

REVIEW ARTICLE

# The meaning of chromosome mosaicism in chorionic villus sampling: A review

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## ABSTRACT

In the field of prenatal cytogenetic diagnosis the study of chromosomal mosaicism has attracted special attention. It is found in 1-2% of viable pregnancies and can be classified into one of three different types: confined to either cytotrophoblast or chorionic stroma, or affecting both. In this paper we review the embryological origin of chorionic villus to clarify the etiology of mosaicism, the role of mosaicism in chorionic villus sampling involving the main viable and unviable aneuploidies, chromosomal rearrangements and marker chromosomes, the importance of uniparental disomy, genomic imprinting and the effects of these factors on the course of pregnancy.

## INTRODUCTION

The development of prenatal diagnosis techniques has permitted a better understanding of pregnancy and its outcome. Nowadays it is well known that placentas and fetuses are identical from a genetic point of view and, based on this finding, researchers have used chorionic villus sampling in the first trimester to identify some genetic abnormalities of the fetus.

In approximately 2% of all gestations there is a condition in which placenta and fetus lose their identity due to an abnormal distribution of chromosomes resulting in chromosomal dichotomy between them (Kalousek, 1994). This genetic inconsistency is known as confined placental mosaicism. The effects of this mosaicism on fetal phenotype and pregnancy development depend on the chromosomes involved, the

distribution of abnormal cells among tissues and the precise stage at which chromosome mutation occurred (Kalousek *et al.*, 1992).

Chromosomal mosaicism is defined by the presence of two or more cell lineages in the same sample or individual. It is the result of postzygotic nondisjunction, anaphase lag or structural rearrangement and it represents the main difficulty in prenatal diagnosis. In the conceptus, the extent of the resultant mosaicism depends on the timing of chromosomal mutation occurrence, the cell lineage affected, and the viability of the mutation (Kalousek, 1985).

Chromosomal mosaicism can occur in two different patterns. The first may arise very early during development, prior to the differentiation of the embryonic and chorionic compartments (Simoni and Sirchia, 1994). It is generalized throughout the entire conceptus, involving both placenta and fetus, and its frequency is 0.1 to 0.3% (Hsu, 1992). The second type is considered to arise later, and may be confined to either the placenta or the fetus and not necessarily in both.

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Since chorionic villus sampling (CVS) was introduced in prenatal diagnosis, the study of chromosomal mosaicism has attracted special attention. The CVS technique may be performed in two ways: the direct method, which utilizes spontaneously dividing cytotrophoblasts (Simoni *et al.*, 1983), and long-term culture, which permits the growth of villus stroma. The literature states that 1-2% of viable pregnancies with CVS abnormalities but with a diploid fetus at 10-12 weeks, show placental mosaicism (Simoni *et al.*, 1985; Mikkelsen and Aymé, 1987). There are three different types: confined to either cytotrophoblast or chorionic stroma, or affecting both cell lineages of the placenta (Kalousek, 1994).

### **The embryology of chorionic villi: two points of view**

A brief review of embryonic development is needed for a better understanding of the etiology of mosaicism. After fertilization of the human ovum in the upper portion of the oviduct, the male and female pronuclei reproduce their DNA prior to mitosis, and undergo the first cleavage in 30 h. Subsequent cell divisions produce the morula within three days, which consists of 16 cells. The morula then produces the inner cell mass and the trophoblast. Transformations occur in the embryo and extraembryonic structures at the same time.

The human morula enters the uterus at about four days postfertilization, loses the zona pellucida, and goes from a loose assembly of cells to a tightly packed mass, at which point the embryo is called a blastocyst. The inner cell mass separates into a hypoblast and an epiblast, while the outer cell mass or trophoblast proliferates to form a thickened polar trophoblast, consisting of a cytotrophoblast which produces the syncytiotrophoblast. The latter invades the uterine wall about eight days postfertilization. The cytotrophoblast divides to form localized clumps of cells known as primary chorionic villi. During the third week post-conception, the extraembryonic mesoderm invades and invaginates the overlying trophoblast. Some mesoderm cells within the villi subsequently differentiate into blood capillaries, forming the tertiary villi (Crane and Cheung, 1988). At the same time, the amniotic cavity develops within the epiblast.

The epiblast begins its development into a embryo, with formation of the primitive streak (linear zone of cell invagination along the midline axis). Cells of the primitive streak form the embryonic endoderm (and germ cells) which grows down the midline of the embryo, leaving embryonic mesoderm and endoderm

to fill in the embryonic body that folds to acquire the shape of a definitive embryo.

The hypoblast divides the inner cell mass as a single and continuous layer down and inside of the trophoblast. The primitive yolk sac is formed when the edges of the hypoblast meet on the side of the blastocyst opposite the embryo. About 13-14 days postfertilization the primary yolk sac breaks up and gives rise to the exocoelomic cyst and Heuser's membranes. The part of the yolk sac attached to the embryo is called the secondary yolk sac, that gives rise to the vitelline duct. The break-up of the primitive yolk sac is the final stage of a process by which the hypoblast gives rise to the extraembryonic mesoderm. Cells leave the hypoblast to migrate along the inner surface of the trophoblast just prior to implantation of the blastocyst. The most important evidence for this was the identification of cells between the basal lamina of the trophoblast and the yolk-sac endoderm, which has no basal lamina. Extraembryonic mesodermal cells originate from the yolk-sac endoderm (Enders and King, 1988), which increases continuously during the first three or four days after implantation.

These explanations about the embryology of the chorionic villi were based on the papers published by Bianchi *et al.* (1993) and Enders and King (1988). In 1988, Crane and Cheung proposed an embryogenic model to explain cytogenetic inconsistencies between villi and fetus, the main difference being the origin of the extraembryonic mesoderm, which is a key structure for the study of the different types of chromosomal mosaicism.

