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Fetal Adrenal Gland Volume in Normal versus Growth Restricted Fetuses

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Abstract:

Introduction: The term "intrauterine growth restriction" (IUGR) refers to a rate of fetal growth that is less than normal given the infant's potential for growth according to the fetus's gender and race. It is typically the result of many negative influences on the fetus or inherent diminished development potential.

Aim of the study: To detect the association of fetal adrenal gland volume with restricted late fetal growth.

Subjects & Methods: This was a case-control study; the study involving 120 pregnant females were eligible for this study and divided into two cohort; 55 eligible pregnant females with fetal growth restriction and 55 women with healthy normal pregnancies within similar gestational age, not having any additional medical disorders or obstetric complication, delivered at term. The study was conducted in Fayoum University Hospital.

Results: Our study compared between IUGR group and healthy control pregnancies regarding the adrenal gland volume (AGV) and medulla width. AGV was significantly higher among fetuses with IUGR as compared with normal estimated fetal weight (EFW) for gestational age in both groups, respectively. Medulla width was significantly larger in the IUGR fetus compared to healthy controls in both groups.

Conclusions: Our study concluded that the fetal AG sizes of the fetuses diagnosed with IUGR showed changes that we had seen. These changes were linked to poor fetal programming, which resulted in long-term postnatal poor health outcomes**.**

Keywords: Growth Restricted Fetuses; Fetal Adrenal Gland; Ultrasound Assessment; Perinatal Outcomes; Fetal Development.

1. Introduction

Fetal growth is a complex process influenced by various maternal, placental, and fetal factors. One of the critical structures involved in fetal development is the adrenal gland, an endocrine organ that plays a crucial role in producing hormones

essential for regulating stress response, metabolism, and electrolyte balance. The fetal adrenal gland undergoes significant development during gestation, particularly in the second and third trimesters. It is responsible for producing corticosteroids like cortisol, which are vital for fetal lung maturation and overall readiness for postnatal life [1].

Monitoring the fetal adrenal gland's size and function may offer insights into the health of the fetus, especially when assessing fetuses with growth restrictions. IUGR is a condition where a fetus does not reach its genetic growth potential, often due to placental insufficiency or other maternal and fetal complications. FGR is associated with increased perinatal morbidity and mortality, and long-term health consequences like cardiovascular diseases and metabolic syndromes [2]. In normal fetuses, the adrenal gland grows in a predictable pattern, reflective of the overall healthy intrauterine environment. Conversely, in growth-restricted fetuses, the size and function of the adrenal gland may be altered as part of a compensatory or stress response to adverse intrauterine conditions [2].

Studying the fetal AGV in normal versus growth-restricted fetuses is important for understanding the adaptations made by growth-restricted fetuses. It may also serve as a potential biomarker for identifying fetuses at risk and guiding clinical management decisions. This comparison offers potential insights into the severity of growth restriction and helps to evaluate the overall fetal well-being [3].

The medulla and cortex, two embryologically different tissues that originate from the neuroectoderm and mesoderm, respectively, make up the AG. The AG in a fetus is comparatively large. It is four times the size of the kidney at 4 months of gestation, but it is only 1/3 the size of the kidney at birth. This happens as a result of the fetal cortex rapidly shrinking at birth. There could be AG anatomic abnormalities. Agenesis of one AG is typically linked to ipsilateral kidney agenesis, and fused AGs are linked to a fused kidney due to the strong connection among the kidneys and the development of the AGs [4].

A previous study measured the sizes of the fetal AGs in cases of IUGR and concluded that the changes in these gland sizes are a result of both chronic hypoxia,

which is linked to uteroplacental failure, and poor programming of the fetus, which is linked to prolonged negative health effects [5].

2. Subjects & Methods

2.1. Subjects

The study included 110 pregnant women who were involved in this study and divided into two cohorts: 55 eligible pregnant women with fetal growth restriction and 55 women with healthy normal pregnancies within similar gestational age (GA), not having any additional medical disorders or obstetric complications, delivered at term. The study was conducted in Fayoum University Hospital.

The women were divided into two cohorts:

- **Cohort [1]:** A sample of 55 eligible pregnant women between 28 and 36 weeks of gestation with a diagnosis of IUGR
- **Cohort [2] (control cohort):** 55 women with appropriate GA fetuses within similar GA (28 – 36 weeks), who did not suffer from other medical conditions or obstetric complications, and delivered at term.

