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Screening (Bi Test, Triple Test, Panorama Test) and Amniocentesis for Early Diagnosis of Congenital Malformations

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Abstract

The genetic consult is very important in the diagnosis of early fetal malformations and its complications at birth and after it. Our research is based on a 3-year research on 6097 pregnant women who underwent screening *Bi-Test or Triple Test*. We discovered 408 pregnant women who were found positive and needed amniocentesis for a diagnostic of certitude. Out of them, 14 had a positive result from which 10 were found with Down syndrome and 4 with Edwards syndrome. In Romania, amniocentesis has become the most used method of prenatal diagnosis for pregnant women at 35 or above with a family history of hereditary congenital anomalies. However, the latest screening test from maternal blood, the Panorama test, can discover many malformations (for chromosomes 21, 18, and 13 and the abnormality of the sex chromosome). The accuracy for false positive is 2% and false negative 98%. In that light, the purpose of our study is to decrease the use of amniocentesis and to introduce the latest tests (Panoramic) for the early diagnosis of fetal malformation, the use of maternal blood, and the avoidance of using invasive medical procedures.

Keywords: screening *Bi-Test, Triple Test, Panorama Test*, amniocentesis for early detection of fetal malformations

1. Introduction

Talking with the patient about his or her family medical history, such as if the couple had a person with Down syndrome in their family or any other malformation, is important. That can be considered as a 'genetic consultation' in order to find out about any possible genetic problems before screening or any other tests. The specialist tries, in the first place, to make the patient understand the nature of his disease he is confronting, what's the most possible evolution of it, and last but not least what are the possibilities of treating it. A major objective of the genetic consult is to make the patient understand what are the factors that lead to the development of the disease, what are the mechanisms that transmit the disease, and how high is the risk of appearance to other family members. The doctor establishes, after running different tests, the correct diagnosis of the disease, its evolution, its prognosis, as well as the possibilities of treatment for a higher quality of life.

The genetic consult is very important in the diagnosis of early fetal malformations and their complications at birth and after it. The consult is necessary for pregnant women with high risk in developing a malformation (e.g., if the woman has in the family history a newborn with malformations, if she gave birth before to a baby with malformations, if she lives in a toxic environment).

In Romania, it is mandatory that every pregnant woman should do the BI-TEST or TRIPLE TEST, depending on the pregnancy weeks.

The cytogenetic prenatal diagnosis refers to early detection of intrauterine fetal abnormalities and genetic malformations, very often determined by genetics, which complicate and threaten the life of 3–5% of newborn. These abnormalities explain the 20% deaths in the newborn period and the much higher percentage of deaths in childhood and puberty [1]. From the fetal abnormalities, 95% are unexpected and appear at pregnancies that are not considered at risk for these situations. They can be light or severe.

The severe abnormalities are not compatible with life or can cause a long-term handicap [2].

There are multiple purposes for the detection of intrauterine prenatal illness such as:

- Establishing the high-risk diagnosis and possibly the termination of the pregnancy (abortion), the pregnancy representing a high risk of death both for the mother and fetus
- Identifying a situation that can influence the date, the place, or the childbirth method
- Identifying fetuses that will benefit of early pediatric intervention
- Identifying situations that can affect future pregnancies

Opinions are different when it comes to knowing the diagnosis; many families decide to keep the pregnancy even if there are severe malformations, thinking that they can fight this problem by taking care of the baby and not terminating the pregnancy. But most of the families decide to terminate the pregnancies and seek treatments for future pregnancies.

In conclusion, the most important thing in the prenatal diagnosis is obtaining very early in the pregnancy of correct informations about the fetus and making a correct and easy decision in conformity with family principles [3].

