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Research Article

Evaluation of Midtrimester Alpha-Fetoprotein and Beta-Human Chorionic Gonadotropin in Cases at High Risk of Intrauterine Growth Restriction

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Abstract

Purpose: The aim of this work was to evaluate mid-trimester maternal serum alpha-fetoprotein and beta- Human Chorionic gonadotropins in cases at high risk of intra-uterine growth restriction (IUGR).

Patients and Methods: This was a prospective study of 117 singleton pregnancies (gestational age range: 14 - 28 weeks) with risk factor to have IUGR. We evaluated serum Alpha-fetoprotein and Beta-Human Chorionic Gonadotropin with ultrasonographic study and uterine, umbilical, middle cerebral artery and ductus venosus Doppler assessment. Statistical analysis was performed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

Results: There was a no significant difference in the group who had IUGR fetuses from the other group who had normal ones in relation to Ductus venosus Doppler indices. But showed significant difference between umbilical artery, middle cerebral artery and uterine artery Doppler indices. Both groups showed significant difference in regard to Alpha-fetoprotein and Beta HCG.

Conclusion: Goal of antenatal monitoring is early detection of IUGR, for better neonatal outcome. Combining Doppler indices with biochemical and clinical parameters improve the prediction of IUGR. There is significant difference in regard to Alpha-fetoprotein and Beta HCG to diagnose IUGR in the high risk pregnancy patients.

Keywords: *Alpha-Fetoprotein; Beta-Human Chorionic Gonadotropin; Intrauterine Growth Restriction*

Introduction

Intrauterine growth restriction (IUGR) is defined as the rate of fetal growth that is below normal in light of the growth potential of a specific infant as per the race and gender of the fetus. It implies a pathological process in which one or more factors inhibit the pre-programmed genetic growth potential. It affects up to 10% of pregnancies [1].

IUGR is pathologic decrease in the rate of fetal growth below 10th percentile for age. IUGR ranks third after prematurity and malformations as cause of perinatal deaths [2].

IUGR causes are maternal, placental, fetal, metabolic or genetic factors. The most frequent etiology for IUGR is abnormal placentation, which is frequently associated with impaired placental blood flow [3,4].

There are three types of IUGR: symmetrical, asymmetrical and mixed [5].

Complications are antepartum (as stillbirth and iatrogenic prematurity), intra-partum asphyxia and perinatal stroke), neonatal (as hypothermia and hypoglycemia) and pediatric (as short stature and cerebral palsy) [6,7].

The goal of antenatal monitoring is early detection of IUGR, so that antenatal management can be optimized for better neonatal outcome. There are currently no accurate predictive tests for IUGR, and it is not recommended to screen low risk populations with routine ultrasound [8].

History Screening for IUGR by clinical risk factor assessment is already routinely performed by obstetrical care providers. Accurate dating is a prerequisite for pregnancy care and the tracking of fetal growth [9].

Investigators tried to improve the prediction of IUGR by combining Doppler indices with biochemical and clinical parameters due to the insufficient predictive value of each marker alone [10].

In the absence of aneuploidy or neural tube defects, mid-trimester ms-hCG and/or ms-AFP associated with adverse pregnancy outcomes [11].

Early dating in the first or early second trimester is important. The transverse cerebellar diameter is the easiest to perform and the most effective, being normal in 75% of 73 previously dated IUGR fetuses [12].

In IUGR, shunting of blood from the splanchnic circulation results in reduced renal blood flow, reduced glomerular filtration rate and hence less liquor [13]. Amniotic fluid volume is believed to be chronic parameter, one week before deterioration 20 – 30 % of cases has oligohydramnios [14].

In normal pregnancy, uterine blood flow increases dramatically from 50 ml/min at 10 weeks gestation to over 1200 ml/min at term. In pregnancies complicated by intrauterine growth restriction, impedance to flow in the uterine arteries is increased [15].

Umbilical artery (UA) Doppler as a standalone standard is not valid anymore because UA Doppler is able to identify Fetal Growth Restriction because of severe placental disease, but it showed poor detection rates in cases of mild placental diseases, which are responsible for a few cases of early-onset IUGR and for a majority of cases of late-onset Fetal Growth Restriction [16].

In fetal hypoxemia, there is an increase in the blood supply to the brain, myocardium and the adrenal glands and reduction in the perfusion of the kidneys, gastrointestinal tract and the lower extremities. However, compensation through cerebral vasodilatation is limited and a plateau corresponding to a nadir of pulsatility index (PI) in cerebral vessels is reached at least 2 weeks before the development of the fetus is jeopardized [17].

