Ospedale Filippo Del
Ponte

AZIENDA SOCIO SANITARIA TERRITORIALE DEI SETTE LAGHI

Sistema Socio Sanitario
Regione Lombardia
ASST Sette Laghi

S.C. Gynecology and Obstetrics

SCREENING AND DIAGNOSIS OF THE FETAL CHROMOSOMIC ANOMALIES

Information for the patient

Approximately 5% of children are born with a congenital disease, which is a condition that is determined during conception or during embryo-fetal development and causes malformative, functional, or metabolic abnormalities. To date, thousands of congenital diseases have been identified, some are evident from birth, while others can be asymptomatic for several years. Congenital diseases can be caused by genetic, environmental factors, or have a multifactorial cause. For many of these conditions, it is not possible to make a diagnosis during pregnancy.

Chromosomal disorders are responsible for 15% of the major congenital anomalies diagnosed during the first year of life and are the cause of 25% of perinatal deaths from congenital anomalies.
Down syndrome (trisomy 21), that is, the presence of three instead of two copies of chromosome 21, represents approximately 50% of all chromosomal pathologies.

Every woman, regardless of her age, is at risk of giving birth to a child affected by this chromosomal abnormality and this risk increases with increasing maternal age (see the table on the side).

Mother's age	Risk of trisomy 21 at term of pregnancy
20	1:1527
25	1:1352
30	1:895
31	1:776
32	1:659
33	1:547
34	1:446
35	1:356
36	1:280
37	1:218
38	1:167

39	1:128
40	1:97
41	1:73
42	1:55

The only way to know with certainty before birth if the fetus is affected by a chromosomal abnormality is to carry out an invasive investigation such as chorionic villus sampling (CVS) or amniocentesis. These procedures have a risk of causing a miscarriage of approximately 0.5-1%.
The Italian National Health Service allows the execution of invasive diagnostic tests such as CVS and amniocentesis without participation in health care costs (exemption from a ticket) only for women who have a basic risk of having a child with a higher chromosomal pathology, for example those who are 35 years of age or older at the time of delivery, or

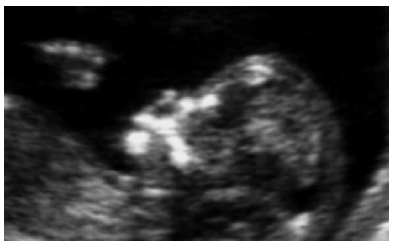
who have been diagnosed with a fetal malformation or who have a high risk estimated by a screening test.
Without prejudice to this choice of health policy, *all* couples, informed of the risks, can decide to carry out an invasive diagnostic investigation if they want to exclude with certainty that the fetus has a chromosomal abnormality and do not accept any risk margin, even if minimal, which the diagnosis is made only after birth.
Chromosomal diseases cannot be cured by therapeutic interventions in uterus, therefore the diagnosis of these conditions during pregnancy has the sole purpose of allowing the option to terminate the pregnancy (within the terms permitted by law) or to prepare to welcome the baby sick in his own life before his birth.

SCREENING TESTS

Screening tests are intended to identify those who are at risk for disease. **They do not provide a certain diagnosis**, but they estimate the individual risk (that is, they calculate the statistical probability) of being affected by a certain condition, specifically trisomy 21.
Screening tests are a useful tool if expectant parents want to get an idea how high is your risk of having a child with Down syndrome (more precisely compared to the calculation made only on the basis of maternal age), before deciding whether or not to expose yourself to the risk of invasive diagnostic tests.
There are two types of fetal chromosome abnormality screening tests: the combined test and the non-invasive prenatal test (NIPT), which is based on the presence of fetal DNA in maternal blood.

<u>COMBINED TEST</u>

It consists of a biochemical examination in maternal blood (called bi-test) associated with the ultrasound measurement of the nuchal translucency of the fetus between 11 and 13 weeks of gestation.



The **Bi-test** measures the concentration of 2 proteins produced by the placenta (freeβHCG and PAPP-A), while

the nuchal translucency is a small accumulation of fluid located on the back of the fetus neck, visible on ultrasound at the end of the first trimester of pregnancy. An increase in the thickness of the nape translucency is associated with an increased risk of chromosomal abnormalities. When the thickness increases greatly, an increased risk of malformative pathologies (for should also be considered

example, of the fetal heart), some of which can only be diagnosed later in pregnancy. Ultrasound evaluation of nuchal translucency alone identifies about 70% of fetuses with Down syndrome.

The risk values obtained by combining ultrasound and Bi-test give a better estimate of the risk of fetal chromosomal pathology than the single examination. If an invasive diagnostic test is performed only when the combined test gives a "high risk" result (defined as a probability of Down syndrome greater than or equal to 1 in 250), **approximately 85% of affected fetuses are identified.**

Like all screening tests, the combined test also has false positives (it is high risk but the fetus does not actually have trisomy 21) or false negatives (it is low risk but the fetus actually has trisomy 21). 5% of fetuses without trisomy 21 are classified as "high risk" (and will undergo an invasive procedure "unnecessarily") and 15% of fetuses with trisomy 21 are identified as "low risk" (and therefore they may not be diagnosed). **The positive predictive value (probability of actually finding the disease if the test indicates a high risk) is 7 to 10%.**

NON-INVASIVE PRENATAL TEST (NIPT) based on fetal DNA

This test attempts to identify the presence of fetuses with trisomy of chromosomes 21,18, 13 from the 10th gestational week; these trisomies represent approximately 70% of all chromosomal abnormalities.

