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CURRENT RISK ASSESSMENT FOR FETAL ANOMALIES IN FIRST A ND SECOND TRIMESTER OF PREGNANCY

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Abstract

Nowadays, I n western world, by influence of many factors, such as information, technology, progress in health care standards and social economic ones, according to statistics of last five years, live childbirths in United States of America (USA) exceeded 4.5 million. During the evaluation of these data, were noticed a steady increase of average of mothers at their first childbirth in the past 4 decades. In 2008, 15% of all neonates were born by women 35 years old or older. These tendencies have been and also are noted in European countries, including the eastern European countries like Albania.

There is enough evidenced based medicine information of the risk of fetal anomalies of the pregnant women in older age. Fetal anomalies can affect different part of human system. Down syndrome (DS) is the most common chromosomal abnormality, af-fecting 1:700 live births. Its frequency is at least a third greater if stillbirths and spontaneous losses, which inherently have a greater burden of aneuploidies, are included.

With the trend aging of the ob-stetrical population the incidence has grown as high as 1:500 live births. Iden-tifying pregnancies at risk for DS has been a major goal of prenatal care since safe prenatal diagnostic testing became available in the early 1970s. Sonographic equipments and medical staff training started in late 1970s, and in mid 1980s and early 1990s obstetrical sonography was part of clinical practice in Albania, specifically in Tirana.

Having noticed this tendency of old age of Albanian obstetrical population influenced by same factors as in western countries, this article brings most current strategies diagnostic testing and management of fetal anomalies. Also, Albania prenatal care in last 2 decades has gone through a real revolution with a tremendous positive changes and impact in prenatal care, such as preconception consults and screening, early diagnosing of major fetal anomalies, and overall reduction of neonatal and maternal death bringing the statistics very close to the ones of developed countries. These data bring our health care system, especially obstetrical and neonatal care, and diagnostic skills and means of early diagnosis of fetal anomalies to the same level of standard care of western counterparts by using contemporary strategies in diagnosing and management.

Key words: Fetal anomalies, Down syndrome, prenatal care, diagnosis.

Introduction

Nowadays, in western world, by influence of many factors, such as information, technology, progress in health care standards, and social economic ones, according to statistics of last five years, live childbirths in United States of America (USA) exceeded 4.5 million. During the evaluation of these data, were noticed a steady increase of average of mothers at birth in the past 4 decades. In 2008, 15% of all neonates were born by women 35 years old or older [1]. These tendencies have been and also are noted in European countries, including the eastern European countries [2]. There is enough evidenced based medicine information of the risk of fetal anomalies of the pregnant women in older age. Fetal anomalies can affect different part of human system. Down syndrome (DS) is the most common chromosomal abnormality, af-fecting 1:700 live births. Its frequency is at least a third greater if stillbirths and spontaneous losses, which inherently

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have a greater burden of aneuploidies, are included. With the aging of the ob-stetrical population the incidence has grown as high as 1:500 live births. Iden-tifying pregnancies at risk for DS has been a major goal of prenatal care since safe prenatal diagnostic testing became available in the early 1970s. Clinical and bio-genetic experts have long recognized that DS occurs more frequently in older women (Table nr.1) [3] and in women with a family history of DS. These two criteria (mater-nal age e"35, and family history) were and unfortunately in many countries still are the traditional risk factors for offering diag-nostic testing when amniocentesis and karyotyping becomes clinically available. Regrettably, these criteria have proven to be poor screening tools for DS, expos-ing 15% to 25% of pregnant women to invasive testing, with its inherent preg-nancy loss rate, while detecting only 25% to 35% of affected pregnancies.In recent times, due to the results of larger population-based studies, countless new options have been introduced for Down syn-drome risk assessment that can be done either in the first trimester or by com-bining first- and second-trimester mea-surements. This article presents options for fetal aneuploidy risk assessment during pregnancy.

