Failure to diagnose the congenital hearing loss at an early age results in impaired verbal, language and perception as well as social and emotional character development (*Arjmandi et al., 2012*). Significant hearing loss is the most common disorder at birth, occurring in 0.1% to 0.3% newborns of the general population and 2% to 4% in newborns who are admitted to a neonatal intensive care unit (NICU) (*Al-Kandari and Alshuaib, 2007 & Paul, 2011*).

The risk factors for hearing loss, according to Joint Committee on Infant Hearing (JCIH) are: premature birth ; low birth weight (<1500 gm); family history of hearing loss; in utero infections; neurological disorder; ototoxic medications, hyperbilirubinemia; craniofacial anomalies; syndromes associated with hearing loss; and severe birth asphyxia (*JCIH, 2000*).

In the absence of a neonatal hearing screening program; severe and moderate hearing loss may not be identified until the first or second year of life and mild loss may not be recognized until school age (*Clemens et al., 2000*). The JCIH recommends that all babies with hearing loss be identified before the end of the first three months of life and receive intervention by the sixth month (*JCIH, 2000*).

Auditory brainstem response (ABR) audiometry is the measurement of electromagnetic waves, generated in response to sound and captured by superficial electrodes attached to the head of the baby. It evaluates the neural integrity of the auditory brainstem pathway (*Volpe, 2001*).

Automated ABR (AABR) testing is recommended for screening at-risk neonates because of the increased occurrence of neural loss (auditory neuropathy/dyssynchrony) in this population, compared with well infants (*JCIH, 2007*).

The wave (I–V) interval is a measure of auditory maturation describing the central conduction time (*Sleifer et al., 2007*). The wave (I–V) interval shows an age-dependent decline up to about 2 years of age, with increased myelination or increased synaptic efficacy of auditory brain stem pathway (*Ponton et al., 1996*). Although it is known that infants admitted to a NICU are at higher risk of developing perinatal complications and abnormal maturational processes, the incidence of prolonged wave I–V interval in NICU infants is unknown (*Coenraad et al., 2011a*).

Delayed maturation of auditory brainstem pathway may lead to misdiagnosis of children with normal peripheral hearing. Furthermore, this may lead to inappropriate use of amplification device in these misdiagnosed children. Accordingly, this study will be conducted to determine the pattern of maturation of auditory brain stem pathway in the NICU neonates, for proper diagnosis in this population.

AIM OF THE WORK

1. To study the auditory brainstem response morphology in NICU neonates.
2. To study the pattern of maturation of auditory brainstem response, in NICU neonates.

DEVELOPMENT AND MATURATION OF AUDITORY SYSTEM IN THE FETUS AND INFANT

The human auditory system is unique and different from the animals. It receives, interprets, and responds to complex language. It also has the capacity to hear, discern, and respond to music. The auditory system supports the development of language and musical skills. The development of hearing requires the auditory experience with voice, language, music, and meaningful environmental sounds during the last 10 to 12 weeks of fetal life "28th to 30th week of gestation" (**Graven and Browne, 2008**).

The development and maturation of the auditory system during the fetal life and early infancy include:

- I- Development and maturation of the peripheral auditory system.
- II- Development of and maturation the central auditory pathways.
- I- Development and maturation of the peripheral auditory system:

The auditory system in the human fetus and infant has its developmental sequences. The structural parts of the auditory system develop early (**Graven and Browne, 2008**). However,

these structures are functioning by the 20th week of gestation (***Pujol and Lavigne-Rebillard, 1992 & Hall, 2000***). The somesthetic (touch), kinesthetic (movement), proprioceptive, vestibular, and chemosensory (smell) systems are structurally and functionally operative before the 20th week of gestation, the auditory system follows these systems in the sequence of development (***Puddu and Fanos, 2012***).

The development and maturation of the peripheral auditory structures include:

- A- Development and maturation of the outer and middle ear.
- B- Development and maturation of the cochlea.
- C- Development of the cochlear ganglion neurons & innervation of the inner ear.

A- Development and maturation of the outer and middle ear:

The ear pinna begins its development later than other components of the ear. Six hillocks appear on either sides of the first branchial cleft at the 5th week of gestation. Three of them arise on the first (mandibular) branchial arch, other three hillocks arise on the second (hyoid) branchial arch, the six hillocks are distinct by the 6th week of gestation (***Wareing et al., 2006 & Patel and Narayan, 2012***). By the 7th week of gestation, the pinna has an identifiable structure (***Sulik and Cotanche, 1995***).