The test directly analyzes fetal DNA (more precisely, the free DNA fragments that come from placental cells) in maternal blood. Unlike amniocentesis or CVS, NIPT ***does not*** provides a conclusive diagnosis or analyzes all fetal chromosomes.

It is a screening test, so it measures the probability of some chromosomal abnormalities. Compared to the combined test, it has a higher sensitivity for trisomy 21 (**identifies 99% or more of affected fetuses**), has a lower false positive rate (less than 1 fetus in 1000 will be "unnecessarily" subjected to an invasive procedure) and a better **positive predictive value (probability of actually finding the disease if the test indicates a high probability), on average equal to 80%** (less if the maternal age is <35 years). A "high probability" result should always be verified with invasive diagnosis. NIPT can also give a false negative result (it is a low risk but the fetus actually has trisomy 21) - this occurs in less than 1% of cases).

NIPT can also detect numerical abnormalities of the sex chromosomes, but the detection efficiency of X and Y chromosome aneuploidies is lower than that of Down syndrome (60-99%).

Sometimes the NIPT may not provide a result, for example due to insufficient fetal DNA in the maternal blood sample (about 2% of cases) or for other reasons - in this case, a consultation will be performed to evaluate the following procedure.

Although the test is technically feasible after 10 weeks, it is advisable to postpone the test after performing the first trimester screening ultrasound (11-13 weeks), in order to exclude structural abnormalities of the fetus that would lead to a diagnostic test. invasive. It is possible

to consult with a medical geneticist before deciding whether to perform this test. The laboratory conducting the test will request the signing of a detailed and specific informed consent for the NIPT.
The following table is intended to help couples choose between the different detection or diagnosis options for fetal chromosomal diseases, illustrating the main characteristics, risks and benefits. More detailed information will be provided prior to taking each of the chosen exams / tests.

It is specified that the carrying out of screening or diagnostic tests for fetal chromosomal diseases is absolutely optional: future parents can freely decide not to carry out any of these tests / procedures.

	DNA FETAL TEST	**BI TEST associated with the eco graphical measure of the nuchal translucency**	**VILLOCENTESI CVS** **AMNIOCENTESI**
When	After 10 weeks	11-13 weeks	CVS 10-12 weeks AMN 15-16 weeks
To whom	Every woman who wants it	Every woman who wants it	At the charge of the SSN only if: Older than 35 High risk to the screening Other risks factors present
How is it done	Mother's blood sampling	Mother's blood sampling	Invasive procedure (Trans abdominal injection)
Risks	None	None	Abort risk: CVS 1/100 – 1/200 AMN 1/200 – 1/500
Percentage of fetus With Down Syndrome individuated	99%	85%	99,99%
False positive	Less than 1%	5%	Less than 1%

Other information that could be found	Trisomy 18 - 99% Trisomy 13 – 79 – 92% Sex chromosomes abnormalities	Trisomy 18 – 80 – 95% Some sex chromosomes abnormalities	Numerical or structural abnormalities of all chromosomes 99,99%
Needed time to get the results	3 – 10 days (depending on the lab)	3 – 7 days (depending on the lab)	CVS direct exam 5 – 8 days Culture exam up to 3 weeks AMN up to 3 weeks
How is the result expressed	Positive /Negative for Trisomes Some labs indicate a Risk Index	Calculated risk based on the biochemical exam + mother age + nuchal translucency measure	Normal/Abnormal Fetal Karyotype
What it is done if the results are: **Abnormal** **inconclusive**	AMN/CVS echography Percentage:0,5 – 4% (more in the obese) Repeat or CVS / AMN	AMN/CVS echography Percentage: less than 1% Generally repeat	Genetic/obstetric Counselling Percentage: less than 1 - 3% Repeat the invasive procedure
Twins pregnancy	Previous counseling	Validated (decreased sensitivity)	Possible even for triplets
Approximately cost	Approximately 600 – 800 Euro	Approximately 50 – 100 Euro per each lab test	Free of charge in a Public Hospital only if there are risk factors

Ponte

AZIENDA SOCIO SANITARIA TERRITORIALE DEI SETTE LAGHI

S.C. Ginecologia e Ostetricia

INFORMED CONSENT

It is delivered to Mrs.

Surname _____

First name _____

The information on screening tests and invasive methods of prenatal diagnosis for fetal chromosomal abnormalities, in order to help the patient make an informed choice in this area. We are fully available to answer the patient's questions or provide further explanations.

Doctor's signature …… Date …….

The undersigned .... born on .....

I declare that I have received, read and understood the information given to me.

From what I have read and from the explanations given to me by the Gynecologist, I declare that I have understood the limits, advantages and disadvantages of invasive and non invasive investigations of prenatal diagnosis.
I therefore consciously declare that:

or Wanting to undergo invasive prenatal diagnosis (villocentesi, amniocentesis)

or Wanting to take the combined test, regardless of my age risk

or Not wanting to undergo any screening test or invasive prenatal diagnosis for the search for fetal chromosomal abnormalities, even though I am aware of the statistical risk of chromosomal pathology associated with the current pregnancy

or Wanting to undergo the fetal DNA research test on maternal blood

Patient's signature …… Date ……