

Antenatal Detection of Fetal Syndromes by Ultrasound: From a Single Piece to a Complete Puzzle

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ABSTRACT

There are hundreds of known fetal syndromes and their variant yet, the real occurrence for most of them is not quite known, only estimated. The real incidence is probably much higher, but many of them are lost due to natural selection early, in the first few weeks of existence. Novel technology, enables us also to exchange information and improve the team's cumulative knowledge. Detection of dysmorphic features and recognizable patterns of fetal malformations and diagnosing syndromes is still big challenge in prenatal as well as postnatal period.

Keywords: Dysmorphic features, Fetal sonographic assessment, Fetal syndromes, Medical ethics, Online databases, Prenatal, Recognizable patterns, Three-/four-dimensional ultrasound.

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INTRODUCTION

To be able to recognize abnormal, we have to be trained to recognize normal fetal appearance on ultrasound imaging and to distinguish one from the other. Knowledge of basic embryology (sonoembryology) and normal appearance of fetal anatomy in given gestational age is essential for understanding the relationship between normal and abnormal embryologic development

and dysmorphology.⁵⁴⁻⁵⁶ For sonographer this means training and practicing hands on, preferably with more experienced sonographer, which would be willing to share tips and tricks of scanning. As the technology and sonographers skills improve, higher the detection rate of fetal syndromes will be. Continuous education is very important to keep up with emerging new technologies, new diagnostic tools, especially in the field of ultrasound, so, this would be part of progress and not limitation. Common terminology used to describe fetal syndromes, sometimes may be confusing as wide variety of terms and definitions are used to describe it.

Defining a Fetal Syndrome

So, what exactly is a syndrome?

The term syndrome is derived from the ancient Greek word syndrome meaning running together.¹ Syndrome is the association of signs, symptoms, dysmorphic features, and/or behaviors which occur together in a specific pattern in the same individual. Syndrome is made of particular combination of major criteria, which are fundamental to the diagnosis and minor criteria, that are just occasionally present (may be absent).² Furthermore, it is important to make a distinction between a syndrome, a sequence and an association.

In syndromes, typically, anomalies, multiple malformations and/or sequences occur together in the recognizable pattern and they are result of a single (often genetic) abnormality (as in trisomy 18 = Edwards syndrome).

A sequence occurs when a single developmental defect results in a cascade of secondary defects, which may lead to tertiary defect and so on (Pierre-Robin sequence: mandibular hypoplasia, glossoptosis and cleft palate = Robin sequence).³ Sequence may be isolated or associated to unrelated defects or part of a known syndrome. It may also have multiple known causes. [Pierre Robin sequence (PRS) may have numerous (mostly still unknown) causes, such as recently identified genetic anomalies at chromosomes 2, 11, or 17].^{3,4}

Associations are nonrandom combination of birth defects, which may have resulted from a number of genetic factors (VATER association = vertebral anomalies, imperforate anus, and esophageal atresia with tracheoesophageal fistula).^{1,4} Clinical dysmorphology is

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the study of abnormal human development with specific accent on rare syndromes causing malformations or alterations in body form.² If there is one unusual feature (suspicion something is different from what we are use to see as normal) we should look further as there could be more. We also have to have in mind the possibility of numerous variations of normal, which sometimes can be recognized in parents too. There are few pathophysiologic mechanisms for fetal maldevelopment.

Malformation is commonly defined as a single localized poor formation of tissue that initiates a chain of subsequent defects (anencephaly). The recurrence risk for malformations generally range from 1 to 5%.⁴ Deformation is a result of extrinsic mechanical forces on otherwise normal tissue (abnormal faces, pulmonary hypoplasia, and limb contractures that result from prolonged oligohydramnios due to oligohydramnios or primary renal agenesis in Potter syndrome). Disruption results from an extrinsic insult, which destroys normal tissue altering the formation of a structure (Amniotic band syndrome). Dysplasia results if the primary defect is a lack of normal organization of cells into tissue (achondroplasia).⁴

Where to Find the Information?

Identifying one anomaly, raises suspicion in existence of more which could be part of a bigger picture as being a syndrome. The trigger to look for this could be known family history or earlier pregnancy with malformed fetus/infant, history of consanguinity, exposure to teratogenic drugs or other agent, trauma or just detecting abnormality by regular US scan.

It is almost impossible to memorize characteristics of all of the fetal syndromes. However, we do have tools to help us and we know which of those syndromes occur more often than the other. They all have specific patterns. Some can be seen by prenatal sonographic examination, diagnosed and confirmed antenatally or direct postnatally, and some do not. Some syndromes are so rare and complex that the definitive diagnosis would be given many years later.

In the last few decades there has been some major breakthrough in the medical research field assisted by impressive evolution of new technologies. Identifying and mapping all of the genes of the human genome is unquestionably one of them.⁵⁻⁷ A great advances has been made also in the field of noninvasive prenatal testing for early detection of fetal aneuploidy by commercially available tests using cell-free fetal DNA from maternal blood.⁸

The recognition of a set of anomalies as a potential syndrome, nowadays can be also aided by online available databases, such as London Dysmorphology Database (LDDDB) or Online Mendelian Inheritance in Man (OMIM) where, among other things, there is a genetic disorder catalog, with all the known syndromes and their features. Search and review genetic resources including POSSUM web, Orphanet and GeneReview. Each every of these help us in finding, diagnosing and better understanding syndromes in their specific way.

There is no doubt, ultrasound with all of its possibilities (2D, 3D, 4D, etc.) is one of the best noninvasive, powerful visualization tools we have available for prenatal detection of fetal anomalies and syndromes.^{85,86} HDlive Flow and HDlive Silhouette imaging (GE Voluson E10) are one of the latest innovation which brings a totally new perspective, as we will show in illustrations, in visualizing structures with exceptional quality and accuracy of imaging just by increasing silhouette mode (Figs 3 to 6). Recently published (Sept 2015) Donald School Atlas of Advanced Ultrasound in Obstetrics and Gynecology with over thousand full color images (including HDlive Silhouette and HDlive Flow technology) and expert comments, is a great synopsis of all up-to-date knowledge and technology available in ultrasound concerning fetomaternal medicine.⁸⁰