The 3 hillocks on the first arch become the tragus, the helix, and the cyma concha. The hillocks on the second arch become the antitragus, the antihelix, and the cavum concha. Then the auricle is gradually repositioned to a more lateral cephalic position with development of the face (**Patel and Narayan, 2012**). The auricle reaches the adult form by the 18th week of gestation. However, it continues growing in the childhood with changes continuing into the adulthood (**Wareing et al., 2006**).

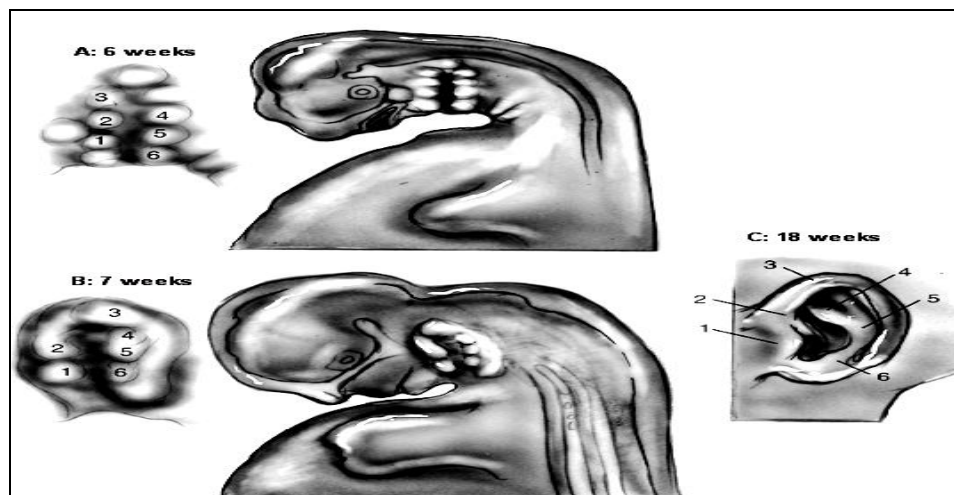


Figure (1): The development of the auricle: (A): Well identified 6 hillocks on the 1st & 2nd branchial arches. **(B):** Identified auricular structures. **(C):** The adult form pinna (**Wareing et al., 2006**).

In the 4th week of gestation, the first branchial cleft forms the primordium of the external auditory canal, it widens with proliferation of the ectoderm forming a pit which is the forerunner of the cartilaginous external auditory canal (**Wareing et al., 2006 & Patel and Narayan, 2012**). In the 8th

week of gestation, the deep portion of the external auditory canal is apparent as a strand of epithelial cells running down to the disk-shaped precursor of the tympanic membrane. Canalization of this epithelial core occurs at the 28th week of gestation allowing communication with the tympanic membrane. The epithelial core is the precursor of the bony part of the external auditory canal (*Van-De-Water et al., 1988*).

The tympanic membrane has a trilaminar origin including: ectodermal origin from the 1st branchial cleft laterally; endodermal origin from the 1st pharyngeal pouch medially, and neural crest mesenchyme with cephalic mesoderm interposed as the fibrous layer (*Noden, 1988*). The bone of the tympanic ring is derived from the neural crest mesenchyme which begins ossification at the 3rd month of postnatal life (*Van-De-Water et al., 1988 & Wareing et al., 2006*).

In the 4th week of gestation, the Eustachian tube and the middle ear are formed as the tubo-tympanic recess, which is an expansion of the endodermal lining of the 1st & 2nd pharyngeal pouches (*Van-De-Water et al., 1988*). In the 5th & 6th weeks, the ossicles are originated from the mesenchyme between the branchial cleft and the developing inner ear. By the 10th week of gestation, the ossicles appears, whereas, the stapes appears slightly before the malleus and incus. The ossicular ossification begins in the 16th week of gestation, and it's completed by the 30th week (*Van-De-Water et al., 1988 & Wareing et al., 2006*).

The development of the tympanic cavity continues, with the expansion of the endodermal pouch surrounding the ossicles, by the 8th month of gestation, it expands with the ossicles lie within an open tympanic space (**Peck, 1994**). Mastoid air cells system appears late during the fetal life (**Wareing et al., 2006**). The middle ear and mastoid air cell system are well developed at birth with a volume of 0.7 to 1.1 mL (**Cinamon, 2009**).

