Gene Determinants and Perinatal Growth Phenotype

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Abstract

Perinatal growth phenotype is largely determined by genes, nutrient supply, placental transport function, environment, and growth hormones. Recently, gene mutation and expression have been reported to play an important role in perinatal growth and development. Perinatal growth epigenetics, a new concept in growth phenotype, has been accepted in fetal programming. This paper outlines the findings of perinatal phenotype in several studies and summarizes fetal growth restriction, birth defects, angiotensinogen gene mutation and pathological phenotypes of placenta, and the occurrence of other pregnancy complications. We review genetic approaches to IUGR, especially those related to growth factor genes, gene mutations and epigenetics with abnormal perinatal characterizations. We also discuss gene study directions, which should be valuable in elucidating mechanisms employed by the fetus and prevent the development of abnormal perinatal outcomes.

Keywords: Gene; Epigenetics; Fetal growth; Birth defect; Placenta

Introduction

Fetal growth is determined by many factors. These include genes, maternal nutrient supply, placental transport function, nutrient concentration gradient between maternal and fetal blood, placental blood flow, etc. Among these factors, gene determinants play an important role. Their mutation and expression are related to the perinatal growth phenotype [1-5]. In this review, perinatal growth phenotype will focus on growth and development from intrauterine pregnancy to the neonatal period after birth.

Regardless of what exactly affects the growth of fetus or infant, one important pathway most likely involved is growth factors and their interaction with their receptors [6-8]. Furthermore, the genes that affect vascular development will affect the vessels in the placenta, a key organ that transports nutrients from mother to fetus, which influences the growth of the fetus [9-11]. In addition, recent studies demonstrated an increasing tendency for neonatal birth defects, which might be considered a result from environmental changes [12]. Scientists believe that gene expression might influence the phenotype, so the term “fetal growth epigenetics”, a new conception of fetal programming influenced by the expression of genes, has been established [13-16].

The perinatal growth phenotype affected by gene determinants or epigenetics might be presented as abnormal growth, such as intrauterine growth restriction, small or large for gestational age, or birth defects. The information in this paper concludes findings in our previous study on perinatal growth and birth defects, reviews the genetic approaches and epigenetics studies in recent years. It would be valuable to elucidate the mechanisms employed by perinatal growth and help to develop interventional strategies that might make early diagnoses or prevent the development of fetal abnormal growth or birth defects.

Genetics and Perinatal Phenotype

Gene mutations and perinatal growth phenotype

Many publications presented that some certain gene mutations are associated with perinatal growth abnormalities (Table 1). Insufficiency of CDK19 gene caused by pericentric inversion of chromosome 6 results in microcephaly, nystagmus, congenital bilateral falciform, retinal folds, and mental retardation [2]. Insufficient expression of NFIA gene, caused by a deletion at chromosome 1p32-p31, can cause ventriculomegaly, abnormality of external genitalia, and IUGR [3]. Smigiel [17] reported two neonates who died of restrictive dermopathy. DNA analysis was performed and compound heterozygous frame shifting mutations were identified in exon 1 and exon 5 at the ZMPSTE24 gene. Autosomal recessive inheritance was confirmed. Insufficient function of Ascl2 affects all three layers of placenta and causes Intrauterine Growth Restriction (IUGR) [18]. The c-fos gene expression is critical in the oxidative stress pathway of placenta and causes Intrauterine Growth Restriction (IUGR) [18].

Table 1: Gene mutations and perinatal phenotypic characteristics.