Inclusion criteria

- **Age:** 20 – 35 years.
- **GA:** 28 – 36 weeks.
- Single fetus.
- History of restricted intrauterine growth, detected by ultrasound (amniotic fluid volume, biometry, or Doppler velocity).

Exclusion criteria

- IUFD.
- Multiple pregnancies.
- Medical disorders.
- Congenital anomalies with ultrasound evidence.
- An irregular fetal heartbeat pattern, a smoker's habit, and the existence of morbidity concomitant with maternal impairment (chronic hypertension, preeclampsia, diabetes, chronic renal disease).

2.2. Study design

This was a case-control study.

2.3. Methods

This study evaluated pregnant women during their third trimester. All women underwent:

History taking including

- Personal history [age, name, parity, residence, special and occupation habits of medical importance].
- History of present pregnancy.
- Menstrual history for last menstrual period, D&C and regularity.
- Past medical history.
- Obstetrical history.
- Family history.

Examination

- General examination (blood pressure, pulse, heart examination, chest examination and assessment of BMI).
- Abdominal examination, including inspection and palpation.
- The cases' weeks of gestation were calculated based on the first day of their most recent menstrual cycle, and this information was verified by measuring the crown-rump length (CRL) in the first trimester.

Diagnosis of IUGR

Measuring EFW below the third percentile led to the recognition of restricted intrauterine growth. When the mean uterine artery PI was more than the 95th percentile, the cerebroplacental rate was beyond the 5th percentile, or the umbilical artery pulsatility index [PI] was more than the 95th percentile, the diagnosis of IUGR was made in cases where the EFW fell between the 10th and 3rd percentile.

Three-dimensional (3D) ultrasound study

3D ultrasonography of the fetal AG was performed. An ultrasound machine is a Voluson S10 GE medical system.

Serial Scanning

Scans were conducted at specific gestational intervals [e.g., every 2–4 weeks] to monitor adrenal gland development throughout pregnancy. Consistent protocols for measuring AGV at each scan were followed to compare changes over time.

Measurement of AGV

After the fetal anatomical assessment, Doppler measures of the ductus venosus, uterine artery, umbilical artery, and

middle cerebral artery were performed, along with measurements of the amniotic fluid and fetal biometry.

3D VOCAL software was used to assess the AGV. The most accurate method for measuring irregularly shaped items is 3D U/S VOCAL, which involves tracing the exterior surface using mathematical calculations. The transverse cross-section showed the fetal AG; the picture was enlarged before measurements, and the medulla's width and length, as well as the fetal AG's overall width and length, were evaluated (**Figures 1, 2**). The ratio of total width to medulla width, as well as cortex width (the half of the variance among the two), was measured.

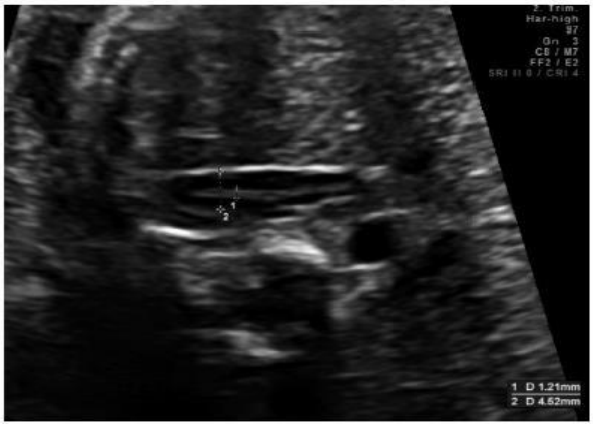

Figure 1: The fetal AG was imaged in the transverse cross-section, with the 28-week and 6-day fetuses expanding by the week of gestation, as shown by the measurements of total width [2] and medulla width [1].