At birth, the external and middle ears are not mature. The peripheral auditory system undergoes a fast developmental period from birth to 12 months (**Kei et al., 2013**). The external auditory canal increases in length and its inner two thirds ossify with age (**Kruger 1987**). The tympanic membrane decreases in thickness, increases in size, and changes its orientation with respect to the external auditory canal (**Eby and Nadol, 1986; Ikui et al., 1997 & Qi et al., 2006**). The volume of middle ear cavity increases linearly throughout childhood (**Molvaer et al., 1978; Ensari et al., 1999 & Wareing et al., 2006**).

The mass and resistance of the middle ear decrease. The mass decreases due to changed ossicular bone density & loss of middle ear's mesenchyme and fluids (**Olszewski 1990**). The stiffness of the middle ear increases due to fibrous structure of the tympanic membrane, changed orientation of the tympanic membrane, fusion of the tympanic ring & tightening of the ossicular joints. The decreased mass & increased stiffness of the middle ear result in a higher resonance frequency of the

external and middle ear with age (**Holte et al., 1991 & Homma et al., 2009**).

B- Development and maturation of the cochlea:

The inner ear is the earliest developing structure of the auditory system. It is formed in the 3rd week of gestation, as a thickening of the surface ectoderm called the otic placode or otic disc appears next to the hindbrain. During the 4th week, the otic placode invaginates to form an otic pit and then a closed, hollow otic vesicle or otocyst which is connected to the surface by a stem of ectoderm. By day 28, the dorsomedial region of the otic vesicle elongates forming an endolymphatic appendage, young neurons delaminate from the ventral otocyst to form the vestibulocochlear ganglion & the rest of the otic vesicle differentiates into an expanded pars superior & a tapered pars inferior (**Eggermont, 1985; Fritzsche et al., 1998; Fekete, 1999 & Baker and Bronner-Fraser, 2001**).

During the 5th week, the ventral tip of the pars inferior elongates & coil forming the cochlear duct (primordium of the cochlea), it also gives rise to the saccule (connected to the cochlea by the ductus reuniens). The endolymphatic appendage elongates over this week forming the endolymphatic sac that is connected to the pars superior by the endolymphatic duct. Late in the 5th week, the pars superior differentiates into the utricle & 3 semicircular (anterior, posterior & lateral) canals, which

are perpendicular to each other. Each canal has a small expansion at one end (ampulla) that houses the sensory cells (*Rubel, 1978; Morsli et al., 1998; Hutson et al., 1999 & Cantos et al., 2000*).