These authors made a synopsis based on human histological studies and blastomere manipulation experiments in preimplantation embryos (Hertig *et al.*, 1956; Lockett, 1978; Gardner, 1978). They suggested that the hypoblast extends beyond the margins of the embryonic disc to form the extraembryonic endoderm, from which the yolk sac is ultimately derived. The epiblast gives rise to three structures: the embryo, amnion and extraembryonic mesoderm. The latter differentiates from the caudal margin of the embryonic disc during the third week post-conception (Lockett, 1978), and ultimately forms the chorion and mesodermal core of the placental villi. According to Bianchi *et al.* (1993), the extraembryonic mesoderm could not originate from the primitive streak because it is well developed by 10-13 days postfertilization, while the primitive streak appears only at 15-16 days. These investigators believe that, if the extraembryonic mesoderm originated from the caudal margin of the embryonic disc there would be a much closer relationship between long-term culture and fetus. However,

when they reviewed two important papers (Miny *et al.*, 1991; Ledbetter *et al.*, 1992) they noted that there are cytogenetic discrepancies between the CVS short term (direct) preparation, long-term culture, amniocentesis and fetal blood. The most important point here is that the clinical conduct in prenatal diagnosis when mosaicism is detected in CVS is the same, but the karyotype obtained from long-term culture may not be equal to the fetal karyotype, which may lead to misinterpretation of results.

most autosomal trisomies and for monosomy and trisomy of the sex chromosomes, and it is commonly detected by amniocentesis after CVS, demonstrating that the fetus is affected (Kalousek, 1994). Data from amniocentesis performed after CVS which revealed mosaicism have shown that the incidence of generalized mosaicism is 0.1 to 0.3% (Hsu, 1992; Pittalis *et al.*, 1994).

### Confined mosaicism

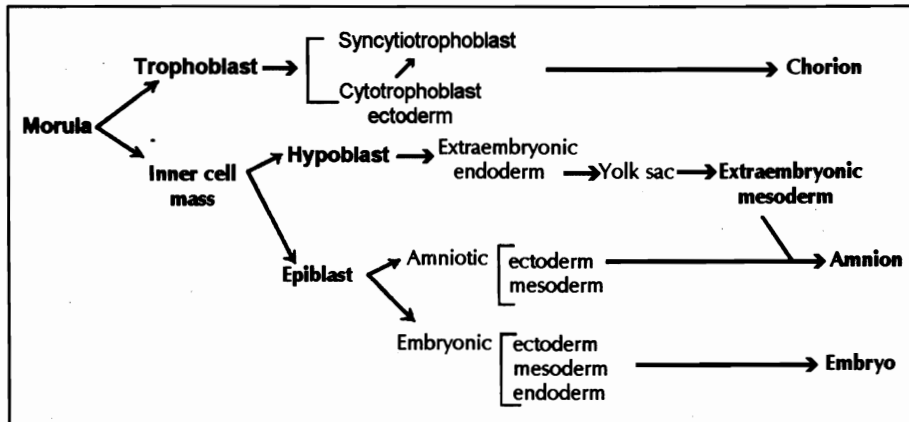


Figure 1 - Synopsis of early development with emphasis on the origin of embryo, chorion and placenta (Crane and Cheung, 1988), modified according to Enders and King (1988).

We may summarize in Figure 1 by stating that the chorion is composed of trophoblast ectoderm and extraembryonic mesoderm from the yolk sac. The placenta is composed of chorionic villi, chorionic plate and amnion, intervillous spaces, outer cytotrophoblastic shell, and decidua. The epiblast gives rise to embryonic mesoderm and endoderm via the primitive streak (Sadler, 1995; Hay, 1995, personal communication).

### Types of mosaicisms

As mentioned earlier, chromosomal mosaicism has been divided into generalized, confined to the embryo or confined to the placenta, and the type of mosaicism will depend on the time at which the mutational event occurred, and which compartments were affected.

### Generalized mosaicism

Generalized mosaicism is a mutational event originating very early during development. In this case the error of cell division occurs before blastocyst formation and affects the progenitors of both embryo and placenta. The general consensus is that when the error occurs at this stage, all tissues of the conceptus are affected. Generalized mosaicism has been described for

The extent of the resulting mosaicism depends on the timing of chromosomal mutation occurrence, the cell lineage affected and the viability of mutation (Kalousek, 1985). Mosaicism confined to the embryo/fetus originates from a mutation that occurred in the progenitor cells of the embryo proper, probably from a small number of embryoblasts in the inner cell mass, and the type confined to the placenta probably occurs as a result of unequal distribution of the embryonic and

placental progenitor cells in a mosaic blastocyst, or viable mutations that occurred in the progenitor cells of trophoblast, extraembryonic mesoderm, or both (Kalousek *et al.*, 1992). Confined mosaicism has been demonstrated not only in first trimester chorionic villi, but also in term placentas.

### Confined placental mosaicism (CPM)

Confined placental mosaicism is the most frequent type of mosaicism. It occurs in 1-2% of all pregnancies (Mikkelsen and Aymé, 1987; Simoni and Sirchia, 1994). It is defined by a partial or complete chromosomal dichotomy between placental tissues (including cytotrophoblast and villus stroma) and the embryonic fetal tissues. According to Kalousek *et al.* (1989) and Kalousek (1994) and considering the techniques used, these discrepancies can assume three different forms:

*Type I* - Mosaic or non-mosaic cytotrophoblast aneuploidy (direct method), associated with normal villus stroma (long-term culture) and fetus. The most common trisomies are for chromosomes 3, 7, 11, 13, 6 and 18, while rare trisomies involve chromosomes 5, 10, 14, 17 and 19. Monosomy in complete or mosaic form is the most frequent finding for sex chromosomes.

*Type II* - Aneuploidy of mosaic or non-mosaic villus stroma (long-term culture), associated with normal cytotrophoblast (direct method) and fetus. Commonly trisomies are for chromosomes 2, 7, 8, 9, 12, 16, 18 and 21 and rare trisomies are for chromosomes 3, 5, 10, 11, 13, 14, 15, 17, 20 and 22. Monosomy has been found as well as triploidy and tetraploidy.

*Type III* - Normal fetus associated with mosaic or non-mosaic aneuploidy cytotrophoblast (direct method) and villus stroma (long-term culture). The most commonly affected chromosomes are 7, 15 and 16, and rare trisomies involve chromosomes 2, 9, 12, 20, 21 and 22.

## Abnormal cells in the placenta

A relationship between the presence of abnormal cells in the placenta and their effects on intrauterine development and/or pregnancy outcome has been considered to occur since Kalousek and Dill (1983) first reported mosaicism associated with growth retardation of the fetus. In those cases the placentas were trisomic and the fetuses were growth retarded.

Several studies have been done to determine if abnormal cells in the placenta are the main cause of delayed intrauterine growth, fetal death, or poor perinatal outcome. Some of them suggested a positive correlation between abnormal cells and adverse pregnancy outcome (Stiou *et al.*, 1989; Reddy *et al.*, 1990; Johnson *et al.*, 1990; Wirtz *et al.* 1991; Wapner *et al.*, 1992). On the other hand, Schwinger *et al.* (1989), based on extensive CVS diagnostic experience, reported that the great majority of pregnancies with CPM proceeded uneventfully, resulting in normal liveborn infants. Wolstenholme *et al.* (1994) were unable to demonstrate a marked increase in adverse pregnancy outcome in cases with CPM in a retrospective collaborative study involving 11775 CVS chromosome analyses and 21 U.K. centers, but they noted that there was a small increase in fetal loss among cases with a chromosomally abnormal placenta.

