

First Trimester Scan by 3D, 3D HDlive and HDlive Silhouette/Flow Ultrasound Imaging

Ritsuko K Pooh

ABSTRACT

Both three-dimensional (3D) and four-dimensional (4D) ultrasound have improved our knowledge regarding the development of the embryo and fetus and of a great number of fetal anomalies. The 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. Furthermore, recent advanced 3D technology has produced exciting new applications of HDlive silhouette and HDlive flow. The algorithm of HDlive silhouette creates a gradient at organ boundaries where an abrupt change of the acoustic impedance exists within tissues. 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 as 'see-through fashion'. Close observation of small embryos and fetuses by advanced 3D technology in early gestation allows us to make diagnoses of various abnormalities. Novel imaging techniques are illustrated in the definition of normal embryonic anatomy as well as in the identification of many of congenital anomalies. Prenatal ultrasound has established sonoembryology and neurosonology, and advanced HDlive and HDlive silhouette and flow imaging added further clinical significance to conventional 3D/4D imaging in those fields. They allow extending the detection of anatomical congenital anomalies to an earlier gestational age, and it is beyond description that noninvasive viewing of the embryo/fetus by all-inclusive ultrasound technology is definitely the first modality in a field of prenatal diagnosis, and help our goal of proper perinatal care and management.

Keywords: Fetus, First trimester, Flow, HDlive, Prenatal diagnosis, Scan, Silhouette, Three-dimensional ultrasound.

How to cite this article: Pooh RK. First Trimester Scan by 3D, 3D HDlive and HDlive Silhouette/Flow Ultrasound Imaging. Donald School J Ultrasound Obstet Gynecol 2015;9(4):361-371.

Source of support: Nil

Conflict of interest: None

President, Clinical Research Institute of Fetal Medicine and Perinatal Medicine Clinic, Osaka, Japan

Executive Director, Asian Regional Director, Japanese Branch Director, Ian Donald Inter-University School of Medical Ultrasound, Croatia

Professor, Department of Human Science, Dubrovnik International University, Dubrovnik, Croatia

Honorary Professor, Pirogov Russian National Research Medical University, Moscow, Russia

Corresponding Author: Ritsuko K Pooh, President, Clinical Research Institute of Fetal Medicine and Perinatal Medicine Clinic Matsushita Building 3F 7-1-24, Uehommachi, Tennoji, Osaka #543-0001, Japan, Phone: +81-6-6775-8111, e-mail: rkpooh@me.com

INTRODUCTION

The prenatal diagnosis of congenital anomalies with ultrasound is based upon identification of a substantial departure of normal anatomy. This has been possible in the second and third trimesters of pregnancy, and this achievement has made the diagnosis of congenital anomalies one of the objectives of modern prenatal care. The definition of the 'normal anatomy' of the human embryo provides the basis for the identification of congenital anomalies at the earliest stages of human development. This goes beyond the mere identification of nuchal translucency, because it is now possible to identify anomalies even in the absence of an abnormal nuchal translucency. Therefore, the scope of prenatal diagnosis during embryonic life has been widened by sonoembryology with three-dimensional (3D) ultrasound.

Owing to prenatal ultrasound technology, there has been an immense acceleration in understanding of early human development. After the introduction of high-frequency transvaginal transducers in clinical obstetrics, the term 'sonoembryology' was first coined in 1990.¹ Three-dimensional sonography performed with a transvaginal approach has expanded the depth of inquiry, and allowed 3D sonoembryology.² A major limitation of embryology is that it has been traditionally based in specimens obtained after embryonic death. Structural and functional early human development has been able to be assessed by 3D and four-dimensional (4D) sonography.³ Modern imaging techniques allow the definition of *in vivo* anatomy including visualization of the embryonic circulation and dynamic feature, which could not be characterized in fixed specimens.⁴ The anatomy and physiology of embryonic development is a field where medicine exerts greatest impact on early pregnancy at present, and it opens fascinating aspects of embryonic differentiation. Recent development of 3D/4D sonography has revealed structural and functional early human development *in utero*.³⁻⁶ Three/four-dimensional sonography moved prenatal diagnosis of fetal anomalies from the second to the first trimester of pregnancy.⁷

THREE-DIMENSIONAL ULTRASOUND, HDLIVE AND HDLIVE SILHOUETTE ULTRASOUND

Three-dimensional transducers take several hundreds or thousands of two-dimensional (2D) ultrasound images

over a short (30–40°) 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 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 interpretation of the scanned region in multiple planes.⁸

Both 3D and 4D ultrasound have improved our knowledge regarding the development of the embryo and fetus and of a great number of fetal anomalies.⁸ The 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, those 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. This combination of light and shadows increases depth perception and produces remarkable images that are more natural than those obtained with classic 3D ultrasound. The virtual light can be placed in the front, back, or lateral sides, where viewing is desired until the best image is achieved. A great advantage is that the soft can be applied to all images stored in the machine's memory.⁹ In obstetrical ultrasound, HDlive could be used during all three trimesters of pregnancy. 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

Recent advanced 3D technology has produced exciting new applications of HDlive silhouette and HDlive flow, released at the end of 2014. The algorithm of HDlive silhouette creates a gradient at organ boundaries, fluid filled cavity and vessel walls, where an abrupt change

of the acoustic impedance exists within tissues.¹⁴⁻¹⁶ 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 as 'see-through fashion'.^{14,16} The examiner can adjust HDlive silhouette percentage with controlling threshold and gain simultaneously for visualizing target organs of interest.

NORMAL MORPHOLOGY DETECTED BY 3D ULTRASOUND

During the early embryonic period, the central nervous system anatomy rapidly changes in appearance. Three-dimensional sonography using transvaginal sonography with high-resolution probes allows imaging of early structures in the embryonic brain. Embryonic brain (Fig. 1) contains three parts: forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). The forebrain (prosencephalon) includes the telencephalon containing cerebral hemispheres and diencephalon containing thalamus, hypothalamus, epithalamus, and subthalamus. The midbrain (mesencephalon) is the most rostral part of the brainstem, and locates above the pons, and adjoins rostrally to the thalamus. The hindbrain (rhombencephalon) is the posterior part of the three primary divisions, which includes metencephalon containing pons and cerebellum and myelencephalon containing medulla oblongata. In 1998, Blaas et al¹⁷ sensationally demonstrated early human

