Morphogenetic assessment of the fetus using ultrasound in the first trimester of pregnancy. Can we save money and time?

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Abstract

Objective. *The purpose of our study was to reconsider the complete diagnostic protocol in some selected cases, highly suspected after first trimester anatomical and biochemical evaluation.* ***Method.*** *We used the three-year data from a first trimester morphologic and genetic prospective study conducted in three university clinics. We considered the first trimester (11-14 gestational weeks) morphological and biochemical findings in the affected singleton pregnancies. The diagnostic of the chromosomal abnormalities was made using quantitative fluorescence polymerase chain reaction (QF-PCR) and multiplex ligation-dependent probe amplification (MLPA) techniques after chorionic villous sampling (CVS) and the genetic results were confirmed by karyotyping.* ***Results.*** *In the vast majority of the cases multiple first trimester morphological markers were found in association to chromosomopaties (90.9%). In almost half of the cases (45.4%) more than six anatomical features were found abnormal and also the biochemical risk was increased. In these cases, the genetic techniques were concordant with the ultrasound morphological presumptive diagnosis. In all these patients we noted a high degree of anxiety related to the time needed for completion of genetic assessment.* ***Conclusions.*** *We consider that an alternative approach in certain socio-economic settings is termination of pregnancy (TOP) followed by genetic diagnostic in cases with ultrasound evaluation revealing typical morphological / functional features for genetic syndromes and altered serum biochemistry.*

Keywords: *first trimester scan, combined test, fetal morphology, genetic markers*

Introduction

Due to technologic improvement of ultrasound machines, the introduction of new markers increased the ability of calculating a more accurate fetal-risk of having a chromosomal anomaly. Thus, fetal medicine has been given a higher role in prenatal care, and physicians are asked to meet the challenges of working in this very important field. Until the early 80's, the most important factor upon which a pregnant woman was investigated for chromosomal anomalies was the maternal age: women over 35 years old were given amniocentesis as the main method of detecting fetal anomalies[(1)]. The introduction of maternal biochemical markers was considered an important step in screening[(2-7)]. The evaluation of nuchal translucency (NT) in early 90's and afterwards the second level ultrasonographic markers - nasal bone (NB), tricuspid regurgitation (TR), ductus venosus measurement (DV), fronto-maxillary facial angle (FMF angle) have imposed high stardards of detection especially in combination with biochemical markers[(11-16)].

The morphological assessment of the fetus increased the efficiency of the genetic screening[(17-21)] and represents an important target of the ultrasound in pregnancy. This is stated as the primary aim of the 18-20 gestational weeks scan in guidelines on routine prenatal care[(22)], but the technical advances allowed the first trimester (11-13 gestational weeks) scan to evolve over the last decades from essentially a scan for measurement of fetal nuchal translucency (NT) and crown-rump length (CRL), to one which includes a summary of the fetal anatomy, with the intention of diagnosing the major abnormalities. Consecutively, anomalies such as absent/hypoechogenic nasal bone, multiple plexus choroid cysts, holoprosencephaly, cystic hygroma, diaphragmatic hernia, cardiac malformations, exomphalos/laparoschisis, single umbilical artery, megacystis have been carefully investigated in large first trimester population groups and proved to be valuable assets in the detection of the chromosomal anomalies in both first and second trimester, as reported in literature[(17-21)].

The purpose of our study was to consider an alternative to the complete diagnostic protocol (containing genetic counseling - ultrasonographic morpho-genetic assessment - biochemical serum investigation - invasive genetic manoeuvres in the high-risk cases - karyotiping/DNA techniques - TOP after a variable time), in cases with typical morpho-

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logic and serologic features for genetic syndromes. In the particular condition of healthcare systems that are not able to financially sustain the genetic investigations, it could lead to financial burden on family budget and additional time needed for genetic confirmation.

Methods

We used the three-year data from a first trimester morphologic and genetic prospective study conducted in our centers between January 2008 and March 2011. Our aim was to investigate the findings of the first trimester combined test (biochemical and sonographic investigation) in the affected pregnancies. Three University public clinics were involved, and sonographers with extensive experience in first trimester genetic screening carried out the morphogenetic scans. The research protocol was approved by each University's Ethics Committee (Figure 1).

Ultrasound evaluation

It consisted in first trimester scan (11-14 gestational weeks) in unselected singleton pregnancies, with detailed ultrasound evaluation (fetal morphology and genetic markers) (Table 1).

Acquisition of ultrasound markers was achieved by Fetal Medicine Foundation certified sonographers using the ultrasound machine Voluson 730 Pro, GE Medical Systems Kretztechnik, ZIPF Austria.

Biochemical parameters

Maternal blood was investigated for biochemical parameters (PAPP-A and free beta-hCG) and evaluation of the genetic risk used Wallac LifeCycle 3, PerkinElmer Life and Analytical Sciences software equipment.

