CURRENT TOPIC

Confined placental mosaicism and intrauterine fetal growth

Valia S Lestou, Dagmar K Kalousek

Fetal growth is a complex and dynamic process regulated by a large number of interactive factors of fetal, maternal, and placental origin. As a result, any abnormality of fetal growth has a complex multifactorial pathogenesis. It has been estimated that about 50% of intrauterine fetal growth is determined by fetal genes.1 Maternal disease, her nutritional intake and behaviours, such as smoking, also influence fetal growth. The placenta develops to its full size during the second trimester, to facilitate the fetal growth acceleration after 20 weeks of gestation. An abnormal pattern of placental growth earlier in gestation may result in abnormal fetal growth in the late second or third trimesters.

A recently described genetic condition, confined placental mosaicism (CPM), has been shown to cause clinically significant intrauterine growth restriction (IUGR) or even intrauterine fetal death. CPM is the most common form of constitutional chromosomal mosaicism which is defined as at least two cell lines with different chromosomal complements in a fetoplacental unit derived from a single zygote. In CPM only the placenta is affected unlike in generalised chromosomal mosaicism where both the fetus and the placenta are involved. Since the first report associating CPM with idiopathic IUGR in 1983, our understanding of its prevalence and origin, as well as its specific effect on fetal growth, has increased exponentially.2

Intrauterine growth restriction (IUGR)

Abnormal fetal growth represents a major cause of perinatal morbidity and mortality. IUGR is defined as a pathological process that affects normal fetal growth and results in an infant whose growth is less than its genetic potential. In contrast, the small for gestational age (SGA) infant is one whose birthweight is less than a specific cut-off point, based on average weight for a specific gestational age, usually between the 10th and 5th percentile.3–5 It is obvious that for prognostic, counselling, and management purposes it is essential to discriminate between an infant for whom intrauterine growth has been restricted and that for whom being small is normal. Given the existing difficulty in accurate differentiation between IUGR and SGA, it is important to identify the specific causes of reduced intrauterine fetal growth to understand the long term implications of the newborn’s condition.6 For the purposes of this article the terms IUGR and SGA follow those in cited references; a number of SGA infants are included in some IUGR studies.

SGA or IUGR neonates have comparatively high levels of perinatal morbidity and mortality.6 7 Recent epidemiological studies suggest a link between reduced fetal growth and the subsequent development of diseases such as diabetes, coronary heart disease, and hypertension.8 9 Fetal adaptation to adverse placental function, of which low birthweight is the most obvious marker, may “imprint” an individual in such a way that internal organs become permanently defective in their structure and function in adult life.

In spite of high quality prenatal care and postnatal morphological examination of the placenta, the cause of abnormal fetal growth in most infants with IUGR remains undetermined. Various environmental and genetic factors, however, have been associated with IUGR. These can be divided into maternal—alcohol, smoking, illegal drugs, malnutrition, essential hypertension, diabetes—fetal—infec-

Developmental aspects of confined placental mosaicism (CPM)

One of the prevailing beliefs dominating the interpretation of the pathogenesis of abnormal intrauterine development has been based on the assumption of a genetic identity between the fetus and its placenta. However, in around 1–2% of viable pregnancies studied by chorionic villus sampling at 10–12 weeks of gestation, a cytogenetic abnormality, most often trisomy, is confined to the placenta and is absent in the fetus.10 11 This genetic diversity in the conceptus is known as CPM. Pregnan
cies
Note that, in theory, a third of cases of meiotic CPM develop this. Figure 2 Principle of origin of fetal uniparental disomy during trisomic zygote rescue.

