Fetal development and growth of the fissula ante fenestram in the human ear

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Abstract
Since the fissula ante fenestram (FAF) is considered as a focus of otosclerotic lesion and a route of perilymph leakage, there are few description of prenatal development of the cartilaginous canal passing though the cochlear wall. We examined the sagittal and frontal histological sections of the ear from 32 human fetuses at 8–37 weeks of gestational age. At 8–12 weeks, in the immediately anterior side of a connection between the cochlear and canalicular parts of the otic capsule cartilage, the FAF appeared as a tear of a cartilage between the basal and second turns of the cochlea. The tear became a slit opening to the scala vestibuli. At 13–15 weeks, the FAF, less than 1.2 mm in length, had the anterosuperior and postero-inferior apertures: the former was near the geniculate ganglion and became closed after 15 weeks, while the latter approached the oval window. Third trimester fetuses, the FAF, 1.5–2.0 mm in length, consistently carried a single, postero-inferior aperture extending along the anterior margin of the oval window and it contained no definite epithelium and vessel. Although it was endochondral ossification, there was no clear zonation in cartilage cells of the FAF. A mechanical stress during three-dimensional coiling of the cochlear ducts seemed to provide the FAF. After the FAF was established, the stapes footplate might use a part of the inferior aperture for the syndesmosis. A specific ossification was seen in the FAF, but it might rarely cause the pathological syndesmosis.

KEYWORDS
cochlea, fissula ante fenestram, human fetus, ossification, oval window

1 INTRODUCTION
The fissula ante fenestram (FAF), a cartilaginous canal in fetuses and a bony canal in children, had been known as an outpouching of a periotic fibrous tissue that lines or passes through the inferolateral wall of the perilymphatic labyrinth. The FAF appears between the 8-week and 10-week stages, and in the fetus of 5 months, it is a definite transcapsular tract communicating between the scala vestibuli and tympanic cavity (Bast & Anson, 1949).

According to Bretlau and Pedersen (1969) and Kohut, Hinojosa, and Ryu (1991), the original description of the
FAF was performed by Siebenmann (1890) and his student Perozzi named it Cozzolino’s zone. However, in Bast (1936), the FAF was first referred by Huschke (1844) and Hyrtl (1845). Anson and Donaldson, 1973 considered the FAF as a transcapsular appendage of osseus labyrinth (Figure 1).

The FAF had been considered as a site of otosclerotic lesion and a route of perilymph leakage (reviewed by Kohut, Hinojosa, & Ryu, 1989; Kohut, Hinojosa, & Ryu, 1991). A newly formed, lamellar bone tissue in the FAF stains deeply acidophilic by hematoxylin–eosin (HE), showing a clear demarcation from the surrounding endochondral bony tissue. This lamellar bone was considered to invade into the surrounding bone and toward the oval window, resulting in ankylosis of the tympanostapedial syndesmosis and consequent clinical otosclerosis (reviewed by Bretlau & Pedersen, 1969).

Bast (1936) classified three different variations in FAF openings to either the: (a) tympanic cavity, (b) vestibule, or (c) oval window or tympanostapedial syndesmosis. He considered the FAF with the third type opening to have a great potential to cause a sudden conductive failure.

Previous studies of the FAF focused on the cartilage content and its ossification in the late-stage fetus, infant, and children (e.g., Bast, 1930, 1936; Bretlau & Pedersen, 1969). There are few descriptions of the prenatal development of the cartilaginous canal passing through the vestibular wall. Does the FAF correspond to a transient structure needed for development and growth of the vestibule? We propose Bast’s three classifications of FAF openings are not individual variations but rather a difference between developmental stages. Consequently, the aim of this study was to describe a developmental sequence of the FAF with special reference to altered topographical anatomy around the FAF.

2 | MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We examined paraffin-embedded histological sections from 32 fetuses (approximately 8–37 weeks of gestational age; 28–310 mm of crown-rump length [CRL]). The specimens were categorized into two groups according to age and size: (a) 20 first and second trimesters’ fetuses at 8–15 weeks of gestational age (CRL 40–120 mm) and (b) 12 third trimester fetuses at 30–37 weeks (CRL 248–310 mm). The parameters used to determine the postconceptional age were CRL (O’Rahilly & Müller, 1996).