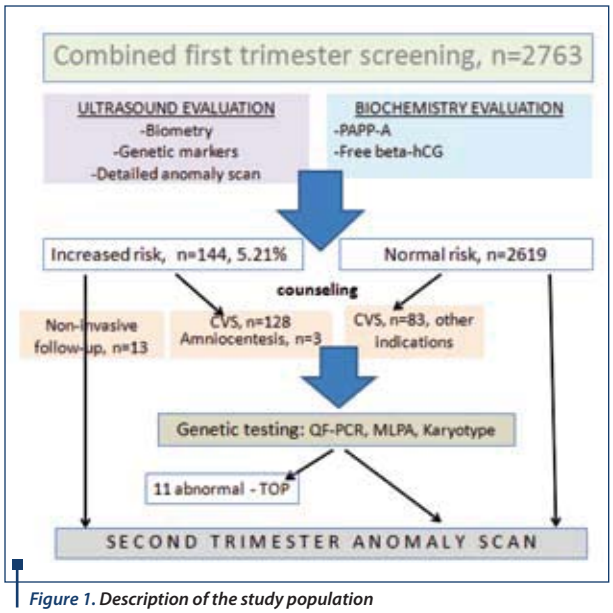

Figure 1. Description of the study population

Prenatal genetic testing for aneuploidy

The prenatal testing of aneuploidy was carried out on chorionic villus samples using two different PCR-based methods in two independent laboratories: quantitative fluorescence polymerase chain reaction - QF-PCR (Genetic Lab, Bucharest) and multiplex ligation-dependent probe amplification - MLPA (Laboratory of Molecular Genetics, University of Medicine and Pharmacy Craiova). All the QF-PCR and MLPA data were compared with the karyotyping results.

All subjects were informed about the aim of using MLPA and QF-PCR for rapid prenatal screening for aneuploidies. All procedures were performed after counseling and written consent of the patient was obtained.

For MLPA testing the human genomic DNA was extracted from trypsin-digested CVS using the Wizard® Genomic DNA Purification Kit (Promega). In order to detect aberrant copy numbers of chromosomes 13, 18, 21, X and Y we amplified polymorphic microsatellite markers along these human chromosomes. We used SALSA MLPA kit P095-A2 Aneuploidy (MRC-Holland) that includes 36 MLPA probes with amplification products between 130 and 454 nucleotides as well as 9 control fragments[8]. MLPA fragments separation and detection were carried out on the Beckman 8000 capillary electrophoresis system.

The quantitative fluorescence PCR (QF-PCR) is now widely used for rapid prenatal diagnosis of the common trisomies[9]. The fetal DNA was extracted using CVS and the QIAamp® DNA Mini Kit according to the manufacturers' recommendations (QIAGEN). Approximately 10-30 ng of fetal DNA were used in a multiplex QF-PCR based technique currently available in our laboratory for the rapid prenatal detection of trisomy 13, 18, 21 and sex chromosomes' aneuploidies. The test is developed based on the published data of Kathy Mann, Erwin Petek and Barbara Pertl and includes specific primers for 26 sequences from the five chromosomes listed above[10]. The PCR products ware separated and visualized by capillary electrophoresis using the automated ABI PRISM® 310 Genetic Analyzer (Applied Biosystems) and GeneMapper® ID Software v3.2, Applied Biosystems. The results interpretation was performed based on the criteria presented in the "Professional guidelines for clinical cytogenetics and clinical molecular genetics - QF-PCR for the diagnosis of aneuplidy best practice guidelines".

The results were obtained in 24 hours after chorionic villi sampling procedure.

Results

The combined screening investigational protocol (ultrasound scan and biochemical profile) was applied in 2763 cases. Using a cut-off risk in screening assessment of 1/250, 144 pregnancies (5.21% of the entire studied population) were

Table 1 Ultrasound protocol for first trimester morphological assessment of the fetus