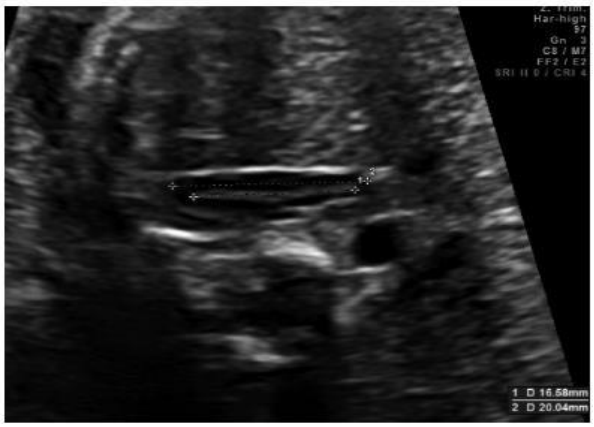

Figure 2: Imaging of the transverse cross-sectional area of the fetal AG. The fetal AG measurements in the 28-week and 6-day fetuses increase by the week of gestation, are the total length [2] and medulla length [1]. The clinician who performed the ultrasound measurements did not participate in the medical management of the cases, nor were fetal AG measurements taken into consideration.

2.4. Statistical Methods

The information was gathered, edited, coded, and added to IBM SPSS, a package of statistics for social science, version 21. The quantitative data were provided as means, ranges, and standard deviations, when their distribution was found to be parametric, whereas qualitative data were expressed as numbers and percentages. The independent sample t-test was utilized to compare two independent cohorts with quantitative data and a parametric distribution. The Mann-Whitney U test was employed to compare quantitative data having a non-parametric distribution among two independent cohorts. The linear association between medulla width and AGV and the other parameters (GA, maternal age, EFW, gravidity, and parity) in the women under study was assessed using Pearson's correlation analysis. Only significant correlations, which are defined as significant at P <0.05, were shown on correlation graphs. When r (the correlation coefficient) has a + signal, the correlation is deemed positive (direct correlation), and when it has a – signal, it is deemed negative (inverse correlation). The relationships were described as strong when r ≥0.65, moderate when r =0.35 – 0.65, and weak when r =0 – 0.35.

3. Results

The current study was designed to detect the association of fetal AGV with late fetal growth restriction among 55 healthy control pregnancies and 55 pregnancies with IUGR.

Table 1 demonstrates the baseline characteristics among the studied pregnant females. There were non-statistically substantial variations between the two studied cohorts regarding their parity, maternal age, gravidity, and GA at time of study enrolment (p >0.05). EFW was remarkably lower among the IUGR cohort (1463.5 ±476.0 vs. 2252.2 ±627.9, p <0.001) in both cohorts, respectively.

Table 1: Features of Baseline of the involved pregnant females (N =110).

Characteristics		Studied Cohorts		p-value
		IUGR N= 55	Control N= 55	
Age [years]	Mean ±SD	31.5 ±3.0	32.3 ±3.2	0.153
	Range (Mini – Max)	27 - 39	27 - 40	
Gravidity	Mean ±SD	3.4 ±1.5	2.8 ±1.4	0.058

	Range (Mini – Max)	1 - 7	1 - 5	
Parity	Mean ±SD	2.4 ±1.5	1.8 ±1.4	0.058
	Range (Mini – Max)	0 - 6	0 - 4	
GA [weeks]	Mean ±SD	33.7 ±3.9	33.9 ±3.7	0.817
	Range (Mini – Max)	26.0 - 38.0	26.0 - 38.5	
EFW	Mean ±SD	1463.5 ±476.0	2252.2 ±627.9	**<0.001***
	Range (Mini – Max)	719.0 - 2335.0	950.0 - 3080.0	

IUGR: Intrauterine growth restriction

Table 2 demonstrated a comparison between the IUGR cohort and healthy control pregnancies regarding the AGV and medulla width. AGV was significantly higher among fetuses with IUGR as compared with normal EFW for GA (364.2 ±67.5 vs. 293.0 ±62.8, p <0.001) in both cohorts, respectively. Medulla width was significantly larger in IUGR fetuses compared to healthy controls (1.6 ±0.4 vs. 1.3 ±0.5, p =0.002) in both cohorts, respectively.

