International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Ultrasound measurement of fetal adrenal gland, umbilical artery doppler in normal and growth restricted fetuses

Osama Ahmed Ibrahim, Ahmed Reda Eladawi, Taghreed Ahmed Sayed Abdelhakim

[1]*Faculty of Medicine, MINIA University, Egypt*

Abstract

Intrauterine growth restriction (IUGR) is characterized by a fetal growth rate that falls below the expected level, taking into account the development potential of a particular newborn based on their race and gender. To ascertain the association among the volume of the fetal adrenal gland & the occurrence of late fetal growth restriction. This study featured a case-control design, involving a total of 110 pregnant women who were separated into 2 equal groups. The investigation was conducted at the Obstetrics & Gynecology Department of MINIA University Hospital. A statistically significant variance exists between the case & control groups in terms of estimated fetal weight (p value<0.05). The research using Pearson association demonstrated that there is a statistically significant moderate positive linear association among maternal age & both medulla width (r=0.390, p=0.003) and AGV (r=0.462, p=0.001). Furthermore, a statistically significant and mild positive linear correlation was seen between gestational age and both medulla and AGV. A moderate positive association exists between the volume of the adrenal gland and the breadth of the medulla, which is statistically significant, as it relates to the gestational age. Although there is no statistically significant distinction among the case & control groups in terms of mother age, gestational age, parity, and gravidity (p value>0.05). Given that the alterations in fetal adrenal gland sizes in fetus diagnosed with IUGR are a consequence of fetal adaptive mechanisms to chronic oxygen deprivation, it is plausible to anticipate worse perinatal outcomes in fetuses that are unable to adjust to the adverse circumstances within the womb.

Keywords: Intrauterine growth restriction (IUGR), Restricted fetuses, Fetal adrenal gland.

Full length article **Corresponding Author*, e-mail: taghreedahmed010065@gmail.com

1. Introduction

IUGR is characterized by a fetal growth rate that is lower than what is considered normal, considering the development potential of a given newborn based on their race and gender [1]. A "normal" neonate refers to an infant whose birth weight falls within the 10th and 90th percentile range based on their gestational age, gender, and race. Additionally, they should not exhibit any signs of starvation or growth retardation [2]. The adrenal gland consists of two separate tissues, the cortex and medulla, which originate from the mesoderm and neuroectoderm, respectively. The size of the fetal adrenal gland is rather substantial, measuring 3 units. After 4 months' gestation, the size of the organ is quadruple that of the kidney, but after birth, it is only 1/3 the size of the kidney. This phenomenon arises due to the fast degeneration of the fetal brain during the process of birth. Adrenal gland may experience anatomical abnormalities [4]. Due to the strong relationship between the development of the adrenals and the kidneys, the absence of one adrenal gland is typically accompanied by the absence of the kidney on the same side. Similarly, the fusion of adrenal glands is similarly linked to the fusion of the kidney.

Kaya and Polat measured the sizes of the adrenal glands of fetuses who were not growing normally inside the uterus. They discovered that changes in the sizes of the adrenal glands seen in women who were diagnosed with intrauterine growth restriction are due to chronic hypoxia caused by uteroplacental failure. These changes also lead to bad programming of the fetus, which is correlated with long-term negative health outcomes [6]. The objective of this study was to identify the association among the volume of the fetal adrenal gland & the occurrence of late fetal growth restriction.

2. Patients and method

This study had a case-control design with 110 pregnant women who were placed into two equal groups. Group 1 consisted of 55 suitable pregnant females among 28 & thirty-eight weeks of gestation who had been diagnosed with intrauterine growth restriction. Group 2: (group serving as a reference for comparison): A total of 55 women, who had fetuses that were appropriate for their gestational age and were between 28 and 38 weeks of gestation, did not have any further obstetric complications or medical illnesses. These

ladies delivered their babies at full term. The investigation was conducted at the Obstetrics & Gynecology department of MINIA University Hospital. Following the approval of the Scientific Research Ethics Committee of the Faculty of Medicine at MINIA University, a total of 110 pregnant women who sought evaluation at the Antenatal Care Unit at MINIA University Hospital were selected for participation in the study. Prior to their inclusion, the women were provided with a detailed explanation of the study's methodology & objectives, & their consent was obtained.