In Albania, use of ultrasound in clinical practice was introduced since late 1970s and early 1980s at University Hospital Center of Tirana what is now called Mother Teresa University Hospital Center, Tirana, Albania. Later on during 1985-1990, Albanian obstetricians were trained and certified from accredited western education institution. In the last 30 years, many positive drastic changes have been introduced in Albanian medical system, especially in the discipline of obstetrics thus many medical doctors are trained competitively with western medical counterparts, thus making a difference in obstetrical patient care of Albanian population.

First trimester risk assessment

Although late onset, restricted, or com-plete lack of prenatal care continue to be challenging even in western world, more than 80% of pregnant women initiate care prior to 12 weeks' gestation.

The interest of first trimester finding of DS is apparent. First trimester risk as-sessment for aneuploidy was introduced in Europe in the mid-1990s. It involves a combination of serum biochemistry and ultrasound measurement of the nuchal translucency (NT) (Figure nr.1). The bio-chemical markers are Pregnancy Associ-ated Plasma Protein A (PAPP-A), which is lower in DS fetuses, and HCg, which is increased in DS fetuses. Although NT or serum markers alone can be used for risk assessment, when taken together with maternal age, Combined First Trimester Screen is the most sensitive technique in the first trimester [10].

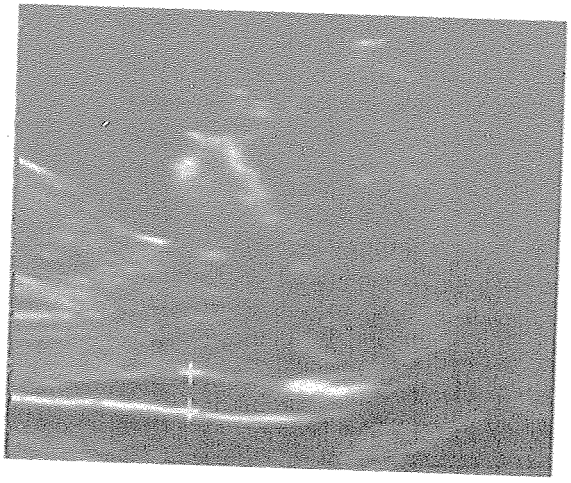

Figure nr.1

Table nr.1 Incidence of Down syndrome by maternal age in singletons

Maternal Age	1st Trimester Risk	2nd Trimester Risk	Live Birth Risk
25	1:616	1:906	1:1250
30	1:415	1:610	1:840
35	1:238	1:256	1:456
37	1:133	1:156	1:217
40	1:56	1:75	1:94
42	1:32	1:46	1:52
44	1:18	1:28	1:30
46	1:10	1:17	1:19
48	1:6	1:11	1:14

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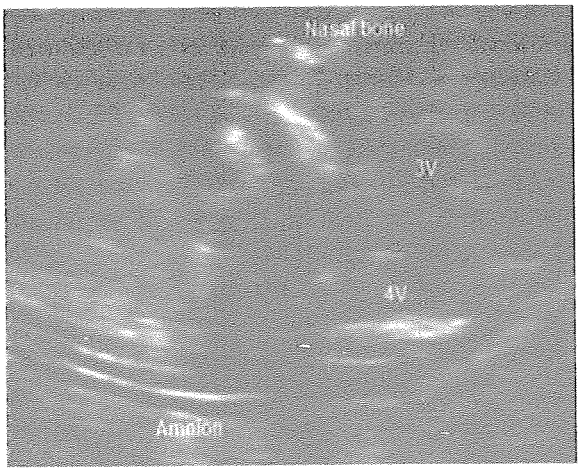