Serial histological sections of first and second trimesters’ fetuses were part of the large collection kept at the Department of Anatomy and Embryology of the Universidad Complutense, Madrid, and were the results of miscarriages and ectopic pregnancies from the Department of Obstetrics of the University. They had been prepared serially and stained with HE, azan, or orange G. The sectional planes were horizontal, frontal, or sagittal. This study was approved by the Ethics Committee of Complutense University (B08/374). Photographs were taken with a Nikon Eclipse 80.

From 12 third trimester fetuses, we prepared paraffin-embedded sections at 50 or 100 μm interval. The sectional planes were sagittal (10 fetuses) and horizontal (2 fetuses) and, all sections were stained with HE. These specimens were parts of the collection of the Department of Anatomy, Akita University, Akita, Japan. These specimens had been donated by their families to the Department from 1975 to 1985 and preserved in 10% (wt/wt) neutral formalin solution for more than 30 years. The available data were limited to the date of donation and gestational age, but there was no information on family name, the name of the obstetrician or hospital and the reason for abortion. The use of these specimens for research was approved by the ethics committee of Akita University (No. 1428). Photographs were taken with a Nikon Eclipse 80.

3 | RESULTS

3.1 | Observations of first and second trimesters fetuses

At 8 weeks, two parts were identified in the otic capsule cartilage: the cochlear and canalicular parts (Figure 2). The cochlear part contained the basal and second turns of the cochlear duct and an incomplete septum separated them. Accordingly, in frontal and horizontal sections, the
cochlear cartilage took an e-shaped appearance. The facial and vestibulocochlear nerves passed along a border area between two parts of the otic capsule. The future oval window was identified as a membrane-like condensation of mesenchymal tissues attaching to the stapes (Figure 2d). Likewise, a linear mesenchyme suggested the future site of the FAF (Figure 2c).

At 9–12 weeks (early fetal phase), the e-shaped cartilage of the cochlea increased in size and a septa of the basal and second turns became thick (Figure 3). The FAF was first identified as a tear between the e shaped primitive cochlea and a cartilage plate connecting with the canalicular part (Figure 3a,b). Later, this plate is involved into cochlear wall. The FAF was identified as a long slit corresponding to the lower gap of “e” (Figure 3c,e). The FAF was located in the inferolateral wall of the cochlea corresponding to the upper and/or middle one-thirds of the medial wall of the tympanic cavity including the future promontory. The long slit of the FAF was in the anterior side of the oval window (Figure 3d) and it extended from the anterosuperior aperture of cochlea to the postero-inferior aperture near the scala vestibuli of the basal turn of the cochlea (Figure 3c).

The superior aperture was near the geniculate ganglion, the tympanic, or horizontal portion of the facial nerve and the future processus cochleariformis of the tensor tympani muscle tendon. The inferior aperture faced the scala vestibuli of the basal turn of the cochlea slightly anterior to the oval window (Figure 3e). Thus, the oval window was seen in sections posterior or inferior to the FAF (Figure 3f).

Slightly later, at 13–15 weeks (mid fetal phase), the postero-inferior end of the FAF became adjacent to the medial margin of the oval window (Figures 4 and 5). The enlarging footplate of the stapes appeared to use a posterior part of the FAF as the attachment, that is, an anterior margin of the oval window. Thus, inferior end of the FAF was seen near the enlarging tympanic cavity. In contrast, the anterosuperior aperture of the FAF, which was near the geniculate ganglion (Figure 5b), became thin or even closed (Figures 4d and 5b). The length of the FAF (less than 1.2 mm) was almost same as or greater than the maximum diameter of the basal turn of the cochlea. The FAF at second trimester was still filled with a loose mesenchymal tissue and, if contained, the vascular structure came from the anterosuperior aperture near the geniculate ganglion (Figure 5f). Although it might be an individual variation, small recesses were sometimes seen near the superior and inferior apertures, respectively. The superior recess tended to be longer than the inferior one.
FIGURE 3  Legend on next page.
3.2 Observations of third trimester fetuses

