Three-dimensional Ultrasound in the Visualization of Fetal Anatomy in the Three Trimesters of Pregnancy

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ABSTRACT

It is now widely considered that three- and four-dimensional (3-4D), namely 3D with a fourth dimension, time, offer too many possibilities to be ignored. Acquisition of a volume or region of interest is the great novelty of 3D technique. And just as exciting is the possibility of studying it in movement during ultrasound examination or afterward; also by other operators in an infinite number of section planes that can all be perfectly reproduced.

This paper aims to provide pictorial documentation of pregnancy monitoring with 3D images, sometimes with the corresponding 2D image, so readers can begin to habituate themselves and hopefully acquire a different and personal key to the 3D image.

Keywords: HDlive, Silhouette, Three-dimensional ultrasound, Visualization of fetal anatomy.

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BIOPHYSICAL MONITORING OF PREGNANCY

An Embryo-fetal Anatomical Study by 3-4D Ultrasound

During the 1970s, the use of ultrasound in obstetric diagnostics was a driving force in the study of the fetus, revolutionizing the concept of prenatal monitoring. The development of increasingly sophisticated techniques such as high frequency, real-time, echo-Doppler flow imaging, color and power Doppler and the second harmonic, was followed in the 90’s by a period of relative immobility for ultrasound up-grading. However, since the turn of the millennium, volumetric probes that store thousands of section planes that can all be perfectly reproduced.

Moreover, the many systems of representing acquired volumes make this technique very similar to computed axial tomography (CAT) and nuclear magnetic resonance (NMR) imaging:

- **Multiplanar scan**: The image can be visualized and studied in the three classical scan planes: coronal, sagittal and transverse;
- **Minimum rendering**: This is the classical 3D image of external embryofetal or other anatomical morphology;
- **Maximum rendering**: This highlights deep echoes to visualize skeletal details;
- **Glass body**: This highlights blood vessels in an anatomical part which is rendered transparent like glass;
- **Vocal**: Enabling volumes to be calculated with great accuracy;
- **Invert**: The transformation of liquid into solid parts;
- **STIC (spatiotemporal imaging correlation)**: Storage of a moving volume over a time interval with the possibility of representing and studying it later in slow motion and in different planes;
- **TUI (tomography ultrasound imaging)** or **multislice**: A field is sectioned up to 27 scans at predefined distances and in real time (like NMR);
- **4D**: 3D represented in time;
- **VCI-c-plane**: Improved tissue contrast resolution in real time (4D), coronal plane imaging (orthogonal plane of the scan plane);
- **B-flow**: The direct visualization of blood reflectors—shas made B-mode flow imaging (B-flow) possible without the limitations of Doppler technology, angle independent;
- **Omni-view**: To study the same volume by VCI—c-plane multiple sections. It is possible to shape the box of observation (linear, curve, etc.) to the region of interest (ROI). This possibility is significant because the human anatomy usually has a curve or round shape. By omni-view we can realize pictures more detailed.\(^1\)

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• **Sono automated volume calculation**: Sono automated volume calculation (SonoAVC) the possibility to detect areas by different color and to calculate the volume of these areas;

• **High-definition live source**: High-definition live source or real-time US (Hdlive), a new ultrasound software, combines a movable virtual adjustable light source in software that calculates the proportion of light reflecting through surface structures, depending on light direction. The light source can be manually positioned to illuminate the desired area of interest. The ultrasound technician can control light intensity to create shadows that enhance image quality. Hdlive is an innovation that will render even more realistic images of fetal anatomy and gynaecologic lesions. Three-dimensional Hdlive further "humanizes" the fetus, enables detailed observation of the fetal face in the first trimester. Hdlive is one the most promising forms of non-invasive diagnostic and embryological phenomena, once matters for textbooks are now routinely recorded with outstanding clarity. New advances deserve the adjective “breathtaking,” including a 4D parallel study of the structural and functional early human development.

• **Silhouette or transparency**: a new advanced tool of Hdlive to evidence the shape of the embryo-fetal body and internal cavity of brain and body. The silhouette is a good ultrasound tool to study the embryo-fetal head in the first trimester. Other possibilities of use are the electronic scalpel which eliminates parts, not of interest and rotates about orthogonal axes.

Today, ultrasound research is so active that new applications have probably been found as these words are being written. One new advance is already available, the electronic matrix probe. The possibilities of electronic rather than volumetric probes, which can combine electronic scans with mechanical movement to cover the area of interest, will provide even more sophisticated images. And the possibility of obtaining volume samples from unthinkable angles and perspectives will be especially useful in cardiology. These innovations, however, require relatively long development periods before they are applied.

The above discourse raises the question whether 3-4D offers greater certainty in embryo study and detection of fetal and ovarian pathology. The scientific community seems unanimous in considering that we cannot yet fully answer this question, but ten years after the finalization of the volumetric probe were acquired many experiences that can make a real contribution to define the role and importance of 3-4D in the study of various embryo-fetal's organs and systems.

However, there are already many papers comparing 2D and 3D, and their results define the use of 3-4D complementary to 2D, with the exception for the neurosonology and fetal cardiology, where can offer the better possibility to explore physiological and pathological fetal anatomy. This technique has unique applications, but it is commonly considered that 3-4D offers an improvement and completion of 2D, of such interest that it cannot be forgone once tried. Hence there are specific situations in which 3D is indispensable, such as when a coronal scan is needed (visualization of the corpus callosum or a fetal profile in anterior occipital position) through a good instrument in the hands of an experienced sonographer can meet all the needs of ultrasound monitoring in pregnancy. Those with long experience with 2D, and subsequently with 3-4D, know the pleasure of working better and obtaining images superior to those obtained by 2D. The possibility of saving a volume and studying it later, discussing it with other operators and visualising it in an infinite number of planes, superior to those obtained with 2D and perfectly reproducible, is
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Figs 2A to D: Weeks 8 + 4 d: (A) HDlive with lateral light; (B) With behind light; (C) Silhouette to evidence the cerebral ventricles; (D) Silhouette, retrovision of embryo with lateral light; the evidence of romboencephalon

Figs 3A to C: Weeks 8 + 5 d: (A) HDlive with lateral light to see cerebral ventricles and yolk sac's cavity; (B) HDlive; (C) Silhouette with frontal light; by posterior vision of embryo, it is possible evidence the prosencephalon and rhombencephalon
Figs 4A to J: Weeks 8 + 6 d: A different point of view of the embryo on HDlive and silhouette
as close as one can imagine to CAT or NMR scans, with the advantage of speed, easy repetition and much lower costs. The old recorded cassette to transmit images of a malformation, for example, cannot compare with the volumetric acquisition. It seems inevitable that in the near future nearly all instruments will be equipped with 3-4D, even if not all sonographers know how to exploit it fully. It is, therefore, necessary to begin to train experts who think and work directly in 3D without having to make the often difficult transition from 2D. Sonographers of tomorrow (today) will undoubtedly obtain better results than those who began with 2D because they will already have in mind the field of interest to explore in 3D.

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FIRST TRIMESTER OF PREGNANCY

From Conception to Week 10

The sophistication achieved by ultrasound instruments associated with clinical and ultrasound knowledge and know-how unthinkable only ten years ago enables us to monitor pregnancy from before conception. For fertility control, 2D ultrasound with power or color Doppler makes it possible to determine with sufficient certainty the following aspects on day:12

- Uterine morphology and myometrial structure; the tridimensional scan in the coronal section is a useful instrument comparable to ISG-RNM to explore the uterine cavity and find the anatomical uterine malformation which represents 3 to 5%; arcuate uterus, bidentalus and bicornuate;
- Endometrial echostructure and morphology by detecting a three-line image characteristic of the ovulatory period and myometrial vascularisation;

Figs 5A to C: Weeks 10 + 0 d: (A and B) Silhouette of the embryo; (C) HDlive of vascular circulation
• Uterine artery flow values which should not have a pulsatility index of less than 3;
• The dominant follicle measuring 16 to 18 mm with peak systolic velocity (PSV) of 5 to 10 cm/sec in neighbouring vessels;
• Four to five antral follicles per ovary with PSV of 6 to 12 cm/sec in stromal vessels (Figs 13 to 15).

By means of 3-4D or better the 4D VCI-c-plane system it is possible to obtain a correct view of the uterine cavity\(^{13,14}\) (Fig. 14). This means that with only one examination, the existence of anatomical-functional conditions for pregnancy can be ascertained. Once conception has occurred, ultrasound monitoring of pregnancy should not necessarily begin in the first weeks of gestation. This type of protocol is usually used for medically assisted conception, however it is possible to follow the progress of pregnancy week by week, acquiring important information on physiological or pathological evolution by monitoring embryo-foetal growth and studying embryo-foetal anatomy. At the present
time, 3-4D volumetric acquisition provides superior images in terms of definition and visual impact, but only slight improvements in diagnostic capacity with respect to 2D.

**An Ultrasound View of the First Trimester of Pregnancy**

In indicating the period of embryo-foetal development, it is correct to distinguish between menstrual age and true gestational age. Menstrual age is counted from the last menstrual period and is unreliable. About 40% of pregnant women, or one in two, have ovulation’s problems for various reasons. Moreover, even in women with physiological ovulation’s patterns, conception may occur between day 11 and day 17 of the menstrual cycle. It is therefore essential to date pregnancy by means of ultrasound parameters during the first trimester. Gestational age is counted from when the gametes fuse and is on average 14 days less than the menstrual age used by embryologists. Internationally, in fact, obstetricians now speak of gestational age when they really mean menstrual age. A compromise is the term ultrasound age, namely age established by ultrasound. When it is desired to indicate the effective period of embryo-foetal life, however, this is usually specified.