Standard planes	Targets of evaluation
Central Nervous System	
Sagittal view of the face	Visualization of fetal profile and nasal bone; measurement of facial angle. Sagittal visualization of sphenoid bone, brain stem, choroid plexus of the fourth ventricle and measurement of intracranial translucency.
Transverse plane of cranium at the level of choroid plexus	Cranium shape and contour; Choroid plexus aspect and median septum.
Transverse plane of cranium at the level cerebral peduncles	Cerebral peduncles aspect (angulations/parallelism).
Oblique-transverse plane of cranium at the level of cerebellum	Cerebellum aspect with special care in curvature.
Sagittal plane of spine on the CRL section	Regularity/irregularity of spine. Presence of cystic masses.
Fetal face	
Transverse/slightly oblique planes of cranium at the level of orbits	Orbits symetry and demonstration of both lenses. Anterior maxilla and when possible upper lip integrity.
Frontal plane	Retronasal triangle (Sepulveda), orbits and lenses if better resolution than in transverse approach.
Cardio-vascular assessment	
Transversal cardiac sweep gray-scale	■ Abdominal situs with the stomach in the left abdominal side and aorta to the left of the spine; ■ The four chambers of the heart with the heart lying on the left side angled at 45° from the midline, occupying one quarter of the chest; atrioventricular valve offsetting; ■ The aorta arising centrally in the heart from the left placed ventricle and crossing to the fetal left side over the ascending aorta; ■ Interventricular septum; when possible - septo-aortic continuity in the left outflow view; ■ The anteriorly positioned ductal arch, converging with the transverse aortic arch on the left side of the fetal spine, with aproximative similar size.
Color-flow Doppler investigation (in order to increase the accuracy and to shorten the examination time)	■ Equal filling of both ventricles in the four chambers view ■ Emergence of aorta with deduction of septo-aortic continuity based on the entire aortic flow arising from the visualized left ventricle; ■ Arterial duct outflow: visualization with power Doppler. 'X' sign (the crossing of the main pulmonary artery with the aorta); ■ The transversal course of the two arches: 'b' sign (the straight line of the pulmonary artery surrounded by aortic arch, when possible with three epiaortic vessel images); 'V' sign (the connection of the aorta and ductus arteriosus).
Pulsat Doppler - investigation (assessment of functional parameters)	■ Tricuspid valve flow assessment, searching for significant regurgitation (occupying at least half of systole and with velocity >80 cm/s). ■ Ductus venosus flow assessment searching for reversed "a"-wave.
Pulmonary areas and diaphragm	
Sagittal, coronal or axial planes	Echogenicity of pulmonary areas. Presence of diaphragm.
Skeleton	
Sagittal, coronal or axial planes	Arms and feet with visualization of the segments and number of digits. Movement assessment.
	Cranium and spine contour, shape, mineralization.
	Thorax shape and subjective dimensions.
Abdomen	
Sagittal and axial planes	**Digestive system** ■ Abdominal situs: stomach and aorta identification. ■ Liver and bowel echogenicity. ■ Abdominal insertion of umbilical cord. **Reno-urinary system** ■ Visualization of both kidneys. In case of poor visualization, Color Doppler was used to highlight the renal arteries. ■ Identification of pyelectasia when present. ■ Bladder and lateral identification of the two umbilical arteries when color Doppler is applied.
Genitals	
Sagittal and axial planes	Determination of fetal sex was not mandatory, but rather at the couple's request.

Table 2 Chromosomaly abnormal cases detected during the study period. Morphological and biochemical features

Nr.	Chromosomal abnormality Detected by molecular methods and classical karyotyping	Morpho-functional abnormal features	Biochemistry results
1	Trisomy 21	absent NB	PAPP-A 0.62 Corr.MoM hCG 1.87 Corr.MoM
2	Trisomy 21	increased NT exomphalos.	PAPP-A 0.71Corr.MoM hCG Corr.MoM
3	Trisomy 21	increased NT, increased FMF, renal pyelectasia, hyperechogenic bowel.	PAPP-A 0.52 Corr.MoM hCG 3.41 Corr.MoM
4	Trisomy 21	increased NT, absent NB, reversed "a" wave in DV.	PAPP-A 1.31 Corr.MoM hCG 2.65 Corr.MoM
5	Trisomy 21	increased NT, atrio-ventricular septal defect, tricuspid regurgitation.	PAPP-A 0.74 Corr.MoM hCG 2.38 Corr.MoM
6	Trisomy 21	increased NT, absent NB, tricuspid regurgitation, reversed "a" wave in DV, increased FMF, exomphalos containing liver, SUA. (Figure 2)	PAPP-A 1.51 Corr.MoM hCG 5.13 Corr.MoM
7	Trisomy 21	increased NT, absent NB, tricuspid regurgitation, reversed "a" wave in DV, megacystis, atrio-ventricular septal defect. (Figure 3)	PAPP-A 0.83 Corr.MoM hCG 4.24 Corr.MoM
8	Trisomy 18	increased NT, increased FMF, bilateral multiple choroid plexus cysts, diaphragmatic hernia, single umbilical artery unilateral forearm lesion (radial hypoplasia), fixed hands in flexed position. (Figure 4)	PAPP-A 0.34 Corr.MoM hCG 0.93 Corr.MoM
9	Trisomy 18	increased NT, absent NB, exomphalos containing liver.	PAPP-A 0.68 Corr.MoM hCG 0.56 Corr.MoM
10	Trisomy 13	laparoskisis, holoprosencephaly, early growth restriction, abnormal heart, low heart rate. (Figure 5)	PAPP-A 0.32 Corr.MoM hCG 0.92 Corr.MoM
11	Monosomy X	severe edema of the head, neck, thorax and abdomen, omphalocele, umbilical cord cyst, diminutive left ventricle, hypoplastic aortic arch. (Figure 6)	PAPP-A 0.41 Corr.MoM hCG 1.38 Corr.MoM

NT, nuchal translucency; NB, nasal bone; DV, ductus venosus; FMF, fronto-maxillary (facial) angle; SUA, single umbilical artery