The sequence of abnormal events that herald adverse perinatal outcome begins with an absence of UA end diastolic flow. Later findings include abnormal Doppler pulsatility of the MCA (with decreased PI) and abnormal ductus venosus flow (absent or reversed flow during atrial contraction) and reversed flow in the UA. These changes are significantly associated with perinatal death. Some pregnancies with intrauterine growth restriction have elevated peripheral maternal vascular resistance in uterine arteries and hence poor fetal growth. Such pregnancies, if resistance values are normalized would have a significantly better outcome [18].

The only available current treatment of IUGR is delivery. The main consideration needs to be appropriate timing, balancing the risk of potential iatrogenic morbidity and continued exposure to unfavorable intrauterine environment [19].

Patients and Methods

This was a prospective study of 117 singleton pregnancies (gestational age range: 14 - 28 weeks) A total of 117 patients, include Patients with chronic hypertension were (22), with history of IUGR were (23), with history of preeclampsia were (64), SLE were (4) cases, chronic renal disease were (2) and with anti-phospholipid disease were (2) cases. Patients were pregnant with singleton between (14 -

28) weeks of gestation. Full physical and obstetric examination was done to all patients with ultrasound biometry (BPD, HC, AC, FL, EFW), biochemical markers were analyzed (AFP and Beta-HCG) and Doppler study of uterine artery, umbilical artery, middle cerebral artery and Ductus Venosus doppler (PSV, EDV, SD ratio, RI, PI). Statistical analysis was performed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp)

Results

Table 1 shows that Out of (117) pregnant patients,

Medical history	IUGR (n = 17)		Normal (n = 100)		Total (n = 117)	
	No.	%	No.	%	No.	%
HTN	4	23.5	18	18.0	22	18.8
History of IUGR	4	23.5	19	19.0	23	19.7
History of PE	8	47.1	56	56.0	64	54.7
SLE	1	5.9	3	3.0	4	3.4
CRD	0	0.0	2	2.0	2	1.7
APD	0	0.0	2	2.0	2	1.7

Table 1*: Distribution of the two studied groups according to medical history.*

- Patients with chronic hypertension were (22) cases, (4) of them were found to have IUGR fetus.
- Patients with history of IUGR were (23) cases, (4) of them were found to have IUGR fetus.
- Patients with history of preeclampsia were (64) cases, (8) of them were found to have IUGR fetus.
- Patients with Systemic Lupus Erythematosus (SLE) were (4) cases, (1) case had IUGR fetus.
- Patients with chronic renal disease (CRD) were (2), with Anti-Phospholipid disease (APD) were also (2) cases, none of them revealed IUGR fetuses.

Table 2 shows significant difference between the two studied groups according to Beta human chorionic gonadotropin (Beta-HCG) and Alpha-fetoprotein.

Mean (± SD) Beta-HCG in miu/ml in group I is 76356.0 ± 28467.6 and 36862.9 ± 29551.5 for group Ⅱ. P value is < 0.001.

Mean (± SD) Alpha-fetoprotein in ng/ml in group I is 180.62 ± 78.08 and 101.66 ± 68.87 for group Ⅱ. P value is < 0.001

	IUGR (n = 17)	Normal (n = 100)	U	p
Beta-HCG in miu/ml				
Min. – Max.	8345.0 - 142700.0	2456.0 - 163233.0	311.0*	< 0.001*
Mean ± SD.	79885.4±33378.7	37862.9±32410.9		
Median	85120.0	25142.5		
Alpha-fetoprotein in ng/ml				
Min. – Max.	105.80 - 332.70	12.40 - 292.30	375.0*	< 0.001*
Mean ± SD.	180.62±78.08	101.66±68.87		
Median	145.70	76.27		

Table 2: *Comparison between the two studied groups according to beta-HCG, alpha-fetoprotein.*

U, p: U and p values for Mann Whitney test for comparing between the two groups

**: Statistically significant at p ≤ 0.05*

Table 3 shows that there is no significant difference in Beta-HCG, Alpha-fetoprotein in relation to the medical risk factor (medical history) of the patients.

Mean (± SD) Beta-HCG in miu/ml in hypertensive patients is 82635.3 ± 45610.2, 86536 ± 13005.5 for patients with history of IUGR and 73142.1 ± 36392.3 for patients with history of preeclampsia. P value is 0.353.