2.1 Criteria for inclusion

Age range: 20 to 35 years. Gestational age range: 28 to 36 weeks. The patient has a single fetus and a history of intrauterine growth restriction, which was diagnosed by ultrasound examination of biometry and amniotic fluid volume. Exclusion criteria include multiple pregnancies, intrauterine fetal demise, medical illnesses, ultrasound evidence of congenital malformations, unreliable pattern of fetal heartbeat, smoking habit, and the presence of maternal morbidity accompanied by morbidity. Each woman had a comprehensive process that included history taking, general examination, diagnosis of intrauterine growth restriction, and a Three-dimensional (3D) ultrasound investigation.

2.2 Quantification of adrenal gland size

Following the fetal anatomical examination, measurements of amniotic fluid, fetal biometry, & ductus venosus, the middle cerebral artery, & uterine artery were conducted. The volume of the adrenal gland (AGV) was quantified using the 3D VOCAL program.3D U/S VOCAL is an optimal method for measuring items with irregular shapes by tracing their exterior surface using mathematical algorithms.

2.3 Quantitative data analysis

The data were gathered, reviewed, encoded, and inputted into the Statistical Package for Social Science (IBM SPSS) version 21. The qualitative data were represented using percentages & numbers, while the quantitative data were represented using measures such as mean, SD, & ranges, but only if their distribution was found to be parametric. The tests employed in the study involved Mann-Whitney U test, the independent sample t-test, Pearson's correlation analysis, and correlation graphs were only generated for statistically significant correlations. We employed receiver operating characteristic (ROC) curve analysis. We employed linear regression analysis. The confidence interval was established at a 95% level, with a permissible margin of error of 5%. The p-value was deemed significant based on the following criteria: P-value up to 0.05 indicates non-significance (NS), P < 0.05 indicates significance (S), and P-value less than 0.001 indicates high significance (HS).

3. Results

As shown in previous table, there is a statistically significant difference between case and control regarding estimated fetal weight (p value<0.05) as it was significantly lower in pregnant women with diagnosis of IUGR (1463gm) than in control with normal baby (2252gm). While there is a non-statistically significant difference between case and control regarding maternal age, gestational age, parity and gravidity (p value>0.05). Table (2) shows an investigation of the link between the medulla width and the volume of the adrenal gland and other variables under study. Maternal age exhibited a statistically significant moderate positive linear correlation with medulla width (r=0.390, p-value=0.003) & with AGV (r=0.462, p-value=0.001), according to Pearson Correlation analysis. Additionally, a statistically significant modest positive linear connection was seen among gestational age & both medulla width (r=0.266, p=0.049) & AGV (r=0.389, p=0.003). The IUGR group exhibited a non-significant linear connection with respect to EFW, gravidity, and parity (p-values >0.05). As shown in previous table, there are mild positive significant correlation between adrenal gland volume & gestational age (r= 0.34 and p value<0.05), also, there are mild positive significant correlation between medulla width and gestational age (r= 0.25 and p value<0.05). & mild and week significant association among adrenal gland volume & both gravidity and parity (r=0.26 0.24 with p value<0.05) respectively. While non-significant correlation was found with other parameters.

4. Discussion

Intrauterine Growth Restriction is a significant contributor to both perinatal death & morbidity. The process of maintaining adequate fetal growth involves an intricate and ever-changing interplay between the maternal, placental, and fetal environments. An asymmetry or deficiency in the coordination of this intricate system might result in IUGR. IUGR is a condition when the growth of the fetus is below the average for both the general population and the expected growth for a specific newborn. Intrauterine growth restriction (IUGR) can manifest as either symmetrical or asymmetrical. Symmetrical IUGR is characterized by low weight, length, and head circumference, which often indicates a developmental issue that originated early in pregnancy. On the other hand, asymmetrical IUGR is characterized by a sparing of head size and length, suggesting that the developmental issues occurred later in gestation [1]. The results of our study revealed that the gestational age of the infants in the IUGR group varied from 26 to 38 weeks. Additionally, the average age of the mothers in this group was 31.5 ±3.0 years. The average age of mothers in the control group was 32.3 ±3.2 years, with a range of gestational ages between 26 and 38 years. Upon study enrollment, there were no statistically significant variances (p-values >0.05) seen in the mother's age, gravidity, parity, & gestational age among the 2 groups under examination. There is a notable statistical distinction among the case & control groups in terms of estimated fetal weight (p value<0.05). Pregnant females diagnosed with IUGR had a considerably lower estimated fetal weight (1463gm) compared to the control group with normal babies (2252gm). Kaya and Polat have verified this by measuring the sizes of embryonic adrenal glands in instances of intrauterine growth restriction.