Evolution in ultrasound imaging technology allows us to assess not only the fetal anatomy to the smallest details, especially the fetal face,^{85,86} but also to follow the fetal behavior and test the functionality of the specific organs and whole systems. Great example of combining those two in one test was done in Kurjak's antenatal neurodevelopment (KANET) test introduced by Kurjak et al in 2008.⁹ Kurjak's antenatal neurodevelopment test is functional test for fetal brain, allows a systematic assessment of fetal neurobehavior, general movement and three signs (neurological thumb, small head circumference and overlapping sutures) that are considered postnatally as a markers, and may separate normal and abnormal behavioral patterns, that could prenatally indicate fetal brain impairment. Kurjak's antenatal neurodevelopment test should be performed in the 3rd trimester of pregnancy, between 28 and 38 gestational weeks. After validation,¹¹ and many multicenter studies in recent years, it is concluded that KANET test can be used in everyday clinical practice for the follow-up of fetuses at neurological risk with the strong recommendation for strict and reliable multidisciplinary postnatal follow-up till the corrected age of at least 3 years and longer whenever appropriate. This way, it is possible to make correlation of prenatal KANET scores with postnatal



neurodevelopmental outcomes.^{11,15} Kurjak's antenatal neurodevelopment test is performed with 4D ultrasound by licensed ultrasonographer for KANET test.⁹⁻¹¹

Very useful as a reference for a sonographer, prenatal diagnostician, to find out information about sonographic finding and differential diagnosis in fetal syndromes is B. Benacerraf's book of 'Ultrasound of fetal syndromes'.¹² Fascinating combination of science, research and new technologies is all together implemented in new research program on the way called: 'Give a face to a syndrome'.¹³

The Facial Dismorphology Novel Analysis (FDNA[®]) is a new technology that facilitates detection of facial dysmorphic features and recognizable patterns of human malformations (postnatal/adult life) to present comprehensive and up-to-date neurogenetic references available online.

Fetal syndromes may be classified on different basis. Typically they are divided in groups of major system involvement, such as syndrome featuring primarily facial anomalies or primarily featuring brain anomalies, craniosynostosis, limb abnormalities, skeletal dysplasia's ones which have in common intrauterine growth restriction or overgrowth or primarily soft-tissue anomalies.¹⁴ We will discuss few of them with typical sonographically recognizable patterns.

First Trimester Sonographically Detectable Anomalies Potentially Recognizable as Syndrome or Sequence

An optimized and systematic approach to the evaluation of the fetus is summarized in International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines for the basic examination.¹⁶ More detailed evaluation of fetal central nervous system (CNS) is indicated for pregnancies at high risk for CNS abnormalities (present in many syndromes) and fetal neurosonogram^{16,17} as well as KANET test should be offered to those.^{15,17} Suspected heart anomalies will require more comprehensive evaluation using fetal echocardiography.⁸³ The use of transvaginal high resolution ultrasound and 3D ultrasound added more accuracy in the fetal assessment and enabled early diagnosis of major fetal anomalies and syndromes.^{18,19}

It is commonly accepted that the single most effective marker of Down syndrome (trisomy 21) and all other major aneuploidies is increased nuchal translucency (NT) at 11 + 0 to 13 + 6 weeks. In combination with other well known parameters in the first trimester screening (maternal age, nasal bone, Doppler assessment of blood flow in the ductus venosus and across the tricuspid valve together with maternal serum free β -hCG and PAPP-A) more than 95% of all major aneuploidies can be identified.²⁰

There are some other anomalies that are frequently seen in fetuses with increased NT (>3.5 mm), such as

omphalocele, hernia diaphragmatica, body stalk anomaly and many syndromes and sequences, such as Noonan syndrome, Smith-Lemli Opitz, fetal akinesia deformation sequence, congenital adrenal hyperplasia and so on.

The intracranial translucency (IT) may be used as an ultrasonographic marker in the first trimester detection of open spina bifida. This is the space between the posterior margin of the brainstem and anterior margin of choroid plexus of fourth ventricle. The intracranial translucency may be absent in fetuses with open spinal canal defect. It is measured at the same period (11 + 0–13 + 6 weeks), in the same plane as that for NT and its parallel to NT (Fig. 1). In the second trimester, in most fetuses with open spina bifida, sonographically we may observe the squaring of the frontal bones (the 'lemon' sign) and caudal displacement and compression of the cerebellum with obliteration of cisterna magna (the 'banana' sign). These three signs, absent IT in 1st trimester and lemon and banana signs in 2nd trimester of pregnancy are the manifestations of (Arnold-) Chiari II malformation²¹⁻²⁴ (Fig. 2). Chiari malformation (I–IV) can be also part of some other syndromes, such as Marfan and Ehlers-Danlos syndrome, Craniocervical hypermobility syndromes, Klippel-Feil anomaly.

Frontomaxillary facial (FMF) angle measurement can be helpful in early detection of the fetuses with facial dysmorphic features, such as midface hypoplasia, which is present in many fetal syndromes (Down syndrome, Edwards syndrome, Patau syndrome and many craniosynostosis syndromes). This is recognized as a shallow FMF angle. The measurement is done in the first trimester, same period as NT and IT (11 + 0–13 + 6 weeks) and the image requirements are the same to those of NT and IT. The use of 3D ultrasound can be helpful in



Fig. 1: Two-dimensional conventional image of a fetus in midsagittal view; assessment of NT, IT and FMF in normal fetus following the Fetal Medicine Foundation criteria