Figure nr. 2. Normal Nuchal Translucency

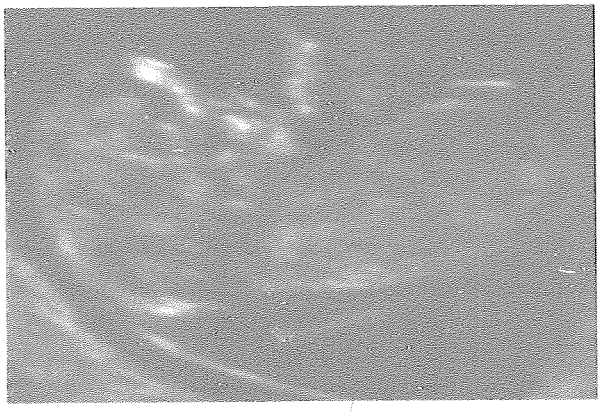

Figure nr.3. Abnormal Nuchal Translucency

NT describes an anechoic area in the posterior nuchal region of the fetus and is typically observed in the first tri-mester (Figures nr.1, nr.2, nr.3). NT increases with gestational age between 10 and 14 weeks. A combination of NT with serum biochemistry between 10 and 14 weeks' gestation in several population-based studies demonstrates 80% to 90% sensitivity for DS fetuses, with a false positive rate of 5% [8,9]. To be useful NT measurements must be performed with accuracy and repro-ducibility. Errors of tenths of a milli-meter can greatly alter calculated DS risk thus we strongly recommend ultrasound scan to be done by professionally certified specialists. As a result, the Nuchal Translucency Quality Review in the U.S.A. and the Foundation for Ma-ternal Fetal Medicine have developed strict criteria, specific cre-dentialing, and quality review for NT measurements (Table nr.2). In clinical practice, the largest NT measurement that meets the criteria should be re-ported to the respective laboratories. The crown-rump length window for NT assessment is between 38 and 84 mm, which correlate between 10 and 13 weeks' ges-tation. NT is also a marker of fetal congenital abnormalities, especially cardiac malformations. Due to the asso-ciation of congenital heart disease with an NT greater than 3.4 mm, it is gener-ally accepted practice to perform a de-tailed evaluation of the fetal heart in the second trimester.

Table nr.2. Ultrasound criteria for accurate NT measurement

1. Margins of NT edges clear,
2.Fetus in mid-sagittal plane,
3. Fetus occupies majority of image
4. Fetal head in neutral position,
5. Fetus observed away from amnion,
6. (+) calipers used
7. Horizontal crossbars placed correctly,
8.Calipers placed perpendicular to long axis of fetus
9. Measurement at widest NT space

Apart from its effectiveness in screening for DS and other chromo-somal abnormalities, first trimester risk assessment may provide many addi-tional benefits. These include either es-tablishment or confirmation of precise gestational age, early recognition and determination of chorionicity in mul-tiple gestations, identification of many major congenital abnormalities; in-cluding cystic hygromas that are asso-ciated with 40-50% incidence of chromosomal anomalies. Furthermore, studies show that, similar to abnormal values of second trimester serum mark-ers, first trimester markers correlate with preterm delivery, preeclampsia, and fetal growth restriction (FGR).

Second trimester risk assessment

Second trimester risk assessment for aneuploidy chiefly involves serum biochemical markers. The association between DS and low maternal serum alpha-fetoprotein levels in the second trimester was recognized since 1984 [4]. This association was extended in the late 1980s, when elevated lev-els of human chorionic gonadotropin (hCG) and decreased levels of uncon-jugated estriol were also reported in DS fetuses. Combining these 3 bio-chemical markers into what is now known as the Triple Screen Test was shown to detect approximately 50-60% of DS fetuses for a 5% screen positive rate when offered to women between 14 and 22 weeks' gestation [5,6].

In the 1990s, Dimeric Inhibin A as a marker for Down's syndrome in early pregnancy was shown to be in-creased in DS fetuses independently of the other biochemical markers [7, 8]. Adding this fourth serum marker to the Triple Screen Test, called the

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Quad Screen Test en-hanced detection of DS fetuses to 85% with a 5% screening false positive rate [8,9] These biochemical markers were also found to be effective in assessing risk for Trisomy 13,18.

Ultrasound risk assessment for DS in the first and second trimester

Fetuses with ultrasound-detected congenital anomalies show an increased risk for DS. Congenital heart disease, cystic hygroma, omphalocele, and duo-denal atresia have the highest burden of aneuploidy, even though at least 50% of infants with DS have no recognizable major congenital anomalies.