Table 1: Baseline characteristics among the studied pregnant women (N= 110).

Characteristics		Studied Groups		p-value
		IUGR N= 55	Control N= 55	
Age (years)	**Mean ±SD**	29.3±**5.1**	28.1±**4.9**	0.34
	Range (Mini – Max)	23-34	22-35	
Gravidity	**Mean ±SD**	2.3±**2.1**	2.8±**1.9**	0.09
	Range (Mini – Max)	1-7	1-5	
Parity	**Mean ±SD**	2.3±1.51	1.8 ±**1.3**	0.057
	Range (Mini – Max)	0-6	0-4	
GA (weeks)	**Mean ±SD**	33.7±**3.8**	33.8±**3.7**	0.80
	Range (Mini – Max)	26-38	26-39	
EFW	**Mean ±SD**	1463±**476**	2252±**627**	**<0.001***
	Range (Mini – Max)	719-2335	950=3080	

* Significant at p value<0.05, IUGR: Intrauterine growth restriction

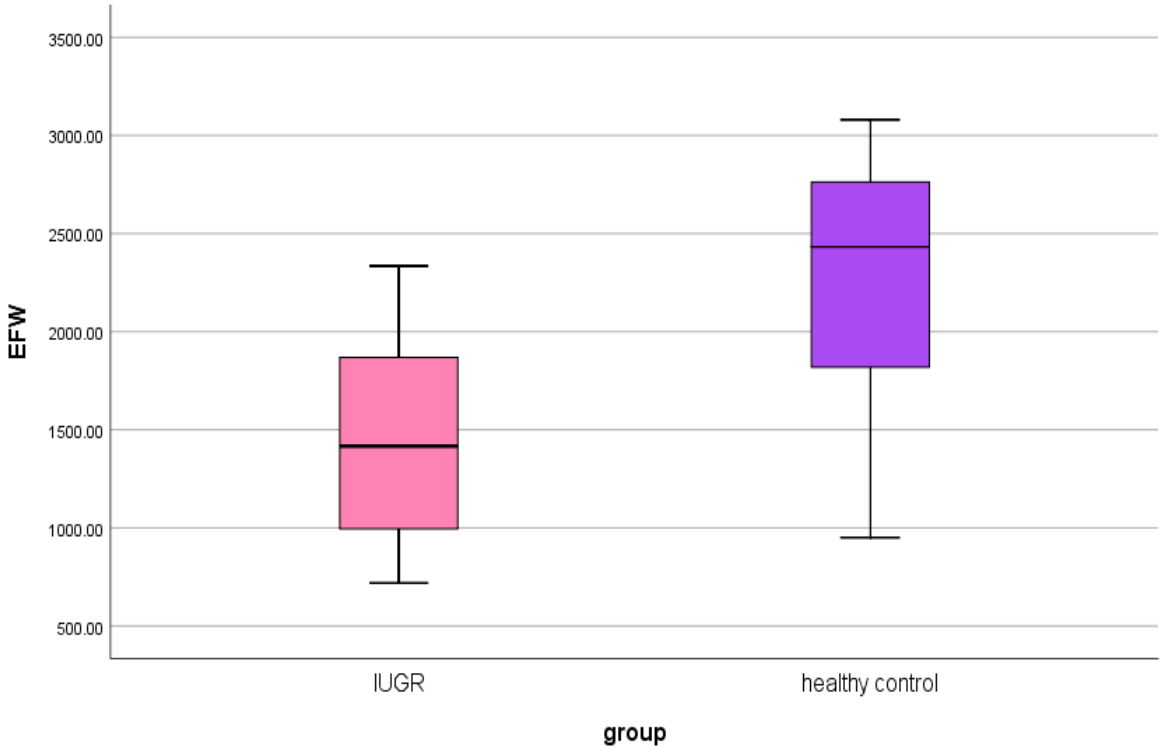

Figure 1: Box plot represent comparison between the studied groups regarding estimated fetal weight

