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The Relationship Of Free ß-hCG, PAPP-A, AFP, ß-hCG, UE3 In Pregnancy With Fac, 50 Gram Glucose Screening Test And Birth Weight

Gebelikte Serbest ß-hCG, PAPP-A, AFP, ß-hCG, UE3'in AKŞ, 50 Gram Glukoz Tarama Testi Ve Bebek Doğum Ağırlığı İle İlişkisi

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Abstract

Objective: It is possible to improve the quality of health and care and to minimize high-cost medical expenses by closely monitoring the complications in infants born with abnormal fetal birth weights. Within the scope of this research, we aimed to elucidate the relationship between first and second-trimester screening tests plasma proteins and 50 g glucose tolerance test values used in gestational diabetes screening with estimated birth weight.
Method: A total of 831 cases with regular antenatal follow-ups in Ankara Atatürk Training and Research Hospital, Gynecology, and Obstetrics Clinic were enrolled. The first- trimester fetal aneuploidy screening determined PAPP-A and free-β-hCG values. The second- trimester triple test determined Alpha-feto protein, hCG, and unconjugated estriol values. Fasting blood glucose was measured at the first visit, and a 50 g oral glucose tolerance test (OGTT) was performed between 24 – 28 weeks of gestation. Pregnancies continued without complications and who gave birth at term (gestational age 37+0 weeks) were included in the study.
Results: When the relationship between the hormonal values used in the first and second-trimester aneuploidy screening and the 50 gr OGTT (mg/dl) values are examined, no correlation between free-beta-hCG and 50 g OGTT (mg/dl) (r= -0.055, p= 0.128). Maternal fasting blood glucose levels (r= -0.055, p= 0.131) did not reveal any relationship with first and second-trimester aneuploidy screening. PAPP-A (r= - 0.011, p= 0.765), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340). (Figure 14), and hCG values (r= -0.051, p= 0.164), also did not present correlation with maternal fasting blood glucose levels.
Conclusion: According to the results of our study, no relationship was found between the hormones used in the first trimester (PAPP-A and free-beta-hCG) and second-trimester (AFP, hCG, and uE3) aneuploidy screening and 50 g OGTT, maternal plasma blood glucose level and birth weight.

Keywords: Gestational Diabetes Mellitus, Abnormal Birth Weight, Trimester, Pregnancy-Associated Plasma Protein-A (PAPP-A), Unconjugated Estriol (uE3).

Özet

Amaç: Anormal fetal doğum ağırlığı ile doğan bebeklerde komplikasyonların yakından izlenmesi ile sağlık ve bakım kalitesinin artırılması ve yüksek maliyetli tıbbi harcamaların en aza indirilmesi mümkündür. Bu araştırma kapsamında, gestasyonel diyabet taramasında kullanılan 50 g glukoz tolerans testi değerleri ile tahmini doğum ağırlığı ile birinci ve ikinci trimester tarama testleri plazma proteinleri arasındaki ilişkiyi ortaya koymayı amaçladık.
Yöntem: Ankara Atatürk Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'nde düzenli antenatal takipleri olan toplam 831 olgu çalışmaya alındı. Birinci trimester fetal anöploidi taraması PAPP-A ve serbest-β-hCG değerlerini belirledi. İkinci trimester üçlü testi, Alfa-feto protein, hCG ve konjuge olmayan estriol değerlerini belirledi. İlk vizitte açlık kan şekeri ölçüldü ve 24-28. gebelik haftaları arasında 50 gr oral glukoz

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tolerans testi (OGTT) yapıldı. Gebelikleri komplikasyonsuz devam eden ve miadında (gebelik yaşı 37+0 hafta) doğum yapanlar çalışmaya dahil edildi.
Bulgular: Birinci ve ikinci trimester anöploidi taramasında kullanılan hormon değerleri ile 50 gr OGTT (mg/dl) değerleri arasındaki ilişki incelendiğinde, serbest-beta-hCG ile 50 gr OGTT (mg/dl) arasında korelasyon saptanmadı (r= -0.055, p= 0.128). Maternal açlık kan şekeri düzeyleri (r= -0.055, p= 0.131) birinci ve ikinci trimester anöploidi taraması ile herhangi bir ilişki göstermedi. PAPP-A (r= - 0.011, p= 0.765), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340) ve hCG değerleri (r= -0.051, p= 0.164) de anne açlık kan şekeri seviyeleri ile korelasyon göstermedi.
Sonuç: Çalışmamızın sonuçlarına göre birinci trimesterde kullanılan hormonlar (PAPP-A ve serbest-beta-hCG) ve ikinci trimesterde (AFP, hCG ve uE3)anöploidi taraması ile 50 g OGTT, maternal plazma kan şekeri düzeyi ve doğum ağırlığı arasında ilişki bulunmadı.