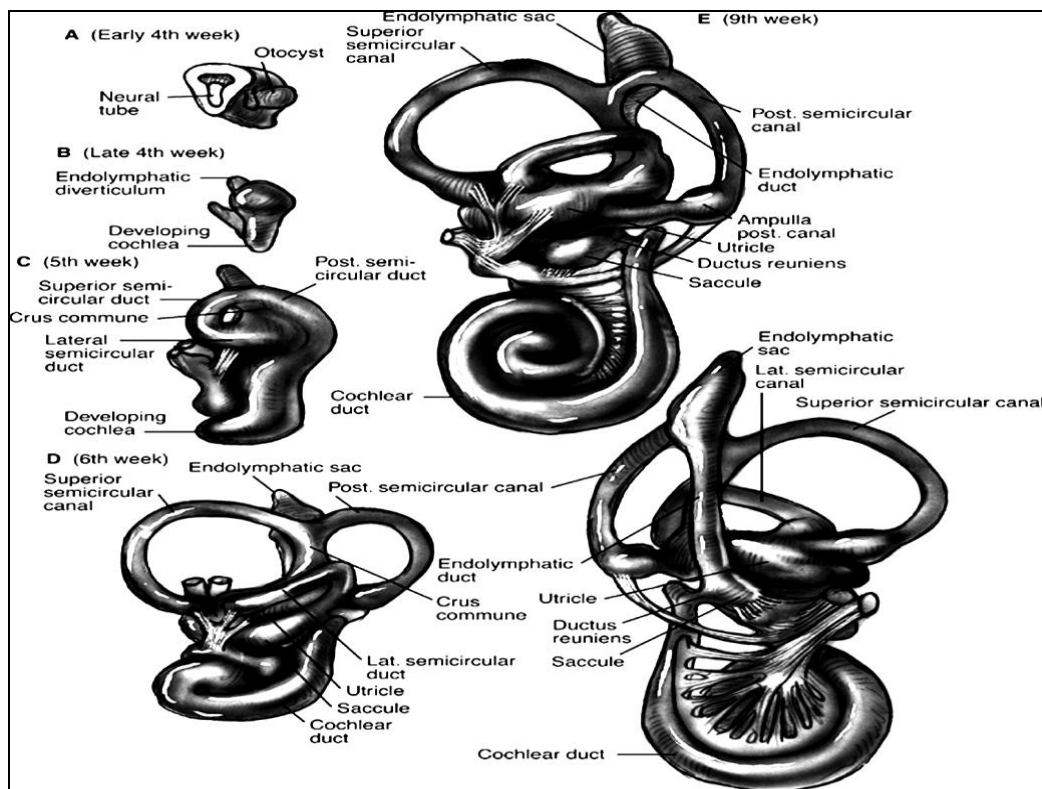


Figure (2): Early development of the inner ear: From 4 to 9 gestational weeks (*Wareing et al., 2006*).

The organ of Corti appears in the cochlear duct at the 9th week of gestation as a ridge of cells with microvilli on their surface (*Iyengar, 2012*). These microvilli are replaced by stereocilia during the next 3 weeks of development (*Bredberg, 1968 & Lavigne-Rebillard and Pujol, 1987*). The hair cells of the cochlea differentiate at the 10th to 12th week of gestation,

proceeding from the base to the apical regions of the cochlea. The inner hair cells (IHCs) complete differentiation earlier than the outer hair cells (OHCs), the IHCs are mature from the functional standpoint at the 15th week of gestation, while the OHCs mature (5 to 7) weeks later (**Hall, 2000 & Kandel et al., 2000c**).

The cochlea attains maturity few weeks before birth (**Eggermont et al., 1996**). During the fetal life, the transmitted sound is analyzed by the basilar membrane depending on the sound frequency, the basilar membrane vibrates differently with tuning each point to a characteristic frequency (**Graven and Browne, 2008**). Each hair cell has a specific frequency at which it achieves maximum stimulation (**Kandel et al., 2000c**). Tuning of most hair cells of the cochlea occurs between the 28th week of gestation and early months of infant life. In utero, most high-frequency sounds are filtered by the uterus, amniotic fluid, and mother's tissues, this protects the hair cells that are tuning to high-frequency sounds from intense high-frequency sounds (**Graven and Browne, 2008**).

C- Development and maturation of the spiral ganglion neurons & inner ear innervation:

As mentioned, young neurons delaminate from the ventral otocyst to form the precursors of the vestibulocochlear ganglionic neurons by the 28th day of gestation (**Eggermont, 1985; Fritsch et al., 1998; Fekete, 1999 & Baker and**

Bronner-Fraser, 2001). A group of neuronal precursors migrate across the basal lamina delimiting the otic vesicle and acquire a position between the developing inner ear and the closely surrounding tissue. These neuronal precursors form the primary neurons of the auditory and vestibular pathways, the cochlear and vestibular ganglia, linking the inner ear and the central nervous system "CNS" (**Rubel and Fritzsch, 2002**).

The IHCs are the true auditory sensory cells, they transform the sound stimuli into nerve impulses that activate the afferent axons for transporting the sensory information to the cochlear nuclei in the brain stem. The OHCs are sound amplifiers and modulators, they are innervated with few afferent axons, while they are largely innervated with feedback efferent neurons from the brainstem nuclei (**Puddu and Fanos, 2012**).