Table 2: Correlation analysis between adrenal gland volume and medulla width with other studied variables among IUGR group (N= 55)

IUGR Group			AGV adrenal gland volume	Medulla width (mm)
	Maternal Age (years)	**r**	**0.462**	**0.390**
		p	**0.001**	**0.003**
	Parity	**r**	0.007	0.038
		p	0.962	0.785
	GA (weeks)	**r**	**0.389**	**0.266**
		p	**0.003**	**0.049**
	EFW (gm)	**r**	0.161	- 0.012
		p	0.241	0.933

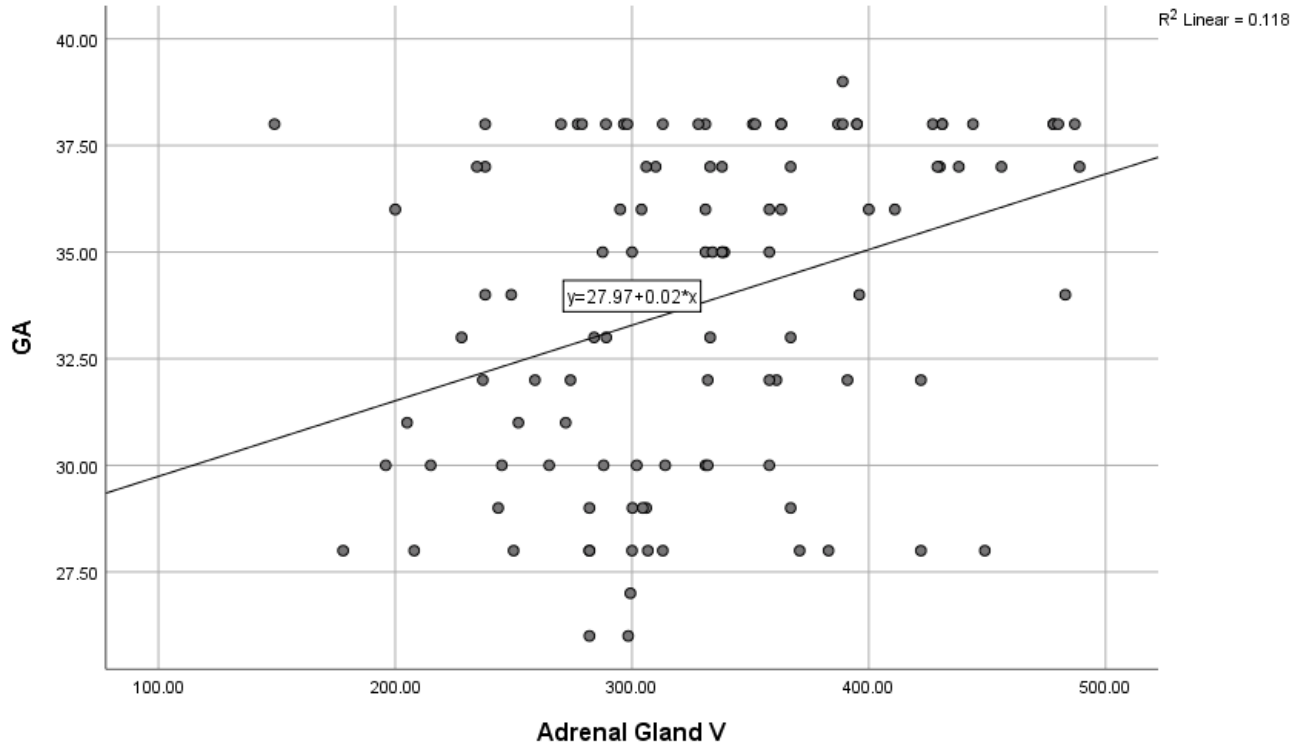

Figure 2: Scatter plot represent correlation between adrenal gland volume & gestational age

