IMPORTANT OF SERUM ADIPONECTIN LEVELS IN THE PREDICTION AND ETHIOPATHOGENESIS OF INTRAUTERINE GROWTH RESTRICTION

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Abstract

Objective: Our aim in this study is to determine the possibility that patients with IUGR (intrauterine growth retardation) will be able to look at the adhesionin levels in the early stages of pregnancy and to have IUGR. In this respect, early diagnosis, treatment and follow-up are aimed to reduce morbidity and mortality due to IUGR

Material Method: The study was carried out between January and March 2010. Zekai Tahir Burak Women's Health Education and Research Hospital 28-40. with 89 patients aged 18-40 years. Groups 44 IUGR patients and 45 normal pregnant patients were divided into two groups. To examine the serum adiponectin level, an average of 3 cc was taken in the gel biochemistry tubes and then centrifuged at 4000 × 10 minutes. The resulting serum samples were collected for the ELISA kit and kept at -80 ° C until the day the patients were collected. In the study, adiponectin levels were measured by serum ELISA (enzyme linked immunosorbent assay) method.

Results: In adiponectin evaluation, mean value was 105.90 ± 19.02 pg / ml for the IUGR group, 65.96 ± 16.5 pg / ml for the control group and 1.6 times higher for the IUGR group (p < 0.001)

Conclusion: In this study, the increased adiponectin levels of IUGR patients were significantly higher than those of IUGR patients, suggesting that pregnancies of IUGR patients can be measured high in the first weeks and if IUGR is high in those weeks, IUGR can be predicted.

Keywords

IUGR, adiponectin, ethiopathogenesis

Introduction

Intrauterine growth restriction (IUGR), is the second leading cause of perinatal mortality after pre-maturity. Perinatal mortality is observed 6-10 times more in fetuses with IUGR than in fetuses with normal development. Growth restriction is determined in about 30% of stillborn fetuses. On the other hand, IUGR is determined in 50% of fetuses showing signs of intrauterine (IU) asphyxia. Adiponectin is an adipocytokine synthesized from differentiated adipocytes and is found circulating in large amounts throughout the body. The adiponectin gene is largely expressed in white adipose tissue. Several experimental and epidemiological studies have shown that adiponectin plays a role in atherosclerosis, angiogenesis, inflammatory responses and in the regulation of insulin resistance. Adiponectin is a polypeptide of about 30 kDa in weight and is synthesized more in the subcutaneous than in the visceral adipose tissue. Adiponectin is found in large amounts in the plasma and constitutes 0.01% of the total protein in human plasma. Numerous adiponectin receptors are present in the placenta over the process of a normal pregnancy. Many studies conducted on animals and humans have determined that throughout the normal gestation period, adiponectin levels in the uterus either decreased or remained unchanged. It was noted that when adiponectin levels remained stable, this was considered an independent protective factor against increased insulin resistance. However, decreasing insulin sensitivity during pregnancy has been attributed to a decrease in adiponectin. In a recent study, a negative correlation was shown between adiponectin and BMI during pregnancy, although in many other studies, no correlation could be found. Although to date it has not been clarified as to which mechanisms are affected, many studies have shown that adiponectin enhances insulin sensitivity. Unlike other adipocytokines, adiponectin has been shown to decrease in obese, diabetic mice and humans. Numerous publications suggest that the anti-inflammatory effect is exhibited by the prevention of the release of the pro-inflammatory cytokines of adiponectin macrophages such as TNF-alpha, interferon gama, and interleukin 6. In the latest studies it has been shown that adiponectin stimulates in vivo and in vitro angiogenesis. Conventional, the progression of pregnancy is characterized by insulin resistance (IR) based on the effects of placental hormones. Diseases such as IUGR, PE, and GDM associated with a deteriorating placental condition can be reasons for the development

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of pregnancy-induced IR. There is convincing evidence to show that in the future the pregnancy disorder of maternal metabolic syndrome can be remedied. However, the underlying pathogenetic mechanisms associated with a normal placental development, IR and metabolic syndrome are still not fully understood. The aim of this study was to look at the adiponectin in IUGR patients and in normal patients without any disease or pathological findings in follow-up, and the difference in their venous blood sample values, and by examining these differences to perceive the prognostic significance of these values for IUGR predictability. In addition, by determining a marker to track the disease before its occurrence, and in the case of the disease, by providing closer monitoring, the long-term morbidity and maximum level of mortality in these patients could be prevented.