In order to better understand ultrasound images, especially for early detection of anatomical structures and embryo-foetal morphology, it is useful to refer to embryology, though naturally the anatomical age is earlier. In practice, it is important to be clear about the terms used.

The first trimester of pregnancy is divided into three periods: pre-embryonic, embryonic and foetal.

**Pre-embryonic Period**

*Embryology:* Days 4 to 19
*Day 4—Morula*
*Days 4 to 7—Implant of avillous morula in the uterus*
*Days 8 to 12—Implant of blastocyst deep in decidua; presence of amniotic and celomatic cavities*
*Days 13 to 19—Presence of chorionic villi, yolk sac (YS) and neural plate.*

**Ultrasonography:** Weeks 3 and 4 of Gestation

Ultrasound detects decidualisation of the endometrium and the luteal body but cannot confirm pregnancy. Endometrial flow can be assessed and when absent suggests lack of implantation (Fig. 16).

**Embryonic Period**

*Embryology:* Days 17 to 49 (seven full weeks)
*Ultrasonography:* Weeks 5 to 9 inclusive (up to day 63)
Figs 9A to G: Weeks 22 + 0 d: “Humanization” of the face by HDlive and silhouette
Figs 10A to E: Weeks 23 + 0 d: Evidence of the umbilical cord by different use of the light on HDlive

Figs 11A and B: Weeks 23 + 0 d: Study of the feet by HDlive and silhouette
Comparison of tissue, organ and system formation detected and studied anatomically during the embryonic period demonstrates the capacities and limits of ultrasound for monitoring the product of conception. Another small distinction between embryology and ultrasound is that in the former case reference is made to exact parameters such as crown rump length (CRL) or the presence of tissues, organs and systems, whereas in the latter gestational age is usually indicated in weeks (the definition of which we have already discussed), with considerable limitations.

Embryology: Days 20 to 23  
CRL = 1.5 to 2.0 mm

Cloacal membranes and posterior cerebral vesicle (rhombencephalon).

Week 5 (Ultrasonographic)

From 4 weeks + 0 days to 4 weeks + 6 days from the last menstrual period

Week 5 of gestation: It is possible to identify the gestation chamber (GC) from 4 weeks + 2 to 3 days in pregnancies with regular menstrual cycles, and by the end of week 5 this is possible in almost 100% of pregnancies. The number of GCs can also be determined. Spiral circulation around the GC can be detected from week 4; using multiplanar 3D with surface rendering it is easier to see
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...vascularisation, combined with hCG monitoring, leave progressively less room for diagnostic uncertainty. It is also possible to visualise vascularisation of the myometrium and decidua and check their homogeneous vasculogenesis, though these observation do not yet have clinical implications.

Detection of a GC measuring 2 to 4 mm in week 5 enables exact dating of pregnancy with an error of only 2 to 3 days. Visualisation of the YS may be possible in the same week and is the first ultrasound-detectable embryonic structure; 2 to 4 days later it is possible to see the embryo as a double bubble. In the following days and in practice from week 6, the yolk sac moves away from the embryo and the amnios is seen to divide the celomatic from the amniotic cavity. The yolk sac appears as a transonic ring above the cephalic pole of the embryo, growing slowly until weeks 8 to 9 without exceeding a diameter of 5 mm and then reducing progressively to disappear between weeks 12 and 14. An absent yolk sac or a large, non spherical, hyperechogenic one with echo-rich internal structure is a condition associated with a poor prognosis for the pregnancy. A GC of mean diameter greater or equal to 20 mm, of lower than expected volume for gestational age, bounded by a thin trophoblast towards the periphery and devoid of embryo suggests blighted ovum syndrome. In such cases it is advisable to repeat ultrasound examination a week later (for diagnosis at week 7).

Embyology: Days 24 to 27

CRL = 4.0 mm, head and body distinguishable;
- Formation of prosencephalic cerebral vesicles or anterior brain, mesencephalon or middle brain and rhombencephalon or posterior brain, which subsequently give rise to:
  - Prosencephalon
  - Median vesicle (diencephalon) that gives rise to third ventricle
  - Two lateral vesicles (telencephalon) that give rise to the hemispheres and lateral ventricles;
- Formation of optical vesicles;
- Formation of falx cerebri;
- Formation of limbs, liver, pancreas, lungs, thyroid and mesonephrium tubes;
- Fusion of two cardiac tubes along the median line and initiation of heart activity (Fig. 17).

Week 6 (Ultrasonographic)

From 5 weeks + 0 days to 5 weeks + 6 days

The GC should still be visible; if not, hCG should be assayed and repeated a week later to determine the possibility of delayed conception or ectopic pregnancy. Bi-, tri-, chorionic multiple pregnancy is readily detected. The...
Figs 15A to K: Different kinds of physiological endometrium at 12 days, a zoom of the three lines and myometrial vascularization and volume by VOCAL. (A) Multiplanar; (B to D) Surface rendering normal uterine shape; (E to H) Luteal phase; (I and J) Vocal; (K) HDlive of bicornuate uterus
YS is detected in almost 100% of cases towards the end of the week and the double bubble image is increasingly frequent with a percentage detection of the embryo of about 20 to 40%. CRL is 1.5 to 4.0 mm at the end of week 6 and embryo heart beat (93-106 bpm) is visible. From now until week 12, CRL is the most reliable biometric value for dating pregnancy; mean error in expert hands is ± 2 to 3 days.

Embryology: 28 to 35 days
CRL = 6 to 9 mm;
slow heart beat evident through chest wall;
the hemispheres increase;
budding of limbs;
primitive intestine present;
first movements of embryo.(Fig.18)

Week 7 (Ultrasonographic)

From 6 weeks + 0 days to 6 weeks + 6 days
The amnios is still distinct from the chorion; the yolk sac is increasingly distant from the embryo, sometimes already compressed between the two membranes; prosencephalon and rhombencephalon detectable; budding of limbs; first movements of embryo.
Embryology: 36 to 42 days
CRL = 11 to 20 mm;

Week 8 (Ultrasonographic)

From 7 weeks + 0 days to 7 weeks + 6 days
The amnios is still distinct from the chorion; the two membranes constrain and envelop the YS, making it disappear when they fuse, which usually occurs at 14 to 16 weeks; choroid plexuses present; herniated intestine in umbilical cord which should resume its intraabdominal position by week 12 (omphalocele differentiation); embryo tachycardia > 110 bpm; evident movements of embryo; facial features detectable; extremities detectable.
Embryology: 43 to 49 days
CRL = 22-30 mm;
Legs form circle with knees turned out and feet in contact (frog attitude);
Formation of eyebrows and external ear (Fig. 20).

Week 9 (Ultrasonographic)

From 8 weeks + 0 days to 8 weeks + 6 days

Figs 16A to E: The number of follicles is easier to determine by 3D in the first part of the cycle (preferably by Vocal and Invert during hyperstimulation) and the morphology and vascularization of the Graafian follicle are more realistic.
The embryo is clearly visible through vaginal and abdominal windows and begins to appear human. Its movements are often jumpy and abrupt. More articulated and refined movements are not seen until development of the neopallium in months 6 to 7. The face is clearly delineated, especially by 3D volumetric scans. In the brain, the hemispheres and ventricles with their posterior (choroid plexuses) and anterior horns are observed developing from the two vesicles of the telencephalon. The brainstem is sometimes detectable. The rhombencephalon persists and is dividing to form the fourth ventricle (metencephalon) and the spinal cord (myelencephalon). The spine and ribs are clearly visible. Differentiation of chorion laeve and chorion frondosum.

The embryonic period comes to an end after week 9, ushering in the fetal period with its rapid longitudinal (hyperplastic) growth that continues until week 20, with further differentiation and organisation of organs and tissues formed in the embryonic period and with acquisition of specific functions (Fig. 21).
Figs 18A and B: Until the end of week 4, it is usually possible to observe transformation of the endometrium into decidua and its vascularization

Fetal period

Anatomy: From day 50 to 84 (8 to 12 full weeks)

Ultrasonography: Until Day 98 (10 to 14 Full Weeks)

Until week 10, the transvaginal route is universally recognised as the acoustic window for embryo study. After week 10, the transabdominal route may also be used with good ultrasound instruments in women with normal fat distribution. By week 10, CRL is no longer precise for dating pregnancy, acquiring an error of ±5 days (due to foetal flexion and extension). From week 11, biparietal diameter (BPD) is therefore preferred, though CRL is still important, for example in measuring nuchal translucence (NT).