| Gene       | Gene mutation effects                                      | Phenotypic effects and complications |
|------------|------------------------------------------------------------|-------------------------------------|
| 11b-HSD2   | Depress glucocorticoid metabolism                          | IUGR, small placenta [4].           |
| Ascl2      | Affect placenta development                                | Three layers malformation, IUGR     |
| CDK19      | Chromosome breakpoints in 6p12.1 and 6q21                   | Microcephaly, congenital bilateral  |
|            |                                                            | falciform fetal folds, nystagmus,   |
|            |                                                            | and mental retardation [2].         |
| GSTP1      | Affect glutathione transferase enzymes pathway              | Fetal growth and neonatal growth    |
| IGF1R      | Novel c.420del mutation in exon 2 of the IGF1R gene        | Reduced IGF1R expression and        |
|            |                                                            | represents haploinsufficiency of the |
|            |                                                            | IGF1R gene. IUGR and neonatal       |
|            |                                                            | growth retardation [8].              |
| NFIA       | Chromosome 1p32-p31 deletion syndrome                       | Ventriculomegaly, corpus callosus   |
|            |                                                            | hypogenesia, abnormal external      |
|            |                                                            | genitalia, and intrauterine growth  |
|            |                                                            | restriction in the third trimester   |
|            |                                                            | [3].                                |
| TFRC       | Affect transferrin receptor function                       | Fetal growth                       |
|            |                                                            | IUGR [13].                          |
| ZMPSTE24   | Fetal growth                                              | IUGR, dermopathy, neonatal death    |

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mice with fetal alcohol syndrome. Administration of alcohol during pregnancy results in altered gene expression through the stress signal pathway. C-fos expression in the decidua increases from 6 to 24 hours after alcohol injection, but does not change in the embryo, which may contribute to alcohol-induced damage in fetal alcohol syndrome (Table 1) [19].

**Epigenetics and perinatal growth phenotype**

Scientists have been considering the evidence from studies in the field of obesity and other areas that elucidate mechanisms by which the environment can modify gene expression which results in an individual’s phenotype. Maternal dietary and behavioral factors determine epigenetic changes in fetuses, neonates, and even adults [21]. DNA methylation and histone modifications are used to determine how the same DNA sequence generates different cells, lineages and organs, i.e., the phenotype. Environmental disturbing factors during pregnancy, such as nutrition, metabolism and behavior, affect epigenetic processes and potentially influence offspring with a predisposition to obesity during adulthood. The mechanisms causing birth weight changes and adverse pregnancy outcomes are complex. In addition to the focus on genetic mutations, epigenetics are associated with perinatal growth phenotype [22] (Table 2).

Many studies have reported that imprinted genes play a central role in placental development and function, and they are related to a variety of perinatal growth disorders [14–16,23,34]. Gene inactivation studies in mice and chromosomal rearrangements in humans have demonstrated that many of these imprinted genes play key roles in placental development and function as well as in fetal growth. Those studies have also demonstrated that imprinted genes act in a complex manner at many levels between the mother and fetus. Animal models support that imprinted genes play a significant role in perinatal growth.

Cell proliferation is very active during the early embryo phase. The proliferation depends on cell division. The quicker division, the shorter phase of G0 and G1 phase. In another words, less proliferation will have more cells in G0 or G1 phases, active proliferation will have more S+G2+M phases. Using flow cytometry to analyze the cell cycle, we found that the ratio of the cells in G0+G1 phases to the total cells was increased and the ratio of the cells in S+G2+M phases to the total cells was decreased in fetal brain, liver and placenta in rabbits exposed to passive smoking. In brain, this change was more prominent. It means that the proliferations of the fetal cells and placenta were inhibited significantly, and the growth retardation of the fetus was the result. It is demonstrated that the cell transformation from G1 to S phase was restricted by smoking [35,36].

During early embryo development, the first embryo differentiation establishes two cell lineages. They are the inner cell mass that forms all the tissues of the adult, and the trophectoderm that eventually produces placental structures. In general, the inner cells become gene hypermethylated while the trophectoderm is hypomethylated and these patterns are preserved throughout the whole period of gestation [37,38].