Figure 1 Mechanisms of origin of mitotic and meiotic CPM. (A) Mitotic CPM arises from a diploid zygote when a postzygotic error occurs in one of the placental cell lineages (trophoblast or mesenchymal stroma). Usually, the placentas with mitotic CPM will have localised trisomic regions and low levels of mosaicism. (B) Meiotic CPM is a result of a localised trisomic region and low levels of mosaicism. At term, placentas with mitotic CPM have high levels of mosaicism or even 100% aneuploidy.

with CPM and a non-mosaic diploid fetus show normal diploid cytogenetic results in amniotic fluid cell cultures in the second trimester. Prenatally diagnosed CPM usually persists throughout gestation and can be demonstrated in the term placenta.11

Based on the origin of the trisomic chromosome in the placenta, CPM can be designated as either mitotic or meiotic (fig 1). In mitotic CPM the trisomic cell line arises from postzygotic mitotic duplication of one chromosome in the progenitors of a placental cell lineage (either trophoblast or extra embryonic mesenchyme) in the developing normal diploid conceptus. In meiotic CPM a trisomic zygote is rescued at the blastocyst development stage by loss of the extra chromosome during mitotic cell division in the embryonic progenitor cells, while the progenitors of the placenta remain trisomic.14 Meiotic CPM may be associated with uniparental disomy, which is defined as the derivation of a pair of homologous chromosomes from one parent. In theory, one third of the trisomic zygote rescues are expected to result in fetal uniparental disomy for the chromosomal pair which is trisomic in the placenta (fig 2). In association with CPM, uniparental disomy may also negatively affect intrauterine growth of the fetus.15

IUGR and CPM

To what extent does the genetically abnormal placenta influence intrauterine fetal growth and pregnancy outcome? There are two types of pregnancy outcome studies describing either detection of CPM at chorionic villus sampling (10 to 12 weeks of gestation) or in the term placenta of pregnancies associated with SGA and IUGR. Both the timing of placental analysis (CVS vs term placenta) and its completeness (both trophoblast and chorionic stroma analysed) should be considered before correlating CPM with pregnancy outcome.

An increase in pregnancy complications as well as completely normal pregnancy outcomes have been documented in clinical follow up studies of CPM diagnosed at CVS.2528 The clinical significance of CPM detection is determined by the type of CPM and specific chromosome involvement. Type I CPM is reported to result in spontaneous abortion, IUGR, intrauterine death or perinatal morbidity in 22% of affected pregnancies.29 Type II CPM is mostly found in pregnancies with a normal outcome and rarely with fetal IUGR or intrauterine fetal death.29 In type III CPM,
Confined placental mosaicism and intrauterine fetal growth

An abnormal outcome of pregnancy outcome with CPM diagnosed at chorionic villus sampling is usually determined by persistence of high levels of the placental aneuploidy (mostly trisomy) throughout gestation. The analysis of term placentas from pregnancies with prenatally diagnosed CPM revealed a 35% prevalence of IUGR when high levels of aneuploid clone were present, while low levels or absence of mosaicism at term correlated with a normal fetal weight. The prevalence of CPM detected at term in IUGR pregnancies without prenatal CVS diagnosis is reported to be between 8% and 60%. The studies including non-idiopathic IUGR pregnancies, such as those with history of heavy maternal smoking, usually detect a low prevalence of CPM. On the other hand, when placentas from idiopathic IUGR pregnancies with birthweights below or equal to the 5th percentile are selected, CPM has been detected in 20% or more. Therefore, for greater efficiency of CPM detection in IUGR pregnancies, only placentas from idiopathic IUGR pregnancies without obvious maternal, fetal, and placental causes should be included. Additionally, both placental cell lineages, trophoblast as well as chorionic stroma, should be analysed before excluding a diagnosis of CPM.

The exact mechanism by which abnormal cells in the placenta affect fetal growth and even lead to fetal intrauterine death remains unknown. Although pregnancies with fetal uniparental disomy are often complicated by IUGR, abnormal fetal growth is probably caused by a highly trisomic placenta rather than just uniparental disomy in the fetus. For example, severe IUGR has been reported for placentas with high level CPM 16 in association with both biparental disomy (16) and uniparental disomy (16) fetuses. The same study reported a low level of CPM 16 in a placenta with a normal birthweight infant with upd16. As CPM and uniparental disomy often occur in association with one another, the effects of each are difficult to discern when only small numbers of affected pregnancies are reported.

