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ORIGINAL SCIENTIFIC ARTICLE

# Recent Advances in 3D Ultrasound, Silhouette Ultrasound, and Sonoangiogram in Fetal Neurology

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## ABSTRACT

New fields of neurosonoembryology and fetal neurology have been established by the remarkable contribution of three-dimensional/four-dimensional (3D/4D) ultrasound technology. A recent evolution in prenatal imaging is HDlive silhouette/flow technology. By HDlive silhouette mode, an inner cystic structure with fluid collection can be depicted through the outer surface structure of the body, and it can be appropriately named "see-through fashion." HDlive flow mode adds more spatial resolution to conventional 3D ultrasound angiogram. We have utilized this technology in neuroimaging and investigated its clinical significance.

HDlive silhouette imaging demonstrated clear images of ventricular system with outer fetal surface structure in early pregnancy as well as in the middle gestation. Silhouette ultrasound demonstration of a thick slice of 3D volume dataset shows a more concrete inside structure of complicated morphology in specific cases. Silhouette ultrasound can also depict a bony structure; therefore, cranial bones and vertebrae of spina bifida can be detected using this technology. HDlive flow imaging can demonstrate the cerebral vascular structure of fine arteries and veins throughout gestation. By HDlive silhouette and flow imaging, inner cystic as well as noncystic structures can be demonstrated with outer surface. HDlive flow imaging can demonstrate fine peripheral brain vasculature.

The degree of gain, threshold, and silhouette or a combination of these makes it possible to create completely different images with different clinical information from a single-volume dataset. This fact expands the flexibility of imaging and demonstration, but at the same time it can create a virtual reality. Although any new technology is not always perfect, HDlive silhouette and flow imaging will greatly contribute to perinatal medicine.



**Keywords:** Fetus, Flow, HDlive, Neurology, Prenatal diagnosis, See-through fashion, Silhouette, Three-dimensional, Ultrasound.

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## INTRODUCTION

Recent advances in prenatal ultrasound technology have contributed to the fields of embryology and fetal anatomy, and have established a field of sonoembryology,[1,2] which is still evolving. Three-dimensional (3D)/four-dimensional (4D) sonography has revealed structural and functional early human development *in utero*[3-6] and moved prenatal diagnosis of fetal anomalies from the second trimester to the first trimester of pregnancy.[7] The 3D transducers take several hundreds or thousands of two-dimensional (2D) ultrasound images over a short (30–40° degree) arc. These images are then transferred to a computer that integrates them into a single image. The first generation of 3D ultrasound lacked the capability to reconstruct images rapidly and with high resolution. These limitations could explain why the method was not very popular initially.[8] With current clinically available equipment, 3D sonographic reconstruction is fast with a high resolution, giving ultrasound the ability to image in real time. Also, 3D ultrasound allows volume data to be stored and manipulated long after the patient has left the examination room. Storage of a single volume of data is easy and quick, yet the stored volume permits the interpretation of the scanned region in multiple planes.[8]

A great achievement in the field of 3D/4D ultrasound is HDlive technology. This technology is a novel ultrasound technique that improves the 3D/4D images. HDlive ultrasound has resulted in remarkable progress in visualization of early embryos and fetuses and in the development of sonoembryology.[9] With HDlive ultrasound, both structural and functional developments can be assessed from early pregnancy more objectively and reliably, and indeed, these new technologies have moved embryology from postmortem studies to the *in vivo* environment.[8] HDlive uses an adjustable light source and software that calculates the propagation of light through surface structures in relation to the light direction.[10] The virtual light source produces selective illumination, and the respective shadows are created by the structures where the light is reflected. There have been several reports on HDlive demonstration of fetal surface.[9,11-13]

Three-dimensional HDlive further "humanizes" the fetus, enables detailed observation of the fetal face in the first trimester, and reveals that a small fetus is not a fetus but a "person" from the first trimester.[13] Detailed structural abnormalities of face, fingers, toes, and even amniotic membranes in the first trimester could be well demonstrated by the HDlive technique.[13,14]

Furthermore, great advances in ultrasound technology have produced new applications of HDlive silhouette and HDlive flow. This article demonstrates detailed and comprehensive structural images and angiograms of normal and abnormal central nervous system (CNS) from the first trimester depicted by 3D HDlive silhouette and flows, which closely resemble those from anatomy atlases or scientific documentaries, and describes clinical significance and pitfalls of those novel applications.