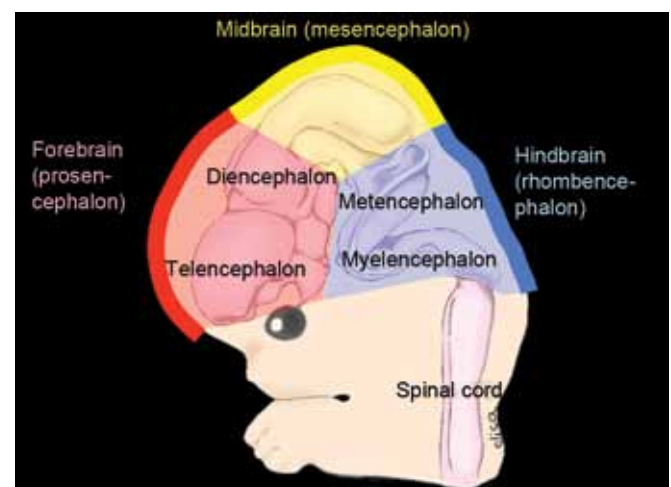


Fig. 1: Schematic picture of embryonic brain. The forebrain (prosencephalon) includes the telencephalon containing cerebral hemispheres and diencephalon containing thalamus, hypothalamus, epithalamus and subthalamus. The midbrain (mesencephalon) is the most rostral part of the brainstem, and located above the pons, and adjoined rostrally to the thalamus. The hindbrain (rhombencephalon) is the posterior part of the three primary divisions includes metencephalon containing pons and cerebellum and myelencephalon containing medulla oblongata

brain vesicles in different colors and measured their volumes by 3D scanning embryos ranged between 9.3 and 39 mm, and performed post-processing procedure. Thereafter, embryonic brain structure was demonstrated by advancing 3D technology of inversion-rendering mode,^{18,19} and 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.²⁰ Three-dimensional images of embryos were generated using the high-frequency transvaginal transducer (Voluson® E8 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.

Figure 2 shows 3D thick-slice and tomographic ultrasound image (TUI) demonstrating brain vesicles at 8 weeks. By using the most up-to-date technology of HDlive and its silhouette, outer surface as well as inner brain changing structure is clearly depicted from crown-rump length (CRL)—19.3 mm embryo to 23.9 mm fetus in the lateral view (Figs 3 and 4). Figure 5 shows frontal HDlive silhouette view demonstrating changing appearance of brain vesicles from CRL—22.3 mm embryo to 23.9 mm fetus. Inner cystic structure of the face is the eyeball. Figure 6 shows the surface HDlive image of fetal face and inner silhouette image of lens and vitreous body within outer surface of the fetal face.

The utilization of post-processing algorithms, such as maximum mode, can be used to demonstrate the fetal skeleton. Chaoui et al²¹ reported clear 3D images for the identification of an abnormally wide metopic suture in the second trimester of pregnancy. However,



Fig. 2: Eight-week normal brain. Left: Three-dimensional reconstructed image of brain cavity. Forebrain, midbrain and hindbrain are well demonstrated. Right: Images from tomographic ultrasound. Axial images (upper) and sagittal images (lower) of brain cavity

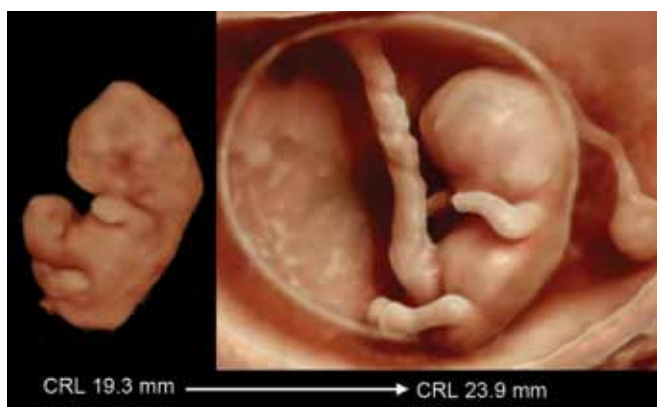


Fig. 3: Embryo to fetus by HDlive imaging. Left: Embryo with crown-rump length (CRL) 19.3 mm compatible to 8th gestational week. Right: Fetus with CRL 23.9 mm compatible to 9th gestational week. Remarkable development is clearly seen

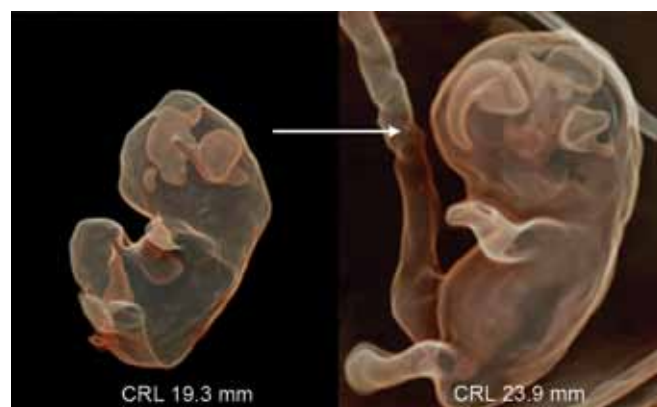


Fig. 4: Early brain development by HDlive silhouette mode. Left: Embryo with crown-rump length (CRL) 19.3 mm compatible to 8th gestational week. Right: Fetus with CRL 23.9 mm compatible to 9th gestational week. The development of three primary brain divisions of forebrain, midbrain and hindbrain is well demonstrated

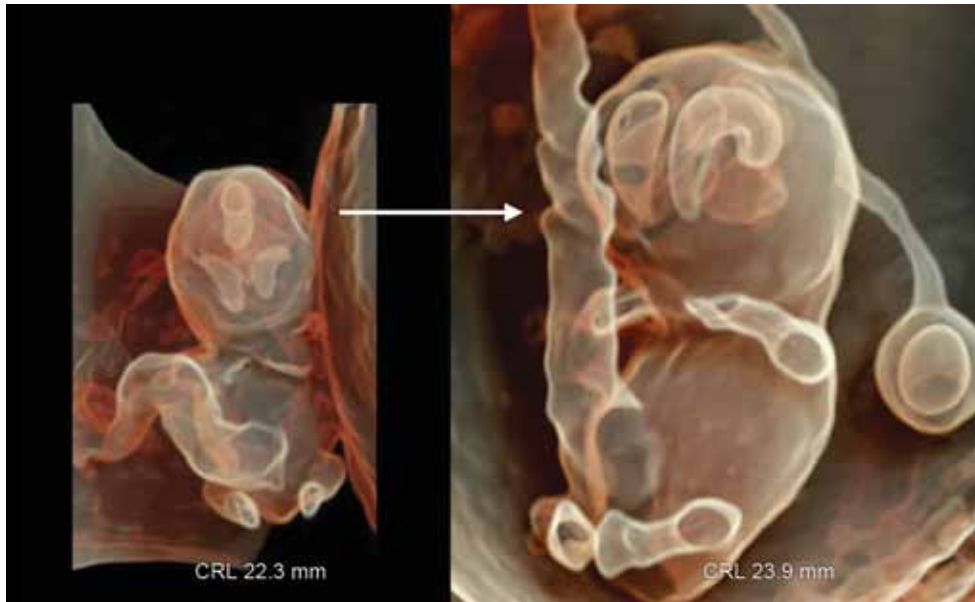


Fig. 5: Frontal view of brain development by HDlive silhouette mode. Left: Fetus with crown-rump length (CRL) 22.3 mm. Bilateral telencephalon (forebrain) and midbrain are well demonstrated. Right: Frontal-oblique view. Rapid development of early brain is comprehensively depicted