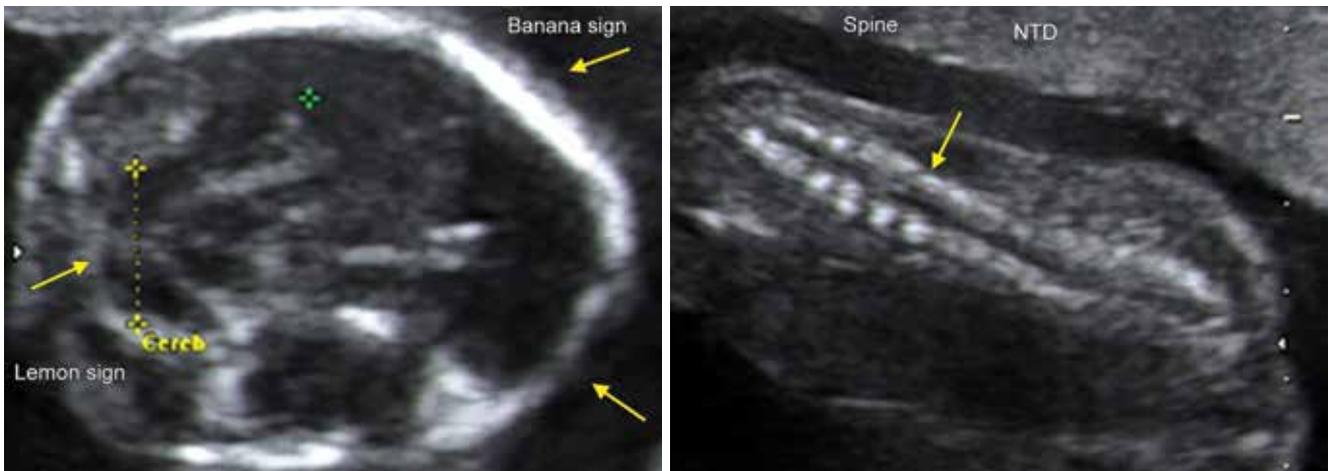
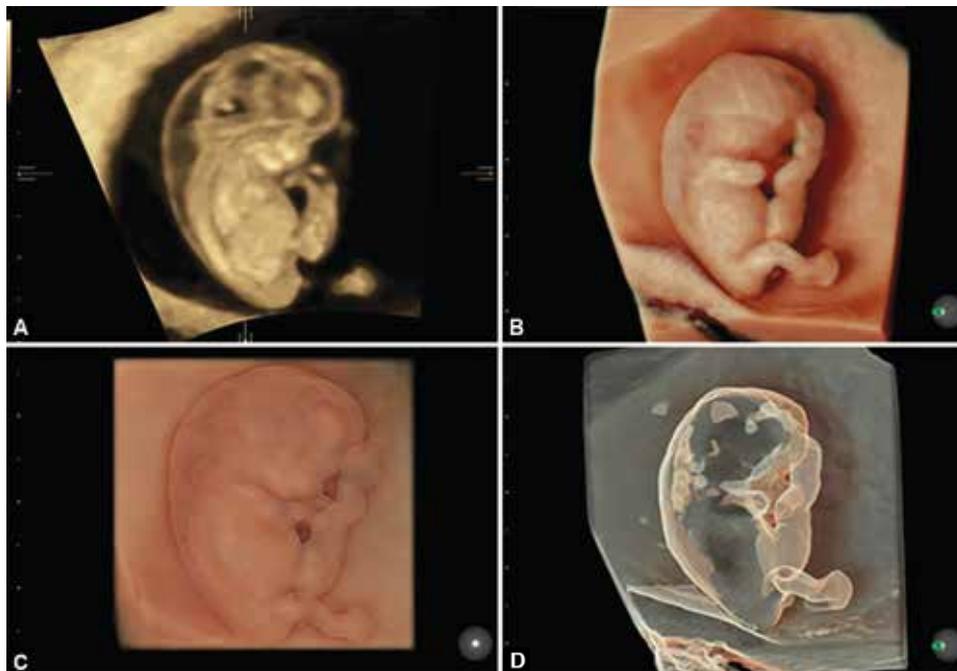


Fig. 2: Chiari type II malformation case with typical lemon and banana signs on the first image and NTD detected at 14 weeks of gestation on conventional 2D image



Figs 3A to D: Images of 9-week embryo with thick NT: (A) VCI sagittal image, increased NT is visible. (B-D)* HDlive silhouette images. With increased silhouette mode, translucent fetus is visible. (Note: Images with the permission of the publisher⁸⁰), *D: Noted the tiny cysts in the increased NT

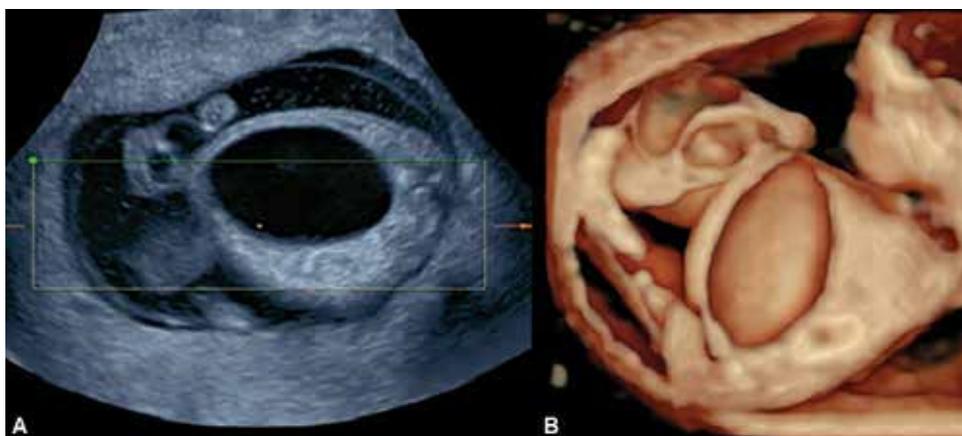
establishing the precise midline section as in the NT and IT measurements.^{25,26}

CLINICAL APPLICATION OF NEW US TECHNOLOGIES

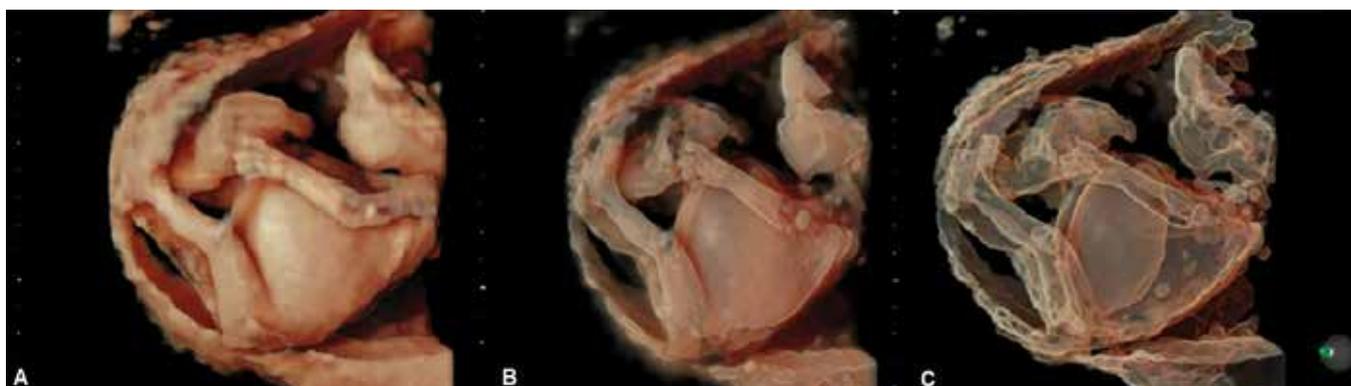
Euroscan group did a large study and collected data from 20 registries of congenital malformations in 12 European countries. They reported that about 50% of the recognized syndromes which are associated with major congenital anomalies (cardiac, renal, intestinal, limb defects, abdominal wall defects and oral clefts) can be detected prenatally by the anomaly scan.^{71,73} The detection rate varies with the type of syndrome and with the different countries policies of prenatal screening.^{66,76-78}