Mean (± SD) Alpha-fetoprotein in ng/ml in in hypertensive patients is 72635.3 ± 29640.6, 183.7 ± 80.4 for patients with history of IUGR and 179.7 ± 83.5 for patients with history of preeclampsia. P value is 0.088.

	Medical history				H (p)
	HTN (n = 4)	History of IUGR (n = 4)	History of PE (n = 8)	SLE# (n = 1)	
Beta-HCG in miu/ml					
Min. - Max.	34657 - 142700	72135 - 103145	8345 - 120456		0.353 (0.838)
Mean ± SD.	82635.3 ± 45610.2	86536 ± 13005.5	75642.1 ± 39121.3	76230	
Median	76592	85432	89122.5		
Alpha-fetoprotein in ng/ml					
Min. - Max.	105.8 - 314.8	109.4 - 253.2	115.8 - 332.7		0.088 (0.957)
Mean ± SD.	195.6 ± 89.9	183.7 ± 80.4	179.7 ± 83.5	115.8	
Median	181.0	186.1	143.0		

Table 3: *Relation between Medical history with beta-HCG, alpha-fetoprotein in IUGR group.*

H, p: H and p values for Kruskal Wallis test

#: Excluded from the relation due to small number of case (n = 1)

Table 4 shows significant difference between of umbilical artery Doppler indices at delivery.

Mean (±SD) PSV in cm/sec in group I is 69.82 ± 7.44 and 57.18 ± 5.92 for group II. P value is < 0.001.

Mean (±SD) EDV in cm/sec in group I is 24.98 ± 4.70 and 30.73 ± 3.18 for group II. P value is < 0.001.

Mean (±SD) SD ratio in group I is 2.78 ± 0.54 and 1.88 ± 0.29 for group II. P value is < 0.001.

Mean (±SD) RI in group I is 0.68 ± 0.13 and 0.59 ± 0.12 for group II. P value is 0.006.

Mean (±SD) PI in group I is 1.23 ± 0.34 and 0.98 ± 0.33 for group II. P value is 0.003.

Umbilical artery	IUGR (n = 17)	Normal (n = 100)	Test of sig.	p
PSV				
Min. - Max.	56.40 - 81.70	46.10 - 70.80	U = 287.0*	< 0.001*
Mean ± SD.	69.82 ± 7.44	57.18 ± 5.92		
Median	71.12	56.17		
EDV				
Min. - Max.	20.48 - 41.10	22.46 - 42.45	U = 514.0*	< 0.001*
Mean ± SD.	24.98 ± 4.70	30.73 ± 3.18		
Median	24.0	30.10		
SD ratio				
Min. - Max.	1.45 - 3.40	1.40 - 2.70	U = 590.0*	< 0.001*
Mean ± SD.	2.78 ± 0.54	1.88 ± 0.29		
Median	2.90	1.80		
RI				
Min. - Max.	0.36 - 0.81	0.30 - 0.89	t = 2.796*	0.006*
Mean ± SD.	0.68 ± 0.13	0.59 ± 0.12		
Median	0.72	0.61		
PI				
Min. - Max.	0.47 - 1.69	0.40 - 1.82	U = 464.50*	0.003*
Mean ± SD.	1.23 ± 0.34	0.98 ± 0.33		
Median	1.39	0.90		

Table 4: *Comparison between the two studied groups according to umbilical artery at delivery.*

t, p: t and p values for Student t-test for comparing between the two groups

U, p: U and p values for Mann Whitney test for comparing between the two groups

**: Statistically significant at p ≤ 0.05*

Table 5 shows significant difference between middle cerebral artery Doppler indices at delivery.

Mean (± SD) PSV in cm/sec in group I is 56.20 ± 9.28 and 51.45 ± 14.27 for group II. P value is 0.043.

Mean (± SD) EDV in cm/sec in group I is 20.90 ± 7.75 and 12.89 ± 4.77 for group II. P value is < 0.001.

Mean (± SD) SD ratio in group I is 3.02 ± 1.15 and 4.49 ± 1.82 for group II. P value is < 0.001.

Mean (± SD) RI in group I is 0.73 ± 0.10 and 0.80 ± 0.05 for group II. P value is 0.003.

Mean (± SD) PI in group I is 1.42 ± 0.33 and 1.63 ± 0.33 for group II. P value is 0.024.