Table 2: AGV and Medulla Width comparison between IUGR cohort and healthy control pregnancies (N =110)

Characteristics		**Studied Cohorts**		***P*-value**
		IUGR N =55	**Control N =55**	
AGV (mm^3)	Mean ±SD	364.2 ±67.5	293.0 ±62.8	
	Range (Mini – Max)	238 – 489	149 – 431	**<0.001***
Medulla Width (mm)	Mean ±SD	1.6 ±0.4	1.3 ±0.5	
	Range (Mini – Max)	0.56 – 2.0	0.6 – 2.3	**0.002***

AGV: Adrenal Gland Volume, IUGR: Intrauterine growth restriction

Table 3 and Figures 3-6 demonstrate a correlation analysis among medulla width and AGV with other studied variables. Regarding Pearson Correlation analysis, maternal age demonstrated a statistically remarkable moderate positive linear relation with AGV (r =0.462, p =0.001) and with medulla width (r =0.390, p =0.003). Also, GA provided a statistically substantial, slight positive linear relation with AGV (r =0.389, p =0.003) and with medulla width (r =0.266, p =0.049). There was no statistically remarkable linear relation with parity, gravidity and EFW among the IUGR cohort (p >0.05).

Table 3: Correlation analysis among medulla width and AGV with other studied measurements among the IUGR cohort (N =55).

IUGR Cohort		Medulla width (mm)	AGV
Gravidity	p	0.718	0.833
	r	0.050	0.029
Maternal Age (years)	p	**0.003***	**0.001***
	r	**0.390**	**0.462**
Parity	p	0.718	0.833
	r	0.050	0.029
GA (weeks)	p	**0.049***	**0.003***
	r	**0.266**	**0.389**
EFW (gm)	p	0.935	0.241
	r	-0.011	0.161

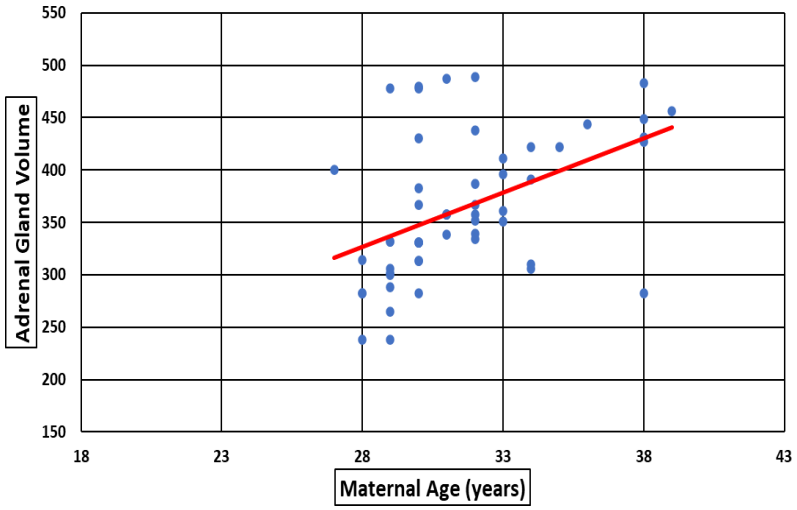

Figure 3: Correlation between AGV and maternal age.

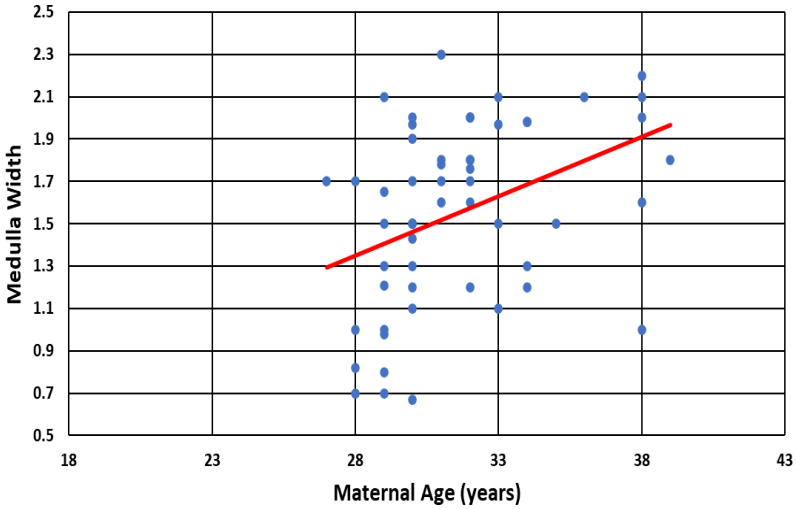

Figure 4: Correlation between medulla width and maternal age.