Three-dimensional compared with 2D ultrasound was done by Merz et al³⁰ and they examined large group of 3472 fetuses evaluated with detailed 2D and 3D US targeted for fetal anomalies. The total number of defects was 1012. Comparing the 2D and 3D technique, 3D US proved advantageous in 60.8% of the defects, which was related to the favorable demonstration of targeted areas in different views (e.g. multiplanar, surface).^{30,31} There is no doubt that 3D sonography can provide additional and more specific diagnostic information on high risk and normal fetuses.⁶⁰

Prune-Belly syndrome (PBS) is a rare, congenital, obstructive, urologic alteration that is associated with megacystic bladder and visible deformity(distention) of



Figs 4A and B: (A) 2D image and (B) 3D reconstructed image



Figs 5A to C: (A) HDlive silhouette images with increased, (B) silhouette mode, translucent fetus, (C) images with clearly visible distended bladder in Prune-Belly syndrome at 13 gestational weeks (*Note: Images with the permission of the publisher⁸⁰*)

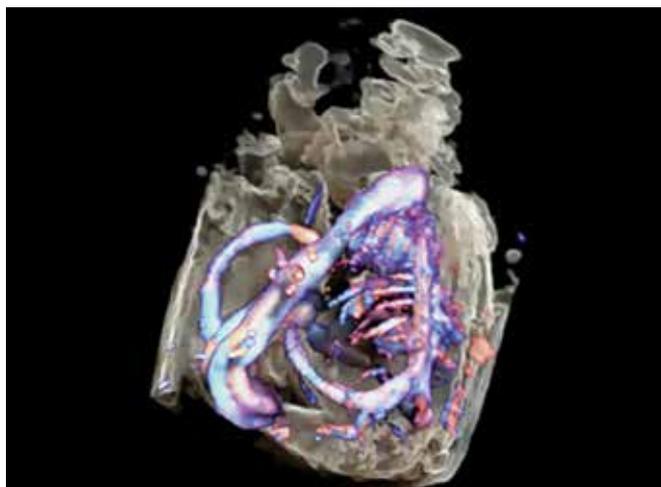


Fig. 6: Prune-Belly syndrome case at 13 gestational weeks, HDlive flow image of intracorporeal circulation (*Note: Images with the permission of the publisher⁸⁰*)

the abdominal wall (Figs 3 to 6). It is frequently associated with other fetal malformations. There is in addition renal hypoplasia (Fig. 7) or dysplasia and pulmonary hypoplasia.²⁷

The incidence of PBS is estimated to be 1 in 30,000 to 50,000 newborn babies, but it is likely to be greater since many fetuses die *in utero* or are aborted. More than 97% of cases are male and only males develop the complete

syndrome. The incidence is four times higher in twin gestations than in singleton pregnancies.²⁷

Syndromes Featuring Primarily Craniofacial Anomalies

These syndromes may be divided in different groups, such as orofacial clefting, craniosynostosis, abnormal development of different branchial arches and simply dysmorphic faces.² How do we decide what is normal and what is not if only discrete differences exist?

Although we all have the same basic features, we have our own distinguishing features and there is evidence that the brain (fusiform gyrus) has a specialized mental module dedicated to face processing. A researcher G Yovel at TAU's Department of Psychology is working on understand how the mechanisms of the fusiform gyrus process information about how we recognize faces and interpret facial expressions.

Dysmorphic fetuses are diagnosed by meeting the criteria which are also used in the postnatal assessment, such as shape of the head and closure of the sutures, asymmetry of the face, hyper-hypotelorism, low set or abnormal ears, micro or retrognathia by measuring the Jaw-Index,²⁸ malformations, such as cleft lip and palate.⁴³

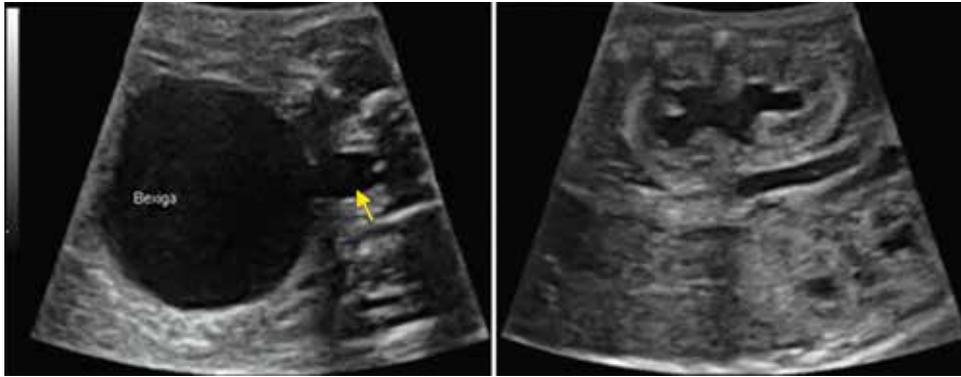


Fig. 7: Conventional 2D image of obstructed urinary tract with massive distention of bladder, megalourethra. The second image shows the same fetus with bilateral hydronephrosis and distended ureters in a case of Prune-Belly Syndrome (Courtesy: Dr RM Nieto)

Cleft lip/palate is one of the most frequent fetal anomalies. It can be an isolated finding (Fig. 8) (less than 50% of the fetuses) or combined with associated anomalies as part of a diverse syndromes. As an isolated defect it can be satisfyingly repaired with plastic surgery. Unfortunately, most fetuses with this anomaly have multiple severe abnormalities and high incidence of chromosomal anomalies. We can differentiate: bilateral complete cleft lip and palate which is easily identified even in 1st trimester, unilateral complete cleft lip and palate, incomplete cleft lip which has only subtle sign and can be easily overseen (Figs 9 to 11). Midline clefts are the most severe anomalies, regularly part of a severe sequence, such as holoprosencephaly and Patau (trisomy 13) and Edward's syndrome (trisomy 18), Aicardi syndrome.³³ Trisomy 13 is the most common chromosomal abnormality associated with alobar holoprosencephaly (facial anomalies: cyclopia, cebocephaly, flat nose and cleft lip). However, a 75% of holoprosencephaly has normal karyotype.²⁹

Mandibular anomalies are common in fetuses/neonates, and micrognathia has been described in more than 100 syndromes.^{4,35}

