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# Effect of Cell Growth and Proliferation Factors (EGF/PDGF Signaling Pathway) on the Etiopathogenesis of Intrauterine Growth Restriction

## Hücre Gelişimi ve Proliferasyonunu Sağlayan Faktörlerin (EGF/PDGF Sinyal Yolağı) İntrauterin Gelişme Kısıtlanması Etiyopatogenezine Etkisi

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### ABSTRACT

**Objective:** It is likely that the subgroups of the epidermal growth factor/platelet-derived growth factor (EGF/PDGF) signaling pathway play a role in the etiopathogenesis of intrauterine growth restriction (IUGR). This study was planned to understand the molecular genetic level of apoptosis in IUGR.

**Method**: The EGF/PDGF signaling pathway gene profile (40 genes) was investigated using a real-time reverse transcriptase-polymerase chain reaction. The gene expressions of the IUGR group were compared both individually and as a group. Individual gene differences were also evaluated. The genes related to cell survival and growth, which include the gene groups of apoptosis, cell cycle, cell differentiation, cell growth, cell motility, and cell proliferation, were investigated using microarray technology.

**Results:** Parity, gestational age at delivery, and APGAR scores at the first and fifth minutes were not significantly different between the IUGR and control groups. However, the women in the IUGR group were younger and slimmer. *PRKCA* was the only gene with a significant difference in expression between the IUGR and control groups. Nevertheless, individual differences were detected in gene expression associated with cell cycle, differentiation, growth, motility, proliferation, and apoptosis.

**Conclusion:** Variations in gene expression during pregnancy cause changes in placental and fetal development by affecting apoptosis and cellular events at different levels. The genetic causes of IUGR can be revealed by investigating these metabolic pathways. This study differs from previous IUGR studies, which focused on one or a few genes, because all the gene groups in the EGF/PDGF pathway that may be associated with IUGR were investigated.

**Keywords:** Intrauterine growth restriction, cell survival and growth, apoptosis, EGF/PDGF, PCR array, RT-PCR

### ÖZ

**Amaç:** İntrauterin gelişme geriliği (IUGR) etiyopatogenezinde epidermal büyüme faktörü/trombosit kaynaklı büyüme faktörü (EGF/PDGF) yolağında yer alan alt grupların rol oynadığı düşünülmektedir. Bu çalışma, IUGR'deki apoptozun moleküler genetik seviyesini anlamak için planlanmıştır.

**Yöntemler:** EGF/PDGF sinyal yolu gen profili (40 gen) gerçek zamanlı ters transkriptaz-polimeraz zincir reaksiyonu ile incelendi. IUGR grubunun gen ekspresyonları hem bireysel hem de grup olarak karşılaştırıldı. Ayrıca bireysel gen farklılıkları da değerlendirildi. Apoptoz, hücre döngüsü, hücre farklılaşması, hücre, büyümesi, hücre motilitesi ve hücre proliferasyonu, gen gruplarını içeren hücre yaşamı ve büyümesi ile ilgili genler, mikroarray teknolojisi ile incelendi.

**Bulgular:** IUGR ve kontrol grupları arasında; parite, gebelik yaşı, ilk ve beşinci dakikada APGAR skorları yönünden istatistiksel olarak anlamlı fark gözlenmedi. Bununla birlikte, IUGR grubundaki kadınlar daha genç ve daha zayıf olarak saptandı. IUGR ve kontrol grupları arasında ekspresyon farklılığı bulunan tek gen *PRKCA* olarak bulundu. Hücre döngüsü, farklılaşması, büyümesi, motilitesi, proliferasyonu ve apoptoz ile ilişkili olan genlerin ekspresyonunda bireysel farklılıklar tespit edildi.

**Sonuç:** Hamilelikte genlerin ekspresyonundaki değişiklikler, apoptoz ve hücre olaylarını farklı seviyelerde etkileyerek, plasental ve fetal gelişimde farklılıklara neden olmaktadır. Metabolik yolakların araştırılması; IUGR'nin genetik nedenlerini ortaya çıkarabilir. Bu çalışma önceki çalışmalardan; IUGR bulunan hastalarda bir ya da birkaç genin araştırılması yerine bir gen yolağındaki (EGF/PDGF) tüm gen gruplarının irdelenmesi ile ayrılmaktadır.