By week 10, the foetus acquires definite anatomical characteristics that will persist for the rest of gestation, albeit with changes in size and function. By week 12, umbilical hernia disappears and by week 14 the YS is hardly visible and the two membranes fuse. In the brain, the choroid plexuses that almost filled the cranial cavity, are relegated to the posterior horns; the brainstem is increasingly evident and the posterior cranial fossa is readily detected by week 14. Although the corpus callosum ceases its formation later and is detectable by ultrasound by weeks 20 to 22, the cavity of the septum pellucidum can be detected. The heart with its four chambers becomes visible from week 12 transvaginally, however not in all cases. The detection percentage increases dramatically by week 14 and indeed more and more centres are delaying transvaginal screening for cardiopathy until weeks 14 to 16. The fetal face is increasingly human and offers striking images by 3-4D. By week 12, BPD is the most reliable biometric value for dating pregnancy, having a mean error of ±1 week. (Figs. 22 to 24)

Embryo-fetal Pathology Detectable by Ultrasound in the First Trimester

The acoustic window of the first trimester of pregnancy (until week 14) offers the possibility of suspecting or diagnosing embryo-foetal malformations, chromosome anomalies and perinatal outcome. The possibilities in the first trimester have been described by Nikolaides et al who concentrated their research on the foetus from week 11 to 14, documenting the many chromosome pathologies and malformations that can be detected. The fact that ultrasonographic diagnosis is becoming possible increasingly early in pregnancy partly attenuates the psychological problem of the mother and her partner when the painful question of whether or not to interrupt pregnancy arises. There have been many examples illustrating the significance of the first trimester for detecting chromosome and/or structural anomalies or at least for selecting populations at risk, whereas the second trimester is more indicated for malformations, for example the heart (for which there is ample documentation that suspected or actual diagnosis is possible in week, 14), spina bifida and Dandy-Walker syndrome. In any case, knowledge of the natural history of malformations is fundamental for understanding missed diagnoses. For example, partial or total agenesis of the corpus callosum cannot be diagnosed until week 22 to 24, when the corpus callosum completes its formation. First trimester ultrasonography (weeks 11 to 14) is increasingly viewed as a time for morphological and structural check-up, similar if not better than second trimester scans, hence increasing use of the term first trimester sonoembryology, meaning the whole of the first trimester (Figs 25 to 30).
Figs 19A to J: Week 5: From gestational sac (GS) to yolk sac. The gestational sac is more evident by 3D, and it is possible to see the external wall of the GS, making it easier to distinguish the GS from the interdecidual space (IS).
Figs 20A to I: (A to H) Week 6: The embryo appears and the double bubble becomes more evident during the week. The embryo moves away from the yolk sac, which remains near the uterine wall and disappears in weeks 12–14; (I) Zoom of embryo head showing prosencephalon (P)

Figs 21A to D: Week 7 (6–12 mm): Embryo anatomy is more complex: note promesorhombencephalon and first image of face. Arms and legs are present, as are the queue and the vertebral column. The amniotic membrane is well formed and divides the amniotic cavity from the celomatic cavity; the yolk sac lies between the amniotic and chorionic membranes
SIGNS PREDICTIVE OF ANEUPLOIDY AND STRUCTURAL EMBRYO-FETAL ALTERATIONS IN THE FIRST TRIMESTER

It is common practice to obtain verbal or written informed consent before determining nuchal translucency. It also seems reasonable to make a similar contract (implying correct counseling and specific request) for predictive markers of aneuploidy in the first trimester, as is customary in the second trimester (so-called “genetic” ultrasonography). In my opinion, consent to scan for structural alterations, the only therapy for which would be interruption of pregnancy, is also advisable. Today, ultrasonography in pregnancy is a powerful instrument for serenity, but may also create gratuitous anguish. Before carrying it out, it is important to discuss it with the woman, not only specifying the limits of the method and of the operator, but also asking clearly what the woman expects and wants from the scan.

TRANSITORY SIGNS

Nuchal Translucency

The problem with screening tests in which nuchal translucency (NT) is a constant component is too complex to discuss in an atlas, however the detection of this transient sign is easier and quicker with multiplanar than with classical 2D. (Figs 31 and 32) The current scientific findings have shown that can detect even an intracranial translucency (fourth ventricle) that seems to offer a sensitivity and specificity of nearly 100% in the early detection of spina bifida22,23 (Fig. 16).

At 11 to 13 weeks’ gestation, during the first trimester screening of chromosomal abnormalities in the mid-sagittal view of the fetal face we can to obtain the nuchal translucency thickness and the nasal bone view; in this view is visible the fourth ventricle. In the normal fetuses the fourth ventricle was always visible and the median anteroposterior diameter increased from 1.5 mm at a crown-rump length (CRL) of 45 mm to 2.5 mm at a CRL of 84 mm. In the fetuses with spina bifida the fourth ventricle space was compressed and no could be seen, we can also be used for early detection of open spina bifida.24

Pending clinical confirmations is important to be able, during a 11 to 14 week scan, to detect these markers that can be considered as an alarm bell to identifying cases at risk assessment of intracranial translucency (IT) in the detection of spina bifida at the 11 to 13-week scan. (Fig. 23 bis)

Ductus Venosus

Measurement of NT in the first trimester has become a consolidated method for identifying fetuses at risk for
chromosomal abnormality. The high percentage of heart defects in fetuses with increased NT, whether isolated or caused by chromosome anomalies, has stimulated considerable interest. The association, together with echo-Doppler modifications of the ductus venosus (DV) in fetuses with increased NT, suggests that altered heart function could play a role in determining an increase in NT.25,26

In particular, inverted flow in the DV during heart’s contraction (A wave) has been associated with increased NT. The DV is a communicating vessel that carries well oxygenated blood of the umbilical vein into the
right atrium, through the oval foramen. This vessel is important for assessing the presence of heart function anomalies. Blood flow in the DV is characterised by high velocity during ventricular systole (S wave) and diastole (D wave) and also by forward flow during atrial contraction (A wave). In heart dysfunction due to heart defects, the A wave is absent or negative.

Assessment of flow in the DV could play a role in secondary screening, permitting further reduction in the percentage of false positives in screening for chromosome anomalies in the first trimester. A major association has been demonstrated between chromosome anomalies and abnormal blood flow in the DV at 11 to 14 weeks of pregnancy in high risk pregnancies. DV flow anomaly associated with heart defects and adverse outcome of pregnancy has also been observed. Some authors suggest that the DV can be an important prognostic factor in fetuses with increased NT and normal karyotype.

In fetuses with chromosome anomalies, whose parents decided to continue the pregnancy, heart dysfunction has been found to be a temporary condition: transitory anomalous flow in the DV, detected by colour
Figs 26A to F: Weeks 13–14: Fetal morphology is clear; note details of face, limbs, fingers, toes and neck. Detailed study of spine is possible.

Figs 27A to I: Omphalocele at weeks 13, 16 and 18. Note difference between normal and abnormal hernia in A and B: umbilical artery starts from top of hernia (color and power glass body mode). Week 16 and 18 images show homogeneous echogenicity of small intestine and stomach.
Doppler, manifested as “reversed flow” during contraction. This marker is detected early, around week 13, and usually disappears by week 20. The dysfunction that caused it aggravates retronuchal oedema and may culminate in foetal hydrops, which could explain some cases of intrauterine foetal death. At 10 to 13 weeks + 6 days the duct anomaly is therefore associated with aneuploidy (80% of Down fetuses versus 5% of euploid fetuses), heart malformations and unfavourable outcome of pregnancy. To study the DV, 3-4D does not offer particular advantages, whereas 2D is fundamental and exclusive for correct detection (Fig. 34).

**Nuchal Edema, Cystic Hygroma and Non-immune hydrops**

Subcutaneous edema detected sonographically in the forms of nuchal edema, cystic hygroma, or non-immune hydrops may be a sign of chromosomal abnormalities.  
Cystic hygroma is a congenital malformation of the lymphatic system characterised by a thin walled cystic
At about 40 days of embryo development, the jugular lymphatic sac forms a connection between the jugular duct and the internal jugular veins which become the terminal portions of the lymphatic and thoracic ducts. According to the theory of obstruction of the jugular lymphatic sac, the connection between the jugular lymphatic sac and the jugular veins does not form in the case of cystic hygroma and the lymph builds up in tissues around the neck, causing the sac to swell. Cystic hygroma is often detected by prenatal ultrasound, though some cases develop in the postnatal period, with an incidence of about 1%. The defect may regress spontaneously during pregnancy, leaving extra skin in the neck region, or progress dramatically towards a form of generalised foetal hydrops.

Fetal cystic hygroma was usually readily diagnosed by transabdominal ultrasound in the second trimester of pregnancy. Today transvaginal ultrasound has increased the percentage of diagnoses in the first trimester. Ultrasound diagnosis of cystic hygroma is based on visualisation of a prominent anechogenic or hypoechogenic area (more than 3 mm thick) in the occipital, nuchal or upper thoracic regions, bilaterally. On the contrary, physiological build-up of fluid or the nuchal bleb is generally considered normal when it is less than 3 mm thick: these build-ups seem to occur in 40% of embryos before week 10 and disappear at week 11.
Cystic hygroma may be single or consist of multiple cysts and is classified as septate and non septate. Though confused for years by various authors, this distinction is important for prognosis, because septate cystic hygroma is strongly associated with aneuploidies.\(^{36}\)

The presence of cystic hygroma in the first trimester is associated with increased risk of fetal chromosome anomalies: about 50% of fetuses with ultrasound diagnosis of cystic hygroma in the first trimester also have a chromosome anomaly. A high percentage of the cases undergoing cytogenetic analysis show Turner syndrome, often associated with trisomy 21, 18, 13 or other structural anomalies. The risk of this transient anomaly increases with increasing maternal age.

As yet there are no ultrasonographic elements for distinguishing cystic lesions that may regress from those that persist. However, when the nuchal cyst is small and non septate and karyotype is normal, it usually resolves spontaneously with good foetal outcome. When septate cystic hygroma is diagnosed early in pregnancy, the risk of chromosome aberrations is much greater and the outcome is therefore worse, also because septate hygroma is often larger and frequently develops into foetal hydrops. Spontaneous regression of cystic hygroma has been reported in chromosomally normal fetuses and in, down, Turner and Robert syndrome fetuses.

