Confined placental mosaicism

Dagmar K Kalousek, Michel Vekemans

In most pregnancies the chromosomal complement detected in the fetus is also present in the placenta. The detection of an identical chromosomal complement in both the fetus and its placenta has always been expected as both develop from the same zygote. However, in approximately 2% of viable pregnancies studied by chorionic villus sampling (CVS) at 9 to 11 weeks of gestation, the cytogenetic abnormality, most often trisomy, is confined to the placenta.1-4 This phenomenon is known as confined placental mosaicism (CPM). It was first described by Kalousek and Dill5 in term placentas of infants born with unexplained intrauterine growth restriction (IUGR). Contrary to generalised mosaicism, which is characterised by the presence of two or more karyotypically different cell lines within both the fetus and its placenta, CPM represents tissue specific chromosomal mosaicism affecting the placenta only. The diagnosis of CPM is most commonly made when, after the diagnosis of chromosomal mosaicism in a CVS sample, the second prenatal testing (amniotic fluid culture or fetal blood culture analysis) shows a normal diploid karyotype. (J Med Genet 1996;33:529-533)

Key words: confined placental mosaicism; uniparental disomy; intrauterine growth restriction.

Types of CPM

There are three types of CPM, categorised according to the placental cell lineage exhibiting the abnormal cell line (fig 1, table 1). Placental mosaicism can be confined to either cytotrophoblast (type I), chorionic stroma (type II), or both cell lineages (type III). CPM is the result of viable postzygotic mitotic mutation(s) occurring in either the progenitor cells of specific placental cell lineages or the true embryoblasts. It can arise in both a diploid conception (mitotic CPM) or in a viable dividing chromosomally abnormal zygote (meiotic CPM). A diploid non-mosaic fetus with chromosomal trisomy confined to both cell lineages of the placenta (type III CPM) implies that the conceptus was originally trisomic (meiotic CPM). At present there is no nomenclature designated for various types of CPM and therefore we propose to label CPM16 as a confined placental mosaicism involving chromosome 16 without specification of its type.

Developmental aspects of CPM

The existence of a discrepancy between the chromosomal constitution of chorionic tissue and embryonic/fetal tissues is the result of complex developmental events during early embryogenesis. Both the cell lineage involvement and the timing of the occurrence of the second viable cell line are equally important in the final cell distribution. It has been shown in rodents that, between the eight cell stage and the blastocyst, the cells situated in the innermost layers contribute more frequently to the inner cell mass formation than do the peripheral cells.6 The elegant experiments with manufactured hexaparental mice performed by Markert and Petters7 have shown that the wall of the blastocyst gives rise exclusively to the chorion and that the complete embryo is derived from only three cells of the inner cell mass. The remaining cells of the inner cell mass contribute to the development.

Table 1. FREQUENCIES OF VARIOUS TYPES OF CVS MOSAICISM AND CELL LINEAGE INVOLVEMENT IN CPM

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>CPM16</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:</td>
<td>51/2612</td>
<td>0.9%</td>
</tr>
<tr>
<td>II:</td>
<td>24/0.9%</td>
<td></td>
</tr>
<tr>
<td>III:</td>
<td>7/0.2%</td>
<td></td>
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</tbody>
</table>

of extraembryonic structures such as the yolk sac, allantois, and some parts of the amnion.

The morphogenesis of human cleavage embryos has not been studied experimentally in as much detail as that of mouse embryos. In both species, however, the histological appearance of the inner cell mass and the pattern of formation of the embryo proper suggests great similarity in the early stages of embryogenesis. The knowledge that only a few embryonic progenitor cells are selected from the inner cell mass at the blastocyst stage profoundly changes our understanding of the development of human mosaic morulas.