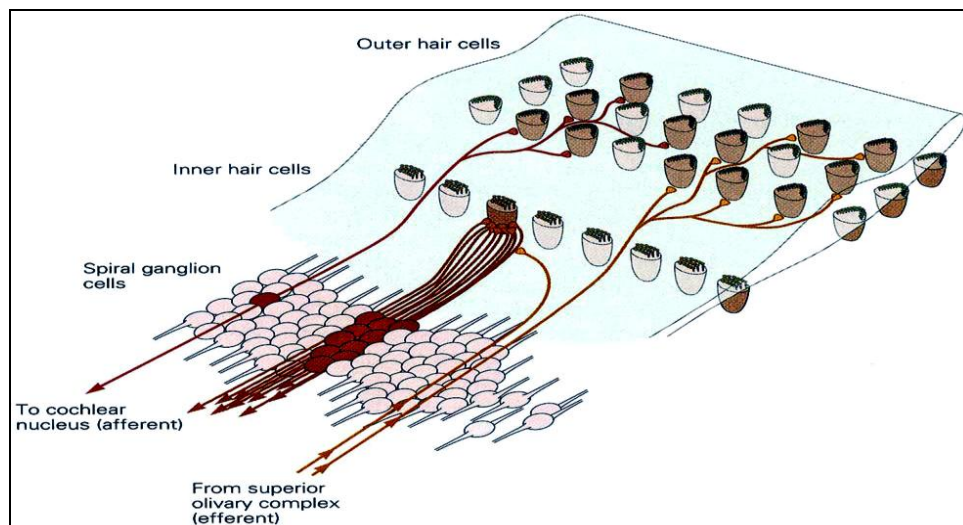


Figure (3): Innervation of the organ of Corti: Most afferent axons end on inner hair cells, Efferent axons largely innervate outer hair cells and do so directly (**Kandel, 2000a**).

The afferent axons (connecting the cochlea with spiral ganglion) appear at the base of the hair cells at the (13th - 14th) week of gestation. Most IHCs are innervated with afferent neurons at the (20th - 22th) week of gestation (**Puddu and Fanos, 2012**). The efferent system (connecting the cochlea with brainstem nuclei) develops at the second trimester "14th - 26th week of gestation" (**Iyengar, 2012**). The fetus & preterm infant have limited ability to modulate the intense auditory signals, as the efferent connections are not functional until near term (**Graven and Browne, 2008**).

Auditory nerve myelination begins by the 24th week of gestation. At the (38th to 40th) week of gestation, most peripheral auditory structures are well myelinated with complete anatomic and physiologic maturation by the first few weeks after birth (**Eggermont, 1985 & Eggermont, 1986**). Like the hair cells, each axon has a characteristic frequency for maximal response. With the IHCs tuning, corresponding spiral ganglionic neurons are tuned to the characteristic frequencies of the IHCs to which they are connected (**Graven and Browne, 2008 & Puddu and Fanos, 2012**).

II- Development and maturation of the central auditory pathways:

All (cochlear, superior olive & inferior colliculus) nuclei of auditory brainstem pathways are identified by the (7th - 8th) week of gestation. The medial geniculate nucleus (MGN) of the thalamus develops by the 8th week of gestation (**Iyengar, 2012**). The cells of all brainstem nuclei begin to mature producing arborizing dendrites by the (24th - 25th) week of gestation. The myelination of the central auditory components (cochlear nuclei, superior olivary complex, trapezoid body, lateral lemniscus, inferior colliculi, brainstem commissures and connecting pathways of the inferior colliculus to the MGN) begins between the 26th & 30th week of gestation (**Weitzman and Graziani, 1968; Starr et al., 1977; Rotteveel et al., 1987 & Moore et al., 1995**).

The perinatal period (3rd trimester to 6th postnatal month) is characterized by the maturation of neurons & axonal pathways of the brainstem. Central myelination and synaptogenesis of the auditory brainstem pathways continue up to 18 to 24 months based on neurophysiologic studies (**Salamy et al., 1985; Madonia et al., 1986; Salamy, 1986 & Iyengar, 2012**). Whereas, MGN afferents to the cortex complete myelination around 4-5 years of age (**Yakolev and Lecours, 1967; Kinney et al., 1988 & Iyengar, 2012**).

During the (27th – 29th) week of gestation, the temporal lobe is discerned as a distinct part of the cortex (**Iyengar, 2012**). By the 37th week of gestation, the medial Heschl's gyrus (the transverse temporal gyrus), that contains the primary auditory cortex, is clearly separated from the lateral part of the superior temporal gyrus where the secondary auditory cortical areas are located (**Moore and Guan, 2001**). Myelination of the auditory cortex begins around 3 months postnatal age (**Pujol et al., 2006**). It is completed around 6 years of age. Yet, the maturation of the auditory pathways has a caudal-to-rostral pattern that parallels the neurophysiologic changes seen with brainstem auditory evoked potentials (**Iyengar, 2012**).

In different critical periods of postnatal life, tonotopic organization occurs in the auditory cortex & the relay nuclei corresponding to the tonotopic organization of cochlear IHCs (**Graven and Browne, 2008**). By the capacity to discriminate sounds at different frequencies, the first cognitive functions are acquired serving in language acquisition (**Shahidullah and Hepper, 1994**).