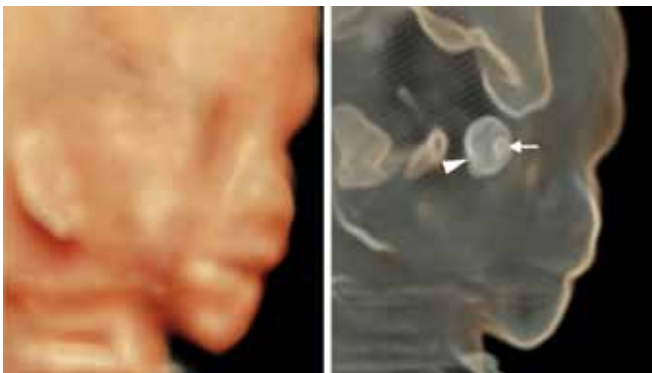


Fig. 6: Eye of 13-week fetus with HDlive silhouette mode. Left: HDlive image of fetal face. Right: Same image with HDlive silhouette mode as the left. Lens (arrow) and vitreous body (arrowhead) are well demonstrated with facial surface

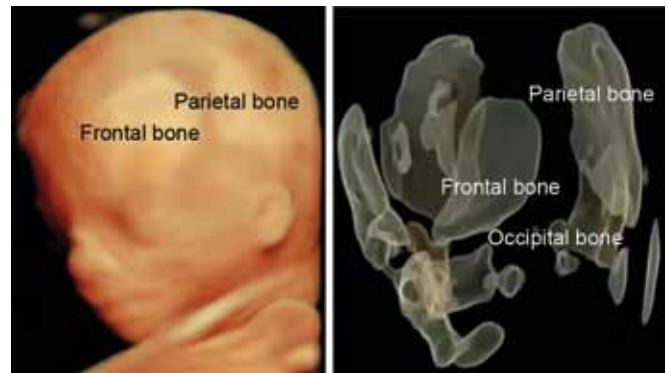


Fig. 7: Cranial bones of 13-week fetus with HDlive silhouette mode. Left: HDlive image of fetal head. Frontal bone and parietal bone are demonstrated through thin skin. Right: Same image with HDlive silhouette mode as the left. Cranial bones (frontal bone, parietal bone and occipital bone) and facial bones are extracted



Fig. 8: Vertebrae and ribs of 12-week fetus with HDlive silhouette mode. Left: HDlive image of fetal back. Middle and right: Same images with HDlive silhouette mode as the left. Skeletal structure is emphasized by silhouette mode

rapid ossification of the craniofacial bones occurs during the first trimester of pregnancy. As described,

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 cystic structure but also hyperechoic structure, such as bones.¹⁵ Figure 7 shows HDlive image of fetal head and HDlive silhouette extracting frontal, parietal and occipital bones from the same volume dataset. The skeletal demonstration by silhouette mode shows posteroanterior view of small fetus in the first trimester, extracting fetal vertebrae and ribs as shown in Figure 8.

Normal Fetal Vascularity detected by 3D Ultrasound

The development of the embryonic circulation became visualized by 3D power Doppler imaging technology.³ In 1993 and 1994, color Doppler detection and assessment

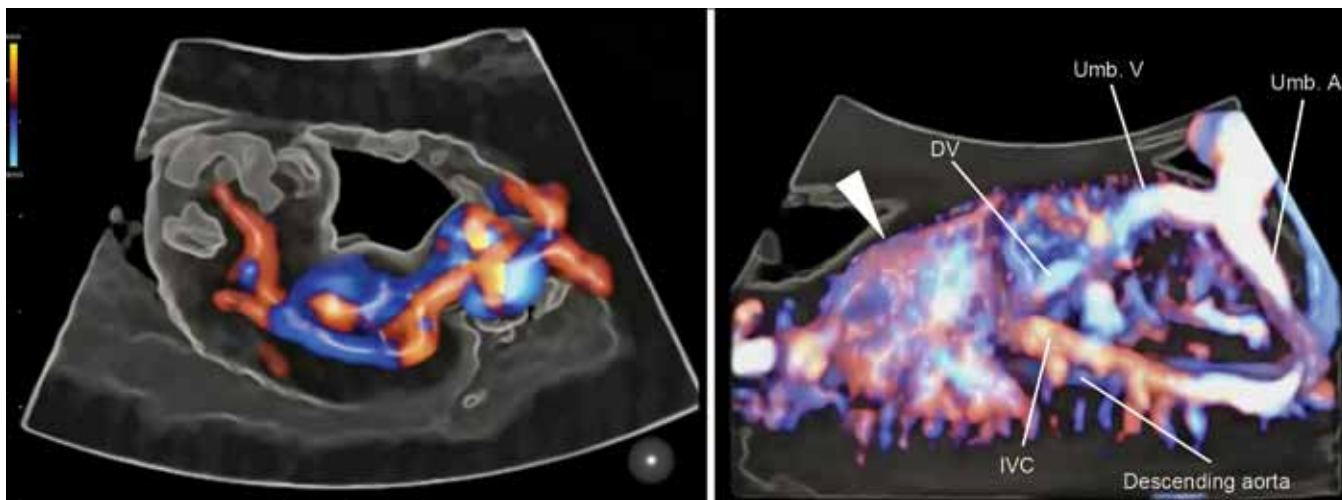


Fig. 9: Intracorporeal hemodynamic structure by HDlive silhouette and flow imaging at 8 and 13 weeks of gestation. Left: 8 weeks. Premature vascular structure is demonstrated with fetal body surface by silhouette mode. Right: 13 weeks. Thoracoabdominal vascular structure demonstrated by HDlive flow imaging. Pulmonary arteries and veins (arrowhead) are well demonstrated (DV: Ductus venosus; IVC: Inferior vena cava; Umb. V: Umbilical vein; Umb. A: Umbilical artery)

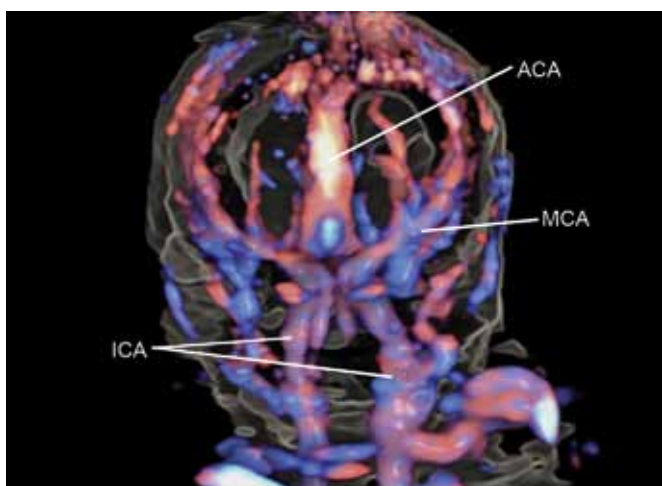


Fig. 10: Cervicocranial vascular hemodynamic structure at 13 weeks of gestation (ACA: Anterior cerebral artery; MCA: Middle cerebral artery; ICA: Internal carotid artery)