Anahtar Kelimeler: Gestasyonel Diabetesmellitus, Anormal Doğum Ağırlığı, Trimester, Gebelikle İlişkili Plazma Protein-A (PAPP-A), Konjuge Olmayan Estriol (uE3).

INTRODUCTION

In 2-3% of pregnancies, major congenital anomalies are identified during pregnancy or immediately after delivery. These anomalies are responsible for 20% of infant deaths and have become the most common cause. Prenatal diagnosis; It is the science that identifies malformations, birth defects, chromosomal abnormalities, and other genetic syndromes in the fetus. The aim of prenatal diagnosis is to improve counseling services and outcomes by providing accurate information about short and long-term prognosis, risk of recurrence, and potential treatment (1). In recent years, thanks to the new developments in prenatal diagnosis methods, detecting many anomalies in the early period has become possible (2).

Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 3-4% of all pregnant women. 90% of this is gestational diabetes mellitus. Babies of mothers with GDM are at risk of developing obesity, impaired glucose tolerance, and diabetes at an early age (2, 3).

The biological function of pregnancy-associated plasma protein-A (PAPP-A), one of the four proteins detected in high concentration in pregnant blood in 1974, was unknown. In 1992, Wald suggested that PAPP-A is lower than normal in pregnancies with Down syndrome (DS) in the first trimester, and it has been used in routine medical practice as part of first-trimester screening tests since the second half of the 1990s. In 1999, it was reported that PAPP-A is the IGF-dependent IGFBP-4 protease isolated from human fibroblast culture medium (3). In the 2000s, it was understood that PAPP-A plays a critical role in growth and development and is involved in many physiological and pathophysiological processes by regulating local IGF concentration (4).

Similar to PAPP-A, various biomarkers have been identified and integrated into screening tests for anomaly screening. In the first trimester (11 – 14 weeks), free beta-human chorionic gonadotropin (f-ßhCG) and PAPP-A biochemical parameters and fetal nuchal translucency (NT) measurements have become almost the standard method to determine the risk of trisomy 21, 13 and 18. Thus, it is possible to detect the risk of trisomy in the early period with an accuracy of approximately 85-90% (5). One of the screening tests used in the second trimester is the triple screening test; its reliability is 61-70% (1). It is used in the determination of trisomy 21, 18, 13, and neural tube defects by looking at alfa-feto protein (AFP), uE3, and ßhCG in maternal serum (6).

As the function of these proteins, which are used in anomaly screening tests in recent years, is understood, various studies have been carried out in order to use them for the pre-detection of

some conditions (preeclampsia, IUGR, gestational diabetes, macrosomia, preterm birth, polyhydramnios, fetal sex, etc.). Placental proteins include ß-hCG, PAPP-A, AFP, uE3, and Inhibin-A. The results of the pregnancy values of these proteins I mentioned in terms of preeclampsia, fetal sex, and gestational diabetes were compared in various studies, and it was evaluated whether there was a relationship between them (7).

Gestational diabetes mellitus (GDM) is a glucose intolerance disorder that first appears during pregnancy or is diagnosed during pregnancy. GDM rate in all pregnancies is 1 – 14%. The main mechanism in the pathogenesis of gestational diabetes is a maximum of 24 – 28. Insulin resistance is triggered by placental hormones and autoimmune origin proteins (HLA-DR 2, 3, 4 antigens) and the inability to meet the increased insulin requirement by maternal pancreatic beta cells. Hormones that increase insulin resistance are human placental lactogen (HPL), growth hormone (GH), progesterone, corticotropin-releasing hormone (CRH), cortisol, and prolactin (PRL) (8).