Micrognathia can be detected as an isolated structural anomaly, as one of the features of a chromosomal abnormality, or a syndrome. Teoh et al reported the prenatal diagnosis of severe micrognathia in a first trimester fetus with Pierre Robin sequence (PRS).³⁶ For diagnosing micrognathia, Jaw-index can be helpful. It is defined by the ratio between AP diameter of mandible and BPD. If the ratio is < 0.23 , diagnosis of micrognathia can be made.²⁸

The PRS primary defect is hypoplastic mandible (occurs between the 7th and 11th week of gestation) which initiate chain of subsequent anomalies due to more posteriorly located tongue that disturbs the physiological closure of the posterior soft palate. The prevalence of PRS is approximately 1 per 8500 live births. As an isolated finding it has a very good prognosis with appropriate care



Fig. 8: Isolated cleft lip at 19 GW detected with HDlive surface view (Note: Image with the permission of the publisher⁸⁰)



Fig. 9: HDlive image of the 21 GW fetus with unilateral left sided cleft lip and palate

and management.¹² The growth of the mandible catches up during the first year of life, however, mandibular hypoplasia resolves and the child attains a normal profile by approximately age of 5 to 6 years.³⁷⁻³⁹ As mentioned earlier, PRS can be feature of different syndromes, and the outcome will depend on the severity of the syndrome and its associated anomalies.¹²



Fig. 10: HDlive surface view of the fetus with Patau syndrome (21 GW) with midline cleft (Note: Images with the permission of the publisher⁸⁰)



Fig. 11: HDlive surface view of fetus with micrognathia, 21 gestational weeks, Pierre Robin sequence as part of a syndrome (Courtesy: Dr Sonal)

More than 40 syndromes with PRS have been described, the most common of which are Stickler syndrome (SS) and 22q11.2 deletion syndrome (Di George syndrome or Shprintzen syndrome). Evans et al (2006) reviewed 115 patients with PRS.³⁹ They have found that 54% (n = 63) of patients were nonsyndromic. Syndromic patients included: Stickler syndrome (18%), velocardiofacial syndrome (7%), Treacher-Collins (5%), facial and hemifacial microsomia (3%), and other defined (3.5%) and undefined (9%) disorders.³⁹

Detecting congenital micrognathia and low set ears together is not rare, on contrary, it is frequent finding especially in those cases with chromosomal aberrations and other syndromes. The connection/link between the two lies in the fact that they arise together from the first pharyngeal (branchial) arch.⁴⁰ Tsai et al reported assessment of the facial features, chin development and mandibular size by 3D ultrasound in the second and third trimesters.⁴¹ A short maxillary length has been associated with trisomy 21.⁴²

Detecting an abnormal shape of the head may be feature of different syndromes (Fig. 13). The 'Strawberry' shaped head is typical finding in Edward's syndrome.

'Lemon' shaped head is caused by a neural tube defect and Chiari II malformation and several syndromes. 'Cloverleaf' head shape is mostly found in skeletal dysplasia's, such as Thanatophoric dysplasia (most common skeletal dysplasia with small faces, short, bowed long bones, narrow chest, short ribs) (Fig. 12) and some syndromes characterized by craniosynostosis, such as Crouzon and Pfeiffer syndrome.⁴³

Craniosynostosis is caused by premature closure of fetal skull sutures and depending on which ones are involved, they result in different shapes of the head. By premature closure and fusion of coronal, sagittal and lambdoid sutures, acrocephaly (the top of the skull assumes a cone shape) is the result as seen in Crouzon syndrome (along with micrognathia, hyperhypotelorism, occasionally with agenesis of corpus callosum, cleft lip and palate). Synostosis of coronal and sagittal sutures results in brachycephaly as seen in Apert (high forehead, flat faces, hypertelorism, ACC, mild ventriculomegaly, syndactily of the 2nd, 3rd and 4th fingers = 'mitten hand', cardiac defects and variable degrees of mental retardation); Carpenter (depressed nasal bridge, micrognathia and low set ears, cardiac



Fig. 12: Three-dimensional image of fetus with Thanatophoric dysplasia

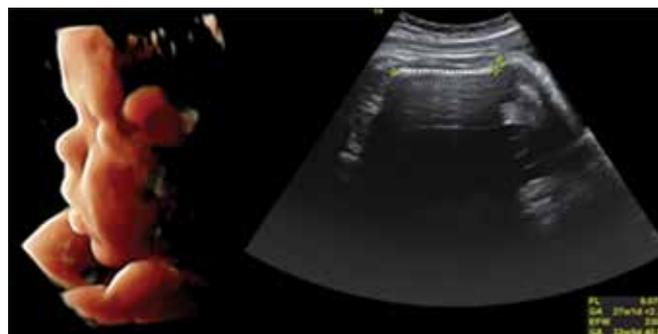


Fig. 13: HDlive surface view of fetal face, fetus suspected of Achondroplasia, notice frontal bossing and depressed nasal bridge; second image by conventional 2D, shows very short femur (length appropriate for 27 GW) at 34 weeks of gestation



Fig. 14: Conventional 2D image of gastroschisis due to Amniotic Band Syndrome: fetal anterior abdominal wall defect with multiple bowel loops fluting free in the amniotic fluid (Courtesy: Dr RM Nieto)

defects, omphalocele, clinodactily, synpolydactyly) and Pfeiffer syndrome (sometimes cloverleaf skull, depressed nasal bridge, hypertelorism, broad hallux and thumb, occasional ventriculomegaly and cardiac defects). Syndromic craniosynostosis are all autosomal dominant conditions. They are differentiated by presence/absence of associated anomalies or by molecular analysis of fetal deoxyribonucleic acid (DNA).⁴⁴

Frontal bossing may be seen in Russell-Silver syndrome (along with asymmetric IUGR of the skeleton with normal size head, short stature) or Achondroplasia (Fig. 13) (rhizomelic limb shortening, autosomal dominant condition usually not apparent until late in 2nd trimester).

Skull asymmetry can be seen in Wolf-Hirschhorn syndrome (deletion 4p) also called 'Greek warrior helmet' syndrome because of the appearance of the forehead. Incidence is estimated at 1 in 50,000 births. However, this may be underestimated because it is likely that some affected individuals are never diagnosed. It affects twice as many females as males. Typical face with hypertelorism, broad, flat nasal bridge continuing to the forehead, micrognathia and microcephaly along with ACC, cleft lip and palate, IUGR are some of the features that may be detectable by ultrasound.

Another syndrome which may cause skull asymmetry is Amniotic Band Syndrome (sequence) (Fig. 14) initiated by premature rupture of the amnion (most likely before 12 weeks of gestation), resulting in wide variety as well as severity of destructive processes depending on where the amniotic band comes into contact (facial clefting, encephalocele, asymmetric anencephaly, micrognathia, gastroschisis, limbs defects and amputations and so on).