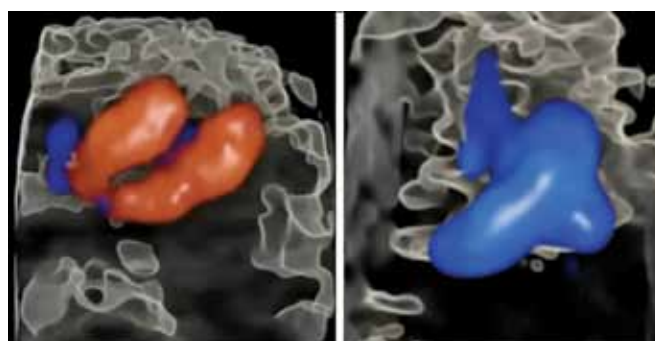


Fig. 11: Normal cardiac hemodynamic imaging by HDlive silhouette and flow at 12 weeks of gestation. Left: Intracardiac angiostructure. Flows of right and left heart are visible. Right: Crossing of great arteries is well demonstrated



Fig. 12: Abnormal midbrain cavity at 10 weeks of gestation. Left: 3D HDlive image of the fetus. Note the prominent top of the fetal head (arrowhead) due to abnormal midbrain. Right: HDlive silhouette image of the fetal head. Abnormal prominent midbrain (arrowheads) is depicted between forebrain and hindbrain

of brain vessels in the early fetus using a transvaginal approach was reported.^{22,23} Clear visualization by transvaginal power Doppler of the common carotid arteries,

internal and external carotid arteries, middle cerebral arteries at 12 weeks of gestation was reported in 1996.²⁴ By using advanced technology of HDlive flow combined with HDlive silhouette, fetal intracorporeal hemodynamic structure can be demonstrated from early embryo (Fig. 9), and comprehensive cervicocranial vascular hemodynamic structure with internal carotid artery, anterior and middle cerebral arteries are well demonstrated in the first trimester as shown in Figure 10. Intracardiac vascular structure is also well demonstrated in Figure 11, showing dynamic flows in each right and left heart and crossing of the great arteries.

Abnormal Morphology and Vascularity detected by 3D Ultrasound

Close observation of small embryos and fetuses by advanced 3D technology up to 14 weeks of gestation allows us to make diagnoses of various abnormalities. As shown in Figure 12, midbrain abnormality can be detected as early as 10 weeks of gestation. Figure 13 shows Meckel-Gruber syndrome detected at

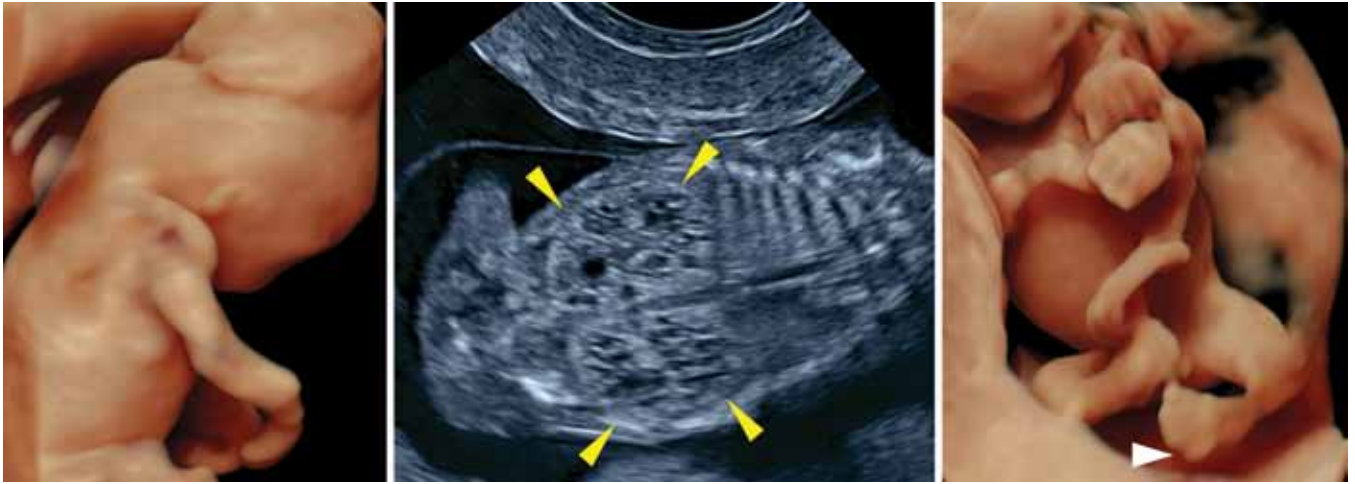


Fig. 13: Meckel-Gruber syndrome (MGS) at 12 weeks of gestation. Left: HDlive image of fetus. Exencephaly is demonstrated. Middle: Two-dimensional sonographic image of fetal kidneys. Multiple cysts are visualized (arrowheads) in bilateral kidneys. Right: Polydactyly (arrowhead) is demonstrated by HDlive mode. Meckel-Gruber syndrome is autosomal recessive genetic syndrome. Therefore, its incidence is 1 out of 4 in the next pregnancy

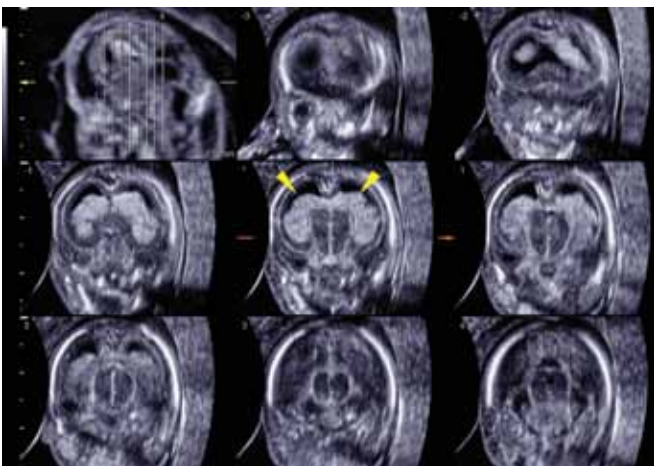


Fig. 14: Holoprosencephaly (semilobar type) at 13 weeks of gestation. Tomographic ultrasound image shows fused choroid plexus (arrowheads) in fused lateral ventricle

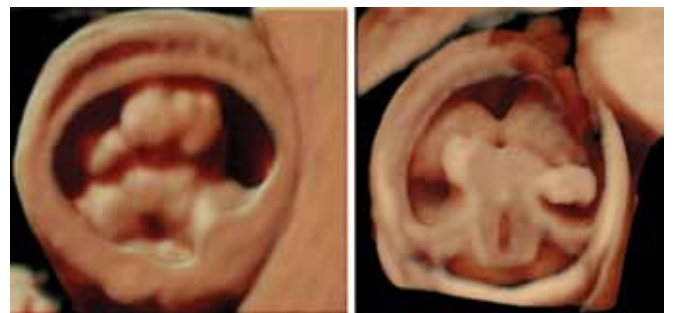


Fig. 15: Holoprosencephaly. Alobar type (left) at 11 weeks and semilobar type (right) at 14 weeks by HDlive imaging