It is possible to improve the quality of health and care and to minimize high-cost medical expenses by closely monitoring the complications that may occur in infants born with abnormal fetal birth weights (9). Within the scope of this research, we aimed to elucidate the relationship between first and second-trimester screening tests plasma proteins and 50 g glucose tolerance test values used in gestational diabetes screening with estimated birth weight.

METHOD

A total of 831 cases with regular antenatal follow-ups in Ankara Atatürk Training and Research Hospital, Gynecology, and Obstetrics Clinic were enrolled. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution.

The first-trimester fetal aneuploidy screening determined PAPP-A and free-β-hCG values. The second-trimester triple test determined Alpha-feto protein, hCG, and unconjugated estriol values. Fasting blood glucose was measured at the first visit, and a 50 g oral glucose tolerance test (OGTT) was performed between 24 – 28 weeks of gestation. Among these cases, 759 cases whose pregnancies continued without complications and who gave birth at term (gestational age 37+0 weeks) were included in the study.

The descriptive data of the pregnant women, age, gravida, and parity values, birth weeks and birth weights (g), and maternal plasma PAPP-A, free-beta-hCG, alpha-feto protein, hCG, and unconjugated estriol values were recorded as MoM. Fasting plasma glucose (FPG) and 50 g OGTT values were calculated as mg/dl and recorded. It was investigated whether there is a relationship between maternal plasma hormone values and FGW, 50 gr OGTT values, and birth weights and hormone values.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T–test" was used for two groups, and the "Pearson Chi-Square Test" was used for the comparison of categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

The mean age of 759 cases was 26.8±4.7 (range 16 – 41). The gravida was 2.2±1.2 (range 1 – 10), and parity was 0.9±0.8 (range 0 – 5). The mean FPG value was 83.6±11.3 (range 49 – 136) mg/dl, 50 g OGTT was 117.0±28.3 (range 53 –224) mg/dl, and birth weight was 3350±449 g. When the relationship between the hormonal values used in the first and second-trimester aneuploidy screening and the 50 gr OGTT (mg/dl) values are examined, no correlation between free-beta-hCG and 50 g OGTT (mg/dl) (r= -0.055, p= 0.128).

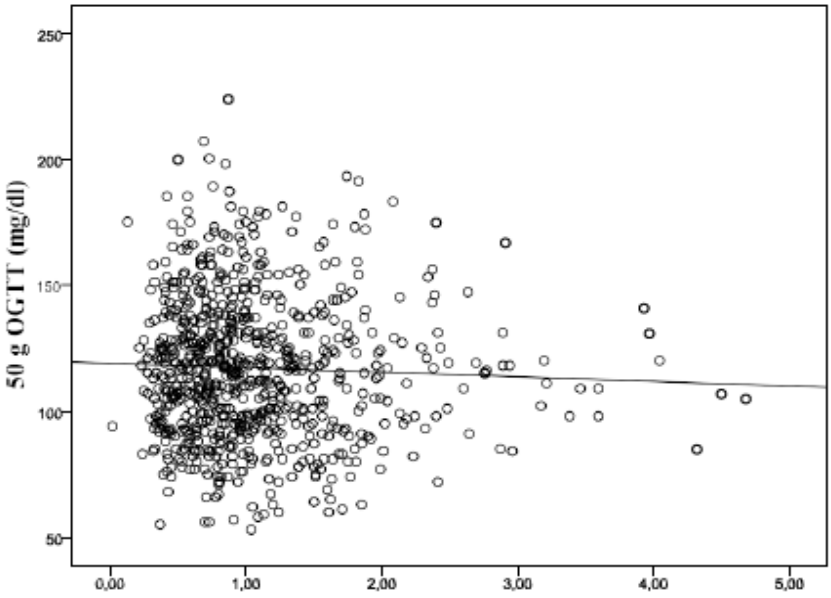

Figure 1. Correlation Of PAPP-A (MoM) With 50 g OGTT (mg/dl)

No correlation was found between PAPP-A and 50 g OGTT (mg/dl) (r= -0.041, p= 0.262) (Figure 2) and between AFP (MoM) and 50 g OGTT (mg/dl) (r= 0.022, p= 0.554) (Figure 1). Additionally, we could not achieve a correlation between uE3 (MoM) and 50 g OGTT (mg/dl) (r= - 0.022, p= 0.540), and between hCG (MoM) and 50 g OGTT (mg/dl) (r= 0.031, p= 0.399).