In order to gain insights of the importance of epigenetic regulation in fetal growth, Lamberti [34] investigated methylation status of imprinted genes by comparing IUGR with normal placentas. They found that the gene length is highly correlated with methylations. Growth restricted placentas have encompassing genes that are actively expressed. Kumar et al. [39] confirmed that the growth promoting imprinted gene expression increased and the growth suppression imprinted gene expression decreased with the advancing of gestational age. He found that the ZNF127 gene expression was up regulated and the PHLDA2 gene expression was down regulated [39]. Another excellent example of imprinted genes can be found in McMinn’s study [40]. He showed that a small group of imprinted genes (PHLDA2, MEST, MEG3, GATM, GNAS, and PLAGL1) and additional genes acting in endocrine signaling (LEP, CRH, HPGD, INHBA), tissue growth (IGF1), immune modulation (INDO, PSG-family genes), oxidative metabolism (GLRX), vascular function (AGTR1, DSCR1) and metabolite transport (SLC-family solute carriers) were affected in IUGR placentas.

Multiple imprinted loci have been reported to have abnormal methylation in association with IUGR, for example, at the IGF2/H19 locus, methylation decreased in IUGR placentas [16,41,42] (Table 2). Besides the imprinted gene expression changes in IUGR, a growing number of animal studies show that specific environment exposure can influence fetal DNA methylation/demethylation [43]. These effects can permanently affect health outcomes later in life and are heritable across generations [44].

Methylation alteration to the environment can occur even before conception [45]. Environment can also influence the remethylation time and pattern after conception [46]. This methylation pattern change can be seen in Wu et al. [47] study that the methylationtransferase activity was increased in the mouse embryos exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxid (TCDD), leading an up-regulation of methylation of H19/igf2 imprinted gene. During the development of the embryo, the embryo demethylates most of its genes between fertilization and implantation but the maintenance of imprinted genes through the preimplanatatin period is essential for normal embryonic development. These effects are important for

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**Table 2: Epigenetics and perinatal phenotypic characteristics.**

| Gene          | Gene expression                  | Phenotypic effects and complications. |
|---------------|----------------------------------|---------------------------------------|
| c-fos         | Decreased expression             | Fetal alcohol syndrome [19].           |
| DIO3          | Type 3 deiodinase, highly expressed in placenta and fetus. | IUGR and hypothyroidism [23].         |
| DLK1          | Growth promoter, increased in placental villi. | Methylation defects associated with IUGR [16]. |
| HBB1-85/PWScr | C/D Box small RNA                | Implicated in Prader Willi, Postnatal growth retardation [24]. |
| HYMAI         | Non-coding RNA, expressed in fetus. | Transient neonatal diabetes and IUGR [25]. |
| IGF2          | Growth Factor, decreased expression in placenta | Placental and fetal growth restriction [26]. |
| KCNQ1OT1      | Non-coding RNA, Control placental Kcnq1 domain | Involved in Beckwith-Wiedemann syndrome [27]. |
| MAGEL2/NDNL1  | Similarity to NDN               | Neonatal growth retardation, altered metabolism [28]. |
| MEST          | Neuronal differentiation         | Fetal growth restriction, smaller placentas [29]. |
| PEG3          | Inhibits WNT-signaling           | Placental and fetal growth restriction and abnormal maternal behavior [30]. |
| PEG10         | Retrottransponson-derived gene   | Severe growth retardation, absence of spongiosotrophoblast layer, embryonic lethality [31]. |
| PLAGL1 Zac1   | Tumor suppressor                 | Skeletal defects, neonatal lethality, IUGR, and disrupted transactivation of igf2 [32]. |
| SFRP2         | WNT signaling                    | Reduction in vitro of extra villous trophoblast invasion [33]. |
the development of the embryo [48,49]. Additionally, demethylation in the embryo might remove epigenetic modification effects from parental gametogenesis. At different times in the uterus, fetal DNA undergoes methylation/demethylation depending on the cell, tissue, or organ based on developmental and environmental factors. Furthermore, some genes predisposing obesity might be affected by maternal diet habits. This effect could be seen in the study to expose mice to a genistein diet leading to an increased methylation of the retrotransposon located in the Agouti gene [43]. Even after birth, the methylation patterns continue to adjust in the somatic cells [50].