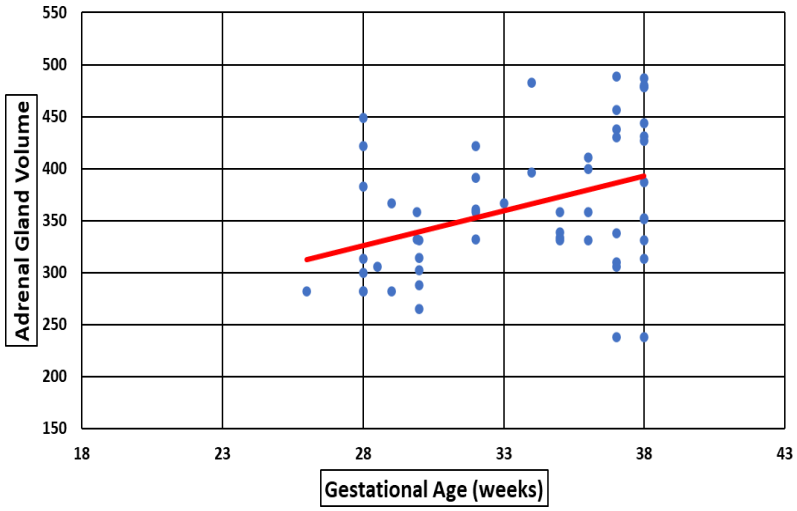

Figure 5: Correlation between AGV and gestational age.

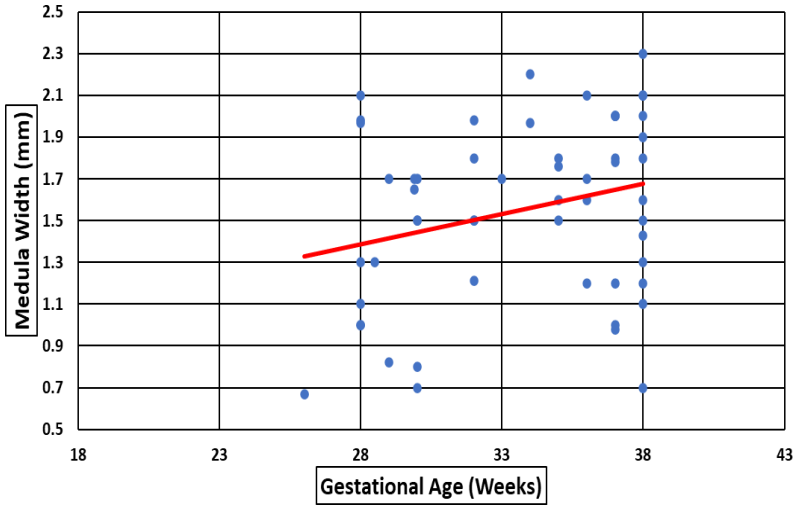

Figure 6: Correlation between medulla width and gestational age.

Using ROC curve analysis, the sensitivity and specificity of AGV and medulla width as indicators and diagnostic predictors for IUGR were evaluated as demonstrated in Table 4 and Figure 7. The AUC of AGV for prediction of IUGR was 0.773 (AUC = 0.773, SE = 0.05, 95% CI: 0.687–0.860). A threshold volume of AG ≥283 could predict IUGR with a sensitivity of 87.3%% % and a specificity of 60%. The AUC of medulla width for prediction of IUGR was 0.665 (AUC = 0.665, SE = 0.05, 95% CI: 0.562–0.769). A threshold volume of medulla width ≥1.35 could predict IUGR with a specificity of 60% and sensitivity of 67.3%.

Table 4: Results of ROC curve analysis for sensitivity and specificity of AGV and medulla width as indicators and diagnostic predictors for IUGR (N =110).

Variables	AUC	95% CI of AUC	Cut-off	Sensitivity	Specificity	p-value
Adrenal gland volume	0.773	0.687- 0.860	≥283	87.3%	60%	<0.001*
Medulla Width	0.665	0.562- 0.769	≥1.35	67.3%	60%	0.003*

AUC: Area under the curve, CI: Asymptotic 95% Confidence Interval of AUC.

