Prenatal cytogenetic diagnosis is the analysis of the fetal chromosomal set (or fetal karyotype) and allows to identify any chromosomal abnormalities in the unborn child.
Prenatal cytogenetic diagnosis can be made by I-trimester CVS or II-trimester amniocentesis. Villocentesis and Amniocentesis are invasive collection techniques.

Both allow the determination of the fetal karyotype with similar reliability of the result.

The main indications for prenatal diagnosis of fetal karyotype are:

- maternal age> 35 years at birth
- parent of the fetus carrying a balanced chromosomal abnormality
- (chromosomal translocation or inversion)
- parents with a previous child or pregnancy with chromosomal abnormality
- altered bi-test or fetal ultrasound abnormalities.

LIMITS OF CYTOGENETIC PRENATAL DIAGNOSIS

What is not diagnosed

- all Mendelian genetic diseases associated with gene mutation (e.g. thalassemia, cystic fibrosis, muscular dystrophy, fragile X, etc.) for which the diagnosis is possible only in the case of documented familiarity and after appropriate specific consultation;

- pathologies associated with submicroscopic or cryptic chromosomal rearrangements, not detectable with routine cytogenetic diagnosis (eg S. of Prader-Willi, S. of Angelman, S. of Di George ...) which can also be diagnosed with specific techniques only in case of documented familiarity or

- ultrasound indication.

POSSIBILITY OF CYTOGENETIC PRENATAL DIAGNOSIS

What is diagnosed

The cytogenetic prenatal investigation, both carried out on chorionic villi taken by means of villocentesis starting from the 10th week + 1 day, and carried out on amniocytes obtained by amniocentesis starting from the 14th week + 1 day, is able to identify any type of chromosomal abnormality present in the fetus: numerical or structural, de novo or inherited from a healthy carrier parent.

The most frequent chromosomal number anomalies are:

Trisomy 21 S. of Down	1/ 1.000 births
Trisomy 18 S. of Edwards	1/ 2.700 births
Trisomy 13 S. of Patau	1/ 6.600 births
Trisomy X	1/ 1.000 females
Monosomy X S. of Turner	1/ 2.500 females
47,XXY S. of Klinefelter	1/ 500 males
47,XYY	1/ 1.000 males

(Orphanet database www.orpha.net)

Unbalanced numerical or structural chromosomal anomalies do not always lead to an altered clinical picture in the affected subject: it is essentially possible to distinguish **3 groups of chromosomal anomalies**:

- Autosomal anomalies (chromosomes from 1 to 22): frequently involve mental retardation of various degrees, dysmorphic / malformations.

- Anomalies of the sex chromosomes (X and Y): despite being characterized by a well-defined clinical picture, they do not involve mental retardation and are considered not serious.

- Chromosomal variants or small supernumerary markers without pathological significance and present with variable frequency in the population.

Mosaic chromosomal anomalies

Mosaic is the coexistence, in the same individual, of cells with normal karyotype and cells with chromosomal anomaly and has an incidence of 2/100 pregnancies. All the anomalies of number can be present in mosaic, but more frequently the X and Y sex chromosomes are involved. In subjects with mosaic the clinical picture is attenuated in relation to the quantity of normal cells present. The mosaic anomaly can be present in different proportions in the different tissues of the same individual, therefore the prenatal diagnosis of chromosomal mosaicism presents aspects that are difficult to interpret. Low-grade chromosomal mosaicism can escape prenatal cytogenetic investigation, both on chorionic villi and amniocytes.
The **table** attached shows the incidence of chromosomal abnormalities at birth and one S. Down, in relation to maternal age at birth. It can be noted that this incidence increases significantly after the age of 35. The frequency of births of children with chromosomal abnormalities should be compared with the invasiveness of the sample described by the number of consequent fetal losses.

VILLOCENTESI and AMNIOCENTESI

Villocentesi is a sampling of chorionic villi which constitute the fetal part of the placenta.

The chorionic villi are therefore placental structures: since a karyotype discrepancy between fetus and placenta (villi) cannot be excluded, the sample is divided into two parts, treated differently, in order to make 2 different tissues making up the chorionic villus available for analysis. . The first part (direct preparation) gives a cytogenetic result within 1 week, the second part (cultivated preparation) gives a result within 20-22 days from the sampling. The results must be in agreement. The discrepancy (1-2% of cases) does not mean 'fetus with anomaly', but it will be necessary to resort to amniocentesis to clarify the fetal karyotype.
In case of results obtained exclusively on the direct preparation (insufficient quantity of villi at sampling, absence of cell growth or maternal contamination in the culture) the reliability of the same is equal to 99%.

Amniocentesis is a sampling of amniotic fluid that is performed in the second trimester of pregnancy. . Amniotic fluid contains amniocytes, cells coming mainly from the fetus, but also from the placenta. These cells are harvested, cultured for 10-15 days. and then analyze. The cytogenetic result is available after approximately 3 weeks from the date of collection.

The most recent data obtained from numerous case series on the techniques used in prenatal diagnosis, are in agreement in identifying an abortion risk between 0.5-1.0% both for amniocentesis and CVS therefore the choice of one or the other sampling technique must take into account of the objective indication for cytogenetic prenatal diagnosis, by personal factors such as maternal anxiety or particular family / social conditions.

Reporting times:

In accordance with the indications given by the Italian Society of Human Genetics (SIGU), the reporting is expected within 21 days from the date of collection.
To be reported only to the CVS: the result of the direct preparation (valid at 99%), available within one week from the date of collection, will be communicated only in the event of a pathological result.

POSSIBLE REASONS FOR IN-DEPTH DIAGNOSTICS

- Parental karyotype control may be necessary to clarify the pathological significance of an abnormality found in the fetus.

-The finding of pseudo mosaic (possible apparent mosaic) in amniotic fluid, or of direct / cultured result discrepancy in chorionic villi provides for a subsequent amniocentesis, or, only exceptionally, a cordocentesis (high invasiveness).

-An inadequate number of metaphases (cells) that can be analyzed or poor cell growth in culture (both in amniotic fluid and in chorionic villi) make the result of the cytogenetic analysis partial or uncertain: it is possible to re-perform an amniocentesis, although, at times, it can not be advised or necessary.

-Contamination from maternal cells can occur in the culture of chorionic villi and, less frequently, in cultures of amniocytes. A follow-up amniocentesis is rarely required.

The cytogenetic prenatal diagnosis is not carried out on the person who requests it, but on a subject who, according to the current legislation has no legal recognition and whose life is placed in the background compared to psychophysical health of the mother (law 194/1978).

CHROMOSOMAL ANOMALIES AT BIRTH IN RELATION TO MATERNAL AGE

MOTHER'S AGE	CHROMOSOMAL ANOMALIES FREQUENCY	DOWN SINDROM FREQUENCY
15	1:454	1:1578
16	1:476	1:1562
17	1:500	1:1565
18	1:526	1:1556
19	1:555	1:1544
20	1:526	1:1528
21	1:526	1:1507
22	1:500	1:1481
23	1:500	1:1447
24	1:476	1:1404
25	1:476	1:1351
26	1:476	1:1286
27	1:454	1:1208
28	1:434	1:1119
29	1:416	1:1018
30	1:384	1:909
31	1:384	1:795
32	1:322	1:683
33	1:286	1:574
34	1:244	1:474
35	1:178	1:384
36	1:149	1:307
37	1:123	1:242
38	1:105	1:189
39	1:81	1:146
40	1:63	1:112
41	1:49	1:85
42	1:39	1:65
43	1:31	1:49
44	1:24	1:37
45	1:19	1:28