**Gene expression and large for gestational age birth**

Placental studies on the expression of human placental Growth Hormone (GH) and chorionic somatomammotropin (CSH) locus, which is situated on chromosome 17q22-24, demonstrated interesting results [51]. Placental GH2, CSH1, and CSH2 genes expression was reduced significantly in preeclampsia cases. However, in pregnancy with large for gestational age newborns or maternal gestational diabetes, a different expression of GH2 was detected. In conclusion, the results demonstrated a consistent relationship of fetal growth regulation, maternal metabolism and the expression of hGH/CSH genes.

IGF-II and relaxin both cause proliferation of human amniotic epithelial cells. Studies showed a relationship of relaxin gene and IGF-II gene expression levels to neonatal birth weight and amniotic membrane surface area. It suggests that relaxin increases the development of fetal membranes. Its expression level was significantly greater in the membranes from macrosomic infants compared to normal infants [52].

**Gene mutation, gene expression and birth defects**

Birth defects are a major cause of perinatal death and disability. Most birth defects are related to gene abnormalities or result from reasons which can cause gene abnormal expression. There are many reports about gene mutations and birth defects. Gripp et al. [53] identified that FOXC1 mutation caused cardiac anomalies in Axenfeld-Rieger syndrome. Until now, only about 20% of congenital cardiac abnormalities can be attributed to chromosomal anomalies, single gene disorders, or teratogens. There were only about 30 genes to have been reported linked to non-syndromal forms of congenital heart disease [1]. Misceo et al. [54] reported on a congenital heart disease with atypical deletion of 1.5 Mb from chromosome 4p16.3. He reviewed seven previously published patients and found them carrying a similar deletion. They consistently presented post-natal growth delay. By investigating and analyzing the birth defects in 13 medical centers in Changsha, China, we found 1050 birth defects among 64101 infants with a birth defect incidence of 16.38% (Table 3). The first five birth defects were dysmelia, chelognathoschisis, auricle malformation, congenital heart disease, and gastrointestinal tract anomalies (Table 4) [12]. There are two significant changes we were concerned with: the increasing rate of birth defects from year to year and the increasing occurrence of congenital heart disease. The reason for these changes is not clear but may result from epigenetics induced by environmental changes.

Yang et al. [55] have similar findings in birth defect investigations of Shanxi Province in West China and concluded that health care service utilization, unhealthy lifestyle factors, and environmental risk factors all seem to be associated with birth defects. The environmental risk factors related to birth defects may include unhealthy lifestyles (such as alcohol, smoking), heavy pollution, drug use, chemical pesticide exposure, etc [55]. According to the National Birth Defects Prevention Study, maternal occupational exposure to organic solvents during early pregnancy may be associated with neural tube defects [56]. Furthermore, different occupations might have significant differences in smoking, drinking, folic acid use, and access to prenatal care. All these could affect the intrauterine fetal growth and neonatal development [57]. Many studies demonstrated a relationship between the specific material exposure, which is associated with birth defects, and the gene expression changes [58-60].

**Gene Approaches and Perinatal Growth**

In an individual embryo, all cells have the same basic set of genetic information stored in DNA, but in different organs the cell proliferation and differentiation depends on the expression of different genes. This small subset of genes allows the cells to produce proteins unique to their functions. Although gene expression is controlled by epigenetic modifications, the gene sequence obviously plays the most important role in the cells proliferation and differentiation.

**Growth factor gene and perinatal growth**

Many studies have demonstrated a relationship of the level of human placentla growth hormones (hPGH), IGF-I, and IGF banding proteins in maternal blood and IUGR [61-63]. Koutsaki et al. [7] aimed to evaluate the expression status of hPGH, (IGF-1), IGFBP-1 and IGFBP-3 genes in placentas from human IUGR pregnancies of no apparent etiology and found that hPGH, IGF1, IGFBP-1, and IGFBP-3 expression is significantly lower than that in the placentas with normal fetal growth, though the causative factors are not known in the alterations of IUGR or that they accompany other pathogenic mechanisms.