**Materials and Methods**

The study was carried out with a total of 89 patients with ages ranging from 18 to 40 who presented at the Dr. Zekai Tahir Burak Women’s Health Education and Research Hospital between January and March 2010. The patients were divided into two study groups. One group consisted of 44 patients between 28 and 40 weeks of pregnancy hospitalized at the Perinatology Clinic with a diagnosis of IUGR. Another group of 45 patients between 28 and 40 weeks of pregnancy attending the Antenatal Polyclinic and showing no disease with normal follow-up were randomly selected for the control. Seven of the IUGR patients were eliminated from the study because of diabetes mellitus (DM) and hypertension (HT). The study continued with Group 1 (IUGR group) consisting of 37 IUGR patients at 28 or more weeks of gestation and Group 2 (control group) consisting of the randomly selected 45 patients at the same gestational weeks. The number of pregnancies, the outcomes of previous pregnancies, blood group, age, disease status (diabetes mellitus, maternal renal, cardiac or any other systemic disease), follow-up status, whether or not related to spouse and if so, degree of kinship, addiction to alcohol or tobacco or other bad habits, weight gain during pregnancy and USG results (BPD, AC, FL, AFI, Doppler) were recorded for all patients in the study. To account for the weeks of gestation of the patients included in the study in terms of standardization, the results of the first ultrasound performed in the patients’ first trimester were used as the basis of calculation for the first pregnancy week. Using the PROSOUND SSD 5500 SV (ALOKA, Japan) USG having a 3.5 MHz convex probe, with the mother in supine position and at a time when fetal movements were absent, biometric measurements and pulsed color Doppler measurements were performed on all pregnant women in the study. The umbilical artery systolic / diastolic ratio was measured using the sites detected as the equi distance of the umbilical artery and of the fetus to the placenta. Pregnant women detected with absent end diastolic flow and reverse flow were noted. In all pregnant women, BPD (biparietal diameter), FL (femur length) and AC (abdominal circumference) measurements were made and estimated fetal weights were determined according to the Hadlock formula. In addition, amniotic fluid indices and placental location were also assessed. Intra uterine growth restriction was diagnosed in patients with estimated birth weight under 10 percentile according to the gestational age calculated by the first trimester USG, using pulsed color Doppler ultrasound. In order to examine blood samples of all the patients in the study for a marker indicating the properties of adiponectin, an average of 3 cc were taken in gel biochemistry tubes, and then centrifuged at 4000 ×/10 min. The obtained serum samples were collected for the ELISA kit and maintained at -80 °C until the working day when the summing-up process of the patients was completed. In the study, the adiponectin levels serum were determined via the ELISA (enzyme-linked immunosorbent assay) method. With this aim, the Millipore Human Adiponectin (ACRP30, Raybiotech) ELIZA KIT was used and adiponectin levels were determined in pg /ml. For the statistical analyses, the SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used. The independent samples t-test, Manny-Whitney U test and frequency distribution were used for the descriptive statistics (mean, standard deviation, median) as well as for the comparison of quantitative data. Confidence intervals of 95% and 99% (p < 0.01 and p < 0.05) were set for the differences between the groups to be considered significant.

**Results**

Table 1 shows that no statistical differences were found between the groups in terms of demographic characteristics (p > 0.05).

When the Independent Samples t-test was applied, the statistical analyses of weight gained during pregnancy, weeks pregnant (actual gestational age) and USG weeks were found to be significant (Table 2).

The average weight gain during pregnancy in the control group (12.04 ± 4.385 kg) was more than in the IUGR group (8.84 ± 4.986 kg)(p = 0.003). The average weeks pregnant for the control group were 34.511 ± 3.1650, while the IUGR group averaged 35.919 ± 2.8125 weeks (p = 0.036). The USG weeks for the IUGR group were 31.784 ± 2.8125, while for the control group they were 34.000 ± 3.0600 (p = 0.000). In the IUGR group compared with the control group, the sonographic measurements were about four weeks behind the actual gestational age, while in the control group these measurements were consistent (Table 2).

According to the Mann-Whitney U Test, the Doppler and amniotic fluid values were found to be statistically significant. The average Doppler for the IUGR group was 3.0314 ± 0.8364, while that of the control group was 2.5444 ± 04803 (p = 0.000). The average amniotic fluid measurement for the IUGR group was 33.322 ± 5.3 mm, while that of the control group was 135.346 ± 10.50 mm, showing the amniotic fluid to be significantly decreased in the IUGR group (Table 2).