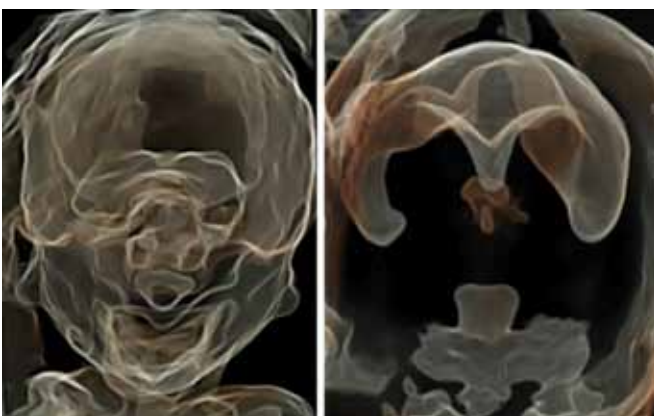


Fig. 16: Holoprosencephaly. Alobar type (left) and semilobar type (right) at 14 weeks by HDlive silhouette mode

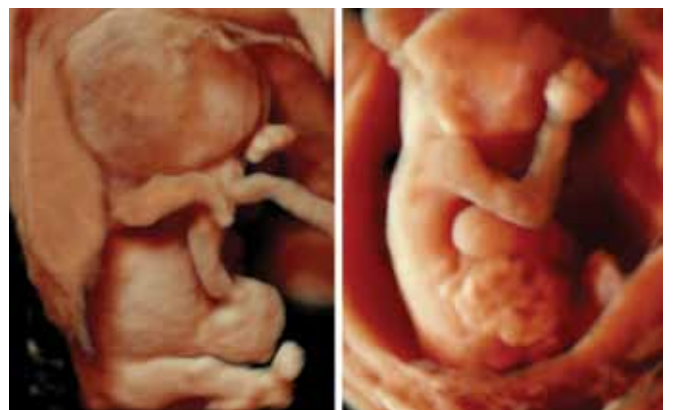


Fig. 17: Omphalocele in cases of trisomy 18 (left) and limb body wall complex (right) at 12 to 13 weeks of gestation. Note the contents of ectopic organs, such as liver and bowel (right), are well demonstrated by HDlive imaging

12 weeks of gestation. Holoprosencephaly is one of detectable congenital anomalies in the first trimester by demonstrating its characteristic features of fused ventricle or a single ventricle, fused choroid plexus and associated various facial anomalies. Figures 14

to 16 demonstrate holoprosencephaly by various 3D imagings of parallel slicing of TUI, HDlive, and HDlive silhouette. Omphalocele is associated with structural malformations and chromosomal abnormalities in 45%^{25,26} and 35%²⁷ of fetuses respectively, and 3D demonstration of omphalocele was published in 2002.²⁸ Advanced 3D HDlive demonstrates the contents of ectopic abdominal organs by creating shadows as shown in Figure 17.

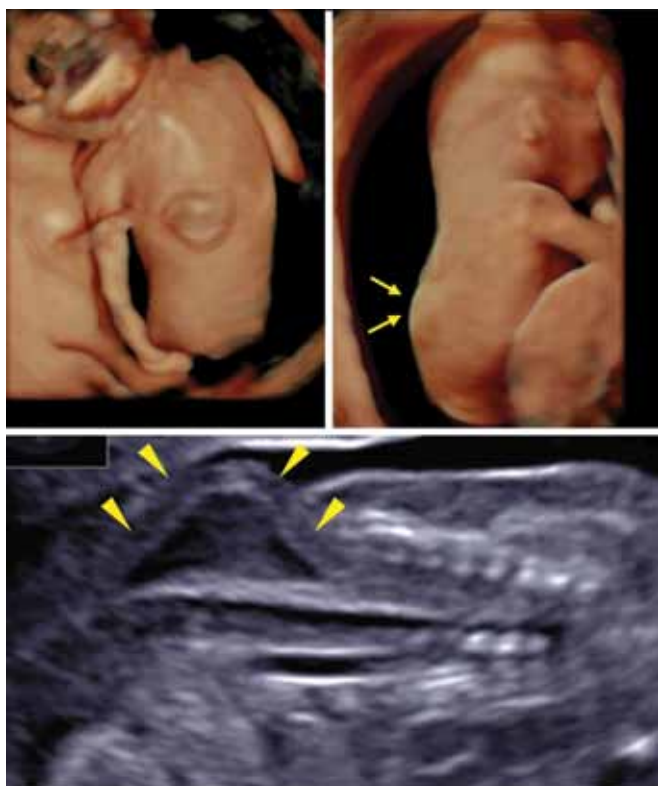


Fig. 18: Myelomeningocele at 12 weeks of gestation. Upper left: HDlive image of fetal back. Upper right: Lateral view. Arrows indicate protrusion of myelomeningocele. Lower: Sagittal section image by two-dimensional sonography. Ectopic spinal cord from spinal canal is well demonstrated (arrowheads)

Spina bifida and myelomeningocele can be demonstrated by 2D/3D ultrasound in the first trimester as shown in Figure 18. However, it is not always possible to demonstrate fetal back as in Figure 18. For early screening of spina bifida, intracranial translucency (IT) (Fig. 19)

indicating the 4th ventricle was proposed as an ultrasound marker for spina bifida in the first trimester by Chaoui et al.²⁹ Thereafter, several articles have been published on IT and spina bifida.^{30,31} It is well known that low-set ear is often associated with various genetic abnormalities and/or congenital anomalies. However, a few articles^{13,32} have been published on fetal low-set ear in the first trimester. The normal external ear position is on the imaginary line between eye slant and occiput even in the first trimester as shown in Figure 20 (left) but low-set ear (Fig. 20: right) located below the imaginary line is occasionally observed, with strong association with congenital genetic aberrations.^{13,32} Micrognathia can be detected as an isolated structural anomaly, as one of the features of a chromosomal abnormality, or a syndrome.³³ Assessment of the facial features, chin development and mandibular size by 3D ultrasound in the second and third trimesters has been reported.³⁴ Micrognathia is usually associated with low-set ear as shown in Figure 21 (left: however, not associated with low-set ear in the specific situation (Fig. 21: right). Cleft lip and palate is usually demonstrated and diagnosed in the second and third trimesters. However, recent advances of the transvaginal 3D ultrasound have provided accurate and informative diagnostic images of cleft lip (Fig. 23). Furthermore, the palate is still created during pregnancy but 3D reconstructed image can demonstrate cleft palate shown in Figure 22. Up-to-date TUI can provide the precise demonstration of palate shown in Figure 23 and the possibility of early diagnosis of cleft palate. Eye abnormalities, such as exophthalmos (Fig. 24: left) or microphthalmos (Fig. 24: right), are often observed with strong association of holoprosencephaly.