Kalousek *et al.* in 1991 proposed an association between different types of mosaicism and intrauterine growth retardation. The authors suggested that when aneuploid cells are present only in the cytotrophoblast (type I) there is no influence on fetal growth. On the other hand, when the abnormal cells are present only in the mesenchyma (type II) there have been some cases of fetal growth retardation, although this situation is less common. The abnormal cells can also be found in both cytotrophoblast and mesenchyma (type III). This type is very rare, but when it occurs the pregnancy is fre-

quently complicated by intrauterine growth retardation and fetal death.

## Aneuploidies and mosaicism

### Rare aneuploidies and mosaicism

Since CVS in the first trimester is an early prenatal diagnosis technique, the probability to detect a chromosomally abnormal fetus by this technique is much higher than with methods used later in pregnancy. Depending on the chromosome involved, fetal survival is totally inviable so that in the second trimester the fetus has already been spontaneously aborted before testing. The presence of aneuploidies in liveborn infants, which will be discussed further on, is a very rare situation. When their presence is detected in prenatal tests, this does not necessarily mean that the fetus is affected, but the clinician should consider the possibility of intrauterine growth retardation, fetal loss or poor outcome.

## Autosomal chromosome mosaicism

### Chromosome involved - Description

#### Trisomy 3 mosaicism

Trisomy 3 mosaicism is very rare at birth, and few cases are known in malformed liveborns (Metaxotou *et al.*, 1981; De Keyser *et al.*, 1988; Gueneri *et al.*, 1989). The phenotypic effect of this mosaic trisomy, when confined to the placental tissues, is unknown. Trisomies related to group A chromosomes probably cause an imbalance involving several genes that do not permit the survival of the fetus. Creasy *et al.* (1976) suggest that trisomy of chromosome 2 or 3 is incompatible with embryo formation, resulting in the production of an empty sac. The almost exclusive association of trisomy 3 mosaicism with direct preparations and the association of trisomy 2 with cultured cells may indicate a cell-lineage-specific non-disjunction mechanism. Alternatively, significant numbers of trisomy 3 cells in the extraembryonic mesoderm layers or trisomy 2 cells in the cytotrophoblast may be incompatible with maintenance of pregnancy (Wolstenholme *et al.*, 1994).

#### Trisomy 4 mosaicism

Complete trisomy 4 represents 3% of all chromosomally abnormal abortions and seems to be inversely correlated with advanced maternal age (Hassold and Jacobs, 1984). Trisomy 4 mosaicism is very infrequent. Marion *et al.* (1990) reported a patient with this mosaicism detected pre- and postnatally and observed that an abnormal lineage was present in some tissues (amniotic fluid, cultures of placenta and forearm skin biopsy) but absent in others (cord blood,

newborn blood). The conclusion of these authors was that this mosaicism can be considered tissue-specific, and it would go unnoticed if the only technique performed were cordocentesis.

### Trisomy 7 mosaicism

Non-mosaic trisomy 7 frequently results in spontaneous abortions during the first trimester (Kajii *et al.*, 1973; Boué *et al.*, 1975). These pregnancies consist of small embryos or empty sacs with membranes but without fetal tissue. Trisomy 7 mosaicism, when detected in prenatal tests, is frequently confined to the placental tissues. In CVS it is common for this trisomy to be either confined to the cytotrophoblast or mesenchymal cells or both, but never to the fetus (Callen *et al.*, 1988; McKinley *et al.*, 1988). Some liveborn infants with trisomy 7 mosaicism have renal abnormalities (Pflueger *et al.*, 1984; Verp *et al.*, 1987). These findings are not necessarily present in the liveborn infant. Hodes *et al.* (1981) reported one without renal anomalies. Based on their experience and previous reports, Reddy *et al.* (1990) suggested that in cases with trisomy 7 mosaicism detected by CVS the couples should be advised of the possibility of false-positive or false-negative results independent of the laboratory method (direct and/or culture) employed, and should be counseled to carefully assess the fetus by serial sonography, and continue the gestation until amniocentesis diagnosis.

### Trisomy 12 mosaicism

This kind of mosaicism is very rare and poses some difficulties in prenatal diagnosis because most gestations are terminated after the first test. The incidence of trisomy 12 in spontaneous abortions is approximately 0.2% (Hassold and Jacobs, 1984). Although complete trisomy 12 has never been reported in a liveborn, multiple cases of trisomy 12p, trisomy 12q, and various other duplicated segments of chromosome 12 have been reported (De Grouchy and Turleau, 1984). The follow-up studies of this trisomy are limited because the trisomic cells are present in some tissues and absent in others. Usually trisomy 12 is found in fibroblasts, but is absent in blood cells (Meck *et al.*, 1994). When detected by CVS this abnormality has been reported to be confined to the placenta (Kalousek *et al.*, 1989; Wyandt *et al.*, 1990). Similar mosaicism has been described in Pallister-Killian syndrome the main feature of which is tetrasomy 12p in fibroblasts, but absent in lymphocytes. The mechanisms common to trisomy 12 and tetrasomy 12p are unknown (Wyandt *et al.*, 1990). A recent review of the literature (Meck *et al.*, 1994) showed 12 cases of trisomy 12 mosaicism diagnosed prenatally. Seven of these were terminated, impairing the follow-up. Among the liveborn infants, only two cases showed trisomy 12 in blood cells, but they carried abnormalities that could be features of other syndromes (Richer *et al.*, 1977; Patil *et al.*, 1983).

### Trisomy 15 mosaicism

Trisomy of chromosome 15 corresponds to about 8% of karyotyped abortions. It seems that maternal age has an influence on the formation of this trisomy because it was observed in mothers who were about 4 years older on average than mothers who had chromosomally normal abortions (Hassold *et al.*, 1984). The most important aspect of this

trisomy is that one of the chromosomes may be lost early on life, so that the trisomy would "revert" in the fetus but the placenta would remain trisomic, resulting in confined placental mosaicism (Cassidy *et al.*, 1992). The fetus could become diploid, with uniparental disomy represented by a chromosome pair originating from the same parent (mother or father).