The indications for prenatal diagnosis are:

- Pregnancy—women at age of 35 or above
- Husband aged 45 or above
- Past pregnancy with a fetus with chromosomal abnormality
- One of the parents has a chromosomal abnormality including being a carrier of a balanced translocation or other structural rearrangements
- Down syndrome
- Pregnancies with risk of Mendelian or polygenic diseases (e.g., Tay-Sachs disease)

- Abnormal fetus diagnosed by the ultrasound procedure within the first weeks of pregnancy
- Maternal anxiety
- Determination of fetal risk in pregnancies with high risk for hereditary x-linked diseases, for that there is not yet a specific prenatal diagnosis (it is obtained better by determining the Y-chromosomal material with the new ADN techniques)
- History of two or more abortions without the possibility of effectuation of the cytogenic analysis to both parents or a noninvasive prenatal diagnosis [4]

The screening programs focus on the most common chromosomal abnormality—the Down syndrome (trisomy 21)—and they not only detect very often other fetal abnormalities.

2. The BI-TEST

The screening of the first trimester is a prenatal text that offers informations about early pregnancy and the risk of the baby to develop some specific chromosomal abnormalities—the Down syndrome (trisomy 21) and the Edwards syndrome (trisomy 18).

The Down syndrome determines a lifetime affectation of the mental and social development and also some physical modifications. As for Edwards syndrome, it is a much more severe condition, and often it is fatal until the early age of 1 year [5].

The screening tests from the first trimester of pregnancy do not evaluate the risk of defects of the neural tube, such as spina bifida.

We do the BI-TEST (the screening of the first trimester in pregnancy) because it can be done much earlier than other tests of screening; the results can be available in the first weeks of pregnancy, which offers the parents much more time in taking the best decision regarding additional tests, medical treatment, and the course of pregnancy [6].

Normally, the screening of the first trimester (the BI-TEST) is made between weeks 11 and 14 of pregnancy. The results of the test are formulated as positive or negative and also like a probability, e.g., 1:5000 risk to have a baby with Down syndrome. In general, the test is considered positive if the risk is 1:300 or above. The BI-TEST implies two steps: a blood test that measures the level of two hormones that are specific in pregnancy (pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG)) and an ultrasound examination which measures the size of the transparent space behind the neck of the fetus (the nuchal translucency) [7]. Correlating the values obtained from the blood tests with the ultrasound examination and some specific parameters of the mother (age, height, weight, blood pressure, smoking, diabetes, assisted reproductive techniques), the specialist can calculate the risk of the mother of having a baby with chromosomal abnormalities [6].

Frequently, a positive result will enforce the performance of secondary diagnosis tests:

- The chorial biopsy—it is done normally in the first trimester of pregnancy, and it is an invasive test which implies cropping a piece of the placenta, with a low

risk of abortion. It is used to detect chromosomal abnormalities, like the Down syndrome.

- Amniocentesis—it can be used to identify chromosomal abnormalities but also defects of the neural tube, like spina bifida. During the amniocentesis, which frequently is done in the second trimester of pregnancy, a small amount of amniotic liquid is estranged. It also had a low risk of abortion [6].

3. The TRIPLE TEST

A continuance of the BI-TEST from the first trimester and the screening TRIPLE TEST (made in the second trimester of pregnancy) is more and more often requested by us. With the help of it, we can evaluate the risks of the baby developing a neural tube disorder (spina bifida) or chromosomal abnormalities such as the Down syndrome (trisomy 21) or the Edwards syndrome (trisomy 18) [6].

Between the 15 and 20 weeks of pregnancy (with optimal results in the weeks 16–18), pregnant women can be tested with a simple blood test known as the TRIPLE TEST (or triple marker test or second trimester screening). It is made in combination with an ultrasound examination [3].

For the triple marker testing, a blood test is required that will measure the levels of:

- hCG (human chorionic gonadotropin) secreted by the placenta.
- Unconjugated estriol, a product of the placenta and the fetus.
- Alpha-fetoprotein (AFP gene) produced by the fetus's liver.
- Sometimes it also tested the inhibin A (produced by the placenta), because it considerably grows the chances of detection of the Down syndrome, which is also known as the quadruple test.