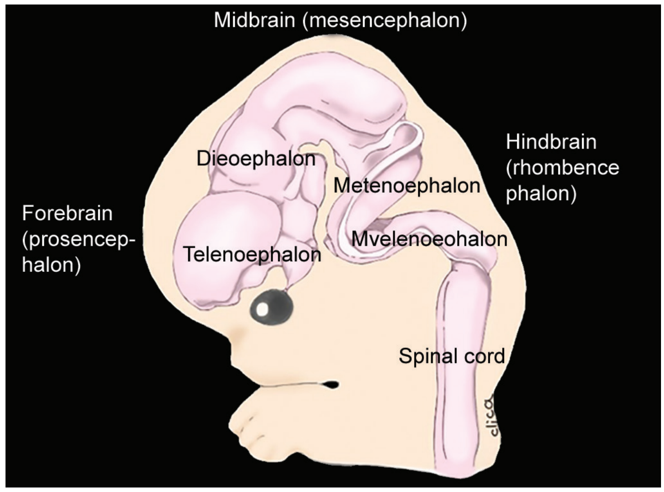


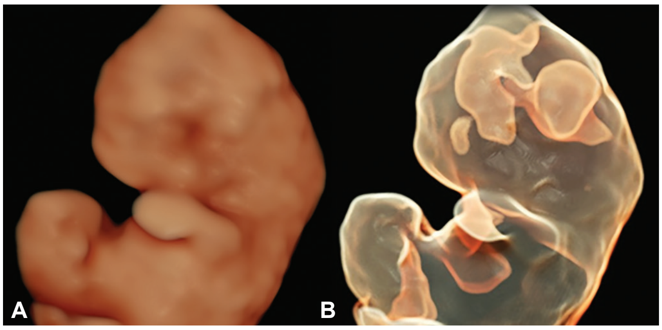

**Fig. 1:** Schematic picture of embryonal brain. Embryonal brain contains three parts of forebrain (prosencephalon), midbrain (mesencephalon) and hindbrain (rhombencephalon)

## WHAT IS SILHOUETTE ULTRASOUND IMAGING?

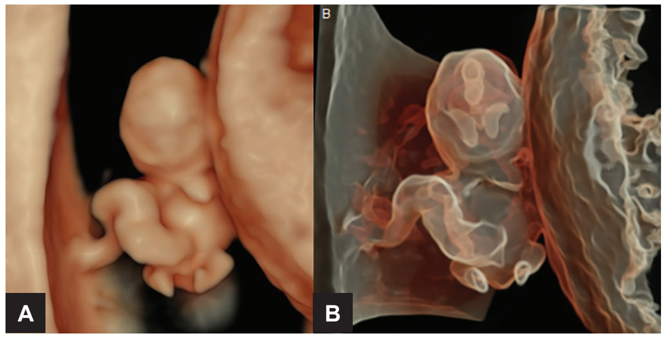
New applications of HDlive silhouette and HDlive flow were released at the end of 2014. The algorithm of HDlive silhouette creates a gradient at organ boundaries, fluid-filled cavity, and vessels walls, where an abrupt change in the acoustic impedance exists within tissues.[15,16] The examiner can adjust HDlive silhouette percentage by controlling threshold and gain simultaneously for visualizing target organs of interest. HDlive silhouette emphasizes the borderlines between organs with different echogenicity; therefore, both the target of interest floating within fluid correction and the cystic area in echogenic organs are simultaneously demonstrated. By HDlive silhouette mode, an inner cystic structure with fluid collection can be depicted through the outer surface structure of the body, and it can be appropriately named "see-through fashion."[15,17,18] The placental surface is demonstrated through the amniotic fluid, and a report on HDlive silhouette imaging of circumvallate placenta was recently published.[19]

### Ventricular System and Abnormal Cystic Structure by HDlive Silhouette Imaging Technology

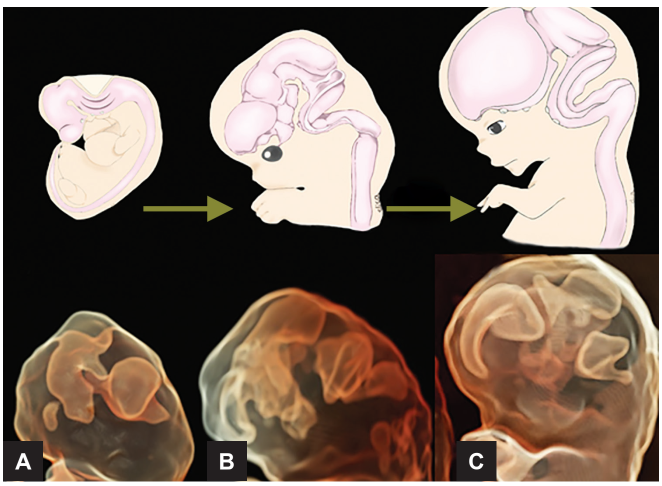
Any cystic area or hypoechoic part can be the target of interest by HDlive silhouette imaging. During the early embryonic period, the CNS anatomy rapidly changes in appearance. Three-dimensional sonography using transvaginal sonography with high-resolution probes allows imaging of early structures in the embryonic brain. Figure 1 is a schematic of the embryonal brain, which contains three parts: Forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). The forebrain includes the telencephalon, containing cerebral hemispheres, and the diencephalon, containing thalamus, hypothalamus, epithalamus, and subthalamus. The midbrain is the most rostral part of the brain stem, is located above the pons, and adjoins rostrally to the thalamus. The hindbrain is the posterior part of the three primary divisions, which includes the metencephalon, containing pons and cerebellum, and the myelencephalon, containing the medulla oblongata. In 1998, Blaas et al[20] sensationally demonstrated early human brain vesicles in different colors and measured their volumes by 3D scanning embryos ranging between 9.3 and 39 mm, and performed a postprocessing procedure. Thereafter, the embryonic brain structure was demonstrated by advancing 3D technology of inversion-rendering mode;[21,22] sonoembryology has become more sophisticated and objective. Advancing imaging techniques allow the definition of *in vivo* anatomy, including visualization of the embryonic features that could not be characterized in fixed specimens.[23] Three-dimensional images of embryos were generated using the high-frequency transvaginal transducer (Voluson® E10 with 6–12 MHz/256 element 3D/4D transvaginal transducer, GE Healthcare, Milwaukee, USA). Transvaginal approach combined with high frequency of 12 MHz with a harmonic-phase inversion method can provide us images with high quality and high resolution, demonstrating detailed embryonal structures, especially brain vesicles. As shown in (Figs 2 and 3), the inside structure of brain vesicles of normal embryos is well demonstrated by the HDlive silhouette mode. Figures 4A to C and 5 show a rapid change in the developing brain vesicles by HDlive silhouette mode at different stages. An abnormal brain structure at 10 weeks is comprehensively detected by HDlive silhouette mode, as shown in Figure 6. The fused ventricle and the single ventricle in semilobar/alobar holoprosencephaly (Fig. 7) are well visualized. Figure 8 demonstrates enlarged bilateral ventricles and third ventricle in a case of hydrocephalus, and Figure 9 shows enlargement of the ventricular system, including third and forth ventricles in a single-volume dataset in a case of Dandy Walker malformation. An eyeball at the outer surface of a fetal face in a case with exophthalmos is depicted in Figure 10.