### Trisomy 16 mosaicism

Trisomy of this chromosome accounts for 31% of all autosomal trisomies, and it is the most common type in spontaneous abortions (Warburton *et al.*, 1991). The mean gestational age for abortion in pregnancies with trisomy 16 is 11.7 weeks, with only minimal embryonic development in abortus specimens. Full trisomy 16 has not been reported in liveborn infants or second-trimester amniotic fluid samples (Garber *et al.*, 1994). Kalousek *et al.* (1993) have suggested that pregnancies which demonstrate pure trisomy of the placenta, and a diploid fetus, are likely to have originated from a trisomic zygote which lost one copy of the trisomic chromosome in early embryogenesis. They found uniparental disomy to occur in 1/3 of diploid fetuses with a trisomic placenta. Chromosome 16 has been one of the most commonly reported trisomies in such cases. The occurrence of trisomy 16 in a prenatal test is completely linked to the origin of the trisomic line, the origin of the disomic line and the possible effects of the abnormal lineage on fetal development. The two lineages, trisomic and disomic, might arise by either a) a trisomic zygote which undergoes postfertilization non-disjunction leading to a disomic cell line or b) a disomic zygote which undergoes mitotic non-disjunction to create a trisomic cell line. The main mechanisms which may cause abnormal fetal morphogenesis associated with trisomy 16 mosaicism include true fetal mosaicism, uniparental disomy, and confined placental mosaicism. The frequent finding of trisomy 16 in abortion specimens supports the idea that trisomy 16 mosaicism originates from a trisomic zygote which has subsequently lost one copy of chromosome 16. Furthermore, several researchers have demonstrated that the trisomic chromosome is of maternal origin in all trisomy 16 specimens studied (Hassold *et al.*, 1991; Kalousek *et al.*, 1993). A very important observation is that trisomy 16 may be found in skin fibroblasts but not in peripheral lymphocytes. This finding demonstrates that there is a greater selection against trisomic cells in blood cells as compared with fibroblasts, occurring either *in vivo* or *in vitro* (Lindor *et al.*, 1993). Furthermore, chromosomally abnormal cells (such as a trisomic cell line) may have a replicative disadvantage when compared to a disomic cell line (Petersen *et al.*, 1991). Thus, a trisomic zygote which undergoes somatic non-disjunction may result in an increasing proportion of cells with 46 chromosomes. This mechanism is likely to occur in rapidly dividing tissues such as blood, making percutaneous umbilical blood sampling a less useful tool in the detection of trisomy 16 (Garber *et al.*, 1994). The trisomic zygote with subsequent loss of one copy of chromosome 16 could be justified by 1) true fetal mosaicism 2) fetal and/or early non-disjunction and selective loss of the trisomic line and/or 3) trisomy 16 mosaicism confined to the placenta. True mosaicism represented by both trisomic and disomic cell lineages might disturb normal development in three ways: the trisomy lineage per se may lead to abnormal morphogenesis,

the death of an aberrant cell as a result of replicative disadvantage may lead to incomplete morphogenesis and the uniparental disomy with genetic imprinting may result in abnormal modification of genetic material. For prenatal genetic counseling it would seem that the prognosis for a pregnancy diagnosed with mosaic trisomy 16 is optimal if the trisomic line is truly confined to the placenta and associated with a normal directed ultrasound evaluation (including fetal echocardiography) and a disomic line containing both maternally and paternally derived chromosomes (Garber *et al.*, 1994).

### Trisomy 17 mosaicism

This mosaicism is a very rare condition even in the first trimester, as demonstrated by a lack of reports after routine CVS and a low frequency among spontaneous abortions in the first trimester (Hassold *et al.*, 1980). It seems that there is a strong selection *in vivo* against this trisomy, which is more frequently observed in pseudomosaicism than in mosaicism (Hsu and Perlis, 1984). Since there are discrepancies between the cytogenetic results obtained with amniotic liquid and lymphocytes or fibroblasts of the fetus/infant, it is possible that selection *in vivo* in determined tissues eliminates the trisomic cell line originally formed by postzygotic non-disjunction. On the other hand, trisomy 17 originating from postzygotic non-disjunction may be tolerated only by certain tissues (Djalali *et al.*, 1991). In CVS, trisomy 17 was demonstrated by some authors to be of extraembryonic origin due to the fact that it was present only in the placenta and not in the fetus (Kalousek *et al.*, 1987). In amniocentesis, this trisomy is not considered to have an important effect on fetal development. In a few cases the fetal mosaicism remains undetected in the cytogenetic analyses and the clinical relevance may depend on the affected tissue and the proportion of trisomic cells (Djalali *et al.*, 1991)

### Trisomy 20 mosaicism

Trisomy 20 mosaicism is one of the most common chromosome mosaicisms diagnosed prenatally, accounting for approximately 16% of all such mosaicisms (Hsu, 1986). Chromosome 20 is also the fifth most frequently observed chromosome in pseudomosaic trisomies (Hsu and Perlis, 1984), but in full trisomy it is very rare in spontaneous abortuses (Hassold *et al.*, 1980). Trisomy 20 mosaicism seems to be relatively common, yet its origin and significance remain obscure. The apparent heterogeneity in the source of the trisomy 20 cells (rectal, esophageal and renal origin), and the absence of any consistent pattern of clinical manifestations suggest that the condition does not always result in a poor pregnancy outcome (Baldinger *et al.*, 1987). The finding of trisomy 20 mosaicism in prenatal tests causes anxiety for clinicians and patients. Early detection has frequently led to pregnancy interruption; however, only a small proportion of fetuses that go to term (15%) have significant anomalies (Hsu *et al.*, 1987; Hsu *et al.*, 1991; Brothman *et al.*, 1992). Calculation of risks for use in genetic counseling is difficult because there are few reported cases of mosaic trisomy 20. Djalali *et al.* (1985) and Hsu *et al.* (1987) suggested that there was a positive correlation between frequency of trisomy 20 cells and major phenotypic abnormalities. On the other hand, Donnenfeld *et al.* (1987) and Baldinger *et al.* (1987) reported cases with more

than 50% trisomy 20 cells detected in amniocytes, that later led to a phenotypically normal fetus. The study of this mosaicism is complex. Park *et al.* (1989) indicate that confirmation in abortions of trisomy 20 which were detected in early prenatal tests is rare, and the lack of reports of postnatal confirmation suggests that the trisomy 20 cells are of extraembryonic origin and do not reflect the cytogenetic status of the fetus. On the other hand, Brothman *et al.* (1992) reported a case of mosaic trisomy 20, detected in amniocyte cultures with a high frequency of trisomic cells (79%), that was confirmed in newborn tissue. The baby was a healthy male delivered at term without dysmorphology or apparent malformations. As mosaicism was present in foreskin (25%) and fetal cord cells (17%) but was absent in newborn blood, these authors believe that the high frequency of mosaicism in this case demonstrates that trisomy 20 cells are of true embryonic origin, though their significance for the embryo still remains unclear. Since renal and cardiac abnormalities have the most important clinical meaning in this mosaicism, morphological ultrasound and echocardiography are recommended for genetic counseling (Hsu *et al.*, 1991).