**Anahtar Sözcükler:** İntrauterin gelişme kısıtlanması, hücre yaşamı ve büyümesi, apoptoz, EGF/PDGF, PCR array, RT-PCR

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## INTRODUCTION

Intrauterine growth restriction (IUGR) is a condition that occurs when a fetus cannot grow as much as it could because of a medical condition or when the estimated fetal weight is less than the 10th percentile for gestational age. In 3-8% of pregnancies, IUGR is observed. IUGR is a significant cause of fetal morbidity and mortality, and the risk increases with the severity of growth restriction (1). IUGR has been linked to adult diseases such as hypertension, diabetes mellitus, and others (2).

Biochemical screening tests for aneuploidy (maybe helpful to detect placental insufficiency), dating and measurement of nuchal translucency with ultrasound in the first trimester, uterine artery Doppler, calculation of estimated fetal weight, measurement of amniotic fluid volume, biophysical profile, and/or studies of umbilical artery Doppler are recommended for screening of IUGR (3). In recent years, most studies have focused on reducing the number of cases of IUGR and finding early signs of IUGR. The factors of cell proliferation, differentiation, and apoptosis [the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) signaling pathways] are thought to play a role in etiopathogenesis. Programmed cell death, or apoptosis, is a key mechanism in tissue hemostasis, development, and immune response. Apoptosis plays a complementary role in the development of an appropriate placenta (4). Parameters such as genes, enzymes, and metabolomics that were thought to be associated with IUGR were particularly investigated in these studies.

This study was designed to examine all genes involved in gene pathways instead of selecting a few genes that would affect IUGR. The etiopathogenesis of IUGR is not clear, no treatment regimes have been created, and perinatal morbidity and mortality have not been prevented. IUGR leads to high health care costs. This study investigated the genetic relationship of IUGR for prediction, thereby determining the risks, shaping the antenatal follow-up, and preventing complications.

In today's conditions, genetic studies have a high cost; therefore, the number of cases was limited, and this study aims to be a preliminary study for future genetic studies.

## MATERIALS AND METHODS

The study was conducted with pregnant women who were followed at The Gazi University Faculty of Medicine, Department of Obstetrics. The EGF/PDGF signaling pathway gene profile (including 40 genes) was extensively studied using RT-PCR. Two groups were designated as the IUGR and control groups. There were six normal pregnant women in the control group and six IUGR-complicated pregnant women in the IUGR group. Patients in the study group who had IUGR were randomly assigned a number from 1 to 6. All women were included in this study after informed consent was obtained. The approval of the Ethics Committee was obtained from the Gazi University Clinical Research Ethics Committee for this study (approval number: 252). Financial support was provided by TUBITAK (the Scientific and Technological Research Council of Türkiye) through the 1002-Short-Term R&D Funding Program.

The inclusion criteria of the study were as follows: The gestational weeks of fetuses were between 37 and 40 weeks, which was confirmed with ultrasonography in the first examination of pregnancy; the ages of pregnant women were between 18 and 35 years; pregnant women had no chronic diseases such as diabetes mellitus, hypertension, heart failure, chronic kidney disease, autoimmune disease, or hereditary anemia; and pregnant women did not use drugs, alcohol, cigarettes, or pills. Fetuses with an estimated fetal weight in the 10th percentile or 2 SD on ultrasound were considered IUGR and included in the IUGR group. TORCH antibodies were tested in all of them, and if TORCH antibodies were found positive in a pregnant woman and her fetus had IUGR, these cases were excluded. The other exclusion criteria were situations that lead to the corruption of uteroplacental perfusions, such as pre-eclampsia, gestational diabetes mellitus, which is determined by an oral glucose tolerance test, anomalies of the fetus, and other obstetrical problems.

The 5 mm3 specimens that were collected with a lancet from the central cotyledon at the placentas were macroscopically normal and had no fibrin or hemorrhage. Samples were taken from pregnant women who gave birth in the delivery room immediately after the births. The specimens were placed in a sterile cup that had been filled with 20 cc of normal saline for cleaning residual tissue. Subsequently, specimens were taken into a 15 mL sterile centrifuge tube, which contained 2 mL of RNA, and they were delivered to the immunology laboratory. They were stored within 15 min in a cooler at -86 °C.

RT-PCR: Human EGF/PDGF Signaling Pathway PCR Array (Qiagen) kits, which were able to calculate on a quantitative level with mRNA, level of protein expression as a growth factor, were used. cDNA was established with an RT reaction using total RNA isolated without tissue culture from samples. RNA isolation kits without genomic DNA were used for this process. Then, cDNA amplification was achieved by PCR. Ultimately, the differences in the expression of protein genes, which are thought to cause IUGR, were determined as a "fold increase" or "fold decrease" in mRNA level. Genes associated with the cell cycle, cell differentiation, cell growth, cell motility, cell proliferation, and apoptosis were investigated.