**Figs 2A and B:** Three-dimensional images of crown-rump length 19.3 mm normal embryo: (A) Conventional HDlive image. Surface rendering with shadow demonstrates the outer surface of the embryo and umbilical cord, and (B) Same image with HDlive silhouette. Premature brain cavity is well demonstrated within the outer surface of embryo




**Figs 3A and B:** Three-dimensional images of crown-rump length 22.3 mm normal embryo: (A) Conventional HDlive image. Surface rendering with shadow demonstrates the outer surface of the embryo and umbilical cord, and (B) Same image with HDlive silhouette. Premature brain cavity is well demonstrated within the outer surface of embryo




**Figs 4A to C:** Lateral view of early brain development by HDlive silhouette mode: (A) Embryo with crown-rump length (CRL) 19.3mm, (B) Embryo with CRL 22.3mm, and (C) Fetus with CRL 23.9 mm. Upper: Schematic illustration showing early brain development (drawn by Clica@CRIFM). The development of three primary brain divisions of forebrain, midbrain, and hindbrain is well demonstrated

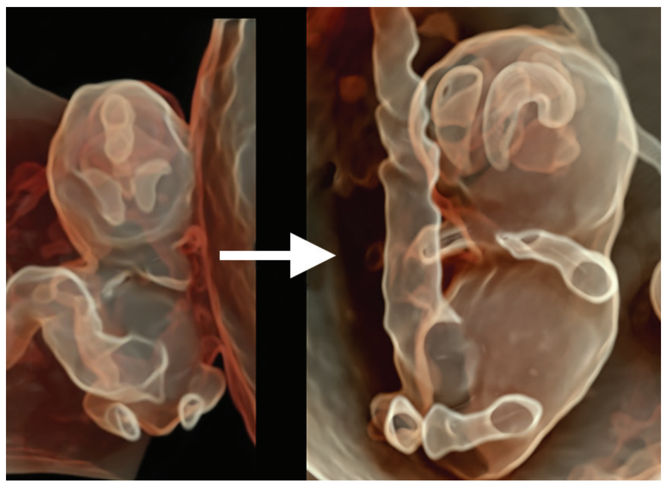


**Fig. 5:** Frontal view of brain development by HDlive silhouette mode: Left: Fetus with crown-rump length (CRL) 22.3 mm. Bilateral telencephalon (forebrain) and midbrain are well demonstrated; Right: Frontal-oblique view of fetus with CRL 23.9 mm. Rapid development of early brain is comprehensively depicted

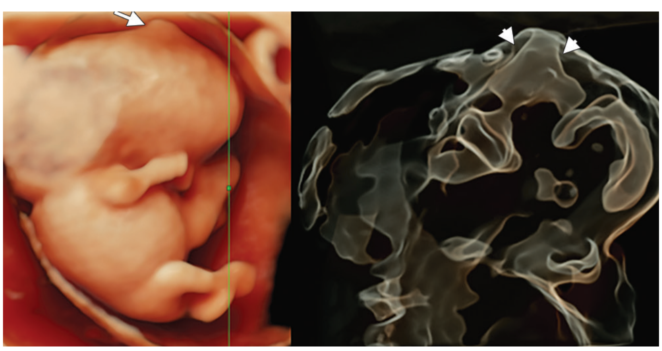


**Fig. 6:** Abnormal midbrain cavity at 10 weeks of gestation: Left: three-dimensional HDlive image of the fetus. Note the prominent top of the fetal head (arrow) due to abnormal midbrain, Right: HDlive silhouette image of the fetal head. Abnormal prominent midbrain (arrowheads) is depicted between the forebrain and hindbrain