The level of each substance present in the blood helps the doctor identify if the fetus is exposed to the risk of developing congenital disorders and chromosomal abnormalities. Exactly as in the case of the BI-TEST, multiples of the median (MoM) is measured depending on the clinical data of the mother (age, height, weight, race, smoker, age of the fetus) [4]. The results of the tests are available in 2 weeks from the blood tests. Usually, if the results of the TRIPLE TEST show a high level of alpha-fetoprotein, it indicates a neural tube defect. The doctor will recommend an ultrasound examination of the fetal cranium and spinal cord. The mother is also purposed to do an amniocentesis, which involves extracting a small amount of amniotic liquid from the uterus for further investigation.

On the other hand, low levels of alpha-fetoprotein (AFP) and unconjugated estriol indicate a high risk of Down syndrome. In this situation, it is recommended that an amniocentesis should be done.

4. Amniocentesis

Amniocentesis is a medical procedure used in prenatal diagnosis of chromosomal abnormalities, in which a small amount of amniotic fluid which contains fetal tissues is sampled from the amniotic sac and which is afterward tested.

It is a two-person procedure which requires a lot of experience and care from the side of the doctor. One of the doctors assures the ultrasound examination, and the

other doctor places the puncture needle. This way, he can manipulate the needle with all the attention and care to attain the desired target. There has to be an incredible collaboration between both doctors, because they have to anticipate each other's moves.

Before the procedure, it is mandatory that the sanguine groups ABO and RH be determined and also to perform an ultrasound examination, which will determine the number of fetuses, the position and viability, the localization of the placenta, the amount of amniotic fluid, and the largest amniotic sac that will be punctured and will assure that the fetus is anatomically normal. Also the gestational age of the fetus by the fetal biparietal diameter, the length of the thigh bone, and the abdominal circumference is determined.

Choosing the place of puncture is made after the initial evaluation. When doing the amniocentesis, it is important to choose the place of the puncture needle in the amniotic cavity wisely, namely by carefully avoiding the placenta, the umbilical cord insertion place and the fetus. Colored Doppler ultrasound can facilitate the choosing of the place for the transplacental puncture, to avoid fetal hemorrhage.

Diagnosis of chromosomal abnormalities and diagnosis of the neural tube defects are the most common indications for amniocentesis in the beginning of the second trimester of pregnancy. As for the evaluation of the fetal pulmonary maturation, it is the most common indication for amniocentesis in the third trimester [8].

At the end of the first trimester and the beginning of the second trimester, the indications for amniocentesis are:

- Cytogenetic diagnosis
- Diagnosis of neural tube defects
- Diagnosis of metabolic disorders

At the end of the second trimester and the beginning of the third trimester, the indications for amniocentesis are:

- Evaluation of the severity of Rh immunization
- Evaluation of fetal pulmonary maturation
- Diagnosis of intra-amniotic infections
- Confirmation of the ruptured membranes

Last, but not the least, the therapeutic purpose of the amniocentesis has indications in the polyhydramnios drainage and the medical treatment of fetal diseases.

Ultrasound examination (localization of the placenta, fetus, and amniotic liquid bag) and the insertion of the needle can take up to 20 min. Extraction of the amniotic liquid can take up to 5 min.

Some women don't feel pain (painless procedure), while other pregnant women feel cramps as the needle punctures the uterus or a pressure sensation during the procedure of extracting amniotic liquid.

Local anesthetic is not normally used. Associated factors to the high level of pain during the amniocentesis are considered to be maternal anxiety, presence of menstrual cramps in the past, an anterior amniocentesis, and the insertion of the needle in the inferior part of the uterus, where the pain is less felt by the patient [9], although there aren't any data to support this practice [10].

5. Panoramic Test

The Panorama Test is a prenatal noninvasive test, which analyzes the fetal DNA from the maternal blood and establishes the risk of common fetal aneuploidies in pregnant women, most interestingly the 21, 18, and 13 chromosomes but also the analyzes the sexual chromosomes X and Y.