### Trisomy 22 mosaicism

Full trisomy 22 in liveborn infants is extremely rare, although it is the second most frequent trisomy in spontaneous abortions, accounting for 10% of cases (Wertelecki, 1990). The clinical findings have not been well established and survival of infants with this trisomy is usually limited to only a matter of days. The identification of one extra chromosome as a complete chromosome 22 in liveborn infants was questioned even with the development of cytogenetic banding techniques (Schinzel, 1981). Even with high quality G banding of prometaphase chromosomes it is difficult to eliminate the possibility that a supernumerary chromosome 22 is not in fact a translocation product derived through recombination with another chromosome, especially if similar size segments with comparable banding patterns are involved (Slater *et al.*, 1993). There is the possibility of misinterpretation of trisomy 22 due to partial duplication of chromosome 22 resulting from 3:1 segregation of the relatively common t(11;22)(q23;q11) translocation (Schinzel, 1984), deleted D groups or partial deletions of chromosome 22. It is currently possible to distinguish these chromosome imbalances of trisomy 22 using FISH (fluorescent *in situ* hybridization) (Slater *et al.*, 1993). The phenotype of trisomy 22 has been reviewed by several authors (Kukolish *et al.*, 1989; McPherson and Stetka, 1990) and includes severe growth retardation, hypertelorism, micrognathia, low-set ears and congenital cardiac defect. The survival to term of these few infants might have been a consequence of undetected chromosomal mosaicism. The fact that the majority of fetuses do not survive to term is more related to insufficient placental function than to incompatibility of fetal development per se.

### Viable aneuploidy mosaicism

Viable aneuploidies are recognized when they are present in a the fetus in non-mosaic state, and allow survival until term. Trisomies 13, 18, 21, and rarely 8

and 9, are the only autosomal trisomies, representing the true fetal karyotype, that can be present in a second trimester diagnosis.

Trisomies for every chromosome except 1 have been described in spontaneous abortions. Some trisomies, such as 15, 16 and 22, occur more commonly, while others, such as 5, 17 and 19, are rare. They share a common feature, i.e., they usually act as a lethal mutation for embryonic development. On the other hand, less than 5% of conceptions with trisomies 13 and 18, and 20-35% for trisomy 21, are liveborn (Bond and Chadley, 1983). It seems that in trisomy 13-18 mosaic conceptions a functional compensation by diploid cells in the cytotrophoblast occurs while the remaining 95% of nonmosaic conceptions are spontaneously aborted prior to reach fetal period. For trisomy 21 the mechanism seems to be slightly different. Trisomic cells in the placenta are less deleterious to its function, so it is common to find viable gestations having trisomy 21 without mosaicism (Kalousek *et al.*, 1989).

## Chromosome involved - Description

### Trisomy 8 mosaicism

Trisomy 8 is an extremely rare condition occurring in 0.12% of all clinically recognized pregnancies and 0.8% of spontaneous abortions (Hassold and Jacobs, 1984). In the liveborn population, this trisomy is almost always found in mosaic form and no relationship has been found between the degree of mosaicism and clinical severity. The clinical manifestations of trisomy 8 include mild mental retardation, abnormalities in bones and joints, cardiovascular and urogenital malformations, deep palmar and plantar grooves and agenesis of corpus callosum (Digilio *et al.*, 1994).

Molecular studies of the etiology of trisomy 8 (James and Jacobs, 1996) showed that there are basically two mechanisms that give rise to this trisomy and these are related to mosaicism and full state. These authors also noted that trisomy 8 is found in liveborns in a mosaic state and in full state in spontaneous abortions. These authors concluded that the origin of full trisomy 8 is similar to other trisomies, usually resulting from maternal meiotic errors; non-disjunction of chromosome 8 in this population is associated with increased maternal age.

The majority of autosomal trisomies result from post-zygotic loss of the additional chromosome from a meiotically derived trisomic conceptus (Pangalos *et al.*, 1994; Robinson *et al.*, 1995). On the other hand, in contrast to the majority of autosomal mosaic trisomies, there is evidence that trisomy 8 comes from postzygotic mitotic gain of the additional chromosome, suggesting that the etiology of mosaic trisomy 8 in the liveborn population differs from that of other autosomal trisomic mosaics and that these errors are not related to increased maternal age (Robinson *et al.*, 1995).

### Trisomy 9 mosaicism

Trisomy 9 mosaicism was first described in 1973 by Haslam *et al.* (1973). Prenatal detection of this mosaicism poses a problem because some cases of this prenatally detected condition have been associated with a lack of phenotypic abnormalities, and because this trisomic condition could be limited to the fetal membranes (Hsu and Perlis, 1984; Pfeiffer *et al.*, 1984). The main features associated with full trisomy 9 include facial characteristics, such as microcephaly, dolichocephaly, prominent occiput, small and up-slanting palpebral fissures, deep-set eyes, a large bulbous nose, micrognathia, low-set and malformed ears, and skeletal abnormalities (Akatsuka *et al.*, 1979).

The prenatal diagnosis of mosaic or non-mosaic trisomy 9 makes genetic counseling difficult since this abnormality can be confined to some tissues, mainly the chorionic villi. It may be present in the fetus with or without phenotypic abnormalities and no relationship has been found between the frequency of trisomic cells and the severity of malformations (Merino *et al.*, 1993).

Saura *et al.* (1995), who reported six cases, proposed that, in genetic counseling, 1) every case of trisomy 9 diagnosed from CVS when ultrasound scan is normal requires further amniocyte investigation; 2) every case of trisomy 9 in a non-mosaic state diagnosed in amniocytes is always associated with ultrasound abnormalities. The option for termination should be discussed with the parents; 3) the diagnosis of mosaic trisomy 9 in blood lymphocytes, even when the rate of mosaicism is low (1%), must be regarded as abnormal, especially in the presence of ultrasound abnormalities. Additional karyotyping from fetal blood lymphocytes associated with amniocyte karyotyping must be performed in case of doubt, and 4) when a newborn shows phenotypic abnormalities suggesting the presence of trisomy 9, the karyotype must be performed on both lymphocytes (100 cells analyzed) and fibroblasts.