Apoptosis: AKT1, BAD, BCAR1, BCL2, BRAF, CASP3, CASP9, FASLG (TNFSF6), FOXO3, IL2, LTA (TNFB), MAPK1 (ERK2), NFKB1, NUP62, PIK3R2 (p85-BETA), PPP2CA, PRKCA, PTEN, RAF1, RASA1, STAT1, and TP53 (P53).

Cell cycle: BCL2, CCND1, DUSP1 (PTPN16), DUSP6, EGFR (ERBB1), HRAS, KRAS, MAPK1 (ERK2), MAPK3 (ERK1), NRAS, PDGFA, PDGFB, PPP2CA, PRKCA, PTEN, RAP1ASHC1, STAT1, and TP53 (P53).

Cell differentiation: FOXO3, IL2, PPP2CA, and TP53 (P53).

Cell growth: BCAR1, CCND1, EGF, HBEGF, IL2, PDGFA, PDGFB, PDGFRA, PPP2CA, RASA1, SHC1, and TP53 (P53).

Cell motility: ACTR2, BCAR1, EGFR (ERBB1), FN1, HBEGF (DTR), MAP2K1 (MEK1), MAPK8 (JNK1), PTEN, STAT3.

Cell proliferation: BCAR1, BCL2, EGF, EGFR (ERBB1), EPS8, GAB1, HBEGF (DTR), IL2, NCK2, NUP62, PDGFA, PDGFB, PDGFRA, PTEN, RAF1, SHC, and TP53 (P53).

### *Statistical Analysis*

An analysis of gene data obtained with the RT-PCR method was performed over delta CT using the statistical analysis portal on the webpage of Sabioscience. "Human EGF/PDGF Signaling PCR Array

Kits" were used for RT-PCR. In the results, p<0.05 values were considered significant.

## RESULTS

Characteristic features of the study and control groups are shown as mean and standard deviation, and differences between both groups are identified as p-values (Table 1).

Significant differences were determined between the groups in terms of maternal age, pre- and post-pregnancy body mass index, and birth weight (p<0.05). There were no differences between the APGAR score, gestational age at delivery, and parity. The mothers were younger and had a low weight; they were in the IUGR group.

Alfa-fetoprotein, which is a component of the second trimester screening test, was statistically different between the IUGR group (59.2 ng/mL) and control group (28.95 ng/mL), (p=0.015).

Expression of only one gene, PRKCA, was found to be statistically significant (p<0.05) in comparison between the IUGR and control groups (Figure 1).

The gene expression differences of patients in the IUGR group were compared individually to those in the control group. *AKT1, BAD, BRAF, CASP9, GAB1, LTA, MAP2K1, MAPK3, NFKB1, NRAS, PIK3R2, PTEN,* and *STAT1* genes were not found to be associated with IUGR in this study, which investigated the effect of the EGF/PDGF signaling pathway on cell survival and growth.

## DISCUSSION

From 3% to 8% of all pregnancies are associated with IUGR. Clinicians who deal with obstetrics have many problems and spend a lot of

**Table 1.** Characteristic features of the study and control groups

| | IUGR (n=6) | Control (n=6) | p-value |
|---|---|---|---|
| Maternal age | 26.50±4.93 | 33.17±1.94 | **0.026*** |
| Parity | 0.50±0.83 | 1.00±0.63 | 0.240 |
| BMI** pre-pregnancy (kg/m$^2$) | 20.22±2.75 | 25.22±3.46 | **0.026*** |
| BMI post-pregnancy (kg/m$^2$) | 24.90±2.76 | 30.96±2.51 | **0.009*** |
| Gestational age at delivery | 37.6±1.98 | 38.4±0.36 | 0.699 |
| APGAR score (1. minute) | 8.83±0.98 | 8.83±0.40 | 0.818 |
| APGAR score (5. minute) | 9.67±0.51 | 9.83±0.40 | 0.699 |
| Birth weight (gr) | 2193±506 | 3323±324 | **0.002*** |

*P<0.05 is statistically significant, ** BMI: Body mass index, IUGR: Intrauterine growth restriction.