Aneuploidies are chromosomal abnormalities characterized by the alteration of the number of chromosomes, for example, more or less chromosomes instead of the exact number of chromosomes; the trisomy, when there is an extra chromosome; or monosomy, when there is missing a chromosome.

Trisomy 21 is caused by the presence of an extra chromosome to the 21st pair, and it's known as the Down syndrome. It is the most frequent cause of mental retardation. The patients with Down syndrome present cardiac disease or other diseases which require surgical interventions or specific medical treatment. Other symptoms are, for example, ophthalmological problems [11].

Trisomy 18 is caused by the presence of an extra chromosome to the 18th pair, and it's known as the Edwards syndrome. It is a serious cause of mental retardation. The majority of the children with trisomy 18 present severe cerebral malformations, severe heart malformations, or severe malformations of other organs. Often, the growth retardation is found, which can lead to the termination of pregnancy (abortion). Most of the children who are born with the growth retardation die within their first year of life. Patients who survive present severe intellectual disability and have problems of growth and development [12].

Trisomy 13 is caused by the presence of an extra chromosome to the 13th pair, and it's known as the Patau syndrome. It is a cause of severe mental retardation. The majority of the patients present serious cerebral and other organs abnormalities. In many situations the pregnancy doesn't get to its due date, and the newborn dies very fast. Half of the born babies die in their first month of life, and 90% from those who survive in the first year of life present heart malformations, renal malformations, and renal malformations.

Aneuploidies of the sexual chromosomes are caused by the presence or the absence of one of the sexual chromosomes. The test can detect the risk for XXX, XYY, XXYY, and XXY (the Klinefelter Syndrome) and for the X monosomy (the Turner syndrome). A significant variability exists in regarding the severity of these genetic conditions, but the majority of the affected individuals are characterized by slight modifications physically and mentally.

During pregnancy some fragments of the fetal DNA run through the maternal blood. The fetal DNA is detectable since the 5th week of pregnancy. The concentration increases successively in the next weeks of pregnancy and disappears right after childbirth. The circulating fetal DNA quantity is found from the 9th to 10th weeks of pregnancy, and it's sufficient to guarantee the relevance and the sensibility of the Panorama Test.

The test is done by collecting a blood sample from the pregnant woman from at least the 10th week of unique and twin pregnancies. In the laboratory a complex analysis is made, where the fetal DNA from the maternal blood is isolated. This procedure identifies the eventual chromosomal abnormalities, like aneuploidy, and cutting-edge sequencing technology is used, along with advanced bioinformatics analysis.

The results obtained in the Panorama Test are:

- “High risk” implies that there is a probability that the fetus can present an aneuploidy of the 21st, 18th, and 13th pairs of chromosomes or an aneuploidy of

X and Y sexual chromosomes. This result indicates that there is a high chance that the fetus can present one of the abovementioned abnormalities, but it is not sure the fetus will have that condition. The endorsed advice is an invasive prenatal diagnosis test, like chorionic villus biopsy or amniocentesis.

- “Low risk” implies that the test detected a risk $<1/10,000$ (0.01%) for the fetus to be affected by a chromosomal aneuploidy.
- In some cases, when the quantity of fetal DNA is not enough, the test can show.
- Incomplete results or no results. In this situation, a new blood sample will be collected for the repetition of the test. In case the sexual analysis is demanded, this result can also be provided.

The accuracy of the Panorama Test

	% diagnosis (sensibility)	% false positive (specificity)
Trisomy 21 (the Down syndrome)	99 (>99%)	< 0.1% (>99%)
Trisomy 18 (the Edwards syndrome)	99 (>99%)	< 0.1% (>99%)
Trisomy 13 (the Patau syndrome)	08/10/16	< 0.1% (>99%)
Determination of the fetal sex	99 (>99%)	< 0.1% (>99%)

The test can detect the risk of a sexual chromosomal aneuploidy with a rate of detection which varies depending on the type of detected aneuploidy: 13th, 18th, and 21st.