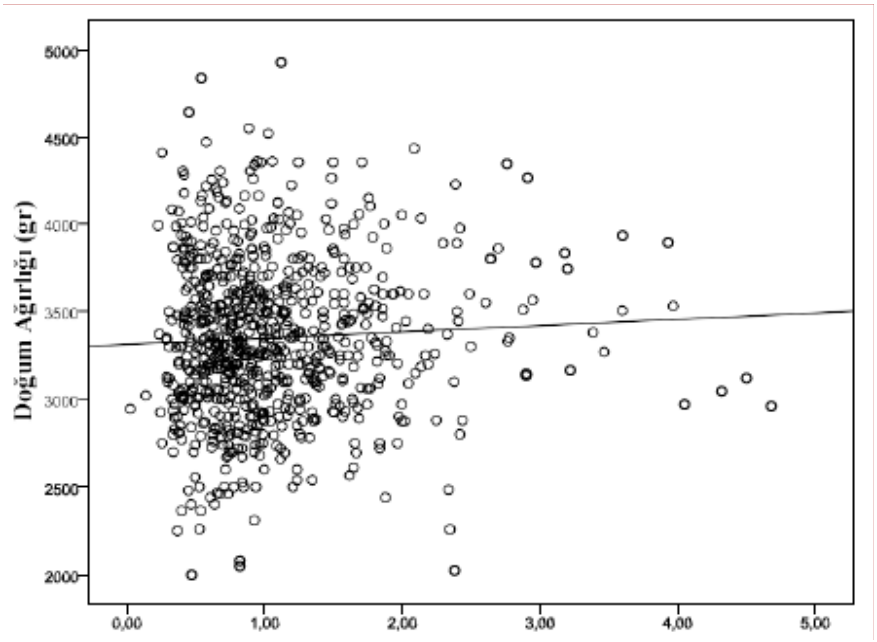

Figure 2. Correlation Of PAPP-A With Birth Weight (g)

When the relationship between hormonal values and birth weight (g) values in the first and second-trimester aneuploidy screening was examined, there was no correlation between free-beta-hCG (r=-0.022, p= 0.542), PAPP-A (r= -0.051, p= 0.159) (Figure 2), AFP (r= 0.012, p= 0.744), uE3 (r= 0.069, p= 0.056), hCG (r= -0.010, p= 0.790) and birth weight.

Maternal fasting blood glucose levels (r= -0.055, p= 0.131), did not reveal any relationship with first and second-trimester aneuploidy screening.

PAPP-A (r= - 0.011, p= 0.765) (Figure 3), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340) (Figure 3), and hCG values (r= -0.051, p= 0.164), also did not present correlation with maternal fasting blood glucose levels.