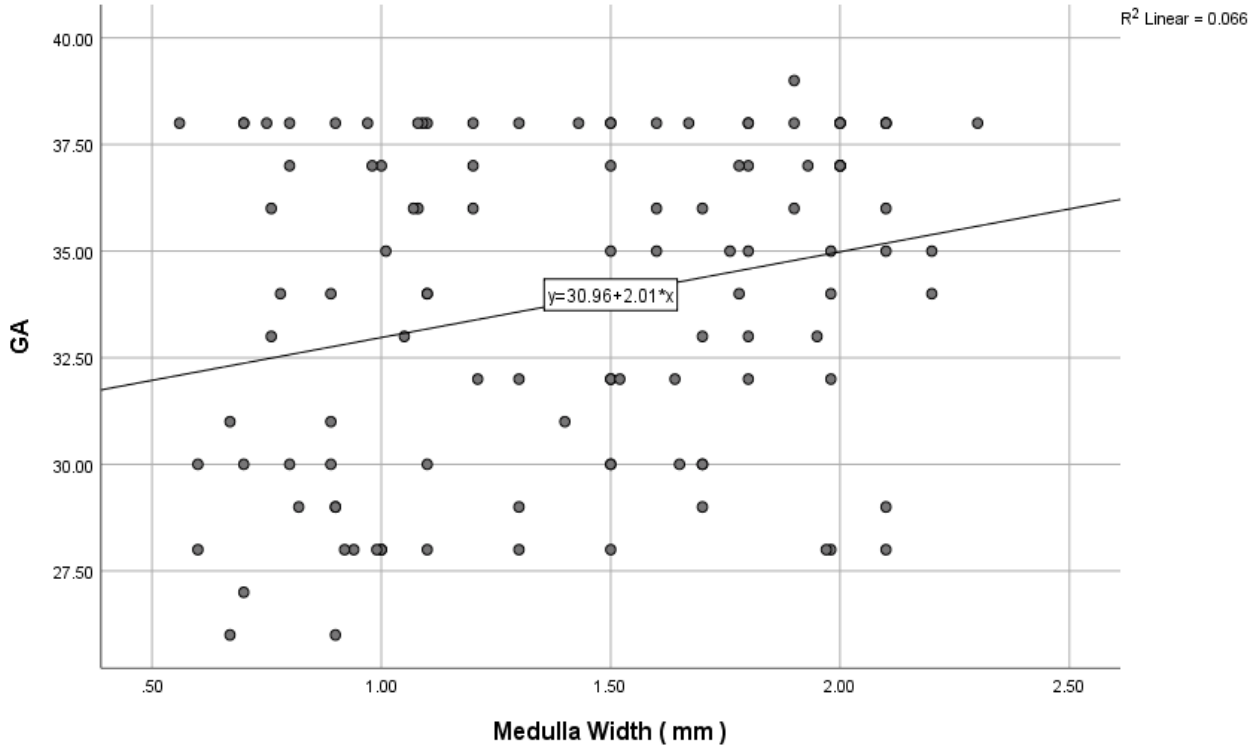

Figure 3: Scatter plot represent correlation among medulla width & gestational age