The IGF-1 receptor (IGF-1R) is widely expressed in fetal and

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**Table 3: Birth defects incidence (Changsha, China).**

| Year | Birth (n) | Birth Defect (n) | Incidence (%) |
|------|-----------|-----------------|---------------|
| 2000 | 13268     | 175             | 13.19         |
| 2001 | 12445     | 150             | 12.05         |
| 2002 | 12598     | 208             | 16.51*         |
| 2003 | 11795     | 193             | 16.36*         |
| 2004 | 13995     | 324             | 23.15*         |
| Total| 64101     | 1050            | 16.36         |

*Compared to 2000, p<0.05; # Compared to 2001, p<0.05

**Table 4: Birth defects constituent (Changsha, China).**

| Defects                  | Occurrence (n) | Constituent Rate (%) | Incidence Rate (%) |
|--------------------------|---------------|----------------------|--------------------|
| Dysmelia                 | 215           | 18.28                | 3.35               |
| Chelognathoschisis       | 148           | 12.59                | 2.3                |
| Auricle malformation     | 125           | 10.63                | 1.95               |
| Congenital heart disease | 95.2          | 1.75                 |                    |
| Gastrointestinal tract   | 76            | 6.46                 | 1.18               |
| Anomalies                | 62            | 5.27                 | 0.97               |
| Hydrocephalus            | 51            | 4.34                 | 0.80               |
| Neural tube defect       | 54            | 2.89                 | 0.53               |
| Urinary malformation     | 17            | 1.45                 | 0.27               |
| Down’s syndrome          | 336           | 28.57                | 5.24               |
| Others                   | 1178          | 100.00               | 18.34              |
postnatal cells. The activation of this receptor after the binding of secreted IGF-I and IGF-II promotes cell proliferation and differentiation. Observations found the IGF-1R gene mutation is associated with low birth weight [64]. Low birth weight and height are found to be related to heterozygous IGF-IR mutations or insufficiency [8,65]. This phenotype presents with family history of low birth weight and a normal increased IGF-I level and/or a normal or increased GH response to GH stimulation test [66,67]. However, it has less response to GH treatment than common small for gestational age short-stature patients [68].

Choi et al. [69] reported a family both with a novel heterozygous mutation of the IGFR1 and a segmental deletion encompassing the entire IGFR1 result in IGF-I resistance, leading to IUGR and postnatal growth failure. During in vitro studies, fibroblasts carrying the IGFR-1R gene mutation clearly demonstrated reduced the expression of this gene and subsequently resist IGF-I. It is considered that IGF-1R gene mutations should be used in the diagnosis of familial IUGR with persistent short stature [69]. Umbers reported that inflammation of the placenta can cause the disturbance of IGF expression, which leads to IUGR [70].

Experiments in mice clearly demonstrated that IGF-I is a major regulator of both prenatal and postnatal growth. Baker et al. [71] reported that isolated invalidation of IGF1 resulted in 45% body weight of the normal ones. Double knockout the IGF gene resulted in more severe growth retardation (Figure 1) [73]. These experiments clearly demonstrated that IGF-1 is a major regulator of both pre- and postnatal growth. Several authors have reported on the IGF-1R gene mutations with the observation of birth weight, height, serum IGF-I and complications (Table 5).

Glucocorticoid gene and perinatal growth phenotype

Prenatal stress or exposure to excess of glucocorticoids might have a link between fetal development maturation and adult pathophysiology [74]. In a variety of animal models (Table 6), prenatal stress, glucocorticoid exposure and inhibition 11β hydroxysteroid dehydrogenase (11β-HSD1) reduced birth weight and caused increases in adult blood pressure, glucose levels, hypothalamic-pituitary-adrenal (HPA) axis activity and anxiety-related behaviors. In humans, mutations in the gene that encodes 11β-HSD2 are associated with low birth weight. Low birth weight is associated with higher cortisol levels throughout life. In addition, over exposure to glucocorticoids induced an increase expression of p73, which is associated with fetal brain growth restriction [75]. Caffeine overconsumption increases maternal glucocorticoid levels. It induces the histone methylation of IGF-1 receptor and decreased IGF-1 mRNA expression and decreased IGF-1 receptor function [76]. Guo et al. [77] uses maternal baboon over expression demonstrate that glucocorticoids receptor and its coregulator-peroxisome proliferator coactivator (PGC-1α) over expression exhibited impaired glucose tolerance at adult age associated with reduced insulin secretion, decreased β-cell mass, and β-cell hypotrophy versus β-cell PGC-1α overexpression from adult age had no consequence on β-cell function [79].