The test was validated for women with unique and twin pregnancies, with at least 10 weeks of pregnancy. This test evaluates just the chromosomal aneuploidies of the 13th, 18th, 21st, X, and Y. In the case of pregnancy with more fetuses, informations about the sexual chromosomes will not be provided. This procedure does not replace the invasive prenatal diagnosis (choriocentesis or amniocentesis).

Also, the analysis cannot highlight the equilibrated chromosomal rearrangements, partial abnormalities of the analyzed chromosomes, structural chromosome abnormalities, fetal or placental chromosomal mosaicism in a small percentage (the presence of two cellular lines with a different set of chromosomes, with a cellular line weakly represented), point mutations, methylation defects, and polyploidy. In particular, the analysis does not reveal the presence of hereditary genetic disorders with the Mendelian transmission. The test can give a false-positive result in the case of chromosomal mosaicism, but this thing can limit itself to the placenta. The sex of the fetus is mentioned as masculine or feminine, based on the presence or absence of the Y chromosome, not on the presence or absence of the SRY gene.

Pregnancies with abnormal ultrasound results should be studied with other types of prenatal investigations, such as fetal karyotype from the chorionic villi or amniotic liquid. Although this test is very precise, the results are not a diagnosis, and they should be evaluated in the clinical context of the patient and the family medical history. The test is limited to offer just informations about the risks of aneuploidies for the analyzed chromosomes.

A “low-risk” result can significantly reduce the possibility for the fetus to present an aneuploidy of the examined chromosomes, but it cannot guarantee that these chromosomes are normal or that the fetus is healthy.

This test can be done for 13th, 18th, and 21st aneuploidies also in case of twin pregnancies and of pregnancies obtained by fertilization in vitro.

This study seeks the degree of accuracy of the prenatal screening which indicates a high risk. The results are established after the confirmation or information of the diagnosis by the invasive diagnosis method for genetical abnormalities, the amniocentesis procedure. The interventions have been made by the obstetrician, helped by different doctors, based on the “2 operatives” technique. The puncture and the extraction of the amniotic liquid will be done by the obstetrician, and the doctor helping him would monitor by ultrasound the whole intervention.

Our study is based on a 3-year research (2012–2015). We evaluated 6097 pregnant women, from which 408 had an indication for effectuation of amniocentesis with the purpose of establishing a correct diagnosis. The dynamics of the number of pregnancies in the analyzed period presents significant decreases from 15%–14.65% in 2014 to 11.15% in 2015.

From the total amount of 408, 114 were made in the year 2012, 102 in the year 2013, 97 in the year 2014, and 95 in the year 2015.

Year	Number of pregnancies	Number of amniocentesis
2012	1641	114
2013	1596	102
2014	1402	97
2015	1458	95
TOTAL	6097	408

Comparing the dynamics of the number of amniocentesis procedures done in 2015 with the amniocentesis procedures done in 2012, they have a pronounced decreasing rhythm, so that in 2013 the level decreased by 10.53%, in 2014 the level decreased by 14.91%, and in 2015 the level decreased by 16.67% due do the apparition of the Panorama Test sampled from the maternal blood.

Year	Number of pregnancies	Number of amniocentesis procedures	Dynamics than 2012	
			Number of pregnancies	Number of amniocentesis procedures
2012	1641	114	–	–
2013	1596	102	97.26	89.47
2014	1402	97	85.44	85.09
2015	1458	95	88.85	83.33
Total	6097	408	–	–

By the fact that, in medical practice, age above 35 years old in pregnant women represents a risk factor; the patients have been divided in two groups such as patients aged until 35 years old and patients above 35 years old.