When a prenatal diagnosis of multicystic dysplastic kidney (MCDK) (Fig. 16) is made by ultrasound, the disease is found to be bilateral in many cases. Those with bilateral disease often have other severe deformities or multisystem malformation syndromes. In bilateral cases, there are typical features of Potter's syndrome⁴⁵ (Figs 15 and 16). The incidence of MCDK is estimated to be 1 in every 4,000 live births, making it rare in terms of the general population.^{45,46}

Meckel Gruber syndrome is lethal autosomal recessive condition, due to pulmonary hypoplasia and neonatal renal failure infants die within a first few days of their life.

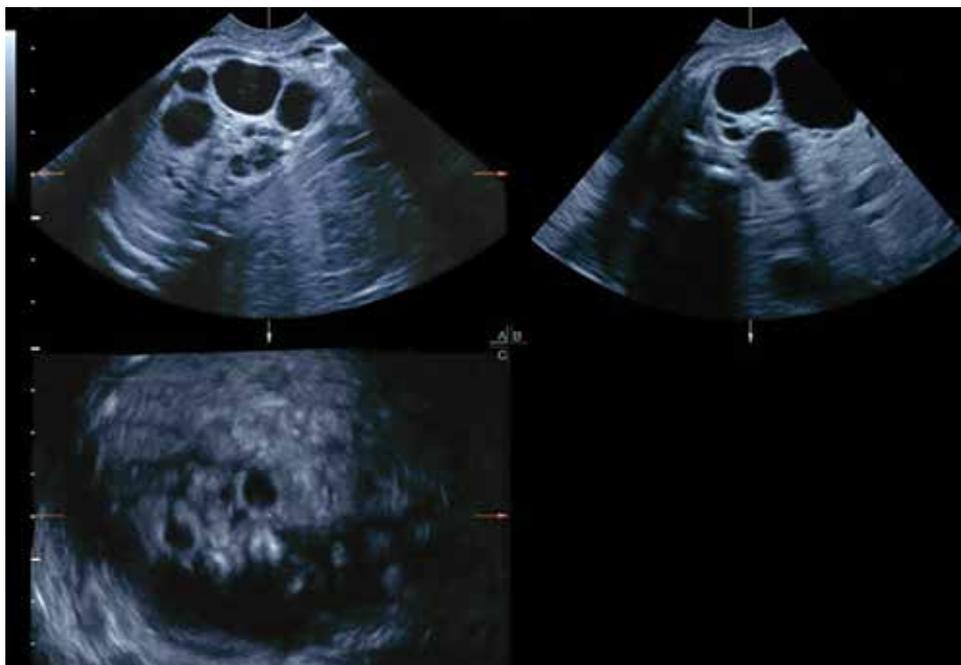


Fig. 15: Conventional 2D split image of fetus and MCDK = Multicystic Dysplastic Kidney, at 26 weeks of gestation, suspected of Potter syndrome

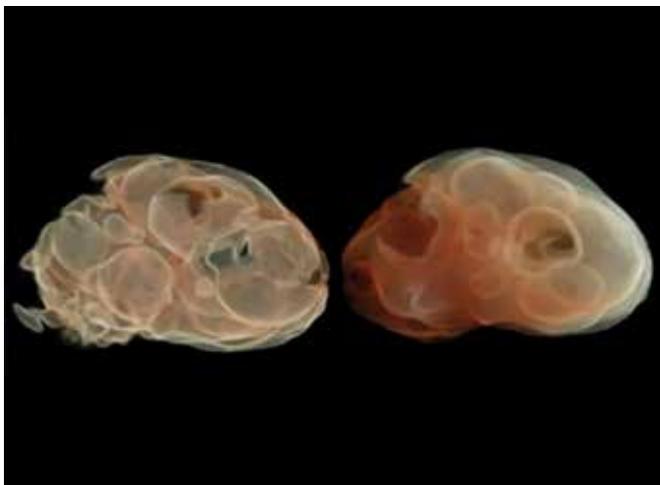


Fig. 16: Multicystic dysplastic kidney at 26 gestational weeks HDlive silhouette images volume extraction (GE, Voluson E10) (Note: Images with the permission of the publisher⁸⁰)

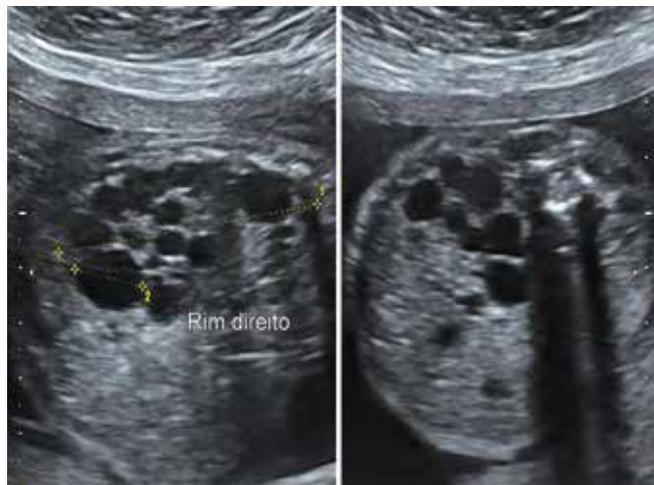


Fig. 17: Two-dimensional conventional split image of fetus with cystic dysplasia of the kidneys at 25 GW, found in fetus with Meckel Gruber syndrome. (Courtesy: Dr RM Nieto)

Typical triads of anomalies pathognomic of this syndromes are occipital encephalocele, cystic renal dysplasia (Fig. 17) and polydactyly. First trimester detection of occipital encephalocele has been often reported. Indeed, due to the normal amount of amniotic fluid early in pregnancy it is much easier to make diagnosis than later in the second trimester as oligohydramnios progresses and this anomalies can be overlooked. If encephalocele is diagnosed, fetal kidneys should be carefully examined. The normal sonographic findings of the kidneys rules the lethal Meckel Gruber syndrome out.⁴⁸ For patients with suspicious findings on basic examination and/or increased risk of CNS abnormalities, fetal neurosonogram should be offered as well as KANET test in 3rd trimester.^{15,17}

Dandy walker malformation (DWM) is posterior fossa abnormality (Figs 18 to 21) that occurs as a part of well known and recognizable syndromes: Walker-Warburg syndrome or Mechel's syndrome which both are associated with chromosomal aberrations.²⁹