### Trisomy 13 mosaicism

In 1960, after the introduction of chromosome analysis, Patau *et al.* (1960) identified a new syndrome with several malformations. Chromosomally the main feature of this syndrome is trisomy 13. The incidence was estimated to be from 1:12000 (Hook, 1980) to 1:29000 (Goldstein and Nielsen, 1988).

It is estimated that trisomy 13 is 100 times more frequent in spontaneous abortions than in liveborn infants (Hook, 1980) and 28% of those that survive to term die during the first week, 44% in the first month and 86% in the first year (Magenis *et al.*, 1968). It seems that the cases which show mosaicism have longer survival because the malformations are rarer than in the full trisomy cases (Zoll *et al.*, 1993).

### Trisomy 18 mosaicism

Trisomy 18 is one of the most common autosomal trisomies, occurring at a frequency of 0.18% among all pregnancies that survive long enough to be clinically recognized. The great majority of conceptions with an additional chromosome 18 or 13 are spontaneously aborted, only 5% surviving to birth (Hassold and Jacobs, 1984). According to Kalousek *et al.* (1989), this frequency

corresponds to the mosaics confined to the placenta, which may facilitate complete embryonic and fetal development through functional compensation provided by diploid cells in the cytotrophoblast. The remaining 95% nonmosaic conceptions would be spontaneously aborted prior to fetal viability. Trisomy 18 is the second most common autosomal trisomy at birth, having a newborn frequency of 1/8,000 (Hook and Hamerton, 1977). The parental origin of the additional chromosome in trisomy 18 has been determined to be maternal (96.8% of cases) (Fisher *et al.*, 1995), demonstrating a strong association with increased maternal age.

### Trisomy 21 mosaicism

Approximately 1 to 2% of all Down syndrome liveborns are mosaics. These individuals show great phenotypic variability which depends on the proportion of abnormal cells. In a few cases, trisomy 21 occurs due to mitotic nondisjunction in the embryo and not due to parental meiotic nondisjunction.

Nondisjunction during first division results in a trisomic cell and a monosomic cell. The latter frequently dies, leading to the trisomic composition of the embryo. Nondisjunction during second division produces two normal cells and a trisomic cell and a monosomic cell. This results in a mosaic individual showing some Down syndrome features. It is estimated that 10% of patients with questionable diagnoses are in fact mosaics. The extent of abnormality varies with the type of tissue and the proportion of trisomic cells (Mange and Mange, 1990).

### Sex chromosome mosaicism

Most couples who seek prenatal diagnosis techniques are concerned with trisomy 21 because their risks are higher than those of the general population or for other reasons.

On the other hand, sex chromosome aneuploidy is present in 1 in 300 newborn infants, and is mostly due to the presence of an additional X or Y chromosome. A small minority of cases is due to presence of a structurally abnormal sex chromosome (Hook and Hamerton, 1977). Among fetal deaths, the situation is quite different. Less than 10% have a sex chromosome abnormality, so that the majority is due to the absence of a second sex chromosome and only a minority is due to the presence of an additional X chromosome (Hassold and Jacobs, 1984). Approximately 15% of all pregnancies that survive to be clinically recognized have a missing sex chromosome and 0.2% have an additional sex chromosome.

When diagnosed prenatally, the prognosis of sex chromosome mosaicism is usually poor and parents ordinarily choose interruption (Verp *et al.*, 1988). In these cases, genetic counseling is complicated because the prognosis is less predictable and the fetus may range

from near normal to presentation of moderately severe handicaps (Robinson *et al.*, 1989).

The main difficulty of these cases is that nobody knows the influence of abnormal cells on the fetal phenotype and frequently the cases diagnosed in prenatal tests are quite different from those diagnosed after birth. In the literature, most reports are of cases diagnosed after birth, provoking a tendency towards the finding of functional and phenotypical abnormalities.

### Chromosome involved - Description

#### XX/XY mosaicism

This is usually a pseudomosaicism resulting from maternal cell growth in a 46,XY pregnancy (Worton and Stern, 1984). This finding is very rare in CVS because maternal cells originate from the decidua which has a very low mitotic index compared to the trophoblast. Studies of parental and fetal chromosome heteromorphisms may allow diagnosis of true mosaicism (or chimerism) vs. pseudomosaicism (Gardner and Sutherland, 1989).

#### X/XY and X/XX mosaicism

The frequency of 45,X/46,XX mosaicism in studies of amniocentesis performed due to maternal age or low levels of alpha-fetoprotein in maternal serum was 1/3000 (Wilson *et al.*, 1989) and the prevalence of this mosaicism among Turner syndrome patients is about 8%-16%, or approximately 1 in 30,000 in the general population (Lippe, 1991).

Full X monosomy is not associated with advanced maternal age (Warburton, 1989). Differently from 45,X/46,XX and 45,X/46,XY mosaicism, the phenotype of prenatally diagnosed 45,X individuals, does not differ much from the postnatally diagnosed group. This is the only full monosomy that is compatible with life in humans. The loss of one X chromosome in cases which survive occurs during the first or second meiotic division, or postmitotically (Amiel *et al.*, 1996). Robinson *et al.* (1995) suggested that the loss of the X chromosome follows a normal disomic fertilization, and that the monosomic lineage arises relatively late in development, resulting in mosaicism. Moreover the parental origin of the remaining X chromosome does not influence the fetal phenotype (Hassold *et al.*, 1992).

The group of prenatally diagnosed 45,X/46,XX individuals was occasionally evaluated when the pregnant women were submitted to this procedure because of advanced maternal age or an other indication not related to Turner syndrome. This group represents the majority of 45,X/46,XX individuals who did not have any indication to seek the procedure. The same is true for the prenatally diagnosed 45,X/46,XX individuals (Wheeler *et al.*, 1988).

The comparison between prenatally and postnatally diagnosed 45,X/46,XY groups revealed that the prenatal group resulted in a predominantly male phenotype, while the postnatal group revealed a female phenotype, with ambiguous genitalia. The postnatal group usually shows great phenotypical variation that ranges from male or female phenotype to Turner syndrome individuals with mixed

gonadal dysgenesis, ambiguous genitalia and increased risk of gonadal neoplasia (Wheeler *et al.*, 1988).

Hsu (1989) and Chang *et al.* (1990) showed that there is a low incidence of genital anomalies among 45,X/46,XY individuals; approximately 90% of these prenatally diagnosed mosaic cases resulted in phenotypically normal men; however, we should consider an uncertainty of 10%. It is important to emphasize that the fertility in men who carry this mosaicism may not be warranted until this group reaches adulthood.