In contrast to the FAF on the posterior side of the tympanic cavity in second trimester fetuses (Figure 5c), FAF was embedded in the medio-superior wall of the cavity in third trimester fetuses (Figure 6a). The FAF consistently had a single aperture adjacent to the oval window (Figures 6a and 7), that corresponded to the postero-inferior aperture in first and second trimester fetuses. The FAF was filled with cartilage and another fibrous tissue. However, because the single aperture was large funnel-like along the supero-inferior axis, the fibrous contents attached to the entire anterior margin of the oval window as well as to both the scala vestibuli and tympanic cavity (Figure 7c vs. a). However, there was no epithelial extension from the tympanic cavity or the scala vestibuli to the FAF. We rarely found thin vessels within the FAF and those that were present appeared to come from bone tissue of the cochlea. The length of the FAF (1.5–2.0 mm) was smaller than the maximum diameter of the basal turn of the cochlea. Comparing sagittal sections at the same magnification (Figure 5b vs. Figure 7c; Figure 5a vs. Figure 6a), the length and thickness of the FAF were not changed or slightly increased between 15 and 30 weeks. However, a course or direction of the FAF was different from that at second trimester fetuses: (a) an oblique or nearly vertical course at second trimester was changed to an almost horizontal course and (b) a postero-inferior aperture opened into the cochlear wall.

Various types of cartilage cells were mixed in the FAF although hypertrophic cells tended to face the calcified zone (Figure 7f). Notably, a mesenchymal tissue sometimes remained in the FAF (Figures 6e and 7f). Conversely, a clear zonal differentiation (Figure 6d) was not evident in the FAF cartilage. A calcified cartilage did not attach to the syndesmosis. Near and around the FAF, inner ear ossification was complete except for the supero-postero-lateral marginal parts in which endochondral ossification was on-going in the remnant otic capsule cartilage (Figure 6b,c). Such ossification also occurred in the upper end of Reichert cartilage. In contrast, membranous ossification was seen along the facial nerve canal (Figure 6f), the carotid canal (Figure 6g), the subarcuate recess or canal of Cotugno (a thickest vascular route from the superior aspect of the otic capsule; Figure 6c) and the tympanic bone. However, since the ossification in and along the subarcuate recess accompanied dense collagen fibers dispersing from the lamellar bone to mesenchymal tissues (Figure 6c), it was not the typical membranous ossification but the woven bone formation.

Finally, we found anomalies in two of the 12 third trimester fetuses examined. One fetus (256 mm CRL) had the anterior crus of stapes connected with the cochlear wall: calcified tissues were continuous between them (Figure 8a). The tympanostapedial syndesmosis was normal and contacted the FAF (Figure 8b). Another fetus (312 mm CRL) carried the usual tympanostapedial syndesmosis adjacent to the FAF anterior margin, but the footplate of the stapes was continuous with the bony cochlear wall (Figure 8c,d). We found no abnormality of the FAF itself.

Figure 9 summarizes the early development, fetal growth, and final location of the FAF. However, a topographical relation of the FAF with the oval window was quite different between Figure 9b,d. After 15 weeks, the postero-inferior aperture of the FAF and the oval window approached mutually to reach their final positions, that is, the postero-inferior aperture adjacent to the anterior margin of the oval window (Figures 4c and 5c). Therefore, the stapes footplate appeared to use a part of the FAF aperture for the syndesmosis. In contrast, the anterosuperior aperture, initially near the geniculate ganglion, was closed and replaced by bone at a stage between 15 and 30 weeks.

4 DISCUSSION

Ossification is categorized into (a) membranous ossification typically seen in the calvaria of skull and (b) endochondral ossification such as occurred in the
vertebra. Endochondral ossification of the FAF was quite different from that in other, major parts of the otic capsule due to poor vascularization to the FAF. The otic capsule ossification is characterized by clusters of short bony columns, each of which surrounds a vein similar to a well-known haversian unit, and this morphology is