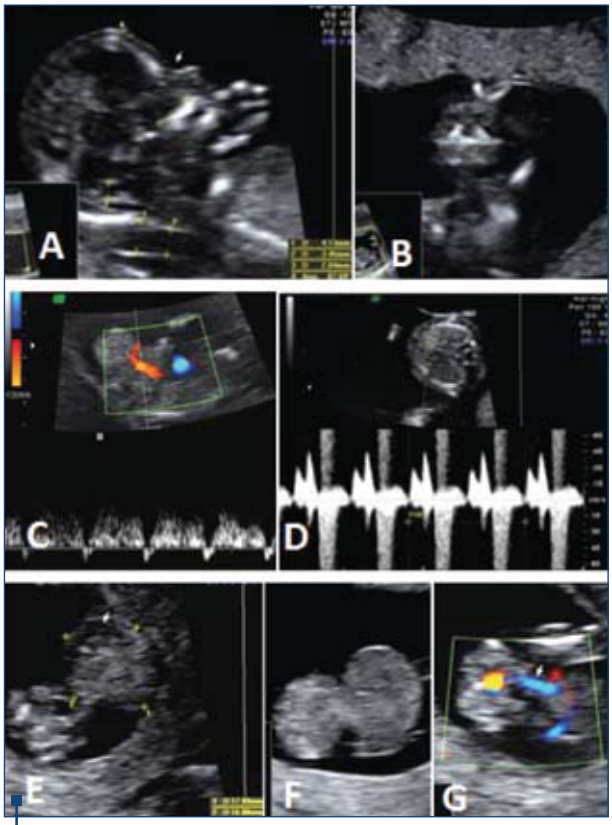

Figure 2. Fetus presenting morpho-genetic T21 markers. A: sagittal sectional plane of the fetal face showing increased nuchal translucency, increased facial angle and absent nasal bone. B: coronal plane confirming the absence of the nasal bone at the level of the retronasal triangle. C: reverse "a" wave in ductus venosus assessment. D: assessment of the tricuspid valve, showing tricuspid regurgitation. E, F: persistent large exomphalos evidenced in transverse sectional planes of the fetal abdomen. G: single umbilical artery

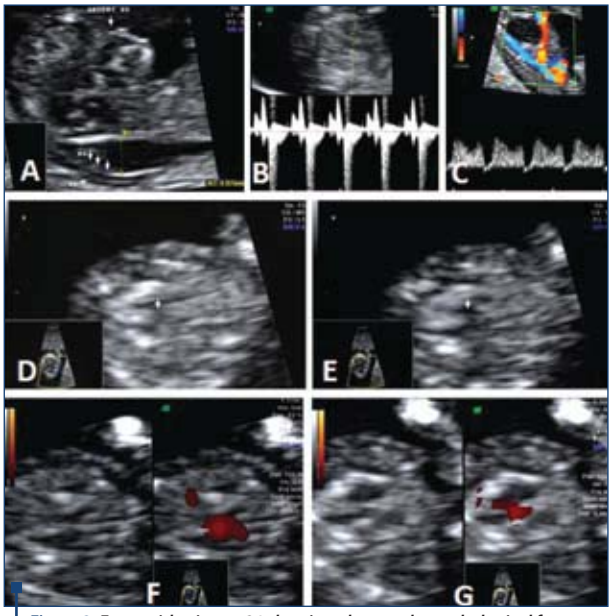

Figure 3. Fetus with trisomy 21 showing abnormal morphological features at 11-14 weeks genetic screening. A: sagittal sectional plane of the fetal face showing increased nuchal translucency and absent nasal bone. B: assessment of the tricuspid valve, showing tricuspid regurgitation. C: sagittal sectional plane of the fetal trunk: reverse "a" wave in ductus venosus assessment by color and pulsed Doppler assessment; megacystis (longitudinal diameter 14.1mm) is obvious in the same plane. D,E: axial plane at the level of the fetal thorax, at the level of the cardiac four-chamber view, suggesting septal defect (arrow). F,G: duplex display (gray-scale and power Doppler) confirming the suspected septal defect

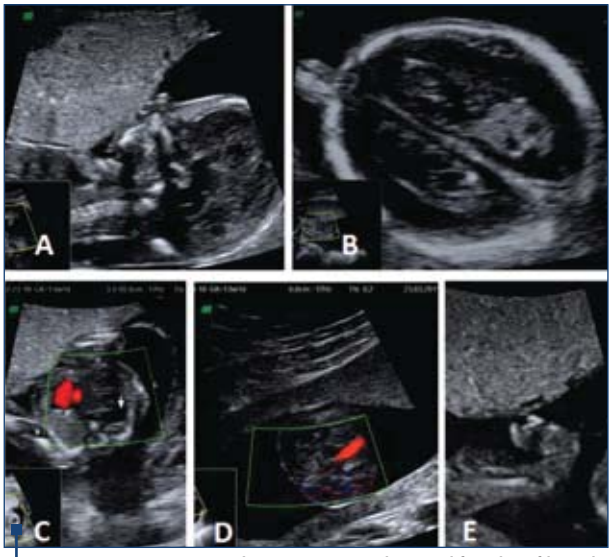

Figure 4. Trisomy 18 in early pregnancy. A: abnormal facial profile and nuchal edema, absent nasal bone. B: multiple choroid plexus cysts. C: axial plane of the fetal thorax with dextroposition of the fetal heart and presence of the stomach in the thorax, both suggesting diaphragmatic hernia. D: single umbilical artery crassing lateral to the fetal blader. E: skeletal abnormality of the fetal arm and persistent hand malposition

screened positive and in the rest of 2619 women the screening was negative (Figure 1). After genetic counseling 128 of the 144 screened-positive pregnant women consent with invasive genetics (88.8%) and 11 chromosomal abnormalities were found, representing 0.39% of the studied pregnancies. From the screen-negative group, 83 invasive maneuvers - CVS (chorionic villus sampling) were performed (Figure 1), mainly for suspected structural anomalies and the rest at the couples' request following the genetic counseling provided by our Genetics department, before the first trimester genetic screening. In this group we did not encounter any chromosomal abnormalities, using the same genetic protocol of investigation.