Fetuses diagnosed with non septate and septate forms, with or without associated malformations, are at high risk of chromosome aneuploidies. The mothers need correct counseling to assess the possibility of cytogenetic tests to determine fetal karyotype, to programme subsequent ultrasound monitoring to exclude morphological anomalies, particularly of the heart and circulatory system, and to evaluate any worsening of edema or its resolution. Fetuses with normal karyotype are usually free of hygroma by weeks 16 to 17 and many have normal phenotypes at birth. Ultrasound parameters such as hygroma size and the time of its disappearance associated with fetal echocardiography may be useful to identify pregnancies at risk for dysmorphic conditions such as Noonan syndrome (Fig. 27).

**PERSISTENT SIGNS**

**Nasal Bone**

In 1866, Langdon Down noticed that subjects with trisomy 21 had a small nose. An anthropometric study on 105 Down patients confirmed that the nasal bone (NB) was smaller than normal in 49.5% of cases. Recent radiological and ultrasound studies have shown that nasal hypoplasia is already present in the uterus.\(^{37,38}\) A study of 105 fetuses with trisomy 21, aborted at weeks 12-25, showed lack of ossification of the NB in 32.4% of cases and hypoplasia in 21.4%. The correlation between absence of NB at weeks 11 to 14 and increased risk of trisomy 21 was reported for the first time in 2001. Indeed, about 65% of Down fetuses lack, or have a small, NB.

The nasal bone can be seen by scan from week 11.\(^{39}\) Many recent studies show a strong association between absence of NB at this gestational age and trisomy 21 and other chromosome anomalies.\(^{40,41}\) We can therefore say that at 11 to 13 weeks + 6 days, fetal profile can be examined correctly in more than 95% of cases and that the NB is absent in about 70% of fetuses with trisomy 21 and in about 55% of fetuses with trisomy 13. The incidence of absence of NB in euploid fetuses is less than 1%. Absence of NB is therefore a major marker of trisomy 21. There are some limiting factors in the ultrasonographic assessment of NB.\(^{42,43}\) Between weeks 11 and 14 from the last menstrual cycle, the probability of visualising the NB increases with increasing gestational age. The presence of NB is not independent of fetal nuchal thickness, since the possibility of visualising it seems to decrease with increasing NT. Finally, ultrasound detection of NB at 11-14 weeks requires much technical skill of the operator, unlike later in pregnancy.\(^{44}\)

Absence of NB has a higher incidence in fetuses of African origin than in Caucasians and decreases with CRL. In calculating individual patient-specific risk of Down syndrome, it is necessary to consider these demographic and ultrasonographic aspects.

If examination of foetal profile to detect NB is associated with NT and maternal serum proteins (free beta hCG and PAPP-A) during first trimester screening for trisomy 21, the detection rate can increase substantially and the false positive rate decrease. For a false positive rate of about 5%, the detection rate increases from about 75% (NT) and 90% (NB + maternal serum proteins) to 93% (NT+NB) and 97% (NT+NB+ maternal serum proteins). For a false positive rate of 1%, the detection rate could be about 57% for NT, 86% for NT + NB and 93% for NT, NB and maternal serum proteins.

In conclusion, the absence of NB or small NB are more common in fetuses with chromosome anomalies. It is therefore clear that NB is becoming a major marker in the prenatal diagnosis of aneuploidies.

There is a statistically significant difference between detection of NB by 2D and 3D techniques. Traditional scan is about 20% less reliable in detecting presence/absence of NB and also for the number of bones detected. This difference can be as high as 40% when 2D is performed with mediopragittal scan of the fetal face, since detection of the NB requires a longitudinal foetal scan as for detection of NT, but in the case of NB the section is 1 to 2 mm from the sagittal median. Further studies seem to suggest greater reliability in the second trimester, with
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SECOND AND THIRD TRIMESTERS

The scan performed in the second trimester, usually around week 20 (range week 18 to 23, depending on the protocol), is used to study foetal anatomy and detect foetal malformations, as well as to evaluate foetal growth by means of biometric parameters. Despite the high expectations of pregnant women about the diagnostic capacity of ultrasound (presumably due to incorrect information in the media and often also from specialists), the various studies on detection of fetal malformations by standard ultrasound in the second trimester show rates that do not exceed 40 to 60% of all malformations detected at birth, with a homogeneous mean prevalence of 2.5%. The Eurocat report, for example, documents a diagnostic capacity of 62% for 11 major pathologies among 4366 malformations in 1,198,519 babies born in 17 European regions in the period 1995 to 1999. Variability was high, ranging from 25% in Croatia to 88% in Paris, with enormous regional differences. Moreover, about 30 to 40% of cases were diagnosed after week 24, for various reasons, not least of which the natural history of malformations. No malformation was diagnosed in all carriers; for example, anencephaly was diagnosed in 94% of cases. It is therefore necessary to be precise and careful when informing women about the intrinsic limits of general ultrasound, as well as individual limits determined by the type of equipment and operator experience. As mentioned for ultrasound in the first trimester, the sophistication of instruments and operator experience also make very accurate and difficult diagnoses possible in the second trimester. Indeed, today the study of foetal anatomy can be much more detailed than in the 1990s. Thus greater experience, attention to districts such as the face, heart and circulatory system, should improve the sensitivity of diagnosis of malformations, though this quite reasonable claim has not yet been demonstrated. Specialists in prenatal diagnosis can also achieve great morphological detail with the aid of sophisticated new instruments with 3-4D technology. For specific use of these instruments, we consider the various systems and organs.

Head

The head offers the possibility of detailed examination of a series of morphological signs by 3-4D. The face is accessible and it is relatively easy to exclude or diagnose

a cut-off of 2.5 mm for NB and the presence of both nasal bones; in the second trimester, 3D plays an important role, making detection of the bones simpler and more reliable (Fig. 35).

Palate

It is possible to investigate the normality of the secondary palate better than the primary palate because it is very difficult to define a normality of the lips in the first trimester (foto 14 settimane). We can detect the secondary palate by two methods: by the evidence of the retronasal angle with a 100% confidence by the authors) using 2D or 3D multiplanar or omni-view and by the Faure method with a coronal/sagittal 3D scan of the foetus’s profile and rotation of the picture avoiding the maxillary shadow and maximum or minimum rendering of the palate by axial section (delta sign) (Fig. 35).

Jaw Bone

In a series 89 Down fetuses compared with a population of 900 euploid fetuses, Cicero (2004) found jaw bones shorter by about 0.7 mm (with variations in growth from 4.8 to 8.3 mm from 11 to 14 weeks) in fetuses with NB and 0.5 mm in fetuses without NB. This characteristic is specific to trisomy 21 and not detectable in other aneuploidies. It is important to assess the jaw correctly by sagittal scan taking the mandibular condyle as reference point.

Single Umbilical Artery

A single umbilical artery in the first trimester of pregnancy is associated with trisomy 21 and especially trisomy 18. Nikolaides et al. showed that an umbilical artery is missing in 77% of cases of trisomy 18 (Fig. 33). The screening tests for Down syndrome in the first trimester with the use of NT and other marker (nasal bone, ductus venosus) have focused the investigator’s attention to the first trimester 11 to 14 week and today it’s possible to diagnose about the 50% of structural foetal malformation that we can detect in the second trimester (Figs 26 to 29).
cleft lip in this period.\textsuperscript{55} Note that 3D technology includes 2D as base, so the capacity to visualise the foetal face by 3-4D in the second trimester is certainly much better than with 2D, with due enhancement and limitation related to foetal position, maternal abdominal fat, the placenta and quantity of amniotic fluid.\textsuperscript{56} Given time (and perhaps more than one session) it is possible to obtain a good image of the foetal face in almost all cases in the period 19 to 23 weeks in 85 to 90\% of cases (our personal percentage for 3540 pregnancies is 92\%). In the next period of pregnancy, the possibility of exploring the foetal face decreases as pregnancy proceeds. Indeed, in the third trimester, after week 35, the face can only be visualised in 30-50\% of cases and sometimes requires two or three sessions in the case of suspected diagnosis (Fig. 36).

Operator experience is critical. After initial successes, considerable difficulty is often encountered in analysing a saved volume: to obtain good images, 3D takes time and application as well as interest and predisposition. 3-4D is much less instinctive than 2D, which gratifies the operator with interpretable images after a few hours of practice (for example, measurement of BPD). The first impression of a face naturally cannot have scientific value, though many facial dysmorphisms depend on genetic syndromes and aneuploidies. Hyper and hypotelorism, a weak chin and low ear position are easily and immediately detectable by 3D and this prompts us to consider the foetus as if it were a newborn. Moreover, with 4D we can observe sucking movements and attitudes, yawning, extraflexion of the tongue and movements of the hands, arms and legs, all characteristic of fetal wellbeing.\textsuperscript{57} Maximum mode rendering enables exact views of bones,\textsuperscript{58} detailed study of cranial bones and sutures, as well as measurement and counting of nasal bones making easier a diagnosis of craniosynostosis.\textsuperscript{59-61} Minimum mode surface rendering can show details such as ear lobes which are markers of urinary system pathology. The study of the fetal face is now the less important and significant field of the three-dimensional study of the cephalic extreme. The so-called “granny” effect that is achieved pleasing images of the fetal face to take home is the playful part of the use of ultrasound that has always existed, even when we were only able to hear the heartbeat. The facial dimorphisms are relevant in certain diseases such as achondroplasia (Fig 37) and in many syndromes (holoprosencephaly, elephant man) where the face is often one of many markers, though often very impressive. Finally today the three-dimensional have bought or better earned its place as a complement or as a significant contribution to the two-dimensional ultrasound diagnostic of malformations.