Group of age	2012	2013	2014	2015	TOTAL
Under 35 years old	74	66	57	54	251
Above 35 years old	40	36	40	41	157
Total number of patients	114	102	97	95	408

In the year of our study, 408 amniocentesis procedures have been made. Two hundred and fifty-one procedures were done on patients with age under 35 years old, which represents a percentage of 61.5%. One hundred and fifty-seven procedures were made on patients with age above 35 years old, with a percentage of 38.5%.

The distribution of the patients based on the pregnancy period and the number of amniocentesis procedures done in percentage:

Weeks of pregnancy	2012	2013	2014	2015	Total	%
Week 15	15	15	14	14	58	14.22
Week 16	36	34	32	39	141	34.56
Week 17	31	28	26	24	109	26.72
Week 18	14	13	10	8	45	11.03
Week 19	9	5	10	6	30	7.35
Week 20	7	5	3	2	17	4.17
Week 21	2	2	2	2	8	1.96
Total	114	102	97	95	408	100%

Even though the number of amniocentesis procedures has slightly decreased, the number of BI-TESTS has significantly increased since year 2012. In year 2013, the increasing number has been a percentage of +115.4%, in 2013 it has been +315.45%, and in the year 2015, it has been 269.2%. In the last 2 years, the percentage for positive tests for Down syndrome in amniocentesis has been 50%. In all our period of research, 35.05% of the patients have effectuated the double-positive test for the Down syndrome.

Year	Number of amniocentesis procedures	Triple Test positive for Down syndrome	Triple Test positive for Edwards syndrome	Percentage of positive Triple Test (minus the number of amniocentesis procedures) for:	
				Down syndrome	Edwards syndrome
2012	114	93	5	81	4.39
2013	102	64	3	62.75	2.94
2014	97	36	1	37.11	1.03
2015	95	33	1	34.74	1.05
Total	408	226	10	55.39	2.45

In the period of our research, the percentage for Down syndrome and Edwards syndrome of the TRIPLE TEST decreased in relation to the number of amniocentesis procedures. In this period the result positive for these tests is considered:

- In 2012 the test for Down syndrome represented 81.58%, and 4.39% for Edwards syndrome.
- In 2013 the test for Down syndrome represented 62.75% and 2.94% for Edwards syndrome.

- In 2014 the test for Down syndrome represented 37.11% and 1.03% for the Edwards syndrome.

Although in 2012 the highest number of amniocentesis procedures (114) was recorded, a single case was recorded in which amniocentesis had as an indication the maternal age, which represents a percentage of 0.88%. In 2013, a slight increase with a percentage of 6.86% is noted (in 2014, 4.12%, and in 2015, 3.16%). In all, there were 15 procedures made after the indication of the maternal age above 35 years old, with a percentage of 3.68%.

Year	Number of amniocentesis procedures	Age of the mother >35	Percentage %
2012	114	1	0.88
2013	102	7	6.86
2014	97	4	4.12
2015	95	3	3.16
Total	408	15	3.68

The distribution of the amniocentesis procedures based on priors:

- Down syndrome in the family
- Prior pregnancy with Down syndrome
- Prior pregnancy with Turner syndrome

Year	Number of amniocentesis procedures	Down syndrome in the family	Prior pregnancy with Down syndrome	Prior pregnancy with Turner syndrome
2012	114	1	1	0
2013	102	0	0	0
2014	97	1	0	1
2015	95	0	0	0

It is observed that in 2012, from the amount of 114 amniocentesis procedures, 2 of them had as indication the pathological chromosomal history. One of the patients presents in her family history a member of the family who has Down syndrome. Another patient had a prior pregnancy with Down syndrome. These indications represent 1.75% of the indications for year 2012. In 2014 two more pregnant women have been diagnosed. One of them was coming from a family with Down syndrome, and the other one had a prior pregnancy with Turner syndrome. These indications represent a percentage of 2.61% for the year 2014.

From a total of 408 pregnancies, the indications for pathological chromosomal history represent a percentage of 0.97%.