Second trimester anomaly scan was performed in all pregnancies from the studied group, except the 11 terminated pregnancies with chromosomal abnormalities.

We present the characteristics of the affected pregnancies in Table 2; all chromosomal abnormal pregnancies were terminated at parents' request in a median interval of 13 days after the diagnosis.

QF-PCR

We analyzed five STR for chromosome 21 - D21S11 (21q21.1), D21S1437 (21q21.1), D21S1409 (21q21.2), D21S1435 (21q21.3) and D21S1411 (21q22.3), six mar-

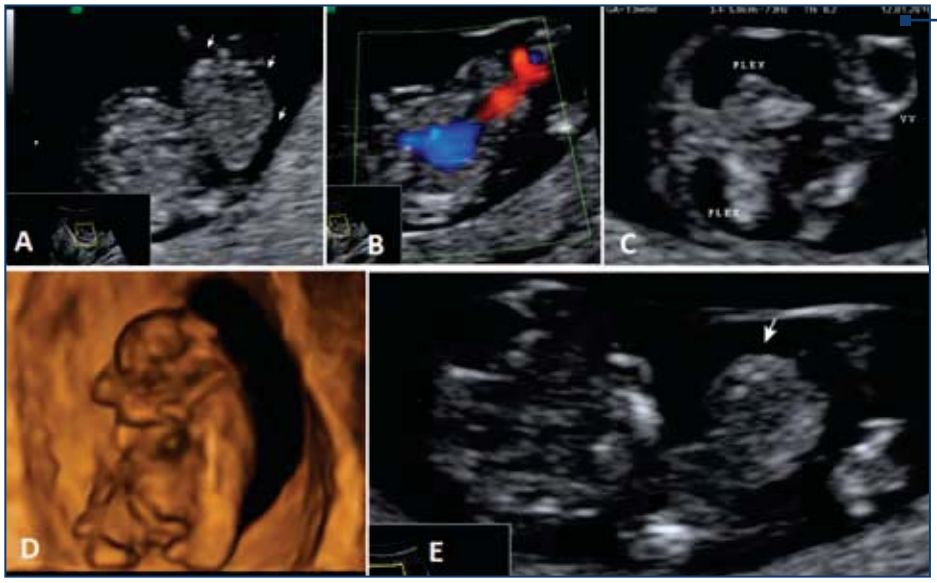

Figure 5. Fetus affected by trisomy 13. A, B: laparoskisis with large exomphalos in gray scale (A) and color Doppler applied (B) to highlite the course of the umbilical vein. C: abnormal cranium and choroid plexus shape and failure in visualizing the normal median septum. D: 3D rendering - surface mode confirming laparoskisis. E: parasagittal view of the affected fetus: abnormal neuronal structures and abdominal defect (arrow).

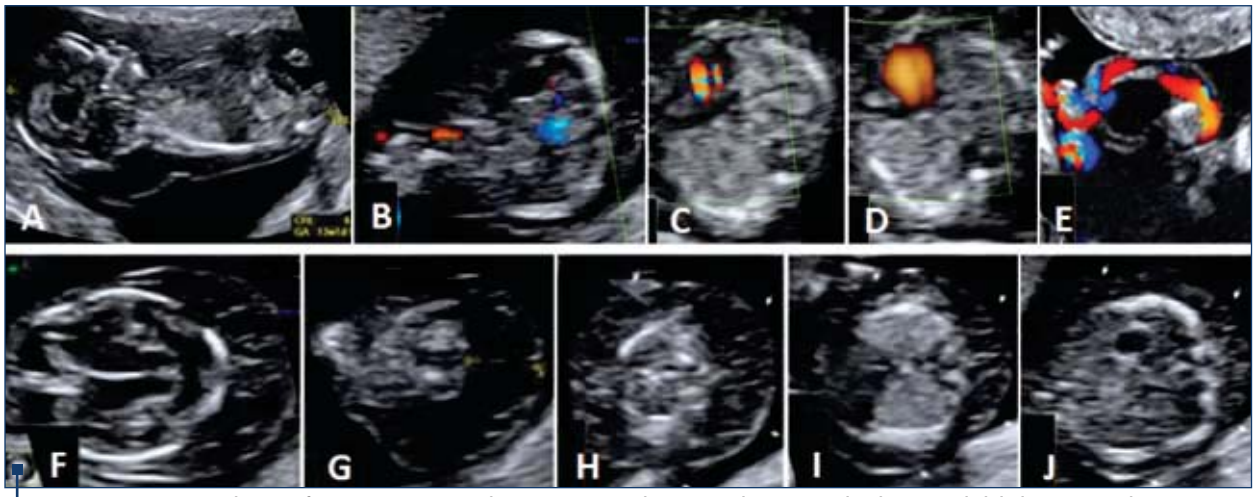

Figure 6. Turner (XO) syndrome in fetus presenting cystic hygroma at 13 weeks. Severe edema is visualized in sagittal global view (A), and transverse views of the head (F), neck (G), thorax (H, I) and abdomen (J). Omphalocele (B) and umbilical cord cyst (E) were also noted. C: Color Doppler at the level of the four-chamber view demonstrating filling of the both left and right ventricles during diastole, confirming the patency of the atrio-ventricular valves; a diminutive left ventricle was remarqued. D: Power Doppler at the level of the four-chamber view; a narrow width of the left ventricle in comparison to that of the right ventricle was confirmed, and a hypoplasia of the aortic arch was further suspected, cardiac anomaly which is sometime associated with Turner syndrome