Blomley et al⁴⁸ showed songraphically that the closure of cerebellar vermis take place early in the second



Fig. 18: HDlive image of DWM suspected at 16 weeks of gestation. Note the abnormal dilatation of posterior fossa (arrow)

trimester (14–18 GW). Even though diagnosis of Dandy Walker malformation should not be made before the 18th week of gestation, sometimes suspicion can exist as early as from 11 weeks of gestation, trisomy 9 mosaicism was confirmed by amniocentesis in that particular case.²⁹

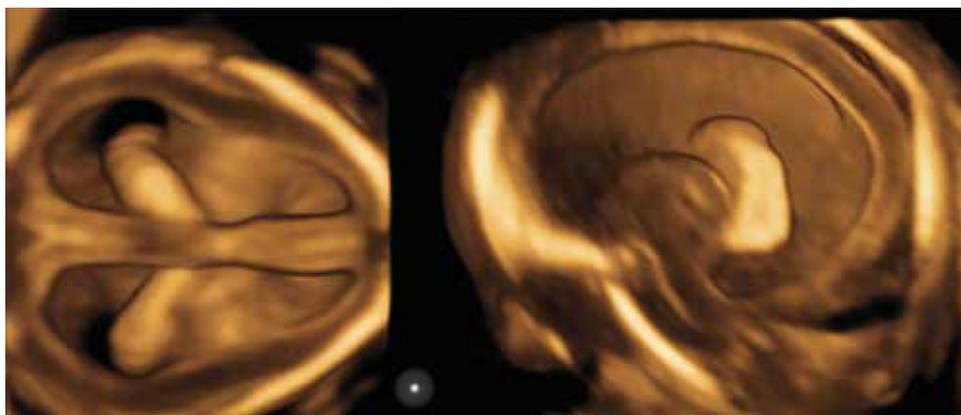


Fig. 19: HDlive image of DWM with ventriculomegaly and demonstration of well preserved choroid plexus

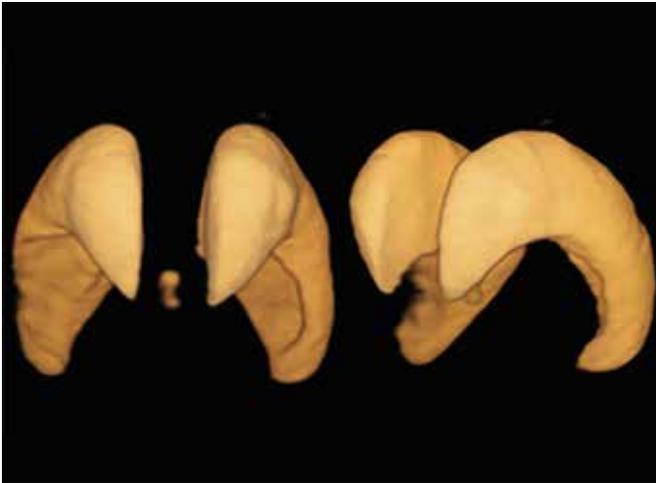


Fig. 20: Three-dimensional volume extraction of the lateral ventricles by inversion mode in ventriculomegaly case of DWM

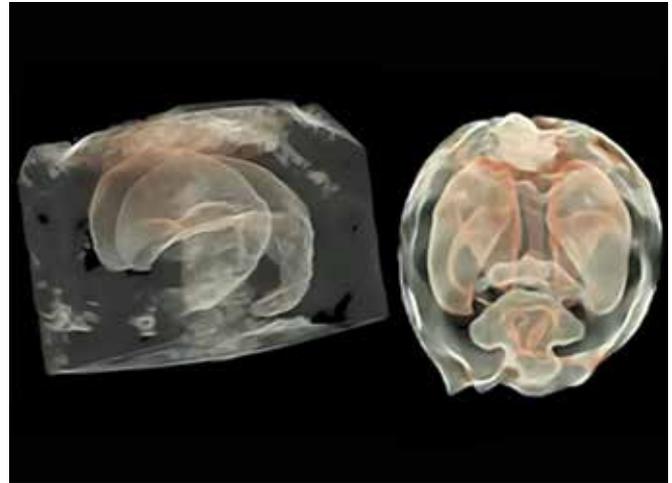


Fig. 21: HDlive silhouette (GE, Voluson E10) in DWM case demonstrating increased volume of 3rd and 4th ventricles in ventriculomegaly at 13 GW (Note: Images 18 to 21 with the permission of the publisher⁸⁰)

Syndromes Featuring Chromosomal Anomalies

According to their etiology, syndromes can be divided in chromosomal or nonchromosomal. A chromosome anomaly, abnormality, aberration, or mutation (Fig. 22) is a missing, extra, or irregular portion of chromosomal DNA. A karyotype refers to a full set of chromosomes from an individual. Humans are diploid species: Two complete haploid sets, which make up 23 homologous chromosome pairs so, typical human somatic cell contains 46 chromosomes. There are many types of chromosome anomalies. Basically, they can be divided into two major groups: numerical and structural anomalies.

Numerical chromosomal abnormality can be aneuploidy or polyploidy.

Aneuploidy: An individual is missing either a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).

Polyploidy: More than two sets of chromosomes per nucleus. Aneuploidy can be either autosomal = happens in autosomes (trisomy 21) (Figs 23 and 24) or sexual = happens in sex chromosomes (e.g. Turner syndrome monosomy X0). Trisomies can occur with any chromosome, but often result in miscarriage, rather than live birth. Trisomy 16 is the most common trisomy in human pregnancies, occurring in more than 1% of pregnancies; only those pregnancies in which some normal cells occur in addition to the trisomic cells (mosaic trisomy 16) survive. This condition, however, usually results in spontaneous miscarriage in the first trimester.⁴⁹

Triploid syndrome (polyploidy) is a chromosomal disorder. A fetus with triploidy has three haploid sets of chromosomes, a total of 69 (instead of the normal 46 chromosomes). Only 1 in 10,000 infants is born with triploidy, and it is estimated that for every live-born infant with triploidy, 1,200 have been lost as miscarriages. There



Fig. 22: Three-dimensional US image of fetus with Pena Shokeir syndrome or FADS, a Fetal Akinesia Deformation Sequence. Biallelic mutations in different genes have been identified in these patients (pseudo-trisomy 18), at 28 gestational weeks, with hyperextension contractures of the lower limbs and on the second image same fetus with arms in fixed flexed position with both clenched hands and camptodactyly. Dysmorphic face with micrognathia (Courtesy: Dr Sonal)



Fig. 23: Two-dimensional image of fetus with duodenal atresia, 'Double Bubble sign' seen in Down syndrome (Courtesy: Dr RM Nieto)



Fig. 24: Three-dimensional surface view of fetus (34 weeks gestation) with low set ears in Down syndrome (Courtesy: Dr Sonal)



Fig. 25: Three-dimensional image of club foot in surface and maximum mode, fetus with diagnosed Edward's syndrome (Courtesy: Dr Sonal)



Fig. 26: Three-dimensional image of 17 weeks fetus with both clenched and club hands and feet diagnosed with Edward's syndrome (trisomy 18) (Courtesy: Dr Sonal)



Fig. 27: HDlive image surface view of fetus with Edward's syndrome. Notice clenched hand and overlapping fingers (Courtesy: Dr Sonal)

are no risk factors. Couples who have one pregnancy with Triploidy do not have an increased risk in future pregnancies. Triploidy is not hereditary.