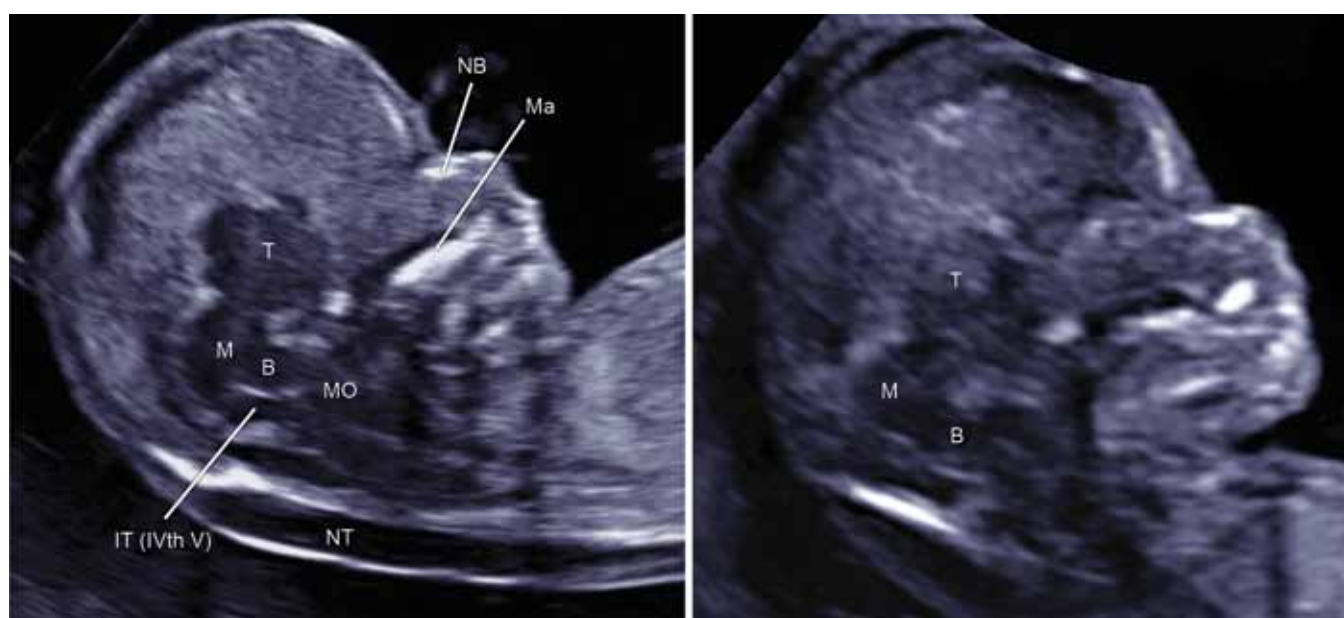


Fig. 19: Midsagittal section of normal fetus (left) and a case of spina bifida (right). Nuchal translucency and intracranial translucency (IT) are visible. In a case of spina bifida, IT disappears due to Chiari type II malformation. Disappearance of IT is useful for screening of spina bifida (NB: Nasal bone; Ma: Maxilla; T: Thalamus; M: Midbrain; MO: Medulla oblongata; NT: Nuchal translucency; IVth V: Fourth ventricle)

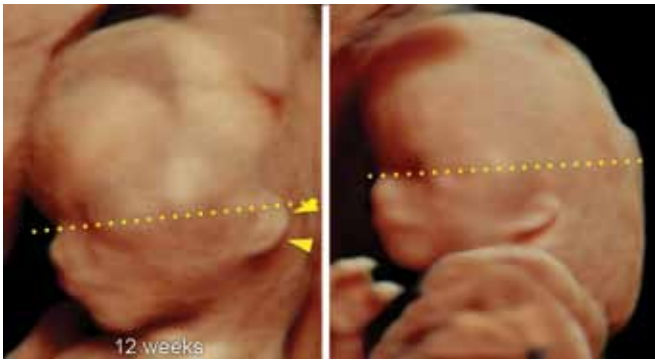


Fig. 20: Normal external ear position (left) and low-set ear (right). Normally, the external ear is located on the imaginary line between eye slant and occiput. Low-set ear is seen in cases of various chromosomal and/or genetic aberration

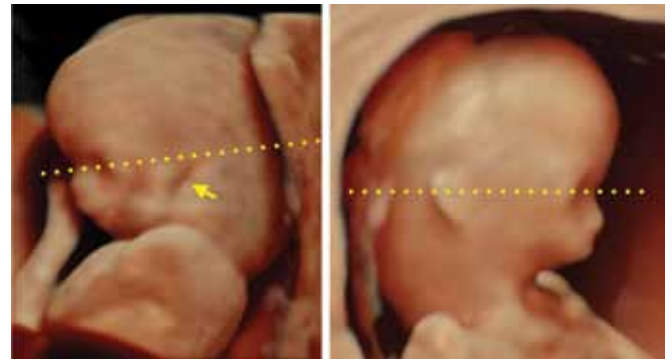


Fig. 21: Micrognathia with low-set ear (left) and micrognathia with normal ear position (right) at 12 weeks of gestation. Left: A case of trisomy 18. Micrognathia is often associated with low-set ear because of abnormal development of branchial arch. Right: A case of Pierre Robin syndrome associated with micrognathia but normal external ear position



Fig. 22: Two cases of cleft lip associated with holoprosencephaly at 12 weeks of gestation

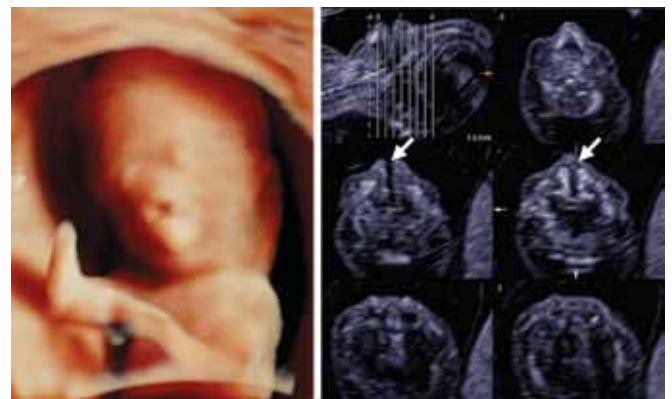


Fig. 23: Cleft lip/palate associated with holoprosencephaly at 12 weeks of gestation. Left: Three-dimensional HDlive image of fetal face. Cleft lip is clearly demonstrated. Right: Tomographic ultrasound image. Outer surface opening of cleft lip and inner structure of cleft palate (arrows) are well demonstrated



Fig. 24: Exophthalmos (left) and microphthalmia (right) in cases of trisomy 13 at 12 weeks



Fig. 25: Wrist contracture seen in cases of trisomy 18 at 12 weeks of gestation. Mild wrist contracture is a specific feature often seen in cases of trisomy 18

Limb abnormalities can occur as isolated findings or as one component of a syndrome or sequence. However, only 5% of congenital hand anomalies occur as part of a recognized syndrome.³⁵ Overlapping fingers, wrist contracture (Fig. 25) and forearm deformities are often associated with a chromosomal abnormality, such as trisomy 18. Most skeletal anomalies are recognizable in the second trimester. However, several reports on congenital skeletal abnormalities (such as sirenomelia and others) in the first trimester have been documented.³⁶⁻⁴⁰

Finger abnormalities, such as polydactyly, oligodactyly and syndactyly, are detectable from the late first trimester with high-resolution by advanced 3D imaging as shown in Figures 26 and 27.

Amniotic membranes can be demonstrated by 3D ultrasound as shown in Figure 3 but membranes fixed



Fig. 26: Finger abnormalities at 12 weeks of gestation. Left: 3rd oligodactyly and syndactyly of 4th and 5th fingers are demonstrated. Right: Amputation of fingers



Fig. 27: Polydactyly seen in a case of trisomy 13 at 12 weeks of gestation. Left: HDlive images. Right: Skeletal images of fingers/toes by maximum mode

on the fetal body depicted by HDlive imaging (Fig. 28) is helpful to suspect the existence of amniotic band syndrome and lead further investigation of fetal surface abnormalities.