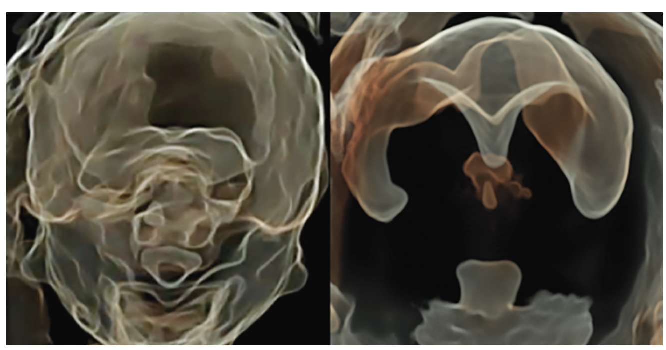


**Fig. 7:** Brain ventricular shape of alobar and semilobar holoprosencephaly by HDlive silhouette imaging at 14 weeks of gestation: Left: Single ventricle of alobar holoprosencephaly demonstrated with HDlive silhouette, Right: Fused ventricle of semilobar holoprosencephaly demonstrated with HDlive silhouette

Thus, any cystic area or hypoechoic part can be the target of interest in HDlive silhouette imaging. This new technology has a great potential to open a new field of "fetal 3D sono-ophthalmology," which has been never invented by conventional ultrasound technology.[17]

Thus, silhouette ultrasound shows a comprehensive structure demonstrating the inner and outer morphologies simultaneously. However, it occasionally appears to demonstrate too many inner structures overlapping one another to understand their relations. The author has cut the volume dataset with a rectangle cube and rendered the cut slice with silhouette ultrasound. The author calls this silhouette ultrasound demonstration of a thick slice of 3D volume dataset "thick-slice silhouette."[24,25] A normal brain image in the coronal cutting section by tomographic ultrasound imaging and a thick-slice silhouette image from the same 3D volume dataset are shown in Figure 11. In Figure 12A, although it is difficult to grasp the abnormal structure by silhouette ultrasound image (Fig. 12B), it is easy to understand by demonstrating the dorsal sac associated with holoprosencephaly by thick-slice silhouette imaging (Fig. 12C). Figure 13 shows thick-slice images of hydrocephalus at 19 weeks of gestation.

## Cranium and Spine by HDlive Silhouette Imaging

Postprocessing algorithms such as maximum mode can be used to demonstrate the fetal skeleton. Chaoui et al[26] reported clear 3D images for the identification of an abnormally wide metopic suture in the second trimester of pregnancy. However, rapid ossification of the craniofacial bones occurs during the first trimester of pregnancy. As described above, HDlive silhouette algorithm creates a gradient at organ boundaries, where an abrupt change of the acoustic impedance exists within tissues. Therefore, silhouette mode can depict not only hypoechoic structures but also hyperechoic structures such as bones.[16] Figure 14 shows HDlive silhouette image extracting frontal, parietal, and occipital bones at 13 weeks, and Figure 15 shows the anterior fontanelle at 16 weeks. The vertebrae and ribs can be visualized from small fetus (Figs 16A to C), and an interestingly extracted skeletal system is demonstrated in the early second trimester in (Figs 17A to C). The image showing extracted bony structure is comprehensive as 3D computed tomography (CT) or X-ray. Figure 18 shows lumber spina bifida by silhouette ultraosund. Thus, silhouette ultrasound can demonstrate

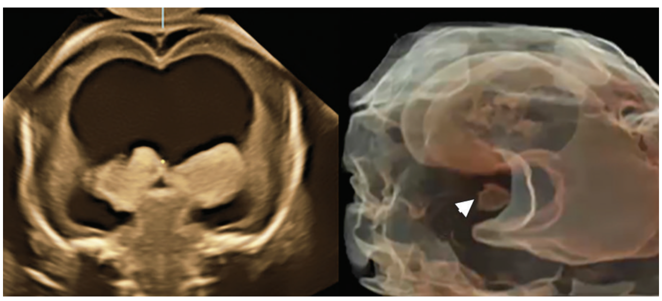


**Fig. 8:** Ventriculomegaly at 22 weeks of gestation: Left: Coronal image of the brain from multiplanar three-dimensional image, and Right: HDlive silhouette image. Bilateral enlarged ventricles and third ventricle (arrowhead) are demonstrated

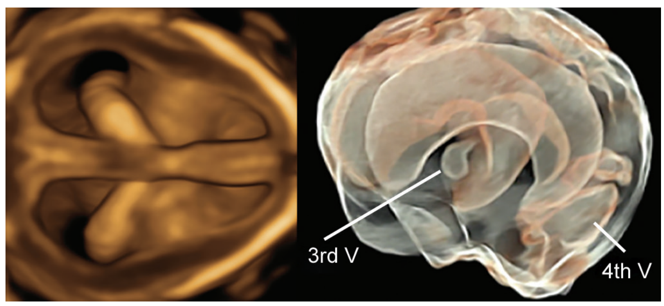



**Fig. 9:** Ventriculomegaly associated with Dandy Walker syndrome at 16 weeks of gestation: Left: Conventional three-dimensional axial image of the brain. Bilateral ventriculomegaly is visible, and Right: HDlive silhouette image. Enlargement of bilateral lateral ventricles, third ventricle (3rd V), and fourth ventricle (4th V) is well demonstrated inside the brain and orientation of ventricular system is well understandable by silhouette ultrasound