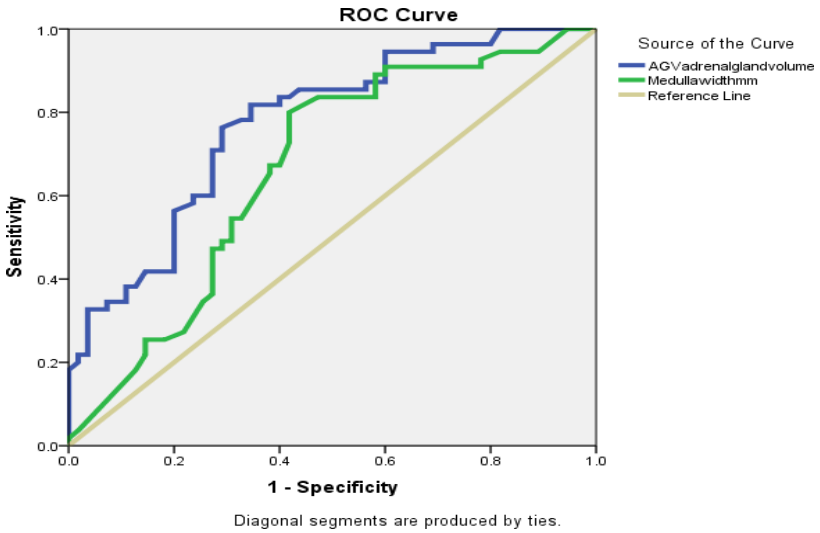

Figure 7: ROC curve analysis for sensitivity and specificity of AGV and medulla width as indicators and diagnostic predictors for IUGR.

As illustrated in **Table 5**, unadjusted regression analysis for factors that could predict AGV showed that parity, gravidity, maternal age, GA and EFW could predict adrenal gland volume at a statistically significant *p*-value, however in the regression model adjusted for maternal age, parity, gravidity, GA and EFW, maternal age, GA and EFW could predict AGV at a statistically significant *p*-value.

Table 5: Adjusted and unadjusted linear regression analysis for predictors of AGV among our involved population

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

4. Discussion

Our study demonstrated that in the IUGR cohort, GA ranged from 26 to 38 weeks, and the mean maternal age was 31.5 ±3.0 years. In the control cohort, the range of GA was from 26 to 38 years, and the mean maternal age was 32.3 ±3.2 years. There were non-statistically substantial variations among both studied cohorts regarding their gravidity, maternal age, parity and GA at time of study enrolment. Additionally, the diameters of the fetal AGs for individuals of restricted intrauterine growth were assessed. Regarding gravida, the week of gestation at diagnosis, maternal age, BMI, and parity, there was no statistically significant disparity among the control and study cohorts [5].

The mean maternal age was 30.6±3.1, whereas the study involved 105 pregnant females with GAs ranging from 34 to 36 weeks; 57% of the females were multigravida and 43% were primigravida, respectively; 54% of the females were multipara and 46% were primipara [6].

According to a previously published paper, the mean GA was 28.4 [5] years in the PE cohort and 29.5 [6] years in the normal cohort. The mean GA in the high-risk cohort was 34 weeks, while the mean GA in the control cohort was 35+4 weeks. There was no statistically remarkable variation in gestation, BMI, or age among preeclamptic and normal-pregnant females [7].

Our study compared between IUGR cohort and healthy control pregnancies regarding the AGV and medulla width. AGV was significantly higher among fetuses with IUGR as compared with normal EFW for GA (364.2 ± 67.5 versus 293.0 ± 62.8, p <0.001) in both cohorts, respectively. Medulla width was significantly larger in IUGR fetuses compared to healthy controls (1.6 ±0.4 versus 1.3 ±0.5, p =0.002) in both cohorts, respectively.

In 2019, Kaya et al discovered that there was a statistically significant variance in the z-scores of fetal AG total length, total breadth, and width of the cortex between the control cohort and the study cohort. Additionally, the study cohort's z-score for the medulla width ratio to total width was substantially higher. The study cohort's fetal AG medulla width z-score was remarkably lower than the control cohorts. The z-score

of the length of the fetal AG medulla did not substantially differ across the cohorts [5].

According to Pearson correlation analysis, maternal age showed a statistically remarkable moderate positive linear relation with AGV (r =0.462, *p* =0.001) and with medulla width (r=0.390, *p* =0.003). Also, GA showed a substantial, slight positive linear relation with AGV (r =0.389, *p* =0.003) and with medulla width (r =0.266, *p* =0.049). But, there was non-statistically significant linear relation with EFW, parity and gravidity among the IUGR cohort. There was a statistically significant positive connection between the weeks of gestation and the fetal AG measurements [5].