Number of amniocentesis procedures	408	100%
BI-TEST	131	32.10%
TRIPLE TEST	258	63.23%
Indication for maternal age 35 years or above	15	3.67%

Down syndrome in the family history	2	0.49%
Prior pregnancy with Down syndrome	1	0.24%
Prior pregnancy with Turner syndrome	1	0.24%

From the amount of 408 pregnancies which underwent the amniocentesis procedure, 149 of them were on their first pregnancy, with a percentage of 36.52%. One hundred and ninety-eight of the pregnant women were on their second pregnancy (48.53%), and 61 were on their third or more pregnancy (14.95%).

Distribution of the patients depending on environmental residence

Environment	2012	2013	2014	2015	Total	%
Rural	16	34	25	20	95	23.28
Urban	98	68	72	75	313	76.72
Total	114	102	97	95	408	100

It is concluded that only 23.28% of the pregnant women came from a rural environment; the rest of 76.72% came from an urban environment.

Distribution of patients depending on chronic diseases

Chronic diseases	Number of patients	%
Diabetes mellitus	11	2.70
Hepatitis A and hepatitis B	5	1.23
High blood pressure	9	2.21
Obesity	10	2.45
Kidney diseases	3	0.74

Distribution of patients depending on vicious behavior

	2012	2013	2014	2015	Total	%
Smoker	38	49	36	37	160	39.22
Non-smoker	76	53	61	58	248	60.78
Total	114	102	97	95	408	100

It can be observed that, despite the fact that smoking affects the pregnancy and the fetus, a quite high percentage of pregnant women smoke (39.22%).

Distribution of the patients depending on the result of the amniocentesis

Result	Number of patients	%
Normal results	394	96.57
Down syndrome	10	2.45
Edwards syndrome	4	0.98
Total	408	100

The percentage of Down syndrome reported to the total number of pregnancies (6097 patients) represents 1.6% above the European statistics. The percentage of Edwards syndrome reported to the total number of pregnancies represents 0.656% above the European statistics.

Maternal ages for women diagnosed with pregnancies with Down syndrome were 28, 31, 32, 38, and 40 years old.

Age of the mother diagnosed with pregnancies with Down syndrome	Number of cases
28	2
31	1
32	2
38	3
40	2

All the patients with babies diagnosed with Down syndrome or Edwards syndrome decided to terminate the pregnancy.

The 14 cases positive for Down syndrome and Edwards syndrome (4 cases positive for Edwards syndrome and 10 cases positive for Down syndrome) were actually found because of the indications of the TRIPLE TEST, 4 more cases positive for Down syndrome were found because of the indications for BI-TEST, and just 1 case of Down syndrome was found because of the indications for maternal age.

Amniocentesis has become the most used prenatal diagnosis method for women aged 35 and above or even for younger women with a family history specific for hereditary congenital abnormalities.

In our studied group, 157 pregnant women asked for a prenatal diagnosis for Down syndrome. They were aged 35 or above 35 and demanded the association of some pathological biochemical markers (double test, TRIPLE TEST).

The frequency of the structural chromosomal abnormalities (translocations, deletions, inversions) did not show a similar numeric relationship regarding the maternal age.

According to the literature, the screening tests have a margin of error in the diagnosis of fetal malformations, so the diagnosis of certainty will result after the amniocentesis.

The majority of the specialists consider that amniocentesis is an invasive procedure, so it is recommended that the number of these procedures should be decreased. In this regard, our study did very well: the result of the utilization of the other methods (BI-TEST, TRIPLE TEST) was positive. The BI-TEST can detect trisomy 21 (the Down syndrome) and trisomy 18 (the Edwards syndrome).

There are tests like Panorama Test which are cutting-edge technology, and they reduce the use of amniocentesis. But the cost of this test is high and not covered by the National Health, which is the reason why it is not accessible for all patients.