Obviously, the epigenetic effects on perinatal growth phenotype exist. Intriguingly, some of these effects seem to be inherited by subsequent generations that are unexposed to exogenous glucocorticoids at any point in their lifespan from fertilization. Adverse prenatal environmental factors can permanently influence the physiological metabolism of the embryo, which demonstrated

| Gene | Gene mutation effects | Phenotypic effects and complications |
|------|-----------------------|-------------------------------------|
| Stat5 | Affects the glucocorticoids receptor function | Dramatic reduction in body size [78]. |
| AKT1/2 | I increased corticosterone and decreased IGF-1mRNA expression | Skeletal growth retardation [76]. |
| p73 | Enhanced corticosterone levels | Fetal brain growth restriction [75]. |
| 11β-HSD1 | Exaggerated cortisol regeneration | Offspring metabolic syndrome [77]. |
| PGC-1α | Influence glucocorticoid receptor function | Reduced insulin secretion, decreased β-cell mass, and β-cell hypotrophy [79]. |
as an increase of cardiovascular, metabolic, neuroendocrine, and psychiatric disorders in adulthood.

**Angiotensinogen gene and placental vascular development**

Small for gestational age has been reported to be associated with insufficient placental circulation, which may be the result from failed maternal physiological changes such as abnormal spiral artery remodeling and reduced maternal blood volume. Morgan reported that spiral artery remodeling might be related to the AGT gene [9]. We examined maternal blood DNA in 174 patients with intrauterine growth restriction, 62 patients with placental abruption, and 60 patients with both preeclampsia compared with the control group comprised 400 consecutive cases of women with term pregnancies and infants with birth weight between the fifth and 95th percentiles. DNA analysis on fetal blood demonstrated high frequencies of Thr235 alleles in IUGR (59.1%) compared with the normal control fetus (37.9%) (IUGR vs control: p<0.01) (Table 7).

DNA analysis demonstrated that maternal and fetal AGT Thr235 allele frequencies are significantly related to IUGR, preeclampsia, and placental abruption [10]. The AGT Thr235 allele may predispose women to deliver growth-restricted fetuses and has a higher frequency of pregnancy complications such as preeclampsia or placental abruption [11] (Table 7). In addition, quantitative pathological studies on placenta found that placental capillary area decreased significantly in homozygous Thr235 placentas compared to the homozygous Met234 placenta (Table 7). In addition, quantitative pathological studies on placenta found that capillary area decreased significantly in homozygous Thr235 placentas compared to the homozygous Met234 placenta (Table 7). In addition, quantitative pathological studies on placenta found that capillary area decreased significantly in homozygous Thr235 placentas compared to the homozygous Met234 placenta (Table 7). In addition, quantitative pathological studies on placenta found that capillary area decreased significantly in homozygous Thr235 placentas compared to the homozygous Met234 placenta (Table 7).

**Table 7: Maternal AGT Thr235 genotypes and pregnancy complications.**

| Groups                     | No. | MM (%) | MT (%) | TT (%) | p value |
|----------------------------|-----|--------|--------|--------|---------|
| Control                    | 400 | 170 (42.5) | 158 (39.5) | 72 (18.0) |         |
| IUGR                       | 174 | 33 (19.0) | 66 (37.9) | 75 (43.1) | <0.001  |
| Preeclampsia+IUGR          | 60  | 11 (18.3) | 24 (40.0) | 25 (41.7) | <0.001  |
| Placental Abruption        | 62  | 9 (14.5)  | 27 (43.5) | 26 (41.9) | <0.001  |

MM: homozygous for AGT Met235 allele; MT: heterozygous TT: homozygous for AGT Thr 235 allele; IUGR: intrauterine growth restriction