The laboratory evaluation kit for adiponectin with the capability of evaluating over 30 IUGR patients and 30 controls was used for synchronization (Table 3). According to the Mann-Whitney U Test, in the evaluation of adiponectin, the average value for the IUGR group was 105.90 ± 19.02 pg /ml, while that of the control group was
Table 1. Demographic characteristics of the groups, showing no significant statistical differences

<table>
<thead>
<tr>
<th></th>
<th>Control (Mean ± SD)</th>
<th>IUGR (Mean ± SD)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 45</td>
<td>n = 37</td>
<td></td>
</tr>
<tr>
<td>Gravida</td>
<td>2.00 ± 0.168</td>
<td>2.19 ± 0.204</td>
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<tr>
<td>Parity</td>
<td>0.76 ± 0.128</td>
<td>0.95 ± 0.173</td>
<td>0.5</td>
</tr>
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<td>Live Births</td>
<td>0.73 ± 0.129</td>
<td>0.84 ± 0.171</td>
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<tr>
<td>Abortions</td>
<td>0.24 ± 0.096</td>
<td>0.22 ± 0.079</td>
<td>0.77</td>
</tr>
<tr>
<td>Curettage</td>
<td>0.02 ± 0.022</td>
<td>0.03 ± 0.027</td>
<td>0.889</td>
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<tr>
<td>Pregnancy</td>
<td>1.04 ± 0.044</td>
<td>1.11 ± 0.075</td>
<td>0.448</td>
</tr>
<tr>
<td>Follow-up Disease</td>
<td>2.1778 ± 0.0915</td>
<td>2.5000 ± 0.2174</td>
<td>0.292</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>1.8444 ± 0.0546</td>
<td>1.9459 ± 0.0376</td>
<td>0.146</td>
</tr>
<tr>
<td>Spousal Kinship Status</td>
<td>2.0000 ± 0.0317</td>
<td>1.9730 ± 0.0270</td>
<td>0.528</td>
</tr>
<tr>
<td>Age</td>
<td>26.51 ± 4.775</td>
<td>27.57 ± 5.824</td>
<td>0.369</td>
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Table 2. Statistical differences determined between groups (p < 0.05 and p < 0.01)

<table>
<thead>
<tr>
<th></th>
<th>Control (Mean ± SD)</th>
<th>IUGR (Mean ± SD)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 45</td>
<td>n = 37</td>
<td></td>
</tr>
<tr>
<td>Weight Gained (kg)</td>
<td>12.04 ± 4.385</td>
<td>8.84 ± 4.986</td>
<td>0.003</td>
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<tr>
<td>Weeks Pregnant</td>
<td>34.511 ± 3.1650</td>
<td>35.919 ± 2.8125</td>
<td>0.036</td>
</tr>
<tr>
<td>USG Weeks</td>
<td>34.000 ± 3.0600</td>
<td>31.784 ± 2.8125</td>
<td>0.000</td>
</tr>
<tr>
<td>Doppler</td>
<td>2.5444 ± 0.4803</td>
<td>3.0314 ± 0.8364</td>
<td>0.000</td>
</tr>
<tr>
<td>Amniotic Fluid (mm)</td>
<td>135.346 ± 10.50</td>
<td>33.322 ± 5.3</td>
<td>0.000</td>
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</tbody>
</table>

Table 3. Statistical distribution of adiponectin between the groups

<table>
<thead>
<tr>
<th></th>
<th>Control (Mean ± SD)</th>
<th>IUGR (Mean ± SD)</th>
<th>p values</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 30</td>
<td></td>
</tr>
<tr>
<td>ADIPONECTIN (pg/ml)</td>
<td>65.96 ± 16.5</td>
<td>105.90 ± 19.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

65.96 ± 16.5 pg/ml, showing the IUGR group to be 1.6 times higher, with a statistical significance of p = 0.001 (Fig. 1).