HDlive flow imaging demonstrates vascular abnormalities, such as excessive coiling cord (Fig. 29) and absent ductus venosus flow (Fig. 30), observed in a case of 45,X. Thus, HDlive flow combined with silhouette mode demonstrates the accurate location of vascularity inside organs. Simultaneous visualization of both structure and vascularity is quite comprehensive, and may add further clinical information of normal and abnormal vascularizations.¹⁴⁻¹⁶

CONCLUSION

Novel imaging techniques of high-resolution transvaginal 3D sonography are illustrated in the definition of normal

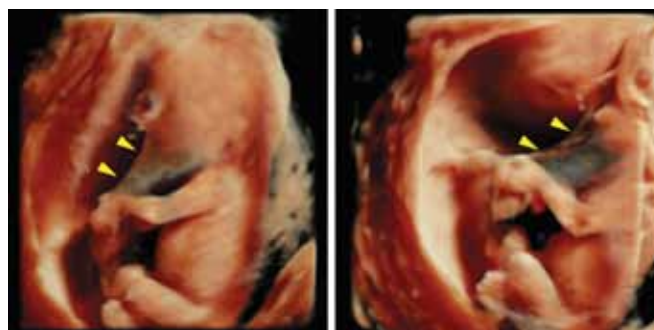


Fig. 28: Amniotic band syndrome at 12 weeks of gestation. Arrows indicate amniotic membranes covering the fetus. In this case, finger amputation, constriction ring and cleft lip are complicated

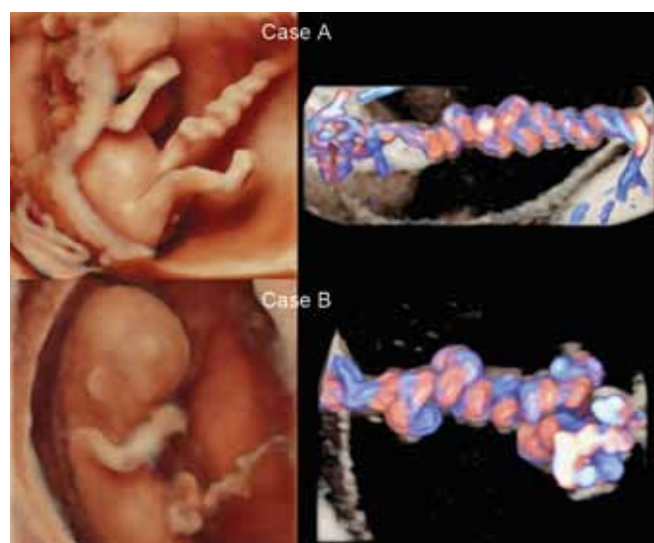


Fig. 29: Excessive coiling cord at 12 weeks of gestation. Left: HDlive images of fetus and cord. Right: HDlive flow images of excessive coiling cord. Note the high-pitch of coils. Both cases died *in utero* several days later

embryonic anatomy as well as in the identification of many of congenital anomalies. Prenatal ultrasound has established sonoembryology and neurosonology, and advanced HDlive, HDlive silhouette and flow imaging added further clinical significance to conventional 3D/4D imaging in those fields. They allow extending the detection of anatomical congenital anomalies to an earlier

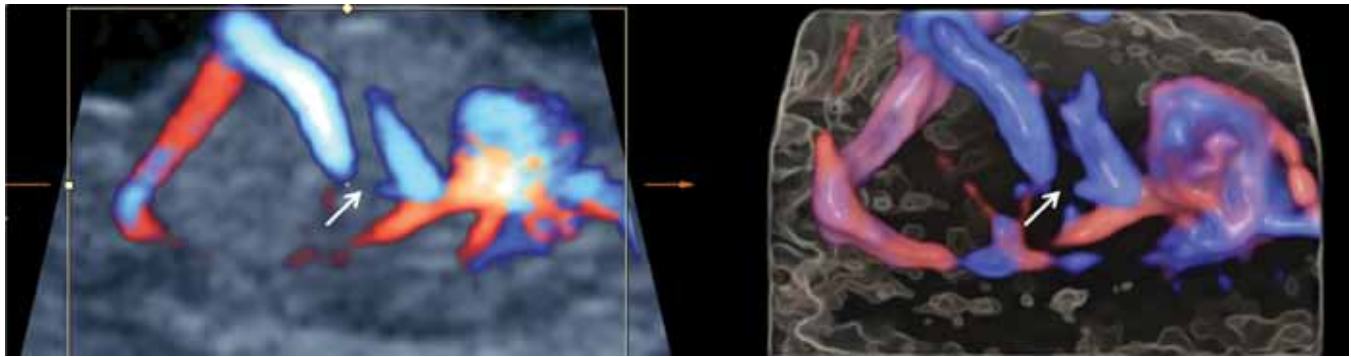


Fig. 30: Absent ductus venosus at 11 weeks of gestation seen in a case of 45, X. Left: Two-dimensional bidirectional power Doppler image. Right: Three-dimensional HDlive flow image. Arrows indicate the original location of ductus venosus. Absent ductus venosus is occasionally seen in cases of Turner syndrome

gestational age, and it is beyond description that non-invasive viewing of the embryo/fetus by all-inclusive ultrasound technology is definitely the first modality in a field of prenatal diagnosis and help our goal of proper perinatal care and management.