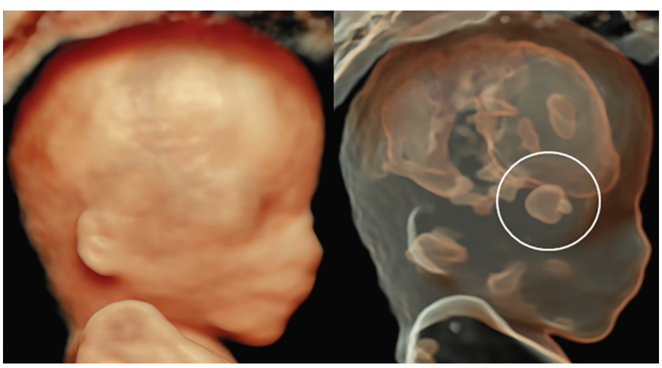


**Fig. 10:** Eye lens and vitreous body at 13 weeks of gestation. Both images are the same volume dataset. Left image is HDlive image and right image is HDlive silhouette image. Silhouette ultrasound demonstrates eye lens and vitreous body (in circle)

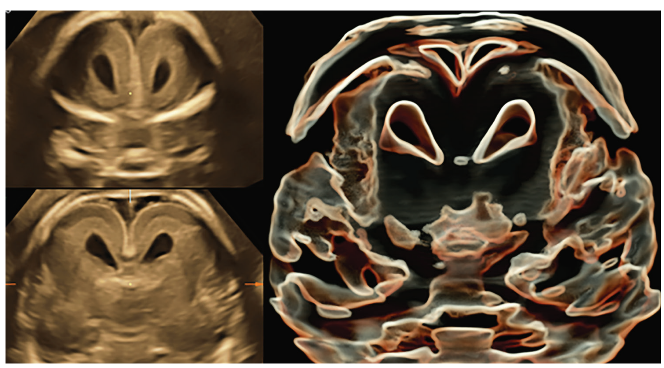
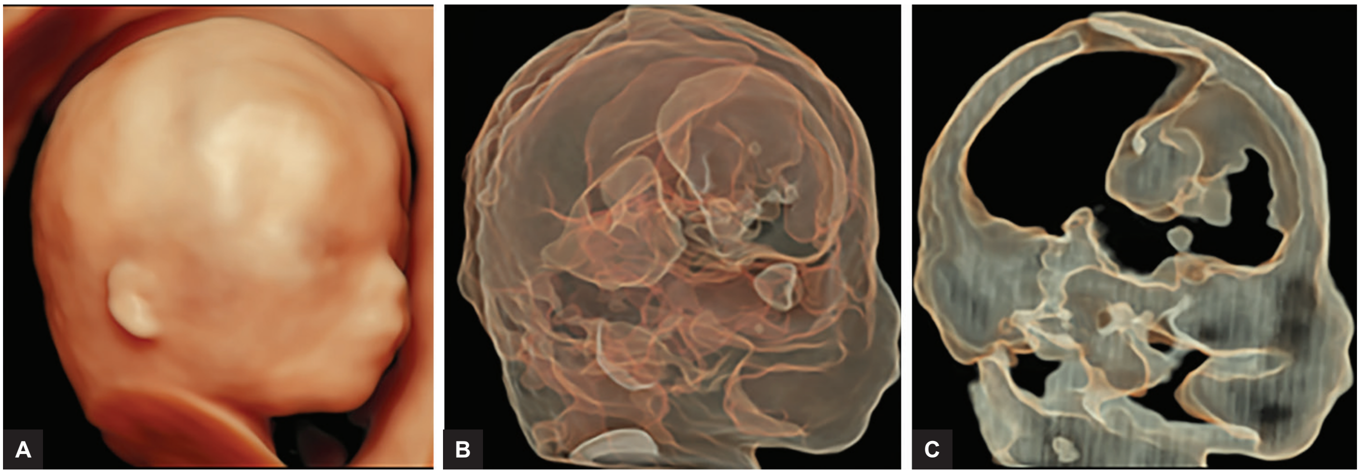


**Fig. 11:** Thick-slice silhouette of normal brain at 18 weeks of gestation: Left: The two images are from three-dimensional (3D) coronal tomographic images; Right: Thick-slice image from the same 3D volume dataset as the left image




**Figs 12A to C:** Different demonstration with HDlive silhouette of holoprosencephaly at 13 weeks of gestation; (A) Surface image of fetal head and face; (B) See-through image of fetal head and intracerebral structure. Abnormally enlarged ventricle with abnormal cystic structure is visible; and (C) Thick-slice silhouette demonstration of sagittal sectioned brain. The huge cystic area continued to ventricle was confirmed as the dorsal sac associated with holoprosencephaly