FIGURE 4 Postero-inferior aperture of the FAF adjacent to the oval window. Horizontal sections from a fetus of 101 mm CRL (13 weeks). Azan staining. Panel (a) displays the most inferior plane in the figure. The right-hand of each panel corresponds to the lateral side of the head. A postero-inferior aperture of the FAF (arrowhead in Panel [a]) opens to the scala vestibuli of the cochlea and it is adjacent to the oval window receiving the stapes (Panel [b]). An anterosuperior aperture (arrow in Panel [d]) is tiny, near the facial nerve and almost closed. Panel (b) exhibits a higher magnification (scale bar: 0.1 mm). All panels were prepared at the same magnification (scale bar in Panel [a], 1 mm)
FIGURE 5  Closing superior aperture of the FAF. A fetus of 100 mm CRL (13 weeks). Sagittal sections. Azan staining. Panel (a) displays the most medial plane in the figure. The right-hand of each panel corresponds to the anterior side of the head. A posteroinferior aperture of the FAF (arrowhead in Panels [a] and [b]) is large and near the oval window, while an anterosuperior aperture (arrow in Panel [b]) is almost closed near the geniculate ganglion. Panel (f) exhibits a higher magnification view of the anterosuperior aperture of the FAF in Panel (b): vascular structures contained in the FAF are coming from a site near the geniculate ganglion. Scale bars 1 mm in Panels (a–e); 0.1 mm in Panel (f). ASC, anterior semicircular canal; JF, jugular foramen; PSC, posterior semicircular canal.
FIGURE 6  Topographical anatomy of the FAF third trimester. A sagittal section from a fetus of 249 mm CRL. Panel (a) displays the FAF embedded in the cochlear wall; note a difference from the second trimester sagittal section (see Figure 4a). The right-hand corresponds to the anterior side of the head. The FAF carries a single aperture opening to the tympanic cavity in this section (arrowhead), but the opening is wide along the mediolateral axis and faces also the base of stapes or footplate (stapes) as well as the scala vestibuli of cochlea in near sections. Panels (b–g) are higher magnification views of squares in Panel (a), respectively. Panels (b) and (d) show endochondral ossification of the otic capsule cartilage remained in the posterolateral end of the inner ear. In contrast, Panel (c) (subarcuate recess), Panel (f) (facial nerve canal) and Panel (g) (carotid canal) exhibit the typical morphology of membranous ossification. The FAF contained non-calcified cartilage as well as a mesenchymal tissue in this section. Asterisks indicate an artificial tear of tissues during histological procedure. Scale bars: 1 mm in Panels (a) and (b); 0.1 mm in Panels (c–g). ICA, internal carotid artery; LSC, lateral semicircular canal.
Figure 7  A single aperture of the FAF in sagittal sections from a fetus of 264 mm CRL. Panel (a) displays the most lateral plane in the figure. Intervals between panels are 0.3 mm (a–b) and 0.4 mm (b,c). Insert exhibits a section near Panel (b): the FAF has a superior branch or recess (stars). Panels (d–f) are higher magnification views of the FAF in Panels (a–c), respectively. The right-hand of each panel corresponds to the anterior side of the head. An aperture of the FAF (arrowhead) is wide along the mediolateral axis and extends from the tympanic cavity (Panels [a] and [d]), via the tympanostapedial syndesmosis (Panels [b] and [e]), to the scala vestibuli of the cochlea (Panels [c] and [e]). The FAF contained non-calcified cartilage, calcified cartilage and a mesenchymal tissue (Panel [f]). Asterisk indicates an artificial space by the histological procedure. Panels (a–c) and the insert (or Panels [d–f]) were prepared at the same magnification (scale bars: 1 mm in Panel [a]; 0.1 mm in Panel [d]).
called “osseous globules” (Sørensen, Bretlau, & Jørgensen, 1992) or “globuli ossei” (Michaels, Soucek, & Linthicum, 2010). The typical zonation of cartilage cells occurs in limited marginal areas of the ear. However, a calcified cartilage in the FAF made an irregularly shaped mass and it was quite different from the globules. Indeed vessels entered the FAF through the anterosuperior aperture until second trimester, but the latter was closed soon later. Because of no or few vessels contained near term, the FAF was unlikely to provide either the globules or woven bone.

The FAF has been considered as a focus of inner ear pathologies causing: (a) abnormal calcification at the tympanostapedial syndesmosis and (b) perilymphatic fluid leakage. The major evidence leading to otosclerosis had been highly eosinophilic calcified cartilage in the FAF as seen in studies by Anson and colleagues (see Introduction). However, a newly formed calcified cartilage must be highly eosinophilic no matter whether it is normal or pathological. Later, the active and delayed ossification toward otosclerosis was defined as a sequential process: (a) “osteocyte-mediated absorption” of the