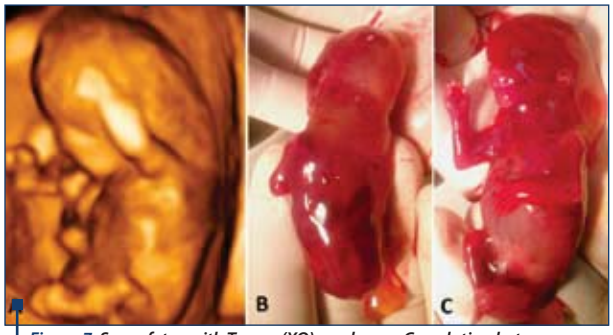

Figure 7. Same fetus with Turner (XO) syndrome. Correlation between in vivo 3D assessment (A) and pathologic aspect after medical induced abortion in posterior (B) and anterior (C) views

kers for chromosome 18 - D18S386 (18q22.1), D18S390 (18q22.3), D18S391 (18q11.31), D18S535 (18q12.3), D18S819 (18q11.2), D18S978 (18q12.3), five markers on chromosome 13 - D13S252 (13q12.1), D13S305 (13q13.3), D13S628 (13q31.1), D13S634 (13q21.33), D13S325 (13q12.12) and ten for sex chromosomes - DXS6807 (Xp22.3), DXS981 (Xq13.1), DXS1187 (Xq26.2), XHPRT (Xp26.2), DXS7423 (Xq28), DXYS267 (Xq21.31; Yp11.31), AMEL (Xp22.2/Yp11.2), SRY (Yp11.31), DYS448 (Yq11.223), DXS1283 (Xp22.3)[10].

MLPA

We used 8 probes for each of the chromosomes 21, 18, X and four probes detecting the human Y