Therefore, many sonographic studies have been attempted to identify DS by unusual ul-trasound features often referred to as obstetrical ultrasound markers. Habitually referred to as a ge-netic sonogram, identification of these markers will significantly alter the risk of DS, providing individual risk assessments for DS rather than age specific risks. However, none of these mark-ers should be considered absolute diagnostic for DS. Likewise, the absence of these markers will reduce the risk of DS by ap-proximately 50 to 80%, although it will not exclude the possibility of aneuploidy.

Combining first and second trimester DS risk assessment

The most competent screening test is one with the highest sensitivity with the lowest screening false positive rate. The most proficient screen-ing for Down syndrome is achieved when both first trimester and second trimester markers are combined. The Fully Integrated Screening model in-volves measuring NT and PAPP-A be-tween 10 weeks and 6 days and 13 weeks and 6 days, followed by serum measurement of AFP, UE3, HCG and Inhibin at approximately 16 to 18 weeks' gestation. A single risk assessment for DS is given at this time. Both the SURRUS and FASTER trials reported a 94% to 95% discovery rate in DS with a 5% false-positive rate [8,9]. Whereas the discovery rates are quite high, the drawback of fully integrated screening is that it leads only to a sec-ond trimester result. Integrated screening would deny a patient the chance to pursue a first trimester diagnosis by chorionic villus sampling (CVS) with earlier and safer terminations if needed.

To offer information to patients after the first part of their screening and allow them the option to follow CVS, the Stepwise Sequential Screening and the Sequential Contingency Screening methods have been introduced (Fig-ures 5 and 6). In the Stepwise Sequential Screening method, the patient is given a result following the first part of her screening (NT plus PAPP-A and hCG). At that point she has the alternative of pursu-ing a diagnostic test if she is at high risk for Down syndrome. If her initial risk is low, she will proceed to the second part (AFP, UE3, HCG and Inhibin) at 16 to 18 weeks of pregnancy. At that time, a final overall risk assessment can be provided. By manipulating cut-offs, Stepwise Sequential Screening is believed to offer a DS detection rate that is very similar to the Fully Integrated Screening approach whereas maintaining a 5% false positive rate [8].