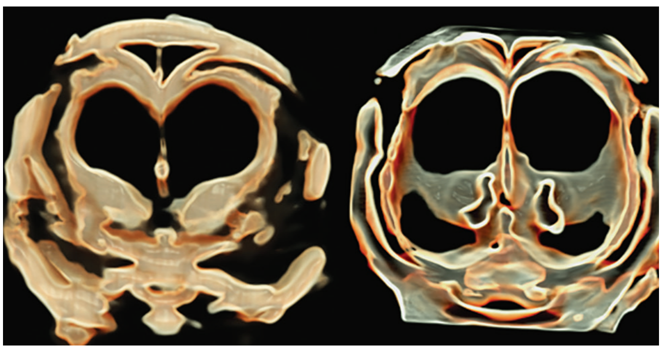


**Fig. 13:** Hydrocephalus at 19 weeks of gestation by thick-slice imaging. Left: Anterior cutting section of coronal section. Right: Posterior cutting section of coronal section

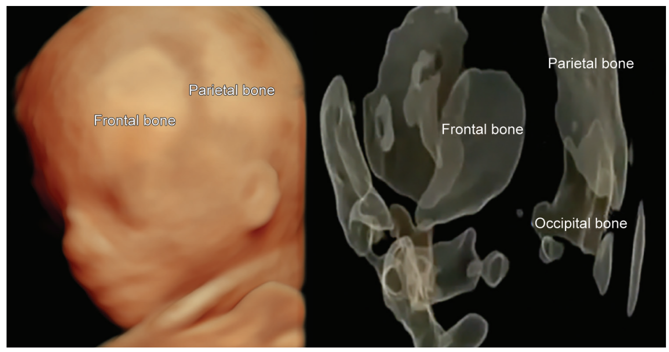



**Fig. 14:** Cranial bones of a 13-week fetus with HDlive silhouette mode; Left: HDlive image of a fetal head. Frontal bone and parietal bone are demonstrated through thin skin; Right: Same image with HDlive silhouette mode as the left. Cranial bones (frontal bone, parietal bone, and occipital bone) and facial bones are extracted

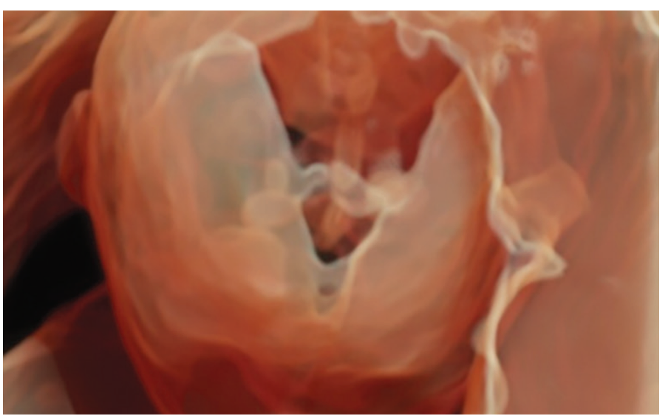
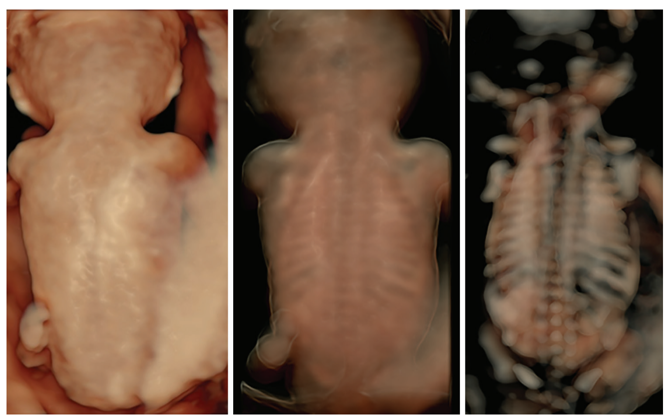


**Fig. 15:** Anterior fontanelle at 16 weeks by HDlive silhouette imaging



**Figs 16A to C:** (A) Vertebrae and ribs of a 12-week fetus with HDlive silhouette; (B) HDlive image of fetal back; and (C) Same volume dataset with HDlive silhouette. Skeletal structure is emphasized by silhouette mode

**Figs 17A to C:** Vertebrae, ribs, and ilia by HDlive silhouette imaging at 18 weeks of gestation: (A) Posterioranterior view; (B) oblique–anterior view, and (C) anteriorposterior view

**Fig. 18:** Spina bifida at 31 weeks of gestation by HDlive silhouette. Vertebral structure is well demonstrated by HDlive silhouette imaging. Though the 5th lumber lamina is closed (green colored), the lamina opening of sacral bones (yellow circle) indicates spina bifida