Internal structures of the brain can be explored in more detail. A correct view of the corpus callosum and pellucid fossa can be obtained in real time by 3-4D with volume contrast imaging in the C-plane. The posterior horns and the vermis can also be explored and their volume calculated.\textsuperscript{62,63} The optic chiasma is easily detected and is

\section*{Figures}

\textbf{Figs 36A and B:} Unusual scan of quadrigeminal pregnancy arising from FIVET of three oocytes: two twins are clearly bichorionic biamniotic (delta sign) and two monochorionic-monoamniotic (T sign) and a distribution of vessels in multiple pregnancy in the first trimester.

\textbf{Figs 37A to C:} Typical face of achondroplasia.
an important prognostic factor in cases of anterior brain anomalies. Brain vascularisation provides much material for future study. The Willis circle and the pericallosa and marginal arteries are easily detected in glass-body mode and angio mode of power or colour Doppler, from the first trimester (Figs 38 to 40).

Detailed study of the jaw and oral cavity is another aspect of the head. We have extensively studied the ears, their size, morphology and position (normal or low), prompted by observations of neonatologists who attribute importance to the anatomy of the external ear (Figs 36 and 41 to 51). Neurosonology represents the area in which the three-dimensional really makes the difference enabling the operator to browse inside the brain structures using multiplanar method; the study of the corpus callosum has become a reality in almost all cases, with the ability to detect the partial agenesis, while both ventricles and posterior fossa are now easier to explore.

Inside the cranium is now possible to highlight structure otherwise unimaginable as the optic chiasm or sphenoid bone (Figs 43H and I), although currently there is a lack of clinical utility but it is representative to signify the depth anatomical study allowed by 3 and 4D. Finally, the study of the palate which today represents a new barrier demolished by ultrasound with a great contribution of the three-dimensional. (Figs 42 to 51)

Renewed interest in the study of primary and secondary palatal morphology has arisen with new ultrasound diagnostic methods in 3 and 4D (64 to 66) and the fact that facial cleft accounts for 13% of all congenital malformations.67 Malformation of the lip and palate may be isolated, associated with other malformations and/or sequences of malformations, associated with chromosome anomalies or with manifestations of a syndrome. Typical facial cleft, including cleft lip, cleft lip/cleft palate and cleft palate, have a prevalence of 9.1/10,000 and 6.4/10,000 births, respectively. Cleft lip accounts for 36% of all lip and palate malformations and the birth prevalence of isolated oro facial clefts accounts for 61.67% of total facial cleft.68 The prevalence is high (about one/1000) and in about two thirds of cases not only involves the lips but also the palate. Unfortunately in 45 to 47% of cases the defect affects the palate only.69 From an epidemiological viewpoint, isolated malformations of the palate are associated with other malformations in about 18% of cases and with syndromes in 27.2%.70 Cleft lip-cleft palate is isolated in 70-79% of cases and in the other 21 to 29% it is part of a syndrome or associated with other malformations.71-73 Chmait 200674 reports 45 cases of cleft lip-cleft palate diagnosed by 2D and 3-4D scan, among which 21.6% of forms diagnosed as isolated
revealed malformations not detected by ultrasound at follow-up. The report EUROSCAN 200075 documents a total ultrasound sensitivity of 27% for cleft lip-cleft palate, a sensitivity of 17% for isolated forms and 7% for isolated cleft palate. Other reports indicate a detection rate of up to 73% for cleft lip by 2D scan performed after week 20 of pregnancy ultrasound but there are papers which report sensitivity for isolated cleft of palate about 0%.76 The prevalence of this malformation and especially the high incidence of associations with other anatomic and genetic malformations has prompted research to improve ultrasound definition of the secondary palate. Usually the amniocentesis for caryotype should be offered in all cases of cleft lip/palate because of the risk of aneuploidy; also the patients should be counselled that ultrasound occult additional anatomic abnormalities might be present with all clefts.77,78

Ultrasonographic detection of the palate

The primary palate includes the lips and jaw bone to the nose root and is the most easily detected part of the anatomy by 2D scan (Figs 52 and 53). Indeed many sustain
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Figs 42A to F: Umbilical cord cyst at week 9. This is a transient soft marker of aneuploidy (about 25% sensitivity—present in about 5% of pregnancies)

Figs 43A to F: The difference between 2D and 3D for detection of nuchal translucency is usual minor: 2D is better for routine scan; 3D sometimes has advantages when the fetus is in an inappropriate position
Figs 44A to E: Weeks 13 and 20. It is easy to find the nasal bone and to detect both bones by 3D in the first and second trimesters; it is more difficult by 2D. The pictures are at 13th and 20th weeks (Abbreviation: nb; nasal bone)

Figs 45A and B: Intracranial translucency 2D and 3D. It is easy with a correct scan to find the IT between two hyperechoic lines

Figs 46A to C: An example of great vessels transposition. The b-flow is not an easy technique but improves the heart defects about pulmonary veins. (Abbreviations: a, aorta; p, pulmonary artery; vci, inferior vena cava; aa, anonymous artery)
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that it is worthwhile visualising the lips, jaw bone and nose root with an oblique coronal scan, scrolling upwards during the routine second trimester scan and it is evident to users of 3D that this suggestion is almost superfluous when a scan of the foetal face is part of the routine (Fig. 54). The secondary palate consists of a hard palate, which runs posterior and horizontal to the incisive foramen and soft palate or velum, which curves downwards and backwards from the posterior aspect of the hard palate and ends in the uvula. In the foetus the hard/soft palate is 2.1 and the soft palate has the similar thickness (Figs 15 to 22). Usually the cleft of the secondary palate

is always midline and results from failure of the palatine processes to elevate and grow (Figs 16 to 18 and 20). Cleft of the secondary palate starts from uvula and soft palate, but it is possible the cleft of soft palate with an intact hard palate (Fig. 19). The severe shadowing of the maxilla made difficult but not impossible the visualization and the diagnosis of clefts of the secondary palate. Shereret et al.\textsuperscript{80} says that visualization of the secondary palate is not difficult by axial plane 2D scan, but he doesn’t report any cases of defects of secondary palate. In this case the new volumetric probe 3D multiplanar and surface rendering offers greater possibilities of study of the normality

Figs 47A to C: Ultrasound flow imaging of the ductus venosus is only feasible by 2D, but 3D provides good images of the vessel. The images show normal A wave in ductus venosus in first trimester and a case of reversed flow (Abbreviation: DV; ductus venosus)

Figs 48A to I: It is possible to control the normal secondary palate in the first trimester of pregnancy by Faure technique 3D (delta sign (D and E) by rendering surface or (C) by omniview) or by retronasal triangle (A to C) by 2D or by omniview)
Figs 49A to C: Maximum and minimum rendering in three cases of l-p cleft. It is easy to understand the extension of the cleft.

Figs 50A to E: In the first and second trimesters, it is easy to find both umbilical arteries at bladder level; 3D color, power and glass body modes provide more realistic images.

and of diagnosis of the cleft of the primary and secondary palate. By 3D it is possible to see the alveolus and maxilla by axial scan and secondary palate by coronal scan by scrolling front-to-back in coronal plane. But with this method there is the problem of the maxillary shadow. Campbell overcame this problem by rotating the face through 180° and scrolling from back-to-front. This technique, described as ‘reverse face view’ eliminate the shadowing of the maxilla, but it offers the possibility to have a good vision of the hard palate but not of the soft palate. Platt et al. found a different technique to see also the soft palate by axial 3D plane (multiplanar and surface rendering) with inverted picture to avoid the shadowing of the maxilla and using a little acoustic box scrolling from chin to nose (flipped-face view’). Uses a sagittal scan and by this technique the mandibula, the tongue, the maxilla,
Three and Four Dimensional

Three-dimensional scans have greater possibilities because a volume can be saved and examined later in an infinite number of scanning planes. Various methods have been proposed:

- Axial surface rendering plane with a small box (“flipped–face view”) and inverted scan to avoid maxillary shadow (scrolling upwards) by sagittal or coronal scan (Figs 55 to 61 and 63 to 70)
- Coronal surface rendering plane, reverse-face (scrolling forwards) or front face (scrolling backwards) scan (Figs 68 and 69)
- TUI tomography ultrasound imaging sagittal scan with angle of 45° (Fig. 70).
Ultrasound technicians will be increasingly called upon to check the integrity of the secondary palate due to the high prevalence of facial defects at birth and the high percentage of malformations, syndromes and chromosome anomalies, associated especially with cleft palate. Three-dimensional techniques offer ways of achieving

Figs 53A to R: The fetal face acquires human features during gestation. The face of the embryo is quite unattractive; whereas in the second trimester, it becomes softer and more pleasant and remains thus into the postnatal period. Facial modeling is related to the formation of facial musculature, fat and the thick consistency of skin due to soaking. 3–4D provides completely realistic images, especially with high quality instruments and experienced operators. It is therefore relatively easy to assess facial symmetry and reliably recognize facial dysmorphisms (e.g. mandibular hypoplasia), which may be of genetic disorders and to diagnose cleft lip or palate.