Using ROC curve analysis, the AUC of AGV for the prediction of IUGR was 0.773. A threshold volume of AG ≥283 could predict IUGR with a sensitivity of 87.3% and a specificity of 60%. The AUC of medulla width for the prediction of IUGR was 0.665. A threshold volume of medulla width ≥1.35 could predict IUGR with a sensitivity of 67.3% and a specificity of 60%.

Prenatal ultrasonography can show the location of the AGs on the upper pole of the fetal kidneys due to relatively larger sizes of the glands throughout the intrauterine era. To predict preterm labor, it has been demonstrated that the sensitivity of the fetal AG sonographic measures influences the beginning of both preterm and mature labors [8].

Unadjusted regression analysis for factors that could predict AGV showed that maternal age, parity, gravidity, GA, and EFW could predict AGV at a statistically significant *p*-value; however, in the regression model adjusted for maternal age, parity, gravidity, GA, and EFW could predict AGV at a statistically significant p-value.

The total volume of the AG and the fetal regional volume of the AG in the fetuses with restriction on intrauterine growth were examined. It was discovered that the fetuses with IUGR had a substantially greater total AGV and a considerably reduced fetal regional volume of the AG than the control cohort [9].

The diameters of the AGs in the fetuses that had been diagnosed with IUGR were examined. The cohort that had been diagnosed with IUGR had considerably larger cortical and total AG widths than the control cohort. Given our findings and the

research state, it is acceptable to conclude that chronic stress and chronic intrauterine hypoxia linked to placental failure stimulate the hypothalamic-pituitary-adrenal axis system, which causes elevated fetal adrenal cortisol synthesis and larger Ads [10].

Fetal adrenal cortisol during pregnancy inhibits the hypothalamic corticotropin-releasing hormone [CRH], which in turn controls the HPA axis's function [11]. Beshay et al. have shown that the fetal AG's production of cortisol causes the placental CRH to be released while blocking the release of the hypothalamus CRH. Furthermore, an increase in placental CRH brought on by adrenal cortisol synthesis aids in the AG's ability to produce cortisol [12].

Another study demonstrated that elevated fetal glucocorticoid levels have detrimental effects on fetal development, growth, and postnatal development, but they also cause the development of the organs required for postnatal life. The elevated fetal levels of cortisol diagnosed with IUGR may be a consequence of persistent hypoxia linked to placental failure. Additionally, they may exacerbate the IUGR by creating a vicious cycle through the release of placental CRH [13].

Blue et al suggested that another explanation for the larger adrenal glands in fetuses diagnosed with IUGR would be that fetal blood flow is directed towards the heart, brain, and AGs in preference as a reaction to placental failure [14].

The AGs have the largest raises in blood flow in the chronic hypoxia sheep model [15]. Malnourishment and chronic hypoxia resulting from placental failure are thought to produce poor programming of the fetus throughout the intrauterine duration and to have long-term health consequences, including stroke, cardiovascular illnesses, and metabolic syndrome. Comparably, one could hypothesize that the rise in fetal AG sizes seen in the condition of placental failure is a sign of factors of intrauterine environmental influencing programming of fetal genetics, which in turn determines the long-term health consequences [16].

Another study also looked into the ability of the IUGR fetuses' diagnoses to detect the unfavorable perinatal results based on the size of their AGs [9]. They noted that the AGV was smaller in those with worse perinatal results than in IUGR fetuses, and they proposed that a non-invasive technique for identifying poor perinatal outcomes in IUGR fetuses would

be to use sonographic examination of the fetal AG during the third trimester. Blue et al looked into the connection between the size of the AGs and poor perinatal results in IURG fetuses. The results showed that there was no such connection [14].

5. Conclusion

We concluded that the fetal AG sizes of the fetuses diagnosed with IUGR showed changes that we had seen. These changes were linked to poor fetal programming, which resulted in long-term postnatal poor health outcomes, and were caused by mechanisms of fetal compliance for an intrauterine environment with chronic hypoxia related to uteroplacental failure. Perinatal outcomes may be anticipated in fetuses that cannot adapt to the poor intrauterine circumstances, given that the alterations in fetal AG sizes seen in IURG fetuses result from the mechanisms of fetal compliance for chronic hypoxia.

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