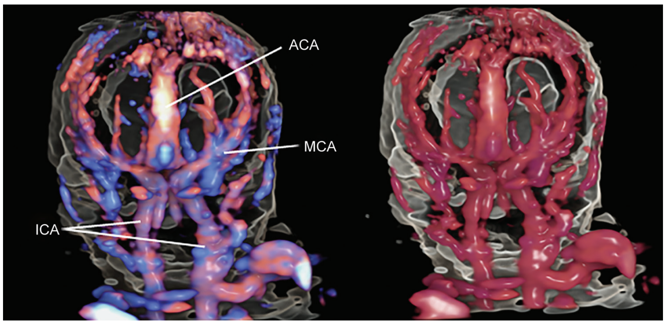



**Fig. 19:** Cervicocranial vascular hemodynamic structure at 13 weeks of gestation: Left: Bidirectional power Doppler HDlive flow image of brain vasculature of a 12-week fetus, and Right: The same ultrasound angiogram dataset with monocolor demonstration; (ACA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery)

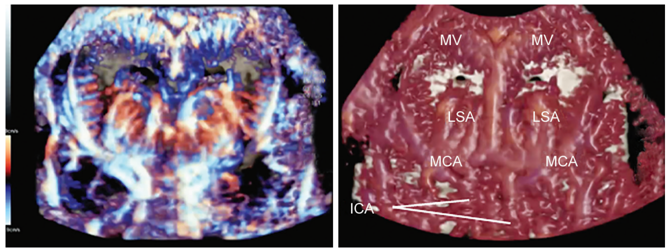



**Fig. 20:** Normal intracranial sonoangiogram at 19 weeks by HDlive flow imaging. Brain vascular networking is well created as early as 19 weeks: Left: Bidirectional power Doppler HDlive flow image of brain vasculature, and Right: Monocolor demonstration; (MCA: middle cerebral artery; ICA: internal carotid artery; LSA: lenticulostriate arteries; MV: medullary veins)

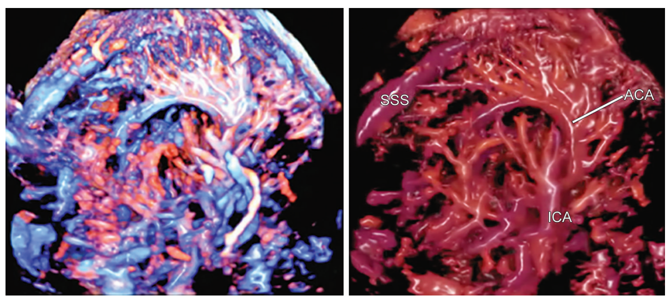



**Fig. 21:** Normal brain vascular structure by HDlive flow imaging at 20 weeks of gestation: Left: Bidirectional power Doppler 3D HDlive flow image of fetal vascular structure, and Right: Mono-color HDlive flow image; (ACA: anterior cerebral artery; ICA: internal carotid artery; SSS: superior sagittal sinus)

the bony structure and may have a great potential for investigating skeletal dysplasia from early pregnancy.

## Neuro-sonoangiogram by HDlive Flow Imaging Technology

The development of embryonic circulation became visualized by 3D power Doppler imaging technology.[3] In 1993 and 1994, color Doppler detection and assessment of brain vessels in the early fetus using a transvaginal approach was reported.[27,28] In 1996, the author reported clear visualization by transvaginal power Doppler of the common carotid arteries, internal/external carotid arteries, and middle cerebral arteries at 12 weeks of gestation.[29]

HDlive flow[14-18] is a recent application of 3D ultrasound technology generating a 3D view of the blood flow and providing a realistic rendering of fine vascular structure. The combination of HDlive silhouette and HDlive flow can be described as a "see-through fashion,"[14] because of its comprehensive orientation and persuasive localization of inner structure as well as of fetal angiostructure inside the morphological structure.

By using the advanced technology of HDlive flow combined with HDlive silhouette, a fetal intracorporeal hemodynamic structure can be demonstrated from early embryo,[24] showing premature vessels toward the midbrain at 8 weeks of gestation. Figures 19 to 21 demonstrate normal intracorporeal angiostructure by 3D HDlive silhouette/flow imaging with bidirectional power Doppler at 13, 19, and 20 weeks of gestation respectively. The umbilical arteries, umbilical vein, ductus venosus, inferior vena cava, descending aorta, as well as rich pulmonary vascularity are clearly demonstrated in a single 3D reconstructed image. Those images indicate the existence of a rich pulmonary vascularity from even before lung maturation from the first trimester.[18]

Medullary veins are well demonstrated between pia matter and subependymal zone at 29 weeks of gestation (Fig. 22). Abnormal brain vascularity and angiostructure in abnormal morphology are demonstrated in Figures 23 to 25. Thus, HDlive flow imaging provides us much more detailed clinical information on the fetal vascularity and hemodynamics than a conventional sonoangiogram.