REFERENCES

1. Timor-Tritsch IE, Peisner DB, Raju S. Sonoembryology: an organ-oriented approach using a high-frequency vaginal probe. *J Clin Ultrasound* 1990;18(4):286-298.
2. Benoit B, Hafner T, Kurjak A, Kupesic S, Bekavac I, Bozek T. Three-dimensional sonoembryology. *J Perinat Med* 2002; 30(1):63-73.
3. Kurjak A, Pooh RK, Merce LT, Carrera JM, Salihagic-Kadic A, Andonotopo W. Structural and functional early human development assessed by three-dimensional (3D) and four-dimensional (4D) sonography. *Fertil Steril* 2005;84(5): 1285-1299.
4. Pooh RK, Shiota K, Kurjak A. Imaging of the human embryo with magnetic resonance imaging microscopy and high-resolution transvaginal 3-dimensional sonography: Human embryology in the 21st century. *Am J Obstet Gynecol* 2011;204(1):77.e1-16.
5. Pooh RK. 3D Sonoembryology. *Donald School J Ultrasound Obstet Gynecol* 2011;5(1):7-15.
6. Pooh RK. Early detection of fetal abnormality. *Donald School J Ultrasound Obstet Gynecol* 2013;7(1):46-50.
7. Pooh RK, Kurjak A. Editorial. 3D/4D sonography moved prenatal diagnosis of fetal anomalies from the second to the first trimester of pregnancy. *J Matern Fetal Neonatal Med* 2012;25(5):433-455.
8. Grigore M, Cojocar C, Lazar T. The role of HD Live technology in obstetrics and gynecology, present and future. *Donald School J Ultrasound Obstet Gynecol* 2014;8(3):234-238.
9. Bonilla-Musoles F, Raga F, Castillo JC, Bonilla F Jr, Climent MT, Caballero O. High definition real-time ultrasound (HDlive) of embryonic and fetal malformations before week 16. *Donald School J Ultrasound Obstet Gynecol* 2013;7(1):1-8.
10. Nebeker J, Nelson R. Imaging of sound speed reflection ultrasound tomography. *J Ultrasound Med* 2012;31(9): 1389-1404.
11. Kagan KO, Pintoffl K, Hoopmann M. First-trimester ultrasound images using HDlive. *Ultrasound Obstet Gynecol* 2011;38(5):607.
12. Hata T, Hanaoka U, Tenkumo C, Sato M, Tanaka H, Ishimura M. Three- and four-dimensional HDlive rendering images of normal and abnormal fetuses: pictorial essay. *Arch Gynecol Obstet* 2012;286(6):1431-1435.
13. Pooh RK, Kurjak A. Novel application of three-dimensional HDlive imaging in prenatal diagnosis from the first trimester. *J Perinat Med* 2015;43(2):147-158.
14. Pooh RK. See-through fashion in prenatal diagnostic imaging. *Donald School J Ultrasound Obstet Gynecol* 2015; 9(2):111.
15. Pooh RK. Brand new technology of HDlive silhouette and HDlive flow images. In: Pooh RK, Kurjak A, editors. *Donald School Atlas of Advanced Ultrasound in Obstetrics and Gynecology*. New Delhi: Jaypee Brothers Medical Publishers Private Limited; 2015. p. 1-39.
16. Pooh RK. Novel application of HDlive silhouette and HDlive flow: clinical significance of the 'See-through fashion' in prenatal diagnosis. *Donald School J Ultrasound Obstet Gynecol* 2015; in press.
17. Blaas HG, Eik-Nes SH, Berg S, Torp H. In-vivo three-dimensional ultrasound reconstructions of embryos and early fetuses. *Lancet* 1998;352(9135):1182-1186.
18. Kim MS, Jeanty P, Turner C, Benoit B. Three-dimensional sonographic evaluations of embryonic brain development. *J Ultrasound Med* 2008;27(1):119-124.
19. Hata T, Dai SY, Kanenishi K, Tanaka H. Three-dimensional volume-rendered imaging of embryonic brain vesicles using inversion mode. *J Obstet Gynaecol Res* 2009;35(2):258-261.
20. Pooh RK. Neurosonoembryology by three-dimensional ultrasound. *Semin Fetal Neonatal Med* 2012;17(5):261-268.
21. Chaoui R, Levailant JM, Benoit B, Faro C, Wegrzyn P, Nicolaidis KH. Three-dimensional sonographic description of abnormal metopic suture in second- and third-trimester fetuses. *Ultrasound Obstet Gynecol* 2005;26(7):761-764.
22. Kurjak A, Zudenigo D, Predanic M, Kupesic S. Recent advances in the Doppler study of early fetomaternal circulation. *J Perinat Med* 1993;21(6):419-439.
23. Kurjak A, Schulman H, Predanic A, Predanic M, Kupesic S, Zalud I. Fetal choroid plexus vascularization assessed by color flow ultrasonography. *J Ultrasound Med* 1994;13(11): 841-844.
24. Pooh RK, Aono T. Transvaginal power Doppler angiography of the fetal brain. *Ultrasound Obstet Gynecol* 1996;8(6): 417-421.
25. Lindham S. Omphalocele and gastroschisis in Sweden 1965–1976. *Acta Paediatr Scand* 1981;70(1):55-60.

26. Nicolaides KH, Snijders RJ, Cheng HH, Gosden C. Fetal gastrointestinal and abdominal wall defects: associated malformations and chromosomal abnormalities. *Fetal Diagn Ther* 1992;7(2):102-115.
27. Snijders RJM, Nicolaides KJ. Ultrasound markers for fetal chromosome defects. In: Nicolaides KH, editor. *Frontiers in Fetal Medicine Series*. London: Parthenon; 1996. p. 21-55.
28. Anandakumar C, Nuruddin Badruddin M, Chua TM, Wong YC, Chia D. First-trimester prenatal diagnosis of omphalocele using three-dimensional ultrasonography. *Ultrasound Obstet Gynecol* 2002;20(6):635-636.
29. Chaoui R, Benoit B, Mitkowska-Wozniak H, Heling KS, Nicolaides KH. Assessment of intracranial translucency (IT) in the detection of spina bifida at the 11–13 week scan. *Ultrasound Obstet Gynecol* 2009;34(3):249-252.
30. Chaoui R, Nicolaides KH. From nuchal translucency to intracranial translucency: towards the early detection of spina bifida. *Ultrasound Obstet Gynecol* 2010;35(2):133-138.
31. Karl K, Heling KS, Chaoui R. Fluid area measurements in the posterior fossa at 11–13 weeks in normal fetuses and fetuses with open spina bifida. *Fetal Diagn Ther* 2015;37(4):289-293.
32. Pooh RK. Fetal abnormality in the 1st trimester. In: Pooh RK, Kurjak A, editors. *Donald School Atlas of Advanced Ultrasound in Obstetrics and Gynecology*. New Delhi: Jaypee Brothers Medical Publishers Private Limited; 2015. p. 111-253.
33. Teoh M, Meagher S. First-trimester diagnosis of micrognathia as a presentation of Pierre Robin syndrome. *Ultrasound Obstet Gynecol* 2003;21(6):616-618.
34. Tsai MY, Lan KC, Ou CY, Chen JH, Chang SY, Hsu TY. Assessment of the facial features and chin development of fetuses with use of serial three-dimensional sonography and the mandibular size monogram in a Chinese population. *Am J Obstet Gynecol* 2004;190(2):541-546.
35. Bolitho DG. Hand, Congenital hand deformities. *emedicine* 2006. Available at: <http://www.emedicine.com/plastic/TOPICT298.HTM>
36. Carbillon L, Seince N, Largillière C, Bucourt M, Uzan M. First-trimester diagnosis of sirenomelia: A case report. *Fetal Diagn Ther* 2001;16(5):284-288.
37. Monteagudo A, Mayberry P, Rebarber A, Paidas M, Timor-Tritsch IE. Sirenomelia sequence: First-trimester diagnosis with both two- and three-dimensional sonography. *J Ultrasound Med* 2002;21(8):915-920.
38. Schiesser M, Holzgreve W, Lapaire O, Willi N, Lüthi H, Lopez R, Tercanli S. Sirenomelia, the mermaid syndrome—detection in the first trimester. *Prenat Diagn* 2003;23(6):493-495.
39. Dugoff L, Thieme G, Hobbins JC. First trimester prenatal diagnosis of chondroectodermal dysplasia (Ellis-van Creveld syndrome) with ultrasound. *Ultrasound Obstet Gynecol* 2001;17(1):86-88.
40. Percin EF, Guvenal T, Cetin A, Percin S, Goze F, Arici S. First-trimester diagnosis of Robinow syndrome. *Fetal Diagn Ther* 2001;16(5):308-311.