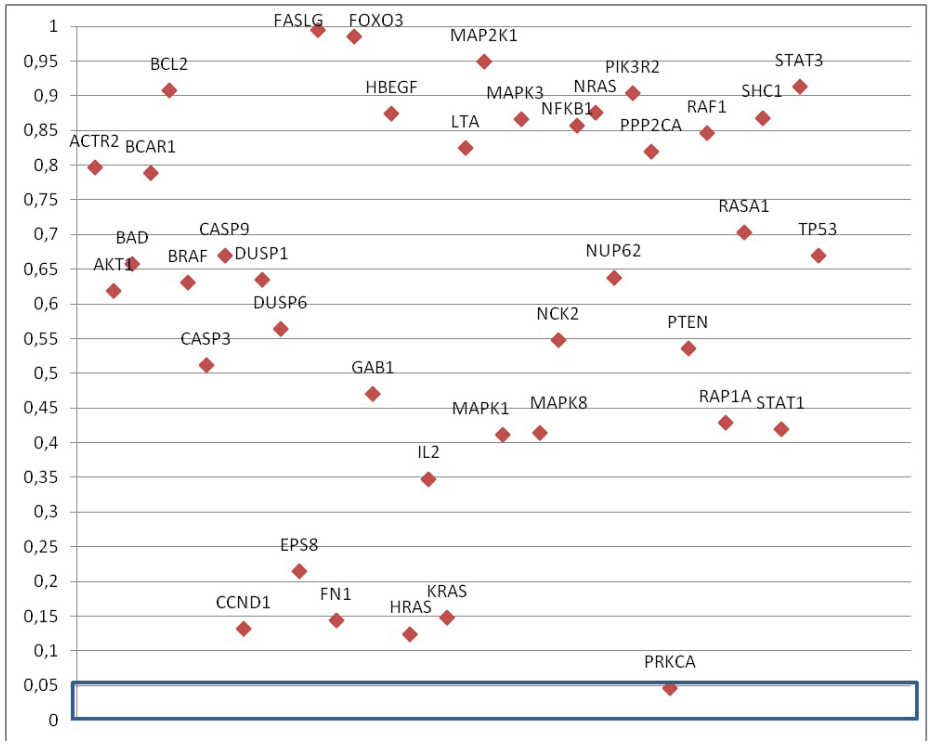



**Figure 1.** P-value of gene expression differences between the IUGR and control groups
IUGR: Intrauterine growth restriction.

time because of IUGR. If the etiopathogenesis of IUGR is determined and treatment modalities are evolved, perinatological follow-up could improve. The aim of this study was to upgrade the previously performed microarray studies with limited genes (5,6), and contribute to the literature with a comprehensive microarray study. The other aim is to aid in the determination of genes associated with IUGR (7,8). We believe that gene disorders associated with IUGR will be individually evaluated in the future and that treatments will be administered accordingly. The final aim of this study was to create the infrastructure described above for the treatment of IUGR.

According to Canadian data, the average hospital cost is $1000 per newborn whose birth weight is 2500 g. Nevertheless, the average hospital cost is $117,000 for a newborn who weighed less than 750 g. Nevertheless, the length of hospital stay for typical newborns increased as birth weight decreased, ranging from two days for babies weighing 2500 g or more to 104 days for those weighing less than 750 g (9). Therefore, if clinicians predict and treat IUGR, disability will be prevented, resulting in decreased health expenditure, and clinicians may spend less time following up.

The increase in apoptosis is well known in IUGR. Our findings, which are described below, support this knowledge. Expression decreases were found in the *RAP1* gene, which affects cell proliferation and adhesion; the *PPP2CA* gene, which provides differentiation and evolution of cells; the *NUP62* gene, which regulates the transition of mRNA and proteins between the nucleus and cytoplasm; and the *MAPK1* gene, which regulates growth and apoptosis. The anti-apoptotic *BCL2* gene and the *BCAR1* gene, which are related to the evaluation of cells, also showed decreases in expression. as well as the increased expression of *FASL* and *IL2* genes, which trigger apoptosis. In addition, decreased expression of BCL2, CCND1, DUSP6, HRAS, KRAS, PPP2CA, PRKCA, RAP1A, and SHC1 negatively affected the cell cycle, cell differentiation, and cell proliferation. These genes are involved in the etiology of IUGR and affect cell function. The *CCND1* gene is effective in cell proliferation; the *DUSP6* gene is effective in cell proliferation and mitosis through MAPKs; the *HRAS* gene regulates cell growth; the *KRAS* gene provides protein activation and proliferation for growth factor proliferation; the *PPP2CA, PRKCA*, and *RAP1A* genes are related to cell differentiation and development; and the *SHC1* gene organizes the cell pathway.

The functions of ACTR2, BCAR1, HBEGF, STAT3, and FN1 modulate cell motility. ACTR2 encodes a major constituent of the ARP2/3 complex, which is placed at the cell surface and is crucial to cell shape and motility through lamellipodial actin assembly and protrusion. BCAR1 is responsible for migration and invasion. HBEGF is expressed by the trophoblast during pregnancy and functions in blastocyst implantation. STAT3 affects angiogenesis and the development of the embryo. FN1 functions on embryogenesis, cell adhesion, and migration. Motility dysfunction is caused by a decrease in the expression of these genes.