### Other sex chromosome mosaicisms

The most frequent karyotypes of sex chromosome mosaicism are 45,X/46,XX, 46,XY/47,XXY, 45,X/47,XXX and 46,XX/47,XXX. When they are detected in amniotic fluid culture they frequently reflect true fetal mosaicism (Hsu and Perlis, 1984). The great majority of cases of true sex chromosomal mosaicism detected at amniocentesis is associated with Y present: male, Y absent: female and normal genital development (Hsu and Perlis, 1984; Wheeler *et al.*, 1988).

### Marker chromosome mosaicism

A small marker chromosome (mar) is frequently described as a small chromosome of unknown origin. The risk of associated phenotypic abnormalities has not been well established. Its presence has been associated with infertility, mental and developmental retardation, but it is also found in phenotypically normal people (Wisniewski and Doherty, 1985).

The identification of marker chromosomes has been limited to morphological or staining characteristics. As they are mitotically stable, they should consist mainly of pericentric chromatin, containing few or no active genes (Rauch *et al.*, 1992).

Usually marker chromosomes have been classified as *de novo* or familial, mosaic or non-mosaic, and satellited or non-satellited (Kaffe and Hsu, 1988). Recently, with the introduction of chromosome-specific probes detected by *in situ* hybridization, rapid and accurate identification of these markers has been possible. Precise identification may lead to a clearer understanding of the derivation of these chromosomes and of their effect on the phenotype of the carrier (Stetten *et al.*, 1992).

The phenotypic abnormalities of the carrier are related to marker size, constitution, staining properties, mosaicism and familial occurrence (Buckton *et al.*, 1985). If a marker is constituted of euchromatin it might result in a partial trisomy for a chromosomal segment (Sachs *et al.*, 1987). Marker chromosomes occur at a rate of 0.01-0.05% among liveborn infants (Buckton *et al.*, 1980) and 0.019 (Warburton, 1984) to 0.1% (Benn and Hsu, 1984) among fetuses.

Generally, familial markers are considered benign; although they are mitotically stable, they do not cause significant phenotypic effects (Carrasco Juan *et al.*, 1990). On the other hand, the effect of a *de novo* marker is much more difficult to predict and the frequency of phenotypic abnormalities is increased in these cases, with an empiric risk of 10% to 15% (Buckton *et al.*, 1985; Callen *et al.*, 1990). As markers show great diversity, it has been observed that in *de novo* cases an increase of phenotypic anomalies occurred, suggesting the existence of functional chromatin. However, imprinting and isodisomy could also explain uncommon manifestations (Dahoun-Hadorn and Delozier-Blanchet, 1990).

Approximately half the markers reported in the literature are derived from the short arms of acrocentric chromosomes and the remainder are small centric fragments dismissed of satellites and, although often benign, they may be associated with a recognizable phenotype (Callen *et al.*, 1990).

Prenatally, marker chromosomes are considered to be a dilemma. If they are of familial origin, the counseling is more tranquilizing. If one of the parents has a 47,+mar karyotype and is phenotypically normal, it can be assumed that no discernibly increased risk for fetal abnormality exists (Tsukahara *et al.*, 1986; Brøndum-Nielsen and Mikkelsen, 1995). It may be useful to know that, in a particular family, its marker chromosome has not been associated with any phenotypic abnormality, a point that may be settled by doing a family study. But when the parent has a marker in a mosaic state, prediction for the fetus is more difficult: the chromosome could be potentially harmful, but the parent might have been protected by a particular tissue distribution (Gardner and Sutherland, 1996). In contrast, if a marker chromosome is identified as a small chromosome derived from 3:1 malsegregation and one of the parents is the carrier of a balanced translocation, serious phenotypic abnormalities are expected (Stamberg and Thomas, 1986). The global risk of phenotypic abnormalities and/or mental retardation for marker chromosomes of non-familial origin detected in prenatal tests is approximately 20% (Warburton, 1984).

Nowadays the identification of marker chromosomes and the elucidation of their clinical significance remain one of the few problems in classical human cytogenetics which will undoubtedly yield to the application of molecular techniques (Daniel *et al.*, 1994).

### Chromosomal rearrangement mosaicism

Chromosomal rearrangement could be a balanced translocation, non-balanced translocation or another category of rearrangement.

The results of large-scale collaborative studies have shown that even though quite rare, prenatally diagnosed structural rearrangement mosaicism occurs in approximately 10% of all cases of chromosomal mosaicism (Hsu *et al.*, 1996). In cases like these, it is most important to perform the parental karyotype to determine if the rearrangement in the fetus is familial or *de novo*. If one of the parents is a carrier of the same balanced rearrangement which was found in the fetus, there is no strong evidence to consider increased risk of fetal abnormalities, but we should consider a low risk (< 1%) due to chromosome defects that would not have been seen in a routine cytogenetic exam. A major difficulty is posed by rearrangement which, at the level of cytogenetic analysis, is "apparently balanced" and involves a submicroscopic abnormality (deletion or duplication, or gene disruption) (Rosenberg *et al.*, 1994).

Prenatal inference is less clear. We should emphasize that the majority of *de novo* inversions and balanced translocations result in normal liveborn. Presumably, these normal cases reflect breakpoints in sequences DNA that do not code for a gene.

In karyotype-phenotype correlations, the clinical result varies depending on the kind of structural abnormality. The data reviewed by Hsu *et al.* (1996) showed that all structurally balanced mosaicism cases, such as balanced translocation, Robertsonian translocation and inversion were associated with a normal phenotypic result. However, this was not true for non-balanced structural abnormality true mosaicism. While the majority of cases 46/47,+i(12p) resulted in abnormal abortuses (compatible with Pallister-Killian syndrome), all 46/46,i(20q) cases resulted in normal liveborn.

The overall risk to fetal abnormality, when the non-balanced structural chromosomal rearrangement mosaicism is found in the prenatal diagnosis, is approximately 40.4%. Hsu *et al.* (1996) suggested that there is an association between the percentage of abnormal cells (non-balanced structural rearrangement) and fetal phenotype. It seems that a high percentage of abnormal cells (> 60%) causes a greater risk of an abnormal fetus than a low percentage of abnormal cells (< 15%).

## Uniparental disomy (UPD)

In 1980, Engel introduced two new concepts in medical genetics: *uniparental disomy* (UPD), i.e., the presence in a diploid offspring, of a chromosome pair derived from only one of the two parents, and *isodisomy* (ID) in which a uniparental pair is a duplicate of the same chromosome.