The significance of the cell lineage involved in the chromosomal mutation and of the timing at which the second viable cell line appears is obvious. These two factors determine whether the mosaic morula develops into a conceptus characterised by chromosomal mosaicism expressed in both the placenta and the fetus or by chromosomal dichotomy between chorionic and embryonic/fetal tissues. When the second viable cell line arises at the first postzygotic division or shortly thereafter, the distribution of the cells of both genotypes in the morula will be more or less even if the cells are distributed randomly. This will result in an increased possibility of generalised chromosomal mosaicism expression in both the embryo and the placental trophoblast and chorion. When, however, the second viable cell line emerges after the third postzygotic division, the position of a mutant cell in the morula determines its impact on the formation of the embryo proper. An unequal distribution of both cell lines in the inner cell mass increases the probability that only one cell line will be involved in the formation of the embryo proper and a mosaicism confined to the trophoblast or the chorion will result (fig 1). Significant confined placental mosaicism can also originate after the morula stage as shown below.

Clinical consequences of CPM

It has been estimated that approximately 16 to 21% of pregnancies with CPM show prenatal or perinatal complications. In particular CPM may be associated with a spectrum of fetal manifestations ranging from normal pregnancy outcome to intrauterine death of a chromosomally normal fetus, IUGR, or even delivery of larger than normal size fetuses. For example, a recent review showed 73, mostly individually reported pregnancies with CPM, to have either IUGR or complications resulting in intrauterine fetal death.

When placental mosaicism detected by first trimester CVS has been associated with poor perinatal outcome, intrauterine growth restriction, and fetal loss, it has been postulated that chromosome specific mosaicism could be responsible for suboptimal placental function and associated pregnancy complications. For example, variable outcome of 84 pregnancies with prenatally diagnosed CPM is shown in table 2. However, other clinical reports suggested that the effect of CPM was minimal or non-existent.

The effects of CPM on development may vary with the timing of the chromosome involved, the type of chromosome abnormality, the proportions of the different chromosome complements present, and the tissues affected. For example, CPM type I is frequent (table 1) and appears to be associated with spontaneous abortion and IUGR. CPM type II is also frequent but its effect on fetal development remains unknown.

The outcome appears to depend also on the nature of the chromosome abnormality as well as the number and the viability of placental cells with an abnormal chromosomal complement. Trisomy 16 is the most common aneuploidy observed in CPM. Other frequently reported aneuploidies include trisomies 2, 7, 9, 15, and 22. Interestingly enough, there is a good correlation for some chromosomes involved in chromosomally abnormal spontaneous abortions and those involved in CPM. This suggests that for some chromosomes CPM is mostly the meiotic type whereas for other chromosomes it is the mitotic type. CPM involving monosomy, except for sex chromosome monosomy, does not occur as frequently, presumably because chromosome loss is likely to result in a viable placental cell progeny but other factors might be involved.

In addition to the previous considerations, the low predictive value of CPM is also explained by data shown in table 3. Overall, CPM is confirmed at term in the majority of originally diagnosed pregnancies in CVS. Among individual chromosomes there is heterogeneity, however, with chromosome 9 and 16 having the strongest tendency to persist to term in a form of trisomy/diploidy mosaic. Since not all prenatally diagnosed CPM persists to term, correlation of pregnancy outcome with CVS diagnosis is limited. An accurate interpretation of the effect of CPM is only possible when the term placenta is analysed extensively and the pregnancy course and outcome is correlated with the extent of aneuploid involvement in the term placenta.

Table 2 Prenatally diagnosed CPM for various chromosomes and incidence of IUGR at birth in 105 pregnancies

<table>
<thead>
<tr>
<th>Chromosome involved</th>
<th>No of cases with CPM</th>
<th>IUGR at birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

$\chi^2=12.81$, df=6, p=0.05. Delozier-Blanchet, personal communication.

Table 3 Correlation of persistence of confined placental mosaicism to term and IUGR in 80 pregnancies

<table>
<thead>
<tr>
<th>Prenatal diagnosis of CPM in 80 pregnancies</th>
<th>IUGR</th>
<th>Normal birth rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS mosaicism only</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>CVS and term placenta mosaicism</td>
<td>16*</td>
<td>44</td>
</tr>
</tbody>
</table>

* Trisomy 2(2), 7(3), 9, 15, 16(8), and 22. D K Kalousek, personal communication.
Genetic consequences of CPM
The genetic consequences of CPM can exert themselves on the fetus, on the placenta, or both. The consequences of CPM on the placenta remain unknown but some information has been gathered concerning the genetical consequences of CPM on the fetus.