Fetuses with structural anomalies often have chromosomal anomaly too. Trisomies are present in 50% of the cases, monosomies in 25%, mosaicism in 10 to 15% and in few percentages of the cases left, usually there is triploidy or miscellaneous aneuploidie.^{81,82}

Nicolaidis et al⁵⁰ have found that fetuses with more than one anomaly are more likely to have chromosomal abnormality, respectively, with one anomaly risk is 2%, with two anomalies 11%, with five anomalies increasing to as high as 66% and with eight anomalies risk jumps to 92%.

Edwards syndrome (Trisomy 18), very well-known syndrome, characterized by multiple organ system malformations. Incidence is 3:10 000 live births. First trimester most common finding is cystic hygroma and lymphangiectasia of fetal head, neck, scalp and so on. In early second trimester some of the detectable anomalies



Fig. 28: Three-dimensional surface view image of fetus with clenched hand detail, Edward's syndrome (Courtesy: Dr Sonal)

include clenched hands (Figs 26 to 28), club feet, (Fig. 25) omphalocele, major cardiac defects, micrognathia and low set ears, choroid plexus cyst.⁴³



Fig. 29: Two-dimensional conventional image of the fetus with cystic hygroma colli, Turner syndrome (Monosomy XO) (Courtesy: Dr RM Nieto)



Fig. 30: Two-dimensional image of fetus with hydrops fetalis at 14 gestational weeks; Turner syndrome was confirmed (Courtesy: Dr RM Nieto)

Choroid plexus cyst is seen in 30 to 50% of the fetuses with trisomy 18. Although trisomy 18 occurs in 1:100 fetuses with choroid plexus cyst, if it is an isolated finding, as Gross et al⁵¹ reported results from the meta-analysis, the risk of trisomy 18 falls on 1:374. Identifying an open hand while scanning can be very helpful finding, as most fetuses with Edward's syndrome are unable to unclench their hands.^{43,51}

Cystic hygroma colli frequently has a chromosomal abnormalities, such as Turner (Fig. 29) and Down syndrome as the underlying cause. Other associated anomalies often found are fetal hydrops (Fig. 30), such as severe subcutaneous edema and pleural effusion.

Nonchromosomal syndromes can be caused by wide variety of agents, some of them are infective agent (Rubella syndrome, CMV syndrome, Parvo B19⁵⁹ and so on), teratogenic drug (Antiepileptic drugs, such as Valproate acid or Phenytoin, some vitamins: Vit A) or addictive substance: alcohol (Fetal Alcohol syndrome).⁵⁸⁻⁶³

On the basis of lethality, fetuses as well as neonates with congenital anomalies and syndromes can be divided into six groups: (1) those who have the potential for total recovery, (2) those with anomalies that would allow for a nearly normal life, (3) those with malformations requiring permanent supervision and/or medical care, (4) those with somatic rest defect and subnormal mental development, (5) those with serious somatic and mental damage, and (6) those with anomalies that are incompatible with life.⁵²

After identifying anomalies and suspect a syndrome, there is next difficult thing. How to explain this to the parents? Naturally, parents are always expecting healthy child. Dealing with difficult situation of having malformed infant with incurable state is distressing and emotionally exhausting either the diagnosis is made pre- or postnatally.^{53,84}

Parents expect you to tell them what it means, the prognosis, recurrence risk, etc. Pediatric books, such as 'Smith's recognizable patterns of human malformations'¹⁴ five is very helpful in providing more detailed information about this.

It would be much easier for the infant's parents and healthcare provider to begin communication before birth. The ability to provide as clear information as possible is of great importance, to avoid confusion in parents, as well as other healthcare providers involved in the care. The aim of this communication between parents and healthcare provider is: to make parents understand the condition of the child, to put everything in the prospective: to inform them about the fetal prognosis, provide genetic counseling, inform them about the need for invasive testing,⁶⁴ discuss the obstetric management plan, short- and long-term neonatal prognosis, neonatal management decisions, possibilities of the treatment, and finally to provide them with the information about the prognosis and outcome.^{67,68} As we mentioned before, as soon as it becomes feasible to identify anomalies at the prenatal stage, questions are raised also about what can and what should be done.^{67,68}

Ethical issues involved. Modern medicine is facing the problem of the possibility to extend the life of many newborns with virtually lethal congenital malformations or other rare diseases, however, the possibility does not always justify the opportunity.⁶⁸ The potential of modern medicine to preserve life of the sickest newborns should not be overestimated, because it raises many ethical issues, which are still waiting to be solved. Why fetal surgery should be restricted to conditions that are life-threatening to the fetus? The obvious answer is to protect mothers. Women should not have to undergo surgery unless it is absolutely necessary.^{68,69}

If major malformations cause stillbirth or infant death in more than 50% of cases, they are considered lethal. If newborn infant with major congenital malformation cannot survive without medical intervention, than malformation is considered severe.⁷⁰

CONCLUSION

From 2D, 3D, 4D to 5th element in recent years it become increasingly difficult to keep up and stay on top of major research development. With a modern communication possibilities, almost in a instant manner, we find, assess and share scientific information easier and quicker than ever before.

Tremendous expansion of possibilities and available diagnostic tools (that can assist us in recognizing fetal anomalies and syndromes) in daily clinical practice, helps us to incorporate and process all the information, use the knowledge to form a unique conclusion in our brain which is the 5th element to complete the whole picture. In a such way, while working, we sharpen our senses, improve our efficiency, increase productivity and finally bring the quality of our work to another level.

We have to keep on improving the technology as well as our skills as it gives as opportunity to research and understand new things. As Vincent van Gogh once wrote... 'After all, there's nothing in the world as interesting as people, and one is never done with studying them.'⁷⁹

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