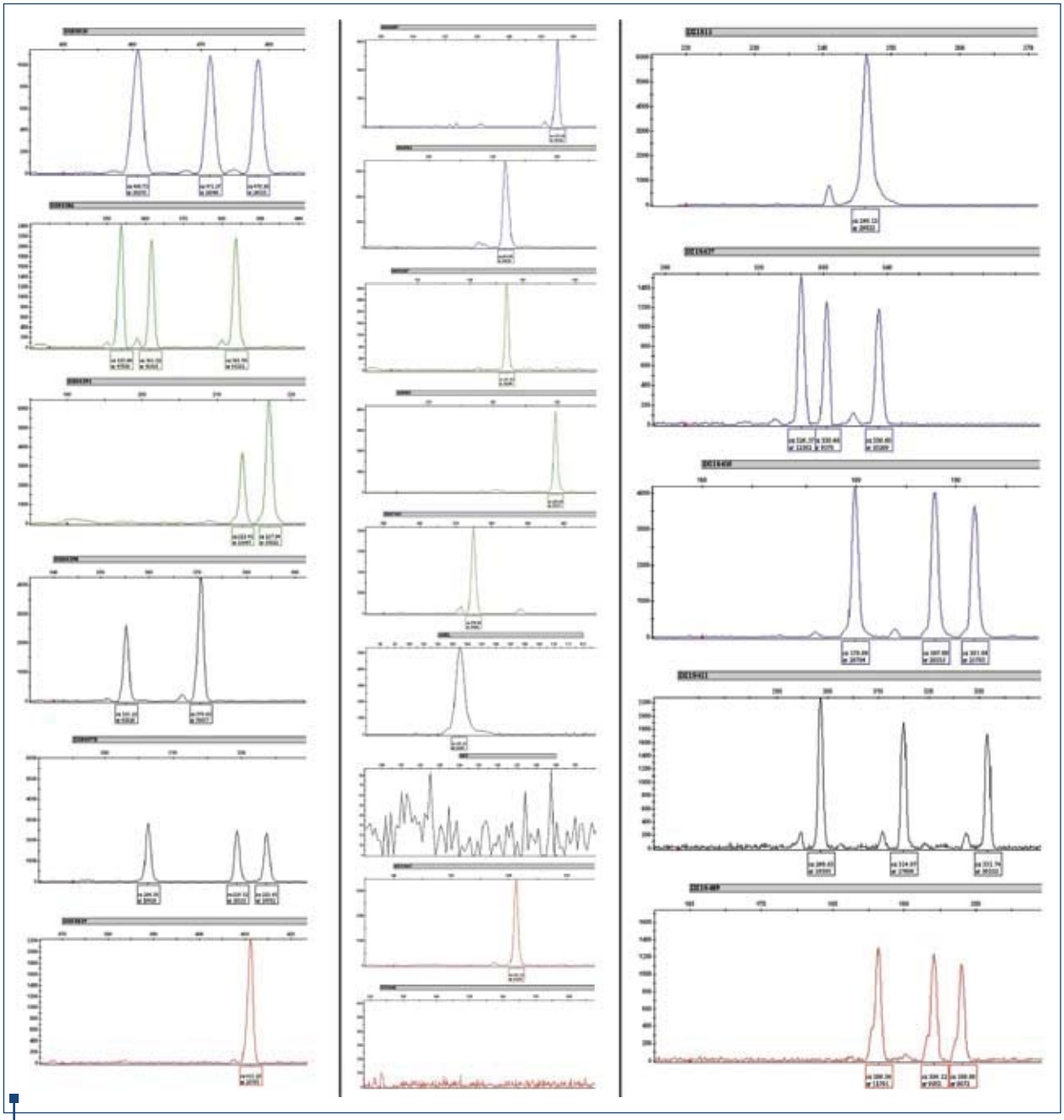

Figure 8. Results of the QF-PCR technique: A. Trisomy 21; B. Trisomy 18; C: Monosomy X

chromosome. Heterozygous deletions of recognition sequences gave a 35-50% reduced relative peak area of the amplification product of that probe (Figures 2-7). For the reported case of monosomy X deletions of the probes' recognition sequences on the X-chromosome led to a 35-50% reduction in relative peak area.

We detected the targeted fetal aneuploidies, with at least two informative (heterozygous) markers on every chromosome tested: 21, 18 and X (see Figure 8 for QF-PCR and Figure 9 for MLPA). The monosomy X patient exibits a monoallelic pattern for all X chromosome' specific markers and the absence of the Y chromosome' markers.

Discussion

In Table 3 is noted the evolution of prenatal genetic screening. Initial polices have emphasized the maternal age as the main factor for invasive procedures. The introduction of serum screening has opened a new, un-invasive way of detecting fetal anomalies and has led to an improvement in detection rate to 75%. Morphological markers and then the use of

Table 3 Evoluation of the detection rate (DR) and false-positive rate (FPR) according to additional functional ultrasound markers

Evaluated markers	Chromosomal anomalies Detection Rate (DR)	
NT alone[12]	76.9%	
NT+PAPP-A+free β-HCG[12]	87% DR at a 5% FPR	
NB alone[12]	69% DR at a 1.4% FPR	
NB+NT+PAPP-A+free β-HCG[11]	92% DR at a 2.9% FPR	
NB+NT+PAPP-A+free β-HCG[13]	97% DR at a 5% FPR	91% DR at a 0.5% FPR
NT+FHR+PAPP-A+free β-HCG[14]	Trisomy 21 - 91% DR at a 3% FPR; Trisomy 13, 18, Turner syndrome 100%	
TR+ NT+FHR+PAPP-A+free β-HCG[14]	Trisomy 21 - 96% DR; Trisomy 18 - 92% DR; trisomy 13, Turner syndrome 100%	
DV+ NT+PAPP-A+free β-HCG[15]	Trisomy 21 - 96% DR at a 2.6% FPR	
NT+PAPP-A+free β-HCG[16]	90% DR at a 5% FPR	85% DR at a 3% FPR
FMF angle+NT+PAPP-A+free β-HCG[16]	94% DR at a 5% FPR	92% DR at a 3% FPR

Table 4 Morphological markers useful in chromosomal anomalies detection

Morphological markers	Chromosomal anomalies Detection Rate (DR)	
Single umbilical artery[17]	■ 3.3% normal fetuses ■ 11.4% trisomy 21 ■ 77.8% trisomy 18 ■ 9.5% other chromosomal defects	
Megacystis[18]	Φ=7-14mm associated with 25% chromosomal defects	Φ>15mm associated with 10% chromosomal defects (invariably associated with progressive obstructive uropathy)
Exomphalus[19]	**Useful in trisomy 18 detection**	
	11-14 week scan - 60% incidence Mid-gestation - 30% incidence Neonates - 15% incidence	
Choroid plexus cysts, pyelectasis and cardiac echogenic foci[20]	**Useful in trisomy 21 detection**	
	sensitivity 18%, specificity 98%, positive predictive values 13%, and negative predictive values of 98%	
Fetal heart rate (FHR)[21]	**Useful in trisomy 13 and 18 detection**	
	Trisomy 13 and Turner syndrome presents tachycardia	Trisomy 18 and triploidy presents bradicardia