Correction of aneuploidy
Among several types of postzygotic mitotic errors that can result in CPM, the most significant is correction of aneuploidy, summarised in fig 2.

As illustrated in this figure, the outcome of the postzygotic loss of the extra chromosome is mainly dependent upon the cell lineage involved, but it is also influenced by the timing of the correction and the nature and type of chromosome involved.

When the trisomic chromosome is lost in the trophoblast progenitors (epithelial lining of the placenta), a viable non-mosaic trisomic infant is delivered (fig 2A). For example, mosaicism involving diploidy in the cytotrophoblast appears to be required for the rescue of trisomy 13 and 18 conceptions.19 If the correction of aneuploidy involves the loss of the extra chromosome in the embryo, a diploid non-mosaic fetus/newborn develops, supported by a trisomic placenta (fig 2B).

Uniparental disomy
Depending on the parental origin of the lost chromosome, the two remaining chromosomes in the fetus may be of both maternal and paternal origin (biparental disomy, BPD) or may be of only one parental origin (uniparental disomy, UPD), as shown in fig 3. The concept of UPD was first introduced and later excellently reviewed by Engel.20

If two different homologous chromosomes derive directly from one parent, the term heterodisomy is used; if both homologues are identified and derived from one parent, isodisomy is used. On average, one third of the aneuploidy correction would be expected to result in fetal uniparental disomy but this might well be chromosome dependent. Using this figure and assuming that all cases of CPM type III result from trisomic zygote rescue, one can estimate that the prevalence of UPD around 9 to 10 weeks of pregnancy in this population of women is about 8/10 000. As mentioned previously, CPM involving monosomy does not occur as frequently. In this instance, however, the correction of the monosomy by postzygotic duplication of the single homologue producing an isodisomy should be considered.

Figure 2 Diagram illustrating trisomic zygote rescue. (A) Intraretinal survival of trisomic fetus correlates with the presence of a diploid cell line in the cytotrophoblast owing to early postzygotic mitotic loss of the trisomic chromosome. (B) A mitotic mutation in the embryonic progenitor cells results in a diploid fetus and trisomic placenta.

Figure 3 Diagram illustrating the difference between biparental and uniparental disomy.
UPD and chromosomal imbalance

The effect of fetal UPD on prenatal and postnatal development in most pregnancies with CPM has not yet been well defined. There are several published reports documenting UPD in pregnancies with CPM for trisomies 7, 14, and 16.21-24 In these reports, however, the phenotypic consequences of fetal UPD may also depend upon the specific chromosome involved in CPM and its effect on fetal or placental functions or both. For example, an association between CPM involving trisomy 16, fetal UPD 16, and IUGR was documented in one out of two cases reported by Bennett et al.,34 and in all four cases reported by Kalousek et al.26 However, studies of CPM for chromosome 16 indicated that IUGR was related to the presence of a high percentage of placental trisomy 16 cells, resulting in placental malfunction, rather than to fetal UPD 16 (table 4). For example, the table illustrates that in cases of CPM with high levels of trisomy 16, IUGR is also found when the fetus has biparental origin of chromosome 16 and a normal birth weight is recorded in an infant with UPD 16 and low level of trisomy 16 in placental cells.