Figs 54A to C: Examination of the corpus callosum is easy and quick by 3D and volume contrast imaging in c-plane; by 2D it is very difficult.
Among those described above, the 3D axial plane is the fastest and easiest to apply, and has been reported to detect the secondary palate in almost all cases in 2 to 3 minutes when echographic conditions do not pose an impediment. Variable fetal position in relation to maternal fat is the only serious obstacle to its correct detection. Today it would seem reasonable to propose study of the hard and soft palate only in cases with suspected or
confirms diagnosis of facial clefting and in cases with a positive family history or after non visualization of the “equals sign” in 2D (Figs 71 to 76).90

**Chest**

The Chest contains the heart, an organ fundamental for human life. Study of the heart, efflux and the circulatory system91 has exploited 3-4D technology and STIC mode (spatio-temporal imaging correlation), which being in four dimensions, cannot be illustrated in an atlas. However, fixed, invert, power, colour and Doppler 3D images and study in real time by tomography ultrasound imaging (TUI) are striking, interesting, and considerably improve diagnostic capacity. At this time the b-flow is the alone possibility to study the vein efflux with low flow and can also become complementary to STIC in heart pathology; but it is not easy to learn the b-flow. Lung volume can be measured by the VOCAL system92,93 improving the prognosis and outcome of fetuses with diaphragm hernia, and is expected to replace thickness as an indication for therapy in utero. With special experience it is possible to correctly visualise the course and morphology of the esophagus. The volume of the thymus, an important foetal organ, can be assessed. The diaphragm is quite evident, reducing diagnostic doubts about hernia.
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Figs 60 A1 to A3: Secondary palate by coronal 3D plane multiplanar and surface rendering; scrolling forwards (reverse face); A1-B1; A2-B2; A3-B3. The arrow points at hard palate

Figs 61 B1 to B4: Secondary palate by coronal 3D plane multiplanar and surface rendering; scrolling forwards (reverse face); A1-B1; A2-B2; A3-B3; A4-B4. The arrow points at hard palate

The gallbladder is also easily visualised (Figs 77 and 78).

**Abdomen**

Visualisation of the viscera and stomach are less exciting than the face, though the vascularisation of the liver is striking. Regarding the urinary system, it is easier to study the renal arteries and parenchyma vessels, and kidney volume is a better index of development than traditional biometry.

**Neural Tube and Limbs**

Volume acquisition is one of the most important technological achievements of the last decade in diagnostic ultrasound and offers a good possibility to study the spine. In particular there is the multi-planar which gives the possibility to navigate within a volumetric space through infinite reproducible imaging planes (including the crown), in real time. There is also rendering which...
Figs 63A to F: By 3D it is possible to detect very small appendix auricularis (an important marker for many other malformations); ear position is important, because low placement or a helix more than 30 degrees out of the skull are a marker of aneuploidy. External ear morphology changes during gestation: until week 20 it is a ring; final morphology is only achieved at about week 29.

Figs 64A to C: (A) The use of 2D, 3D and color Doppler offers a good possibility to diagnose the l-p cleft. It is suggestive of the passage of amniotic fluid directly from oral to nasal choana; (B) Sagittal scan power-color to demonstrate the normality of secondary palate during swallowing; (C) The amniotic fluid crosses through the palate.

Figs 65A and B: Different planes of axial 2D scan for the jaw and the tongue. (A) The maxilla; (B) The proximal part of the maxilla and the eyes.

has the ability to represent surfaces, as well as the VCI-c-plane that makes it possible to dissect an orthogonal plane with ultrasound scanning by integrating multi-planar and rendering. A further step forward is the VCI-Omni view, which has the ability to model the source of 3D insonation by adapting to the structures of the fetal body that are normally represented by curved and straight lines (also the median line at the bottom is an artifact ultrasound). This technique allows direct and relatively simple scans which adapt to the adjustable thickness of the structures corpus studied (20 mm spine). There is no doubt that with a 3D to 4D instrument equipped with VCI-c-plane.
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Figs 66A to D: (A) A correct axial 2D scan for the maxillary bone; (B) The tongue and the uvula; (C) The secondary palate with the uvula by 3D flipped-face view multiplanar; (D) Surface rendering

Fig. 67: Picture of Berkowitz (2006) shows the different possibilities of facial cleft. It is important to note that the palate-cleft starts from the uvula until the primary palate

Fig. 68: Beautiful 2D pictures of uvula-cleft; the uvula-cleft is always associated with palate-cleft

adapted to insonation, can produce virtually overlapping results in terms of detecting anatomical structures in almost all three trimesters, also if with significantly reduced times using the omni-view in the second trimester. The VCI-Omni view, sharing the latest technological achievements, allows one to specify the anatomical study
Fig. 69: The study of the nose and the lips is very easy in the second trimester of pregnancy by 3D.

Fig. 70: The sagittal section of secondary palate shows the two portions of hard and soft palate with the uvula.

Figs 71 A to C: Secondary palate by coronal 3D plane multiplanar and surface rendering: scrolling backwards (Abbreviations: h, hard palate; s, soft palate)
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Figs 72A to C: (A) Tomographic ultrasound imaging (TUI) of the secondary palate in the coronal plane; (B) TUI of the secondary palate in the axial plane; (C) Omniview of the secondary palate in the axial plane

Figs 73A and B: Axial 3D plane multiplanar and surface rendering (flipped view) to see the maxilla (delta sign) and hard palate at 12 weeks by (A) sagittal and (B) coronal scan
of the fetus by choosing the ideal section plane. Regarding the multiple planes, that being in 3D and 4D in the same volume, it can better yet follow the natural curves and angles of the structures, while rotating like a real scanner box that can focus on very small points, which would otherwise be very difficult to explore.

The detailed study is therefore quite superior since it can easily and quickly visualize the structures, that with 3D to 4D can be sometimes detectable only under particular conditions.

Study of the vertebral column and possible anomalies is much more convenient with 3-4D maximum mode which provides easy visualisation of all bones including the phalanges, as well as faster identification of any anomalies (platyspondyly, hemivertebrae, kyphosis, scoliosis such as absence (agenesis) or extra elements (Fig. 52 to 79). The osteochondrodysplasias have a prevalence of approximately 2.4 per 10,000 births and are represented in about 70% of four conditions: thanatophoric dysplasia, achondroplasia, achondrogenesis, osteogenesis imperfecta Tip. II (Fig. 80).

The use of 3D doesn’t offer a better condition to study the long bones, even if it is a good tool to store a volume and to explore by infinitive planes; but the study of dimension of the long bones, for instance the femur and the humerus for the suspicious of down syndrome is the same by 2D or 3D. Instead the control of the extremity is a good field of exploration for three-dimensional scan. The club foot varus or valgus meet 415 syndromes in London medical databases; it is an important malformation because is often associated with other malformations or in about 2% with aneuploid malformation and in the last decade the detection rate of club foot achieve approximately 80% with about 15% of false positive rate. It is reasonable to think that the use of 3-4D, by tools maximum mode and omni-view, will be possible improve the diagnosis of malformation of the extremity (feet and hands) and decrease the false positive rate, because three-dimensional scan is better in the study of anatomical detail (Figs 81 to 85).

Genitals

The genitals are a new field of study. It is relatively easy to diagnose sex in the second trimester by 2D and to determine descent of the testicles at 26-28 weeks (third trimester), however diagnosis of pathology of the external genitalia, such as hypospadias, is much easier with 3D (tulip sign)98 (Fig. 86).

Placenta and Umbilical Cord

Detection of cord pathology (such as cysts), retrocervical position and number of twists is especially easy and reliable with power colour glass-body mode (Fig. 87). Also the study of position and vascularity of the placenta is easier by 3-4D99,100 (Fig. 88).

The above is not intended as a scientific evaluation of the merits of 3-4D with respect to 2D, however almost all researchers report improved sensitivity and a better detection rate using 3-4D to measure volumes, determine orientation and definition of vessels and more precise definition of malformation, study coronal planes and the
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Figs 76A to D: Bilateral l-p cleft with TUI and rendering surface

Figs 77A to D: (A to C) 3D images of amniocentesis; (D) Gives a good idea of the difference between 2D and 3D

Figs 78A and B: The axial 3D plane by multiplanar and surface rendering “flipped view face” to see a cleft-lip cleft alveolar ridge
foetal face, diagnose heart malformations (by STIC), visualise limbs and fingers and study embryo-fetal anatomy (especially neurosonology). All this does not establish a “need” for 3D for the structural study of the foetus, but certainly indicates that 3D instruments can improve ultrasound and make examination easier and more pleasant.

Motor Activity and Facial Expression

The structure of the foetal brain is in the process of development and in each phase of intrauterine life it has a maximum functional level. The first regions to mature are those necessary for life, such as sucking, swallowing and breathing. A first growth spurt is recognised between
Figs 80A to C: Monolateral cleft-lip and cleft-palate by axial 2D scan

Figs 81A to C: Axial 3D plane, inverted image, “flipped view face”, sagittal scan: (A) Cleft lip; (B) Cleft alveolar ridge; (C) Cleft palate

10 weeks of gestation and 18 months of neonatal life, with synapse formation and myelination.

