UPD AND TFM AFTER DETECTION OF MOSAICS IN CVS:
CHROMOSOME SPECIFIC RISKS FROM 52.673 DIAGNOSES
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INTRODUCTION
Chromosome mosaicism is the bane of cytogenetics prenatal diagnosis (PD). It’s detected in 1-2% of chorionic villi samples (CVS) and can involve different numerical and structural chromosome abnormalities and feto-placental cell lineages. Most time it turns out to have been a false alarm such as in the case of confirmed placental mosaicism (CPM) 1. It can be caused by a mitotic error in a normal conceptus or by a mitotic error with a subsequent mitotic event generating a normal cell line. Trisomy rescue of an abnormal conceptus can also be seen in unilateral dysmorphism (UPD) in the fetus 2. The distribution of the normal and abnormal cell lines in fetus and in placenta depends on the time and place of the mitotic error. To define if mosaicism are CPM or generalized to fetus (TFM) a confirmatory amniocentesis is advisable, although Daniel et al. 3 have reported that 10% of CVS interpreted as CPM may reflect a cryptic fetal mosaicism which might or might not have phenotypic consequence.

AIM OF THE STUDY
We report a retrospective survey of 52.673 consecutive prenatal diagnoses on CVS performed in a single center (TOMA laboratory) from 2000 to 2012. In this study we included 1,386 mosaics on CVS, of these 866 were followed by amniocentesis with the aim to explore the risk of TFM and UPD in relation to:

1) distribution of the abnormal cell line in placental tissues
2) chromosome abnormality
3) chromosome involved.

MATERIALS AND METHODS
Chromosome analyses were performed in agreement with the Italian Guidelines which are consistent with the European ones. Standard protocols were used to set up the cultures and chromosome preparations, the applied banding techniques were QFQF- karyotype was formulated following the ISCN2 indications progressively updated during the survey period. CVS analysis was performed combining short-term culture (STC) and long-term culture (LTC) while for amniotic fluid (AF) samples in situ cultures were harvested. A condition of mosaicism was defined as the presence of at least two cells with the same numerical or structural chromosome and chromosome TFM was defined as the presence of at least one colony showing the same abnormality previously observed in CVS. UPD was explored in all cases involving a proposed or documented imprinted chromosome (chromosomes 2, 6, 7, 11, 14, 15, 16 and 20) by microsatellite segregation analysis from parents to fetus. The present survey includes also all cases previously reported by Grati et al. 4,5 and the data are presented in the same format of “EUCROMIC study” 6 to facilitate the comparison.

RESULTS
All cases of mosaics on CVS, the number of cases followed by AF and all TFM cases detected are reported in Table 1. The B86 cases followed by AF were classified into six classes of mosaicism on the basis of tissue involved (Figure 1) and the relative frequencies are reported in Table 2. The risk of fetal involvement also considering mosaicism (MA) and non mosaic abnormalities (NMA) are reported in Table 3. Tables 4, 5, 6 and 7 report all B86 cases of CPM and TFM divided on the basis of chromosome abnormalities. UPD was detected in 6 cases involving a proposed or documented imprinted chromosome, see Table 8.

DISCUSSION

General Frequencies
- The frequency of chromosome mosaicism on 52673 cases of CVS and LTC was 2.14% similar to the frequencies reported by other authors 12. Nowadays not combining the two methods this percentage was redefined as 1%.
- The general risk of fetal involvement (TFM) was 12.7%, comparable with EUCROMIC one (10.4%). This value can decrease or increase on the basis of the distribution of the abnormal cell line in placental tissues (Table 3).
- The difference between TOMA and EUCROMIC studies as shown in table 3 are the risk of TFMIV (4.35% vs. 3.3%). These differences could be caused by the different maternal age.
- Trisomies 2, 3 and 7 were the most common autosomal trisomies detected in TFM in mosaic condition was always confirmed as TFM (6 cases).
- After detecting a mosaic 47,XXY karyotype on CVS, the risk of TFM was 32% (611 cases).

Structural Chromosome abnormalities and markers
- The highest frequency of TFM was detected in the karyotype with mosaic supernumerary marker chromosome 35% (9546) with similar frequency of sat and no sat confirmed at amniocentesis.
- The risk of TFM in the presence of RbAbalanced rearrangement is low 5%, while among TFM cases with a 46, balanced near karyotype two involved a Robertsonian translocation and two a reciprocal translocation.

Polyploidies and multiple trisomies
- Only triploidies were confirmed, on AF while tetraploidies were always CPM. There are rare clinical reports of fetus/infants with mosaic tetraploidy consequently we suggest to consider this finding only in the presence of ultrasound abnormalities.
- In the presence of multiple autosome trisomies with normal cell line as reported by Partal (personal communication, 2002) a fetal involvement is never seen.

UPD risk
- UPD was detected in 6 cases (2.35%) involving chromosomes 4, 15 and 16. 5/6 UPD cases were CPM.
- The two cases of UPD14 were both CPM with a low level of trisomy 14 in the cytogenohraphy. Consequently these cases were be underestimated if STC were not harvested or if analysis was performed combining LTC and QF-PCR for common aneuploidies, as most laboratories now offer.

The indication for prenatal diagnosis was advanced maternal abnormality

CONCLUSION
Despite of the majority of mosaicism identified at CVS does not presage an abnormal baby, we have presented the risk of TFM related to the type of chromosome abnormality detected and the distribution of the abnormal cell line in placental tissues. We think that our experience could be used as a reference during genetic counseling to the couple after detecting a mosaicism at CVS.

REFERENCES