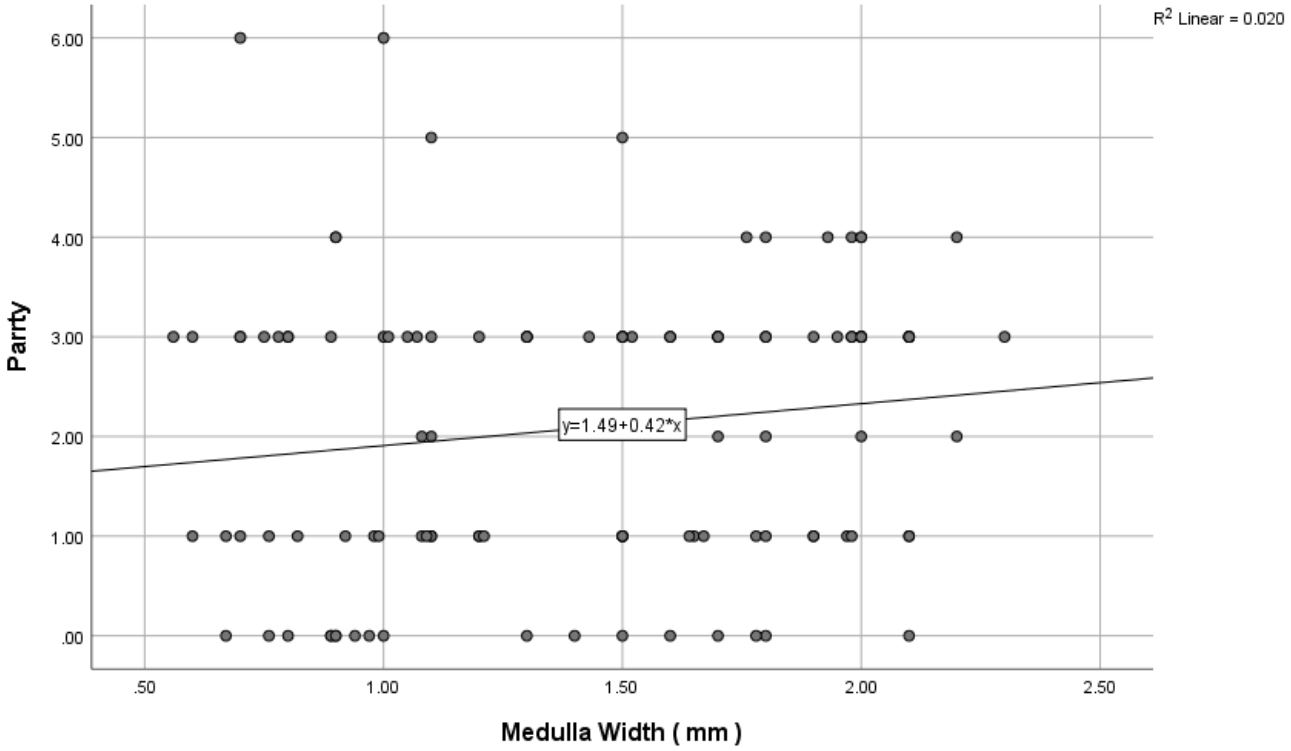

Figure 4: Scatter plot represent correlation among medulla width & parity.

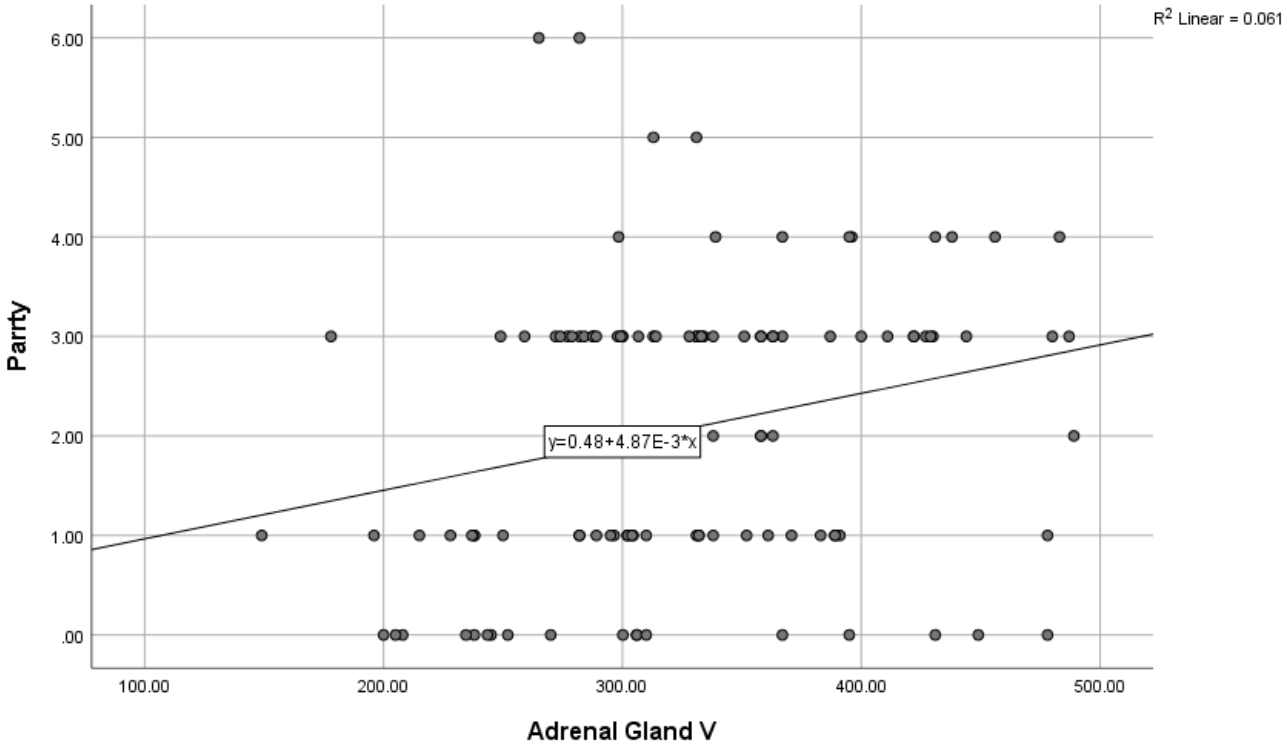

Figure 5: Scatter plot represent correlation between adrenal gland volume and parity