Fetal movements can be divided into primary motor patterns and primary automatisms. The former are present in the first half of pregnancy and are genetically determined, whereas the latter depend on interaction of the foetus with its environment and occur from week 10 of gestation into the first years of estrauterina life.
in the 24-hour period is a sign of neurological maturation. Ultrasound can assess a foetal biophysical profile composed of foetal movements, muscle tone, respiratory movements, placental maturation and amount of amniotic fluid.

Doppler flow imaging plays a fundamental role in assessing foetal wellbeing, by evaluating alterations in blood flow in the placenta, foetus and mother. Robles de Medina et al. sustain that male and female fetuses do not show behavioural differences. Dynamic 3D scan (4D) can be useful together with 2D to study foetal behaviour in the second trimester of pregnancy.

**Brain Function**

Though up to a few years ago the study of foetal brain function and hence motor activity, attitudes, posture and facial expression were of little interest, now, with 4D techniques that enable more accurate visualisation in real time of everything the foetus can do in utero, studies of foetal activity have become increasingly numerous. These studies are concerned with activity from the point of view of physiology as well as brain pathology. We now know much about foetal cognitive and emotional development from observation of premature babies who now survive from as early as 22 to 23 weeks of gestation. Clearly, extrauterine life involves stressors that force the premature baby along the path of brain development, often
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Fig. 84: Cleft-lip by “reverse face” mode and “front face” in the same case, of course change the position of the cleft

Figs 85A and B: The omniview and STIC are good tools to explore the heart

Figs 86A to L: The chest and abdomen from the oral cavity to the esophagus are conveniently examined by 3-4D. The esophagus can be viewed from the oral cavity to the stomach by 3D, aiding diagnosis of stenosis-agenesis. All organs (lung, diaphragm, heart, thymus and bowel) are realistically represented by 3D (Abbreviations: a, aorta; b: bowel; c, gallbladder; d, diaphragm; e, esophagus; h, heart; t, thymus)
with irremediable delays due to anoxia. Observation of premature babies therefore cannot be taken as validation of the physiological evolutionary milestones of the foetal brain. Renewed interest in this field has been spearheaded by Kurjak, who foresees major clinical benefits for 4D study of foetal behaviour. We personally have studied the moment when laterality, the predominance of one hemisphere over the other, is established. Laterality has been the same all over the world for thousands of years. No scientific explanation of the predominance of the left over the right hemisphere has yet been found, if not an ancestral genetic mutation. Today there have been many papers, especially from Scandinavia, associating predominance of the right hemisphere, and hence predominant use of the left side of the body, with a significant increase in mental disorders. 4D scan enabled us to determine laterality in about 90% of fetuses between weeks 10 and 11.

Figs 87A and B: It is possible in the first trimester to study the bones of the skull. (A) Occipital bone at 12 weeks or the total skeleton with the spina; (B) The skeleton at 12th weeks by maximum mode

Figs 88A to H: The glass body tool enhance the fetal circulation and thoracic conformation (Abbreviations: a, aorta; p, pulmonary artery; vci, inferior vena cava; u, umbilical artery
Behavior, Senses and Response to Stimulation in the Second and Third Trimesters

As mentioned, much is now known about foetal behaviour at various gestational ages from the study of premature babies. However, the possibility of observing the foetus in its natural habitat in real time by 3-4D has led much research that may help us to assess foetal wellbeing and specifically, the degree of neurological development in physiological situations and in the presence of CNS pathology. It is fairly easy to detect a foetus who yawns, puts out its tongue, touches itself and its surroundings, developing its sense of touch, pulls faces after ingesting amniotic fluid (taste), opens its eyes (attempts at seeing?), responds to sounds (hearing), responds to manual stimulation (many sustain that parental stimulation of the foetus by stroking or patting the maternal abdomen leads to faster and more intense development of neuronal function), starts (from weeks 11 and 12 the foetus can be observed reacting whenever its fingers and toes touch the wall of the uterus), hiccups, smiles, grimaces, frowns and expresses pain or serenity. The foetus therefore sends us many messages through its behaviour. Though much progress has been made, no scientifically demonstrated clinical applications of behaviour have yet been developed. It is certainly fascinating for parents and specialists to observe a foetus by 4D, and it reinforces the hedonistic aspect of ultrasound examination in pregnancy.

REFERENCES

1. Dyson RL, Pretorius DH, Budorick NE, Johnson DD, Sklansky MS, Cantrell CJ, Lai S, Nelson TR. Three-dimensional ultrasound in the evaluation of fetal anomalies. Ultrasound Obstet Gynecol 2000;16(4):321-328.
2. Merz E, Bahlmann F, Weber G, Macchiella D. Three-dimensional ultrasonography in prenatal diagnosis. J Perinat Med 1995;23(3):213-222.
3. Merz E, Welte C. 2D and 3D Ultrasound in the evaluation of normal and abnormal fetal anatomy in the second and third trimesters in a level III center. Ultraschall Med 2005;26(1):9-16.
4. Pitu GL, Ghi T. Preliminary experience with advanced volume contrast imaging (VCI) and OmniView obstetric and gynecologist ultrasound. GE Healthcare, 2010.
5. Bonilla-Musoles F, Raga F, Osborne NG, Bonilla F Jr; Caballero O, Climent MT, Wallraf SH, Castello JC. Multimodality 3-dimensional volumetric ultrasound in obstetrics and gynecology with an emphasis in Hdlivetechnique. Ultrasound Q 2013;29(3):189-201.
6. Pooh RH, Kurjak A. Novel application of three-dimensional Hdlive imaging in prenatal diagnosis from the first trimester. J Perinat Med 2015;43(2):147-158.
7. Grigore M, Mares A. The role of Hdlive technology in improving the quality of obstetrical images. Med Ultraso 2013;15(3):209-214.
8. AboEllail MA1, Tanaka H1, Mori N1, Hanaoka U1, Hata T1. Hdlive silhouette mode in antenatal diagnosis of jejunal atresia. Ultrasound Obstet Gynecol 2015 Sep 4.
9. Forsberg F, Berghella V, Merton DA, Rychlak K, Meiers J, Goldberg BB. Comparing image processing techniques for improved 3-dimensional ultrasound imaging. J Ultrasound Med 2010;29(4):615-619.
10. Michailidis GD, Papageorgiou P, Economides DL. Assessment of fetal anatomy in the first trimester using two- and three-dimensional ultrasound. Br J Radiol 2002;75(891):215-219.
11. Xu HX, Zhang QP, Lu MD, Xiao XT. Comparison of two-dimensional and three-dimensional sonography in evaluating fetal malformations. J Clin Ultrasound 2002;30(9):515-525.
12. Downey DB, Fenster A, Williams JC. Clinical utility of three-dimensional US. Radiographics 2010;20(2):559-71.
13. Campbell S. Doppler and 3D ultrasound in infertility - do they alter the outcome for the patient? Ultrasound Obstet Gynecol Vol 22 suppl. 1;2003 pag. 24.
14. Rosignoli L, Periti E, Centini G. 3D Omniview sonography in the pre-assisted reproductive medicine programme. Ultrasound Obstet Gynecol 2010;36(Supp.l):52-167.
15. Timor-Tritsch IE, Fuchs KM, Montagudo A, D’Alton ME. Performing a fetal anatomy scan at the time of first-trimester screening. Obstet Gynecol 2009;113:402-407.
16. Hafner E, Metzenbauer M, Stumpflen I, Waldhör T, Philipp K. First trimester placental and myometrial blood perfusion measured by 3D power Doppler in normal and unfavourable outcome pregnancies. Placenta 2010;31(9):756-763.
17. Souka AP, Pilalis A, Kavalakis Y, Kosmas Y, Antsaklis P, Antsaklis A. Assessment of fetal anatomy at the 11-14-week ultrasound examination. Ultrasound Obstet Gynecol 2004;24:730-734.
18. Tonni G, Centini G, Taddei F. Can 3D ultrasound and doppler angiography arteries be included in second trimester ecocardiographic examination? A prospective study on low-risk pregnancy population. Echocardiography 2009;26(7):815-822.
19. Centini G, Sollazzi S, Rosignoli L, Ciani V, Imperatore A, Petraglia F, Lituania M, Tonni G. Capacità diagnostica eco-grafica dei processi mal formativi nel primo trimestre di gravidanza: è proponibile l’ecografia morfologica dalla 11a alla 14a settimana? Il Ginecologo 2010;5(1-2):22-29.
20. Merz E. Spina bifida aperta—detection of a shallow defect of the spine by 3D sonography. Ultraschall Med 2007;28(3):246-7.
21. Tonni G, Centini G. Three dimensional first-trimester diagnosis of alobarholoprosencephaly associated with anophacele in a 46,xx fetus. Am J Perinat 2006.
22. 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.
23. Chaoui R, Benoit B, Mitkowska-Woziak H, Heling KS, Nicolaides KH. Ultrasound Obstet Gynecol 2009;34(3):249-252.
24. Schramm T, Goning KP, Minderer S, Tutschek B. 3D ultrasound in fetal spina bifida. Ultraschall Med 2008;29(5):289-290.
25. Bicaldo CM, Muller MA, Zikulnig L, Schipper M, Hecher K. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. Ultrasound Obstet Gynecol 2001;17:288-294.
26. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol. 2004 Jul;191(1):45.
27. Matias A, Gones C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: the
role of ductus venous blood flow. Ultrasound Obstet Gynecol 1998;12:380-384.

28. Borrell A, Martinez JM, Serès A, Borobio V, Carrañach V, Fortuny A. Ductus venous assessment at the time of nuchal translucency measurement in the detection of fetal aneuploidy. Prenat Diagn 2003;23:921-926.