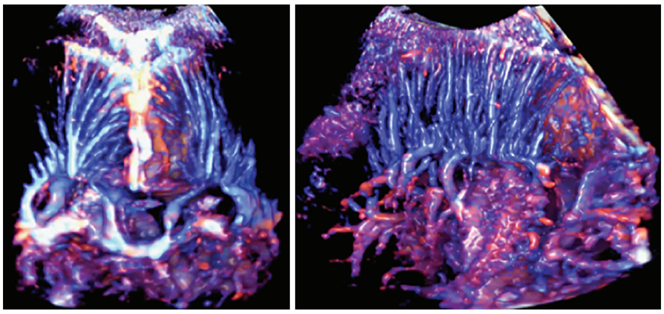


**Fig. 22:** Normal cerebral medullary veins by HDlive flow imaging at 29 weeks of gestation: Left: Coronal image, and Right: Sagittal image. Numerous fine medullary veins between cerebral surface and subependymal zone are well demonstrated

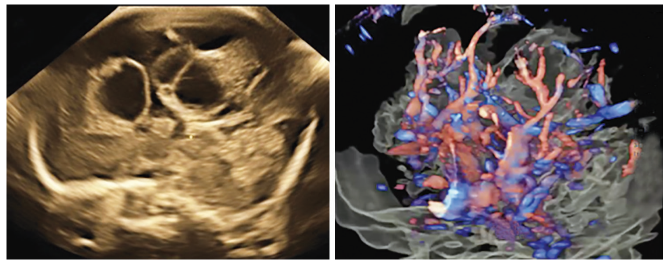


**Fig. 23:** Abnormal intracranial vasculature in a case of agenesis of the corpus callosum with interhemispheric multicysts at 30 weeks of gestation: Left: Sagittal cutting section. Multiple cysts are visible, and Right: Chaotic angiostructure in the sagittal view; (ICA: Internal carotid artery)

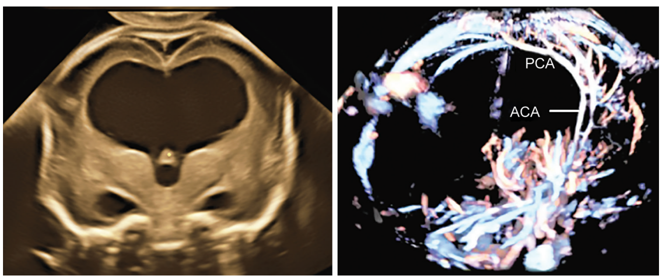



**Fig. 24:** Angiostructure in a case of ventriculomegaly at 22 weeks of gestation: Left: Coronal cutting section of the brain. Bilateral ventriculomegaly with 3rd ventriculomegaly is demonstrated, and Right: Oblique–sagittal view of intracranial angiostructure. Abnormally oppressed pericallosal artery (PCA) from anterior cerebral artery (ACA) is demonstrated

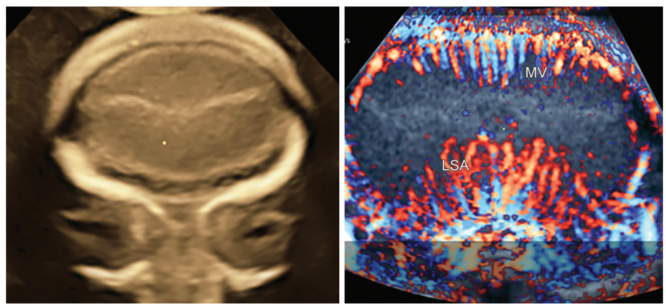



**Fig. 25:** Angiostructure in a case of holoprosencephaly at 20 weeks of gestation: Left: Anterior coronal section of the fetal brain. No separation of hemisphere is well visible, and Right: Angiogram by HDlive flow. The lenticulostriate arteries (LSA) and medullary veins (MV) are well developing within quite abnormal brain structure

### Clinical Significance and Pitfalls of HDlive Silhouette and Flow Imaging

As described in this article, "see-through fashion" imaging technology provides us comprehensive orientation and persuasive localization of inner morphological structure as well as of angiostructure inside the fetal organs. However, examiners should consider pitfalls of HDlive silhouette imaging. The degree of gain, threshold, and silhouette or a combination of these makes it possible to create completely different images with different clinical information from a single-volume dataset.[14] This fact expands the flexibility of imaging and demonstration; however, it can create a virtual reality. For obtaining accurate clinical information, examiners should be cautious that they might create false images and incorrect clinical information.

## CONCLUSION

Prenatal ultrasound has established neuro-sonoembryology and neurosonology. By using HDlive silhouette imaging, the inner structure can be demonstrated along with the outer surface without cutting the image. Furthermore, noncystic as well as cystic structures can be demonstrated, such as bony structure. Skeletal image by HDlive silhouette may be similar to 3D-CT; therefore, investigation of skeletal system diseases. HDlive silhouette imaging with noninvasive technology will be one of our challenges in prenatal imaging diagnosis. HDlive flow imaging demonstrates fine peripheral blood vessels of the brain. Moreover, HDlive flow combined with silhouette mode demonstrates the precise location of vascularity inside the fetal brain and may add further clinical information of vascularization.

HDlive silhouette and flow technologies allow extending the detection of congenital anomalies to an earlier gestational age, and it is beyond description that noninvasive direct viewing of the embryo/fetus by an all-inclusive ultrasound technology is definitely the first modality in a field of prenatal diagnosis and helps our goal of proper perinatal care and management, even in the era of molecular genetics and advanced sequencing of fetal deoxyribonucleic acid in the maternal blood.[24]

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