Table 3: Unadjusted and adjusted linear regression analysis for predictors of adrenal gland volume among our studied population

	Unadjusted Analysis			Adjusted Analysis		
	Coefficients	**t-test**	**p-value**	**Coefficients**	**t-test**	**p-value**
Maternal Age	0.341	3.770	**0.001***	0.363	4.865	**0.001***
Gravidity	0.259	2.785	**0.006***	0.127	1.706	0.091
Parity	0.259	2.785	**0.006***	0.127	1.706	0.091
GA	0.344	3.808	**0.001***	0.654	7.010	**0.001***
EFW	-0.118	-1.230	**<0.001***	-0.582	-6.129	**0.001***

No statistically significant variations were found in the weeks of gestation at diagnosis, parity, gravida, BMI, or maternal age among the study & control groups (p>0.05) [6]. The characteristics of the previous patient were comparable to those observed in the study performed by Rossi et al. This study included 105 pregnant females with a gestational age between 34+0 and 36+0 weeks. The average age of the mothers was 30.6±3.1 years. Among the participants, 43% were experiencing their first pregnancy (primigravida) and 57% had been pregnant before (multigravida). Additionally, 46% of the women were giving birth for the first time (primipara), while 54% had given birth previously (multipara) [8]. Furthermore, Addley et al. validated the characteristics of our patient, since the

average gestational age in the high-risk group was 34+0 weeks, whereas the average gestational age in the control group was 35+4 weeks. Furthermore, it was shown that there wasn't statistically significant disparity in BMI, age, or gestation period among females in the normal pregnancy group & females in the group with preeclampsia [9]. According to Pearson correlation analysis, there was a statistically significant moderate positive linear relationship among maternal age & medulla width (r=0.390, p=0.003), as well as among maternal age and AGV (r=0.462, p=0.001). Also, a statistically significant and moderate positive linear correlation was seen between gestational age and both medulla width (r=0.266, p=0.049) & AGV (r=0.389, p=0.003). However, in the IUGR group, there wasn't statistically significant linear relationship observed among EFW, gravidity, & parity (p-values > 0.05). The dimensions of the developing adrenal glands and the gestational age were found to be directly correlated, as demonstrated by Kaya and Polat, who reported a statistically significant positive association between these variables (p<0.001) [6]. Maternal age, gravidity, gestational age, parity, & estimated fetal weight were identified as statistically significant predictors of adrenal gland volume in the initial regression analysis. However, after adjusting for maternal age, parity, gravidity, gestational age, & estimated fetal weight, only maternal age, gestational age, & estimated fetal weight remained as statistically significant predictors of adrenal gland volume. Heese et al. performed a study on the diameters of adrenal glands in Embryos diagnosed with IUGR. The group with IUGR had significantly bigger cortical and total adrenal gland widths compared to the control group [10]. Based on the current state of research and our findings, it is reasonable to deduce that ongoing lack of oxygen in the uterus and ongoing stress caused by placental failure activate the hypothalamic-pituitary-adrenal axis system. This, in turn, leads to increased production of cortisol in the fetal adrenal glands, resulting in larger adrenal glands in the fetus. During pregnancy, the production of cortisol by the fetal adrenal gland suppresses the release of corticotropin-releasing hormone (CRH) in the hypothalamus. This hormone is responsible for regulating the activity of the hypothalamic-pituitary-adrenal (HPA) axis [11]. Beshay et al.'s research indicates that the synthesis of cortisol by the fetal adrenal gland stimulates the release of placental corticotropin-releasing hormone, while simultaneously inhibiting the release of hypothalamic corticotropin-releasing hormone. Moreover, the rise in placental corticotropin-releasing hormone, triggered by adrenal cortisol production, enhances the adrenal glands' capacity to generate cortisol [12]. In 2019, Blue and colleagues explored the link between big adrenal glands and poorer perinatal outcomes in fetuses diagnosed with IUGR. Their findings revealed a lack of association between the two variables [13].