Uniparental disomy is important for prenatal diagnosis. The cytogenetic analyses are performed by chorionic villus sampling, and by determining which cells of the mesenchyma represent tissues of extraembryonic origin, and which amniocytes or fetal blood cells are derived from the embryo/fetus proper. However, when samples of fetal origin show a diploid karyotype, this does not necessarily mean a normal chromosomal complement uniparental disomy should be considered. Since uniparental disomy may not be detected cytogenetically, molecular techniques should be used (Kalousek and Barrett, 1994).

Several probable mechanisms that give rise to UPD have been proposed: the loss of one chromosome in trisomy (early postzygotic loss of a homologue by a trisomic conceptus) and complementation of gametes (chromosome duplication in a monosomic zygote) (Engel and Delozier-Blanchet, 1991).

Postzygotic mitotic errors during embryo development are responsible for discrepancies between fetal karyotype and placenta, resulting in a confined placental mosaicism. Mechanisms for correction of the trisomy and restoration of the original diploidy in the fetus are thought to occur. It is expected that uniparental disomy is present in one third of these lineages (Hall, 1990; Engel and Delozier-Blanchet, 1991).

Uniparental disomy and isodisomy may go unnoticed. If the identical segments lack deleterious recessive genes, there might even be unexpected beneficial consequences, as may also occur with inbreeding. However, UPD is associated with genetic pathology due to i) autosomal recessive disorders in infants, particularly when only one parent is a carrier, ii) parental imprinting of genes of one chromosome whose origin is uniparental. In the latter case the phenotype will vary according to the maternal or paternal origin of the condition (Antonarakis, 1993).

Genetic imprinting may be defined as specific modifications of structurally normal genes and/or chromosomal regions, resulting in a different functional expression depending on the parental origin (Cattanach and Kirk, 1985). There are several studies suggesting that development of fetal and extrafetal tissue needs the functional presence of both the maternal and paternal genomes, or at least parts of each. Chromosomal regions cannot be replaced by a parental "equivalent", probably because those segments are imprinted. From studies on mice, it was possible to conclude that certain genes are essential for the development of trophoblastic tissues and are transmitted by the paternal genome, while genes responsible for embryo development are transmitted by the maternal genome (Kalousek and Barrett, 1994).

The homozygosity of recessive alleles justifies some cases of UPD. Some examples are UPD for chromosome 7 which is related to cases of cystic fibrosis (Spence *et al.*, 1988; Voss *et al.*, 1989), complement deficiency with UPD for chromosome 6 (Welch *et al.*, 1990) or rod monochromacy with DUP for chromosome 14 (Pentao *et al.*, 1992).

Genomic imprinting has been described in humans for the whole maternal and paternal sets of chromosomes, as well as for specific chromosomal regions (Hall, 1990). Complete moles which are composed mostly of trophoblast tissue contain only a reduplicated paternal complement of chromosomes (Lawer, 1982), while ovarian dermoids which do not show placental elements contain a reduplicated complement of maternal chromosomes derived from one unfertilized oocyte (Linder, 1975).

Prader-Willi and Angelman syndromes are classical examples of genetic diseases caused by imprinted genes, although other genetic syndromes have also been reported, such as Beckwith-Wiedemann syndrome (paternal UPD for region 11p15.5). Prader-Willi (PWS) and Angelman (AS) syndromes are two human genetic syndromes with different features of development and behavior but which are considered "sister" syndromes due to their closely similar etiology. In both there is a deletion of 15q11q13 which is cytogenetically indistinguishable. In PWS the deletion occurred in paternal chromosome 15 while in AS it occurred in the maternal homologue (Knoll *et al.*, 1989). Recent high-resolution mapping of the minimal deleted regions supports the hypothesis that PWS and AS are caused by two very closely linked but distinct genes (or gene clusters), which are oppositely imprinted (Knoll *et al.*, 1993). Additional evidence for genomic imprinting in the two syndromes was produced by detection of PWS cases with maternal disomy for the entire chromosome 15 (Nicholls *et al.*, 1989) and AS cases with paternal disomy 15 (Malcolm *et al.*, 1991).

UPD has been identified for 12 autosomes and for chromosome X. The indication for UPD study in most cases has been either a genetic pathology in an individual, such as PWS and AS, or an abnormality detected by prenatal diagnosis (mosaic or complete aneuploidy in CVS involving chromosomes other than 13, 18, and 21; presence of Robertsonian translocation). Some cases have been accidentally identified when DNA analysis is performed for other reasons (Spence *et al.*, 1988; Voss *et al.*, 1989).

A recent study (Jones *et al.*, 1995) reported a case of maternal uniparental disomy of chromosome 10. Using DNA from the couple and the baby, these investigators proved that maternal UPD for chromo-

some 10 does not produce any major imprinting effect on *in utero* growth and development, although they agreed that long-term follow-up and additional cases are necessary to assess mild imprinting effects.

## CONCLUSIONS

Chromosome mosaicism continues to be a difficulty in prenatal diagnosis and should be considered in terms of several aspects. When detected in first trimester tests like CVS, the clinicians should consider the chromosome involved and the proportion of abnormal cells. They should offer the parents follow-up tests such as amniocentesis or cordocentesis to determine the type of mosaicism (confined or generalized). If the second trimester tests do not show the mosaicism it means that the abnormal cells were confined to the placenta. In these cases the prognosis is good because the great majority of these pregnancies proceed uneventfully and result in normal liveborn infants. On the other hand, if the second trimester tests confirm the mosaicism, "true mosaicism" is considered to be present and the prognosis may not be good because there is a tendency to confirm the lineage which is in highest proportion. Mosaicism may cause early abnormal embryo preimplantation, spontaneous abortions, intrauterine growth retardation and fetal death; nevertheless, there are other cases in which the normal line cells dilute the effects of abnormal cells and the condition may remain undetected, without consequences to the pregnancy.

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## RESUMO

O mosaicismo cromossômico tem recebido atenção especial na área do diagnóstico citogenético pré-natal. É encontrado em 1-2% das gestações viáveis em um dos três diferentes tipos: confinado ao citotrofoblasto ou ao estroma coriônico, ou em ambos. Neste trabalho apresentamos uma revisão da literatura sobre: a origem embriológica da vilosidade coriônica para esclarecer a etiologia do mosaicismo, o papel do mosaicismo na amostra de vilos coriais envolvendo as principais aneuploidias viáveis e não viáveis, rearranjos cromossômicos e cromossomos marcadores, a importância da dissomia uniparental e impressão gênica, e os efeitos destes fatores na evolução da gestação.

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