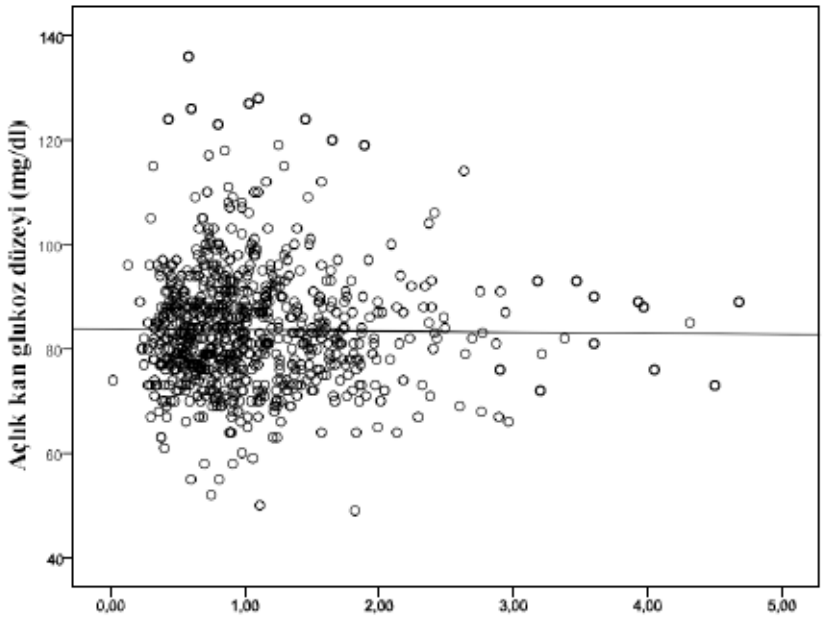

Figure 3. Correlation Of PAPP-A With Maternal Fasting Blood Glucose Level

DISCUSSION

Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 3-4% of all pregnant women. 90% of this is gestational diabetes mellitus. Babies of mothers with GDM are at risk of developing obesity, impaired glucose tolerance, and diabetes. It is a metabolic disorder that can cause morbidity and mortality ranging from congenital malformations to in-utero death in the baby, from hypoglycemia in the mother to diabetic ketoacidosis, increased retinopathy, and nephropathy when adequate glycemic control is not achieved (10).

The main mechanism in the pathogenesis of gestational diabetes is insulin resistance triggered by placental hormones and proteins of autoimmune origin (HLA-DR 2,3,4 antigens) and the inability to meet the increased insulin requirement by maternal pancreatic beta cells. Hormones that increase insulin resistance are HPL, growth hormone, progesterone, CRH, cortisol, and PRL (11). HPL is the main hormone responsible for insulin resistance in pregnancy, and it achieves this effect by decreasing the affinity of insulin for its receptor, although it is not certain. It also reduces the use of carbohydrates for energy by increasing lipolysis in adipose tissue. Thus, glucose and amino acids are stored for the fetus (12). As a result of increasing insulin resistance during pregnancy, the amount of insulin secreted from the pancreas to provide maternal euglycemia increases more than two times compared to non-pregnant women. This situation can be tolerated physiologically in normal pregnant women, it cannot be compensated

during pregnancy in diabetic women and many women who were not known to have diabetes before, and the balance of carbohydrate metabolism is disturbed (13).

It shows its hCG activity through the LH/hCG receptor, and its major function is to provide progesterone production (14). Increased progesterone with hCG contributes to insulin resistance. In previous studies, it was reported that hCG-ß promotes growth. With this effect, it can be thought that it can directly contribute to birth weight. Another effect of the placenta is the prolongation of the half-life of hCG, a glycoprotein carrying a carbohydrate side chain (15).

Compared to normoglycemic individuals, a history of macrosomic infant delivery is three times more common in diabetics. These babies have excessive fat accumulation on the shoulders and trunks. The main factor in the development of macrosomia is fetal hyperinsulinemia developing in response to maternal hyperglycemia. About 80% of maternal glucose levels also occur in the fetus. Thus, fetuses of hyperglycemic mothers synthesize more insulin. In the fetus, tissues sensitive to insulin, such as the liver, adipose tissue, muscle tissue, heart, adrenal glands, and pancreas, undergo hypertrophy and hyperplasia. The same change is not seen in the length of the brain, kidneys, and femur (16). Similarly, maternal amino acid use decreases as a result of insulin resistance and hypoinsulinemic state in diabetics, and fetal development accelerates as a result of increased circulating amino acids passing to the fetus and stimulating insulin secretion. GDM, which may develop with the effect of these hormonal stimuli, can be detected by evaluating with 50 g OGTT performed between 24 – 28 weeks (17).

Insulin-like growth factors (IGFs), which stimulate cell proliferation and differentiation, exert the most important effect on fetal growth. Serum IGF levels in the prenatal period are lower than in the postnatal period, increase during pregnancy and show a positive correlation with birth weight. Placental somatotropins (placental lactogens) stimulate the synthesis of IGF-I and IGF-II (18).