29. Matias A, Montenegro N. Ductus venous blood flow in chromosomally abnormal fetuses at 11 to 14 weeks of gestation. Seminars in Perinatology 2001;25:32-37.

30. Toyama JM, Brizot ML, Liao AW, Lopes LM, Nomura RMY, Saldanha FAT, Zugaib M. Ductus venous blood flow assessment at 11 to 14 weeks of gestation and fetal outcome. Ultrasound Obstet Gynecol 2004;23:341-345.

31. Gezer C, Echin A, Gezer NS, Ertas IE, Avuc ME, Uyar I, Ciftci S, Taner CE. Prenatal karyotype results of fetuses with nuchal edema, cystic hygroma, and non-immune hydrops. Clin Exp Obstet Gynecol 2015;42(5):586-589.

32. Chevernak FA, Isaacson G, Blakemore KJ, Breg WR, Hobbins JC, Berkowitz RL, Tortora M, Mayden K, Mahoney MJ. Fetal cystic hygroma: cause and natural history. N Engl J Med 1983;309:822.

33. Mathias B, Forrester BS, Ruth D. Merz MS. Descriptive epidemiology of cystic hygroma: Hawaii, 1986 to 1999. Southern Medical Journal 2004;97:631-636.

34. Bernstein HS, Filly RA, Goldberg JD, Golbus MS. Prognosis of fetuses with a cystic hygroma. Prenat Diagn 1991;11:349-355.

35. Podobnik M, Singer Z, Podobnik-Sarkanski S, Bulic M. First trimester diagnosis of cystic hygroma using translational ultrasound and cytogenetic evaluation. J Perinat Med 1995;23:283-291.

36. Rosati P, Guariglia L. Transvaginal ultrasound detection of septated and non-septated cystic hygroma in early pregnancy. Fetal Diagn Ther 1997;12:132-135.

37. Farkas LG, Katic MJ, Forrest CR, Litsas L. Surface anatomy of the face in Down’s syndrome: linear and angular measurements in the craniofacial regions. J Craniofac Surg 2001;12:373-379.

38. Stempfel N, Hutten Y, Fredouille C, Brisse H, Neussman C. Skeletal abnormalities in fetuses with Down’s syndrome: a radiographic post-mortem study. Pediatr Radiol 1999;29:682-688.

39. Rosignoli L. An early diagnosis of trisomy 18 by 2-3-4D at 10th week. Ultrasound Obstet Gynecol, London 3-7 September 2006.

40. Sonek J, Nicolaides KH. Prenatal ultrasonographic diagnosis of nasal bone abnormalities in three fetuses with Down syndrome. Am J Obstet Gynecol 2002;186:139-141.

41. Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11-14 weeks scan. Ultrasound Obstet Gynecol 2004;23:218-223.

42. Kelekci S, Yazicioglu HF, Oguz S, Inan I, Yilmaz B, Sommez S. Nasal bone measurement during the first trimester: Is it useful? Gynecol Obstet Invest 2004;58:91-95.

43. Peralta CF, Falcon O, Weszryn P, Faro C, Nicolaides KH. Assessment of the gap between the fetal nasal bone at 11 to 13+6 weeks of gestation by three-dimensional ultrasound. Ultrasound Obstet Gynecol 2005;May; 25(5):464-467.

44. Cicero S, Binda R, Rembouskos G, Spencer K, Nicolaides KH. Integrated ultrasound and biochemical screening for trisomy 21 at 11 to 14 weeks. Prenat Diagn 2003;23:306-310.
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78. Mulliken JB, Benacerraf BR. Prenatal diagnosis of cleft lip: what the sonologist needs to tell the surgeon. J Ultrasound Med 2001;20(11): 1159-1164.

79. Berkowitz S. Cleft lip and palate: Diagnosis and management. Berlin, Springer-Verlag, 2006.

80. Sherer DM, Sokolovski M, Santosu PG, Dalpoul M, Abulafia O. Nomograms of sonographic measurements throughout gestation of the fetal hard palate width, length and area. Ultrasound Obstet Gynecol 2004;24:35-41.

81. Shipp TD, Mulliken JB, Bromley B, Benacerraf B. Three-dimensional prenatal diagnosis of frontonasal malformation and unilateral cleft lip/palate. Ultrasound Obstet Gynecol 2002;20:290-293.

82. Centini G, Rosignoli L, Faldini E, Volotolini C, Tonni G. Comparison between three different methods of scan to visualize the secondary foetal palate by three-dimensional ultrasonography. 17th World Congress on Ultrasound in Obstetrics and Gynecology. Florence. ISUOG 2007

83. Centini G, Rosignoli L, Faldini E. L’ecografia del primo e secondo trimestre in 3D.: 82-104. Vol. Diagnosi Prenatale Ed Paletto. 2006.

84. Campbell S, Lees C, Moscoso G, Hall P. Ultrasound antenatal diagnosis of cleft palate by a new technique: the 3D “reverse face” view. Ultrasound Obstet Gynecol 2000;25(1): 12-18.

85. Platt LD, Devore GR, Pretorius DH. Improving cleft palate/ cleft lip antenatal diagnosis by 3-dimensional sonography: the “flipped face” view. J Ultrasound Med 2006;25:1423-1430.

86. Faure JM, Captop G, Baumlmer M, Boulou P. Sonographic assessment of normal fetal palate using three-dimensional imaging: a new technique. Ultrasound Obstet Gynecol 2007;29(2): 159-165.

87. Pilu G, Segata M. A novel technique for visualization of the normal and cleft fetal secondary palate: angled insonation and three-dimensional ultrasound. Ultrasound Obstet Gynecol 2007;29(2): 166-169.

88. Tonni G, Centini G, Inaudi P, Rosignoli L, Ginanneschi C, De Felice C. Prenatal diagnosis of severe epignathus in a twin: case report and review of the literature. Cleft Palate Craniofac J 2010;47(4):421-425.

89. Campbell S. Prenatal ultrasound examination of the secondary palate. Ultrasound Obstet Gynecol 2007, 29(2): 124-127.

90. Wilhelm L, Borgers H. The ‘equals sign’: a novel marker in the diagnosis of fetal isolated cleft palate. Ultrasound Obstet Gynecol 2010;36(4):439-444.

91. Cohen L, Mangers K, Grobman WA, Gotteiner N, Julien S, Dungan J, Fonseca L, Platt LD. Three-dimensional fast acquisition with sonographically based volume computer-aided analysis for imaging of the fetal heart at 18 to 22 weeks’ gestation. J Ultrasound Med 2010;29(5):751-757.

92. Ruano R, Martinovic J, Dommergues M, Aubry MC, Dumez Y, Benachi A. Accuracy of fetal lung volume assessed by three-dimensional sonography. Ultrasound Obstet Gynecol 2005;26(7):725-730.

93. Ruano R, Benachi A, Joubin L, Aubry MC, Thalbard JC, Dumez Y, Dommergues M. Three dimensional ultrasonographic assessment of fetal lung volume as prognostic factor in isolated congenital diaphragmatic hernia. Brit J Obstet Gynaecol 2004;111(5):423-429.

94. Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. The assessment of normal fetal liver volume by three-dimensional ultrasound. Ultrasound Med Biol 2003;29(8):1123-1129.
95. Rosignoli L, Periti E, Tonni G, Centini G, Tassinari M. VCI-Omniview e studio della colonna vertebrale. XVII Congresso Nazionale Società Italiana Ecografia Ostetrica-Ginecologica (SIEOG) 17-20 Ottobre Sorrento 2010.

96. Piliu GL, Ghi T. Preliminary experience with advanced volume contrast imaging (VCI) and OmniView obetric and gynecologist ultrasound. GE Heliccare 2010 White book.

97. Lauson S, Alvarez C, Patel MS, Langlois S. Outcome of prenatally diagnosed isolated clubfoot. Ultrasound Obstet Gynecol 2010;35(6):708-714.

98. Cafici D, Iglesias A. Prenatal diagnosis of severe hypospadias with two-and three-dimensional sonography. J Ultrasound Med 2002;21(12):1423-1426.

99. Costa J, Rice H, Cardwell C, Hutte Ag, Ong S. An assessment of vascularity and flow intensity of the placenta in normal pregnancy and pre-eclampsia using three-dimensional ultrasound. J MaternFetal Neonatal Med 2010;23(8):894-899.

100. Huster KM, Haas K, Schoenborn J, McVean D, Odibo AO. Reproducibility of placental volume and vasculature indices obtained by 3-dimensional power Doppler sonography. J Ultrasound Med 2010;29(6):911-916.

101. D’Elia A, Pighetti M, Moccia G, Santangelo N. Spontaneous motor activity in normal fetuses. Early Hum Dev 2001;65(2):139-147.

102. Robles de Medina PG, Visser GH, Huizink AC, Buitelaar JK, Mulder EJ. Fetal behaviour does not differ between boys and girls. Early Hum Dev 2003;73(1-2):17-26.

103. Kuno A, Akiyama M, Yamashiro C, Tanaka H, Yanagihara T, Hata T. Three-dimensional sonographic assessment of fetal behaviour in the early second trimester of pregnancy. J Ultrasound Med 2001;20(12):1271-1275.

104. Blaas HG, Eik-Nes SH. Sonoembryology and early prenatal diagnosis of neural anomalies. Prenat Diagn 2009;29(4):312-325.