Figure 1. Distribution of adiponectin

Discussion

The aim of this study was to determine the variations shown in the angiogenic, anti-inflammatory, insulin sensitizing, antiatherosclerotic effects of adiponectin found in the serum level of the IUGR patient group and according to this result, to be able to predict the IUGR outcome or to propose possible ideas about the etiopathogenesis of IUGR. It emerged that factors like gravida, parity, live births, abortions, curretage and follow-up status were each independent risk factors for IUGR, thus increasing the reliability of this study\(^\text{18}\). The weeks pregnant, USG weeks, amniotic fluid, Doppler and weight gain during pregnancy of the demographically matched groups were found to be statistically significant. However, no significant difference was found for the others. The average age of the IUGR patient group was 27.5, while that of the control group was 26.5. The amount of weight gain for the IUGR group was found to be about 4 kg less compared to the control group (p = 0.003). In this study, the serum adiponectin levels examined were found to be increased almost 2-fold in the IUGR group (p = 0.001). Impaired placental perfusion and endothelial injury are known to be present in IUGR. This might be due to secondary damage, possible placental inflammation or insulin resistance and it was thought that the adiponectin, with its angiogenic, anti-inflammatory and insulin-sensitizing properties, could be increased in order to reduce these effects. Upon examination of the literature, IUGR serum adiponectin levels emerged in a wide spectrum; and publications reached the conclusion that in IUGR, increased, decreased or unchanged levels were all possible. IUGR is defined as the genetic inability...
of the fetus to achieve growth potential. IUGR is recognized as an obstetric problem due to the increased perinatal mortality together with its morbidity and long-term adverse effects; thus, defining it and understanding its pathogenesis is important. The findings of Evagelidou et al., in their study of 70 patients, 35 IUGR and 35 AGA, were in parallel with those of the present study. In the cases of detected IUGR, serum adiponectin levels were significantly higher. In the same study, examination of the lipids, leptin and insulin resistance index of the groups revealed that, while no differences in their leptin levels were detected, a significant increase in the insulin resistance index was revealed. The idea was also put forward that as a compliance mechanism, the insulin sensitizing effect of adiponectin may have caused the increased primary insulin resistance levels.

Suliman et al. in their study found increased levels of serum adiponectin, insulin and C-peptide in IUGR patients; also in the same study, defects in insulin receptors were detected in these patients.

Fasshauer et al. evaluated second trimester patients with impaired uterine perfusion and anticipated the possibility of developing IUGR and preeclampsia. For the study, 18 pregnant women between 18-21 weeks with impaired uterine perfusion and a control group of 18 non-pregnant women with the same characteristics were selected, and these pregnant patients were followed until term. In addition, a repeat Doppler ultrasound was performed at week 24 and it was confirmed that uterine perfusion was impaired. Although only six of these patients developed IUGR, no preeclampsia was observed. Serum adiponectin levels taken in the second trimester in the patients with impaired uterine perfusion were significantly higher, while no difference was detected in the IUGR group in the third trimester. It was argued that adiponectin levels in the second trimester may be increased as a response to impaired uterine perfusion and endothelial damage. Nicolaides et al. investigated the serum adiponectin and leptin levels of three groups of women in 23-25 weeks of pregnancy, including 44 patients with normal uterine artery Doppler values, 49 cases with abnormal uterine artery Doppler values but no growth restriction and 15 cases with abnormal uterine artery Doppler values and growth restriction. No significant differences between serum adiponectin levels were detected. As a result, they stated that adiponectin was not an important molecule in mid-trimester IUGR and the pathogenesis of pre-eclampsia. Therefore, when selecting patients, those in the early weeks of pregnancy were not included in this study. Kyriakakou et al. studied two groups of 40 patients that included twenty cases of growth restriction determined in the later weeks and 20 other cases at comparable weeks. First, the adiponectin and leptin levels were examined in serum samples taken from the maternal blood, from the umbilical cord at birth and postnatally from the infants. An increase in leptin levels was found, while the levels of adiponectin decreased. They noted that the chronic stress and inflammation in the IUGR mothers was reflected in their fetuses, and they stated that in this situation, the suppression of adiponectin production was due to chronic stress.

Suliman et al. showed concretely that various genetic mutations in patients with IUGR are the cause of insulin resistance. As mentioned in the study of Evagelidou et al., adiponectin, which has a proven sensitizing effect, could be increasing in response to this pre-existing primary insulin resistance. The main objective of this study was to obtain insight into the pathogenesis of IUGR; therefore, based on this data set, it can be said that insulin resistance has a place in IUGR pathogenesis. The impaired placental perfusion and endothelial damage in IUGR is recognized. Because of its angiogenic properties, adiponectin may again have been increased for this secondary damage. It must be emphasized that the OGTT tests were normal for both of the groups in this study.

In conclusion, the significantly increased adiponectin levels of the IUGR patients in this study provided further clarification and information concerning the pathogenesis of the disease.

Author Contributions

Alper Başbuğ (literature review), Çiğdem Kılıç (oversight), Gülşen Kutluer (data collection), Hacer Cavidan Gülserman (oversight), Ishak Artar (literature review)

References