**FIGURE 8** Anomalous bony connection near the oval window found in two third trimester fetuses. HE staining. Panels (a) and (b), sagittal sections from a fetus of 256 mm CRL; Panels (c–e), horizontal sections from a fetus (312 mm CRL). The right-hand of each panel corresponds to the anterior side of the head. In Panel (a), the anterior limb of stapes connects to the cochlear wall by a bone tissue (arrows). The tympanostapedial syndesmosis is normal and contacts the FAF (Panel [b]). In Panels (c–e), the footplate of stapes is continuous with the bony cochlear wall at the posterior end (arrows in Panel [e]). A syndesmosis is present at the anterior end of the oval window and it is adjacent to the FAF. All panels were prepared at the same magnification (scale bar in Panel [a], 1 mm).
prenatally developed endochondral bone; (b) deposition of “woven bone” in the enlarged perivascular space; (c) proliferation of vessels and production of lamellar bone (reviewed by Merchant & Nadol Jr., 2010). Therefore, the FAF did not contain a woven bone structure in the present specimens. Moreover, a calcified cartilage of the FAF did not attach to the syndesmosis. Actually, the fetal tissue of the FAF at the lower magnification may be similar to the fenestral type of otosclerosis in high resolution imaging such as shown by Sanghan et al. (2018). We incidentally found congenital tympanostapedial fixation in two fetuses. Nevertheless, the fetal tissue of the FAF was quite different from the histology of otosclerosis (Merchant & Nadol Jr., 2010; Quesnel et al., 2013).

Endolymphatic hydrops is likely to occur in combination with otosclerotic pathology at the oval window (reviewed by Merchant & Nadol Jr., 2010). Kohut, Hinojosa, and Ryu (1989) hypothesized that a loose arrangement of the FAF content allows the perilymphatic fluid leakage from the scala vestibuli to the tympanic cavity. Actually, at second trimester fetuses, the scala vestibuli is most likely to secondarily develop by an invasion of high potassium fluids from the cochlear duct (Kim et al., 2011). However, third trimester fetuses, a mesenchymal tissue did not occupy the entire FAF, but it provided a small island. Moreover, the residual mesenchymal tissue was much tighter than that at second trimester fetuses. A mesenchymal tissue in the FAF third trimester was likely to originate from a site near the geniculate ganglion when vessels entered at second trimester fetuses (Figure 5f). Conversely, the mesenchymal island in the third trimester fetuses FAF was unlikely to take a degenerative change similar to the scala vestibuli.

Although the FAF is well known, previous researchers seemed not to consider how the fissure develops. A border area between the cochlear and canalicular parts of the otic capsule cartilage developed into a large “hilus” of the inner ear including the internal meatus, the facial nerve canal and, the oval and round windows. The anterosuperior aperture of the FAF also opens to the hilus although it was closed at and around 15 weeks. We noted a coiling process of the cochlear turns. Depending on enlargement of the basal turn of the cochlea, an “e” shaped appearance of the cochlea became evident and it appeared to draw up a border area cartilage toward the cochlear wall. Simultaneously, a septum between the basal and second turns, corresponding to the center of “e,” became thick and provided a tear of cartilage, that is, an initial FAF. Therefore, the FAF seemed to be a product by a mechanical stress during a change from a two-dimensional cartilage loop to a three-dimensional coil. In the process, the topographical relation drastically changed between the oval window and the FAF inferior aperture: later, a further approach between them made the FAF open to both the scala vestibuli and the tympanic cavity (Figure 7). Similar to the FAF, the round window also seemed to enlarge with receiving a mechanical stress during the three-dimensional coiling. Overall, the FAF was most likely to be a remnant gap of cartilage caused by the three-dimensional cochlear development. Variations in opening site of the FAF according to Bast (1936) correspond to
development stages observed by us. We considered that they might represent remnants of the FAF from these stages of development.

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CONFLICT OF INTEREST
The authors declare no interests.

AUTHOR CONTRIBUTIONS
José Francisco Rodríguez-Vázquez: Conceptualization; formal analysis; investigation; supervision; validation; writing - original draft; writing-review & editing.

Maria Cruz Iglesias-Moreno: Data curation; resources; software. Adriana Poch: Data curation; resources; software. Gen Murakami: Conceptualization; investigation; methodology; supervision; validation; writing - original draft; writing-review & editing. Hiroshi Abe: Conceptualization; methodology; validation; visualization. Yohei Honkura: Conceptualization; formal analysis; investigation; supervision; validation.

ETHICS STATEMENT
This study was approved by the Ethics Committee of the Complutense University (B08/374) and Akita University.

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