IUGR is seen in mothers who are younger than 35 years or older than 35 years (10). Similar to the literature, mother age was related to IUGR. The maternal age in the IUGR group was smaller than that in the control group; therefore, this finding may be useful for predicting IUGR.

The IUGR group had lower body mass indices before and after pregnancy than the control group when we were compared (p=0.026 vs. p=0.009). The literature has similar results regarding weight gain and IUGR (10,11). Strauss and Dietz (12) showed that lower weight gain in the second and third trimesters was associated with a greater risk of IUGR. Low weight gain or poor increases in body mass index are striking features of IUGR; therefore, weight measurement is important for preventing IUGR in primary health care.

EGF has been found to play a role in stimulating placental growth. This means that EGF plays a role in placental growth and in regulating physiological changes in placental function and many hormone secretions during intrauterine fetal development. It was found that IUGR pregnancies had less EGF expression in the placenta than normal pregnancies (13). Wang et al. (14) showed in their study that the EGF levels in non-pregnant women were lower than those in pregnant women. Furthermore, pregnant women with IUGR had lower EGF levels in maternal blood, cord blood, and amniotic fluid than those in the normal birth weight group. However, EGF levels showed no difference between the fetal macrosomia group and the normal birth weight group (14).

PDGF is a protein that regulates cell division and growth. PDGF plays a role in angiogenesis, blood vessel development, cell proliferation, migration, and embryonic development. Poor vascular development leads to low vascular resistance throughout the placental villi with fibrosis, and this situation causes intrauterine death. Abnormal angiogenesis is associated with IUGR (15). Hence, it is possible that mutations, damaged genes, or expression changes of genes in the EGF and PDGF pathways are involved in the etiopathogenesis of IUGR.

The proteins generated by the genes show individual variety; therefore, gene studies should be tailored to each person, and each case should be examined separately. Difficulties in the development of gene therapy are due to these variations. In this study, we compared the increases and decreases in gene expression. In addition, each case in the IUGR group was compared with the control group. We determined differences in gene expression except for the *LTA* gene. Only the expression of one gene, protein kinase alpha (PRKCA), was statistically significant between the IUGR and control groups. PRKC family members phosphorylate a wide variety of protein targets and are known to be involved in diverse cellular signaling pathways. PRKCA has been reported to play roles in many different cellular processes, such as cell adhesion, cell transformation, cell cycle checkpoints, and cell volume control (16). We investigated the *PRKCA* gene in a subgroup of apoptosis and the cell cycle. This pathway should be effective in IUGR, and the *PRKCA* gene should be effective to apoptosis and the cell cycle. When the patients in the IUGR group were compared with the control group, expression variations were determined at the genes that were studied. Therefore, expression variations of genes act on apoptosis and cellular events, so changes occur in the development of the placenta and fetus.

### *Study Limitations*

In this study, there were six pregnant women in the control group and six pregnant women with IUGR. Because of the high cost of such studies, the sample size was small in this study.

In the IUGR studies, only a few genes were investigated in several samples, but gene pathways involving 40 genes were examined

despite the small sample size in this study. Therefore, this study was designed as a guide for future clinical studies. The study should be considered a laboratory study rather than a clinical study.

## CONCLUSION

This study is one of several that are simultaneously investigating many associated genes with the etiopathogenesis of IUGR. We intend to guide future studies by forming an infrastructure for such research. Because of the high cost of such studies, the case and control groups consisted of some subjects. We believe that this kind of study will be conducted with more patients and more genes. This is also one of the most important issues to consider in gene studies, which focus on individual analysis rather than group comparison in the search for diseases and treatments. Currently, targeted therapies are applied to individualized treatments such as cancer. The genetic origin of IUGR and other diseases will be determined during pregnancy, and treatments will be developed.

### *Ethics*

**Ethics Committee Approval:** The approval of the Ethics Committee was obtained from the Gazi University Clinical Research Ethics Committee for this study (approval number: 252, date: 17.10.2012).

**Informed Consent:** All women were included in this study after informed consent was obtained.

**Peer-review:** Externally peer-reviewed.

### *Authorship Contributions*

Surgical and Medical Practices: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Concept: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Design: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Data Collection or Processing: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Analysis or Interpretation: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Literature Search: S.C.İ., E.D., M.Y., E.Ü.B., M.B., Writing: S.C.İ., E.D., M.Y., E.Ü.B., M.B.

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