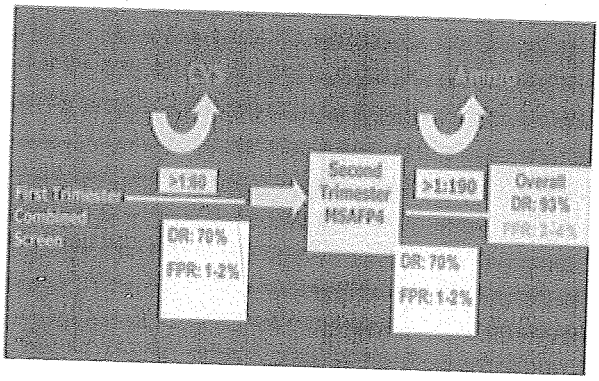

Figure nr.5 Stepwise sequential

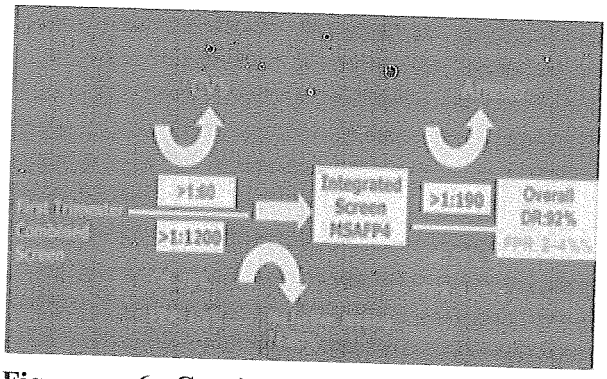

Figure nr.6 Contingency risk assessment risk assessment

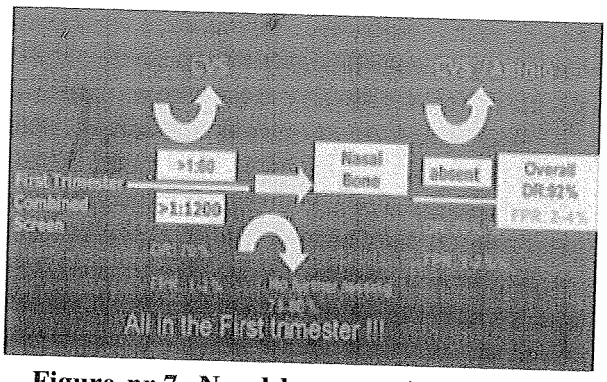

Figure nr.7 Nasal bone contingency risk assessment

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The Genetic Sonogram can also be used to assess DS risk, and it can be used either sequentially or contingently alone or in addition to second trimester serum markers [11].

Nuchal translucency measurements may not be obtainable in 10% to 15% of patients. In these cases Serum Inte-grated Screening should be considered. This option is similar to Fully Inte-grated Screening but without the NT is provided only after the second trimester biochemical markers have been evaluated. The FASTER trial reported an 87% DS detection rate, which was better than MSAFP4, with the same 5% false-positive rate [12].

At 11 to 14 weeks' gestation, the nasal bone is reportedly absent in about 60% to 70% of fetuses with DS, while absent in less than 1% of chro-mosomally normal fetuses. Significant population variation has been noted. A nasal bone contingency test has been proposed which appears to have similar effectiveness for DS detection with the further advantage of completing screen-ing and diagnostic testing by the end of the first trimester [13,14] Investigations continue exploring ad-ditional ultrasound parameters for DS risk assessment [15], and recent studies have found that blood flow through the fetal Ductus Venosus [12,16], fetal tricuspid re-gurgitation, and the frontomaxillary facial angles [17] are all promising. However, all of these techniques are still unavailable for large-scale population screening and re-main investigational at this time.

Conclusions and recommendations

In Albania, having being at least 10 year behind in use of up to date tools in diagnosing in early 1990s, today we use most up to date means in diagnosing and management of fetal anomalies as in western countries. First trimester combined testing (NT plus serum markers) gives the earli-est results but leaves approximately 15% of DS cases undetected. The sec-ond trimester quad test and the genetic sonogram are appropriate for late reg-istrants but leave 20% to 25% of DS cases undetected. The integrated test has the highest detection rates but leads only to a second trimester result, which may be unacceptable to many patients. Stepwise Sequential testing detection rates are very close to the integrated test and allow women with very abnor-mal first trimester results to undergo early invasive testing, but it requires two tests. The contingency test may have slightly lower detection rates than stepwise sequential testing, but higher than first trimester combined testing alone, and it allows most women to complete screening after a single study early in pregnancy. Again, this test-ing is not currently clinically available. All studies that require first and second trimester results require significant well ad-ministrative coordination.

The nasal bone contingency test, which can be completed in first-tri-mester visit, appears to have high de-tection rates and significantly reduced screen positive rates. This testing re-quires performance by an individual with expertise not only in NT measure-ment but also in nasal bone assessment, thus this scan must be done only by proficient experts.

Additionally, the presence or absence of the fetal nasal bone varies with ethnic-ity; this affects more multi ethnic countries. So, this form of screening requires fur-ther study.

Moreover, some patient factors can direct the testing performed. In order to offer the best care for the patient, a professional multi dimensional approach to the patient must done by having a multi level disciplinary clinical approach, as a single testing approach does not fit all situations.

It must be emphasized that explicit answers rely on a diagnostic test. All risk assessment strategies are intended only to establish the risk of a prob-lem, and they will always have less than 100% sensitivity. As long as the only definitive way of diagnosing the karyotype of a fetus involves an inva-sive procedure that can cause the loss of a normal pregnancy, there simply is no substitute for explaining the options and their downsides to all patients. Patients will in turn be empowered to make de-cisions that are best for them and their pregnancy.

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