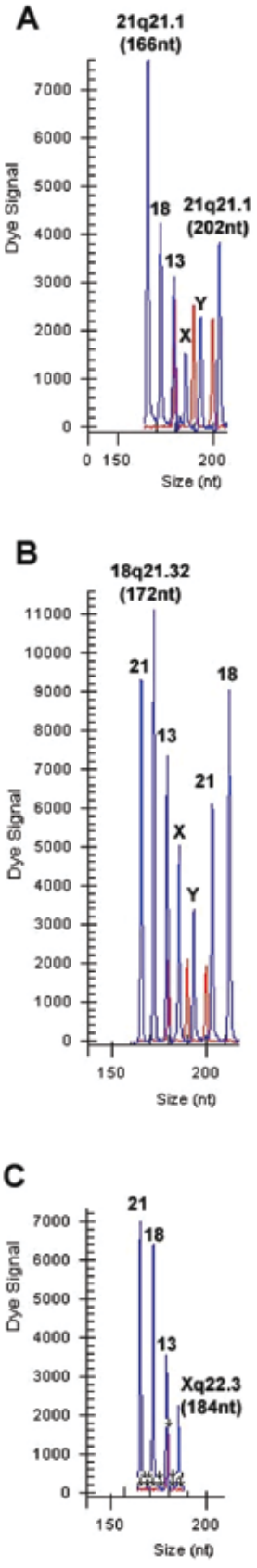

Figure 9. Multiplex Ligation-dependent Probe Amplification (MLPA) peak patterns for the same group of targeted DNA markers (blue peaks) in three different aneuploidies: A. Trisomy 21; B. Trisomy 18; C. Monosomy X. The peaks of interest are labeled with the chromosomal location. The lower part of figure shows the length of fragments on the X axes and the signal level on the Y axes. The signals from the size standard DNA (GenomeLab™ DNA Size Standard Kit - 600) are presented as red peaks

biochemical and morphological markers in "combined", "integrated" or "sequential" screening tests, offered an increase of detection rates to about 97% for trisomy 21 and 100% for trisomy 18, trisomy 13 and Turner syndrome, with concomitant decrease of false-positive rate to less than 5%.

A check-list of morphological features can be visualized by ultrasound at 11+0 – 13+6 weeks and certain structural anomalies were used to increase the efficiency of chromosomal anomalies detection (Table 4). The use of serum biochemical markers (free β-HCG+PAPP-A) + all ultrasonographic functional markers (NT+NB+DV+TR+FMF angle) + morphological marker likelihood ratios for chromosomal anomaly have pushed the detection rate only slightly lower than that of CVS, which is 99.7%[26], but without the afferent costs and complications related to the invasive genetic maneuver.

Prenatal services providers and patients are therefore faced with a multitude of tests incorporated in screening procedures. The new guidelines[22] changed radically the way patient, physician and healthcare system interact with each-other. Although the physician explains all screening procedures, the patients have to make a decision by weighing the risks and benefits of the noninvasive and invasive procedures that they may not fully understand. The patient's need for a doubtless genetic result could lead to an increase in invasive procedures and eventually a higher loss rate of normal fetuses[24]: 2% in CVS procedure and 1.9% for amniocentesis[27]. When using CVS we should also take into account the rate of false-negative results that is reduced only by using both short- and long-term cultures[28].

As the improvement made in the first trimester morphological screening determined an increase in the detection of chromosomal defects, we decided to perform a detailed first trimester examination of fetal morphological and functional features, in order to increase the efficiency of first trimester genetic and structural screening. In all genetically abnormal cases detected during the study period, ad least one anatomical feature related to chromosomal anomalies was found and the vast majority of the chromosomopaties associated multiple first trimester morphological markers (90.9%). Nuchal translucency was the most valuable genetic marker in ultrasound evaluation; abnormal aspect was present in 81.8% of the diagnosed cases. In almost half of the cases (45.4%) more than six anatomical

features considered in the standard protocol were found abnormal and also the biochemical risk was increased. In the presented cases, the QF-PCR and MLPA genetic techniques performed after CVS were concordant with the morphological presumptive diagnosis. In all these cases, the couples expressed a high degree of anxiety related to the time needed for completion of genetic assessment.

We are aware that a limitation of our study is the small number of the chromosomally abnormal fetuses. However, considering the figures, maybe a new strategy in altered ultrasonographic morphological and functional markers + abnormal biochemical serum markers would be more cost-effective: TOP with consecutive genetic investigation of curettage removed product, without invasive maneuvers, expensive genetic testing and 10 to 14 days waiting time for the parents. Our research made in this field has shown that a significant combination of ultrasound markers and abnormal biochemical features is associated with fetal genetic anomalies and determine TOP at the couples' request. Also, the balance between performing the "gold standard" and the financial limitations has become an important issue in prenatal medicine. Therefore, we believe that the possibility of pregnancy termination based on biochemical and ultrasound markers should be taken into consideration by decision-making specialists especially in cases with multiple morphological abnormalities associated to abnormal biochemical profile in healthcare systems with lower financial possibilities. Genetic confirmation of chromosomal disorder may be efficiently performed after TOP, avoiding the cost of invasive procedures, and the mental stress of the parents/pregnant women until genetic confirmation following CVS; also the inconclusive results of the genetic technique would be avoided.

Conclusions

Despite decades of research made in the field of prenatal screening, strategies concerning the best way of detection are constantly changing. We believe that the recommendation of TOP in high-risk pregnancy with evident morphological affected fetuses could be feasible in some cases using only first trimester combined screening, with detailed ultrasound evaluation. Genetic diagnostic and consecutive counseling may be carried out from the curettage product. Pregnancies without severe prognostic would have an invasive screening procedure followed by genetic testing before taking any decision. ■

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