**Table 8: AGT genotype and placental pathological phenotype.**

| AGT genotype | MM | MT | TT |
|--------------|----|----|----|
| No. of placentas | 8  | 13 | 14 |

**Clinical findings:**

| Maternal age (yrs) | 26.0 ± 4.7 | 26.6 ± 6.6 | 29.8 ± 6.5 |
|-------------------|------------|------------|------------|
| Gestational age (wks) | 36.2 ± 4.5 | 36.6 ± 1.9 | 36.7 ± 3.1 |
| Fetal birth wt. (g) | 2730 ± 967 | 2642 ± 541 | 2620 ± 535 |

**Placental quantitative findings:**

| Villous volume/cm³ placenta (cm³) | 0.668 ± 0.034 | 0.626 ± 0.022 | 0.587 ± 0.059*** |
|----------------------------------|---------------|---------------|-----------------|
| Capillary volume/cm² placenta (cm³) | 0.131 ± 0.029 | 0.107 ± 0.034 | 0.070 ± 0.030** |
| Intervillos volume/cm³ placenta (cm³) | 0.332 ± 0.034 | 0.374 ± 0.022** | 0.413 ± 0.059**# |
| Volume of trimmed Placenta (cm³) | 324.8 ± 120.8 | 355.2 ± 80.3 | 374.1 ± 70.2 |
| Villous total volume per placenta (cm³) | 215.8 ± 81.8 | 222.1 ± 50.7 | 219.9 ± 52.6 |
| Intervillos space per placenta (cm³) | 108.9 ± 47.8 | 133.1 ± 31.1 | 154.2 ± 38.6* |
| Villous capillary volume per placenta (cm³) | 45.1 ± 27.4 | 41.4 ± 23.2 | 26.6 ± 14.4* |
| Percentage of villous capillary volume (%) | 19.81 ± 5.12 | 17.41 ± 7.3 | 12.06 ± 5.45* |
| Villous surface area per placenta (m²) | 9.029 ± 3.285 | 9.560 ± 2.031 | 10.370 ± 2.725 |

Data are demonstrated as mean ± SE; *Compare to MM, p<0.05; **compare to MM, p<0.01; # compare to MT, p<0.05.

**Genetics and Perinatal Growth-Problems and Future Directions**

Most birth defects and perinatal growth anomalies are multifactorial and arise through various combinations of genetic and environmental contributors. Only a small part of birth defects and growth anomalies can be attributed to chromosomal abnormalities or single gene disorders. For gene studies, there were only limited numbers of genes studied among the thousands of genes that are expressed. In fact, a lot of genes are associated with the perinatal growth phenotype. To evaluate their roles in affecting perinatal growth we still need the accumulation of multiple collections of the mutation, phenotype, epigenetics, metabolotics of the perinatal growth characteristics. Furthermore, most of the pathways in altering gene expression altering are undiscovered. Basic study on the pathways involved in the genes may help us to understand why and how the phenomenon occurred at the molecular level.

Although the definition and diagnosis of perinatal growth abnormal can be simply defined with the normal growth chart, perinatal growth is still an extremely complex phenotype to dissect because of many factors, such as maternal, fetal, placental, and environmental factors. Almost all gene expression studies were based on small numbers of samples. Though studies on gene expression found gene dysregulated in abnormal perinatal growth, most of these genes, such as IGF-1, IGFBP1, corticotropin-releasing hormone, etc. are supported by reports identifying genes related to regulating cell division and proliferation. We still are unable to know if it is a compensated response to the fetal restricted growth or a reason induced by fetal growth restriction. Using the transgenic engineering technique in animals to study some specific gene may provide an ideal model to study the phenotype related to these genes found in clinical human beings.

Some specific imprinted genes are related to abnormal perinatal growth. Their function could be classified in two categories. The first
decreases fetal growth as a disturbing factor and the second increases fetal growth as a compensatory response when sensing the fetus is at risk. We expect to reduce negative gene expression effects and increase the expression of positive genes to improve perinatal outcomes. It will be a long distance from the basic animal model studies to clinical applications to reach this point using gene-regulating techniques.

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