PAPP-A is secreted by trophoblasts in the placenta; It has been found to be IGF-dependent IGFBP-4 protease. IGFBP-4 has a high affinity for IGFs and prevents cell growth by binding IGF and preventing them from interacting with IGF-I receptors. It is also an inhibitor of IGFBP. PAPP-A severely reduces its affinity for IGFs by cleaving IGFBP-4 in the middle. This mechanism may account for the increase in birth weight at high PAPP-A levels (19). The study of Savvidou and Nicolaides et al. reported the relationship between first-trimester maternal serum f-βhCG and PAPP-A levels and gestational diabetes was examined, and no correlation was found between them. As a result, it was found that low βhCG levels in the second trimester were associated with gestational diabetes (20). Our study showed a difference between first-trimester f-βhCG and OGTT.

While no significant relationship was found, no significant relationship was found between second-trimester βhCG values and FPG and OGTT. Significant results can be obtained in studies performed by setting a threshold value for second trimester βhCG values (above 0.81 MoM). The relationship between serum PAPP-A values and gestational diabetes revealed that the relationship between low PAPP-A values and gestational diabetes was significant (21). Another stated that low PAPP-A levels in the first trimester were associated with possible gestational diabetes (22).

Birth weight is directly related to maternal race, age, body mass index, number of births, smoking, and pre-pregnancy DM in relation to the gestational period. The large size of the fetus complicates the delivery and puts the mother at risk. Identifying the factors that control fetal growth will be beneficial in understanding the pathophysiology of the disease, preventing complications, and treatment. In the past, it was argued that the variability observed in fetal

growth occurred mainly in the second half of pregnancy when antenatal care was given (23). Later studies have reported that embryos and fetuses smaller than expected in the first trimester are more prone to complications such as growth retardation and premature birth (24). In published studies, a significant relationship was found between birth weight percentiles and adjusted PAPP-A values. Habayeb et al. showed a positive correlation between first-trimester PAPP-A MoM values and birth weight (25). Pregnancies with increased PAPP-A MoM values were observed to have higher birth weights. A study also states a positive correlation between PAPP-A and birth weight in complicated pregnancies with maternal diabetes (26). In our study, no significant relationship was found between birth weight and PAPP-A value; Although there was no difference in material method with studies with positive correlation, it was mentioned in one study that a cutoff value was used for PAPP-A MoM (<0.55 MoM).

Bader et al. reported a significant negative correlation between AFP and birth weight (27). However, babies born under 2500 g were not included in their study. In other similar studies, it has been determined that high maternal serum AFP levels may be associated with the birth of a baby with intrauterine growth retardation (28, 29). In our study, no relationship was found between AFP and birth weight. The studies with positive correlations did not include maternal systemic disease, drug use, genetic reasons affecting growth, GDM, multiple pregnancies, and pregnancies without follow-up. Despite this, studies also show no relationship between maternal serum AFP and birth weight at any gestational week (30). In this study, AFP was measured in umbilical cord blood, and an inverse relationship was found between birth weight and birth weight.

We could not find a relationship between our parameters and birth weight in our study, despite the significant results previously determined, maybe the inclusion of a heterogeneous patient population.

CONCLUSION

According to the results of our study, no relationship was found between the hormones used in the first trimester (PAPP-A and free-beta-hCG) and second-trimester (AFP, hCG, and uE3) aneuploidy screening and 50 g OGTT, maternal plasma blood glucose level and birth weight.

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Competing interests: The authors declare that they have no competing interests.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. As this was a retrospective research no informed consent has been obtained from participants.

Abbreviations

AFP : Alfa-feto protein
CRH : Corticotropin-releasing hormone
DS : Down Syndrome
FPG : Fasting plasma glucose

f-ßhCG : Free beta-human chorionic gonadotropin
GDM : Gestational diabetes melltus
GH : Growth hormone
hCG : Human chorionic gonadotropin
HLA : Human leucocyte antigen
HPL : Human placental lactogen
IGFs : Insulin-like growth factors
IUGR : Intra-uterine growth retardation
NT : Nuchal translucency
OGTT : Oral glucose tolerance test
PAPP – A : Pregnancy-associated plasma protein-A
PRL : Prolactin
SPSS : Statistical Package for the Social Sciences
uE3 : Unconjugated estriol

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