5. Conclusion

Given that the alterations in fetal adrenal gland sizes in fetuses detected with IUGR are a consequence of fetal adaptive responses to persistent oxygen deprivation, it is plausible to anticipate worse perinatal outcomes in fetuses that are unable to adjust to the adverse circumstances within the womb.

References

[1] K. Kesavan, S.U. Devaskar. (2019). Intrauterine growth restriction: postnatal monitoring and outcomes. Pediatric Clinics. 66(2):403-23.

[2] P. Anand, T. Sahoo, K.M. Gulla. (2019). Which growth charts to use to classify neonates as small-for-gestational age at birth?. Indian Journal of Child Health. 28:636-42.

[3] S. Van Slycke, K. Van Den Heede, E.-A. Vandenwyngaerden. (2022). Adrenal Glands: Anatomy, Physiology, and Pathophysiology. In Endocrine Surgery Comprehensive Board Exam Guide. Springer. pp 437-455.

[4] A.A. Fanaroff, J.M. Fanaroff. (2019). Klaus and Fanaroff's Care of the High-Risk Neonate: Klaus and Fanaroff's Care of the High-Risk Neonate E-Book. Elsevier Health Sciences.

[5] Y. Nakashima, M. Shiratsuchi, I. Abe, Y. Matsuda, N. Miyata, H. Ohno, M. Ikeda, T. Matsushima, M. Nomura, R. Takayanagi. (2013). Pituitary and adrenal involvement in diffuse large B-cell lymphoma, with recovery of their function after chemotherapy. BMC Endocrine Disorders. 13(1): 1-7.

[6] B. Kaya, İ. Polat. (2019). The investigation of fetal adrenal gland sizes in the pregnancies complicated with the intrauterine growth restriction. Perinatal Journal. 27(3): 176-182-176-182.

[7] R.J. Martin, A.A. Fanaroff, M.C. Walsh. (2014). Fanaroff and Martin's neonatal-perinatal medicine e-book: diseases of the fetus and infant. Elsevier Health Sciences.

[8] E. Orlandi, C. Rossi, A. Perino, G. Musicò, F. Orlandi. (2014). Simplified first-trimester fetal cardiac screening (four chamber view and ventricular outflow tracts) in a low-risk population. Prenatal diagnosis. 34(6): 558-563.

[9] S. Addley, A. Ali, S. Ong. (2017). An Assessment of Fetal Cerebral and Hepatic Perfusion in Normal Pregnancy and Pre-Eclampsia Using Three-Dimensional Ultrasound. The Ulster Medical Journal. 86(1): 10.

[10] S. Heese, K. Hammer, M. Möllers, H.A. Köster, M.K. Falkenberg, M. Eveslage, J. Braun, K. Oelmeier de Murcia, W. Klockenbusch, R. Schmitz. (2018). Adrenal gland size in growth restricted

fetuses. Journal of Perinatal Medicine. 46(8): 900-904.

[11] C. Melau, J.E. Nielsen, H. Frederiksen, K. Kilcoyne, S. Perlman, L. Lundvall, L. Langhoff Thuesen, K. Juul Hare, A.-M. Andersson, R.T. Mitchell. (2019). Characterization of human adrenal steroidogenesis during fetal development. The Journal of Clinical Endocrinology & Metabolism. 104(5): 1802-1812.

[12] V.E. Beshay, B.R. Carr, W.E. Rainey. (2007). In The human fetal adrenal gland, corticotropin-releasing hormone, and parturition, Seminars in reproductive medicine, 2007; Copyright© 2007 by Thieme Publishers, Inc., 333 Seventh Avenue, New York, NY …: 2007; pp 014-020.

[13] N.R. Blue, M. Hoffman, A.A. Allshouse, W.A. Grobman, H.N. Simhan, O.M. Turan, S. Parry, J.H. Chung, U. Reddy, D.M. Haas. (2019). Antenatal Fetal Adrenal Measurements at 22 to 30 Weeks' Gestation, Fetal Growth Restriction, and Perinatal Morbidity. American journal of perinatology. 38(07): 676-682.