Our study has been made on a large segment of the population which had access to all the screening tests (BI-TEST, TRIPLE TEST), but not all of the patients had this possibility.

The TRIPLE TEST in pregnancy can help in tracking down the neural tube defects and chromosomal abnormalities such as trisomy 18 and trisomy 21. So, if a high level of alpha-fetoprotein (AFP gene) is found in the blood, it is likely that the fetus presents a neural tube defect (more exactly the brain and the spinal cord), defects such as spina bifida or anencephaly. If the results of the TRIPLE TEST show a low level of alpha-fetoprotein (AFP gene) and estriol, it can indicate trisomy 21 (the Down syndrome), trisomy 18 (Edwards syndrome), or other chromosomal abnormalities.

Before we proceeded with the amniocentesis procedure, we acquired from every patient and her partner a written consent after informing them about what the procedure implies.

In obstetrical practice the risk of carrying out an amniocentesis is evaluated permanently, compared to the individual risk of numerical chromosomal abnormalities or structural chromosomal abnormalities. We recommend the amniocentesis as an invasive diagnosis prenatal method when the risk of a detectable abnormality is higher than the risk of the procedure itself.

It is important that the patient should be informed about the pain felt during the amniocentesis.

Numerical chromosomal abnormalities (aneuploidies)—in the case of amniocentesis procedures done to pregnant women with age 35 or above from our consignment—have a frequency of 3.18% (5 cases out of 157).

The majority of the patients questioned said that the procedure was a painful method. Pain is a multidimensional sensation and complex, which varies in quality, intensity, duration, localization, and inconvenience from an individual to another. The intensity and inconvenience of the pain is not directly connected to the nature and the extension of the tissue lesion. Cultural, genetic, familial, growth, psychological, and social variables have a strong impact in the perception of the pain and in its expression from the patient.

The objective quantification of the pain is difficult. Before any invasive procedure effectuated throughout pregnancy, the biggest concern of the patient is the risk and the intensity of the pain during procedures.

Ultrasound conclusions in cases of chromosomal abnormalities

Trisomy	Ultrasound conclusions
Trisomy 21 (Down syndrome)	<ul style="list-style-type: none">• Duodenal atresia, tracheoesophageal fistula, and hydramnios are present usually if there are gastrointestinal damages• Heart abnormalities—defects of the atrial septum• Hypoplasia of the middle phalanx of the 5th finger of the hand• Conclusions from the second trimester: increased cervical skinfold (>6 mm), ratio of the actual femur (length), and the expected femur = 0.91
Trisomy 18 (Edwards syndrome)	<ul style="list-style-type: none">• Growth retardation in uterus• Hydramnios• Hand wrapped with superimposed fingers (the index covers the third finger, and the fifth finger covers the fourth finger)• <i>Ankle equinus</i> with prominent calcaneus and clubfoot.• Heart abnormalities: ventricular septal defect• Omphalocele, diaphragmatic hernia• Cyst of the choroid plexus
Trisomy 13 (Patau syndrome)	<ul style="list-style-type: none">• Holoprosencephaly (defects of the facial break line)• Cleft palate• Heart abnormalities such as ventricular septal defect• Polydactylism• Omphalocele• Polycystic kidneys

6. Conclusions

In conclusion, all the pregnant women who underwent the amniocentesis procedure and had a negative result had an on-term pregnancy and delivered healthy newborn babies.

As for the pregnant women who underwent the amniocentesis procedure and had a positive result, all of them decided to terminate their pregnancy due to existent fetal malformations.

The purpose of our study was to decrease the use of amniocentesis procedures and to introduce a cutting-edge technology, which is the Panorama Test for early diagnosis of fetal malformations. We tried to implement a noninvasive method (Panorama Test made from the mother's blood sample) over an invasive method which is the amniocentesis.

Our purpose has been achieved by the decrease of amniocentesis and by increasing the use of cutting-edge technology without affecting the final results in the percentage of the fetal malformations statistics worldwide.

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