UPD and genomic imprinting

One effect of UPD on the prenatal or postnatal development is dependent on the presence of “imprinted” genes carried by the involved chromosomal pair. The term “genomic imprinting” refers to an epigenetic phenomenon which sets a parental signature on a specific DNA segment during gametogenesis or before fertilisation so that it is modified and functions differently, depending on the parental original of the DNA segment. One of the characteristics of genomic imprinting is that this differential allelic expression is observed also when biparental heterozygosity is preserved. Among the first and most general indicators of the effect of genomic imprinting were observations that both complete maternal and paternal sets of chromosomes are essential for undisturbed embryonic and fetal development in mice.27 28 Neither androgenic (diploid paternal) nor gynogenic (diploid maternal) embryos could complete normal intrauterine development. Gynogenic embryos constructed by replacement of a male pronucleus with a female pronucleus were found to grow normally only to early somite stages with unusually small extraembryonic placental tissue. An inverse situation was observed in androgenic embryos induced by transplantation of a male pronucleus into a zygote from which the female pronucleus had been removed. These gave rise to predominantly extraembryonic placental tissues with severely stunted embryos. From these experiments it was concluded that certain genes which are essential for growth of trophoblastic tissue are expressed preferentially from the paternally transmitted genome, while the maternally transmitted genome can provide all the essential genes needed for early development of the embryo proper. More specific evidence for the non-equivalence of maternal and paternal genomes came from breeding experiments using strains of mice which carried various Robertsonian translocations. In appropriate crosses it was possible to produce UPD for particular chromosomes or chromosomal regions and to show an abnormal phenotype for certain UPD regions.29 Clinical observations in humans correspond to those seen in experimental animals.30 31 The expression and consequence of UPD and genomic imprinting in man is probably best exemplified in two genetic syndromes, Prader-Willi syndrome (PWS) and Angelman syndrome (AS).32 33 Most often, both syndromes result from chromosomal deletion in bands 15q11-13, paternal chromosome 15 being deleted in PWS and maternal in AS. PWS also results from maternal UPD for chromosome 15 and AS is phenotypically expressed with paternal UPD for the same chromosome. Thus, in the cases of CPM 15 reported by Purvis-Smith et al.,34 Cassidy et al.,35 and Morichon-Delvallez et al.36 maternal UPD of chromosome 15 resulted, as expected, in a PWS phenotype. For chromosomes other than chromosome 15, phenotype findings associated with UPD can include abnormal growth in some cases, mental retardation, non-distinctive minor anomalies, and less often congenital abnormalities, as reviewed by Schinzel in 1993.31

UPD and loss of heterozygosity

Another consequence of UPD is the expression of a recessively inherited mutation. For example, autosomal recessive disorders have been shown to be associated with UPD, including methylmalonic acidemia, transient neonatal diabetes mellitus, and UPD 6.37 38; cystic fibrosis or Silver Russel syndrome and UPD 7;39 40; rod monochromacy and UPD 14;41 Bloom syndrome and UPD 15; and haemophilia and UPD X.42 Knowing the frequency of isodisomy and the frequency of a recessively inherited mutation, one can estimate the frequency of an association of UPD and the expression of an autosomal recessive condition.43 Interestingly, the lower the frequency of recessively inherited mutation, the higher the probability that its expression will be associated with UPD. This is somewhat equivalent to what has been observed for cousin marriage.

In summary, the clinical significance of fetal UPD for each specific chromosome needs to be carefully studied in a larger number of cases and correlated with findings in the term mosaic placentas before any definite conclusions about CPM and UPD can be made and used for prenatal counselling.

### Table 4 Frequency of fetal IUGR and UPD 16 compared to frequency of IUGR and CPM 16

<table>
<thead>
<tr>
<th></th>
<th>At birth</th>
<th>IUGR</th>
<th>UPD 16</th>
<th>BPD 16</th>
<th>CPM 16</th>
<th>Diploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalbirth weight</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

IUGR and UPD: $X^2=1.06$, df=1, p=0.30. IUGR and CPM: $X^2=11$, df=1, p<0.001.

Conclusion
It is important to apply molecular cytogenetic methodology that allows efficient evaluation of both placental lineages involved and the distribution of mosaicism in term placentas. Use of interphase analysis for the evaluation of the distribution of mosaicism within the term placentas contributes to our understanding of the variable clinical outcomes reported in pregnancies with CPM. Further studies of term placentas and fetal DNA are needed in pregnancies with both normal and abnormal fetal growth to determine the role of CPM and fetal UPD in intrauterine fetal growth and survival.

It is a new role for the clinicians, the paediatricians, the obstetricians, and the geneticists, to teach their colleagues the importance of complete placental examination in cases of any abnormal pregnancy course or outcome. Placenta from such pregnancies requires not only morphological but also cytogenetic and molecular examination. The use of molecular cytogenetic techniques allow rapid and inexpensive detection of any significant chromosomal defect confined to placental tissue. Only the future will show us how many paediatric consultations will find the knowledge of placental genetic make up useful.

The financial support of Medical Research Council of Canada grant MA-12152 and March of Dimes Birth Defects Foundation grant 6-FY95-0131 is acknowledged.

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doi: 10.1136/jmg.33.7.529

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