Detection of CPM

To make an accurate diagnosis of CPM all three embryonic cell lineages (trophoectoderm, extra embryonic mesenchyme, embryo proper) should be cytogenetically evaluated. The trophoectoderm lineage is represented by the trophoblast (cytotrophoblast or syncytiotrophoblast). Fibroblasts of chorionic stroma and chorionic plate represent extra embryonic mesenchyme lineage. All fetal cells and the amniotic epithelium are derived from the embryonic progenitors.

For postnatal investigation of placentas from pregnancies complicated by idiopathic IUGR and fetal death, the most effective approach currently available is comparative genomic hybridisation (CGH). CGH is a technique which offers a molecular approach to cytogenetic analysis and allows the entire genome to be screened for chromosomal imbalances in a single experiment, thus avoiding tissue culture artifacts and culture failures. CGH involves co-hybridisation of differentially fluorochrome labelled placental DNA (such as FITC, green) and normal control DNA (TRITC, red) to normal metaphase chromosome preparations. The ratio of the two fluorochromes (TRITC:FITC) is estimated at each chromosome position to provide a percentage of copy number difference. CGH is particularly useful in IUGR pregnancies and both are associated with high risk of having uniparental disomy for that chromosomal pair which is trisomic in the placenta.

Key Messages

- IUGR and SGA occur in about 10% of pregnancies and both are associated with an increased risk for perinatal morbidity and mortality.
- Environmental and genetic factors are known to be associated with IUGR, although the aetiology of most IUGR remains unexplained.
- In over 20% of pregnancies with idiopathic IUGR, chromosomal mosaicism confined to extra embryonic tissues (CPM) has been observed. The type of CPM (I–III), the particular chromosomal involvement and the origin of trisomy (mitotic/meiotic) in the aneuploid clone correlate with specific pregnancy outcomes. When meiotic CPM involving trisomy is detected in the placenta, the fetus/neonate has a high risk of having uniparental disomy for that chromosomal pair which is trisomic in the placenta.
- It is important to study placentas from pregnancies with idiopathic IUGR for the presence of CPM using molecular cytogenetic methods.
- Detection of CPM not only explains the pathogenesis of fetal IUGR but also provides important information for postnatal follow up.
Lestou, Kalousek

The role of specific chromosomal mosaicism in the fetal growth restriction and teaches us about the IUGR can unveil the contribution of CPM to central studies in pregnancies with idiopathic disomy and evaluation of its e.

When CPM is diagnosed after delivery of an IUGR neonate, DNA analysis of parents, infant, and placenta can determine the origin of placental trisomy and fetal disomy. While a mitotic origin excludes the possibility of fetal uniparental disomy, a meiotic origin of placental trisomy indicates high risk of fetal uniparental disomy for the involved chromosome. It is important for both obstetricians and pediatricians to request appropriate genetic diagnostic tests for neonates and stillborns with idiopathic IUGR to provide the crucial information required for management of IUGR infants and genetic counselling in case of intrauterine death.

Conclusion

The incidence and the phenotypic effects of CPM in human pregnancies with idiopathic IUGR has been underestimated for a long time. To date, both the research and clinical findings show that idiopathic IUGR is probably associated with type III CPM. As the common chromosomal defect in type III CPM is trisomy of meiotic origin, the fetus/newborn carries a risk of uniparental disomy for that chromosomal pair which is trisomic in the placenta. The possibility of clinical detection of uniparental disomy and evaluation of its effect on the postnatal development of the IUGR neonate represents the greatest advantage of saving the placental sample at the time of delivery of a neonate with idiopathic IUGR. Complete placental studies in pregnancies with idiopathic IUGR can unveil the contribution of CPM to fetal growth restriction and teach us about the role of specific chromosomal mosaicism in the regulation of placental and fetal growth.

We thank I J Barrett and B L Lomax in the Research Molecular Cytogenetics Laboratory for their technical and editorial assistance. The financial assistance of the March of Dimes Research Foundation (FY96-1034) is gratefully acknowledged.