Middle cerebral artery	IUGR (n = 17)	Normal (n = 100)	Test of sig.	p
PSV				
Min. - Max.	29.11 - 83.46	25.53 - 123.40	U = 589.50*	0.043*
Mean ± SD.	46.26 ± 14.49	51.45 ± 14.27		
Median	43.83	51.76		
EDV				
Min. - Max.	9.59 - 36.50	4.30 - 24.12	T = 2.453*	< 0.001*
Mean ± SD.	20.90 ± 7.75	12.89 ± 4.77		
Median	19.58	12.60		
SD ratio				
Min. - Max.	1.54 - 6.16	1.49 - 9.79	U = 303.0*	< 0.001*
Mean ± SD.	3.02 ± 1.15	4.49 ± 1.82		
Median	2.78	3.93		
RI				
Min. - Max.	0.51 - 0.89	0.75 - 0.90	U = 468.0*	0.003*
Mean ± SD.	0.73 ± 0.10	0.80 ± 0.05		
Median	0.75	0.79		
PI				
Min. - Max.	0.91 - 2.04	1.0 - 2.30	U = 559.5*	0.024*
Mean ± SD.	1.42 ± 0.33	1.63 ± 0.33		
Median	1.42	1.64		

Table 5: *Comparison between the two studied groups according to middle cerebral artery at delivery.*

t, p: t and p values for Student t-test for comparing between the two groups

U, p: U and p values for Mann Whitney test for comparing between the two groups

**: Statistically significant at p ≤ 0.05*

Table 6 shows significant difference between two groups according to uterine artery Doppler indices at delivery.

Mean (± SD) PSV in cm/sec in group I is 69.03 ± 11.94 and 57.82 ± 7.41 for group II. P value is < 0.001.

Mean (± SD) EDV in cm/sec in group I is 19.94 ± 3.37 and 27.58 ± 2.22 for group II. P value is < 0.001.

Mean (± SD) SD ratio in group I is 3.50 ± 0.57 and 2.21 ± 0.27 for group II. P value is < 0.001.

Mean (± SD) RI in group I is 0.69 ± 0.13 and 0.62 ± 0.07 for group II. P value is 0.030.

Mean (± SD) PI in group I is 1.16 ± 0.40 and 0.91 ± 0.11 for group II. P value is 0.02.

Uterine artery	IUGR (n = 17)	Normal (n = 100)	Test of sig.	p
PSV				
Min. - Max.	43.70 - 82.30	34.37 - 69.80	U = 185.0*	< 0.001*
Mean ± SD.	69.03 ± 11.94	57.82 ± 7.41		
Median	72.70	59.04		
EDV				
Min. - Max.	12.70 - 23.77	22.20 - 35.64	U = 582.5*	< 0.001*
Mean ± SD.	19.94 ± 3.37	27.58 ± 2.22		
Median	21.30	27.32		
SD ratio				
Min. - Max.	2.79 - 4.83	1.66 - 2.77	U = 579.0*	< 0.001*
Mean ± SD.	3.50 ± 0.57	2.21 ± 0.27		
Median	3.50	2.22		
RI				
Min. - Max.	0.47 - 0.91	0.47 - 0.76	t = 2.369*	0.030*
Mean ± SD.	0.69 ± 0.13	0.62 ± 0.07		
Median	0.64	0.63		
PI				
Min. - Max.	0.72 - 2.01	0.62 - 1.16	t = 2.537*	0.022*
Mean ± SD.	1.16 ± 0.40	0.91 ± 0.11		
Median	1.11	0.91		

Table 6: *Comparison between the two studied groups according to uterine artery at delivery.*

t, p: t and p values for Student t-test for comparing between the two groups

U, p: U and p values for Mann Whitney test for comparing between the two groups

Table 7 shows significant difference between two groups according to gestational age at delivery.

Mean (± SD) gestational age at delivery in weeks for group I is 33.53 ± 2.10 and 37.98 ± 0.93 for group II. P value is < 0.001.

	IUGR (n = 17)	Normal (n = 100)	t	p
GA at DELIV				
Min. - Max.	31.0 - 39.0	36.0 - 40.0	8.615*	< 0.001*
Mean ± SD.	33.53 ± 2.10	37.98 ± 0.93		
Median	33.0	38.0		

Table 7: *Comparison between the two studied groups according to Gestational age at delivery.*

t, p: t and p values for Student t-test for comparing between the two groups

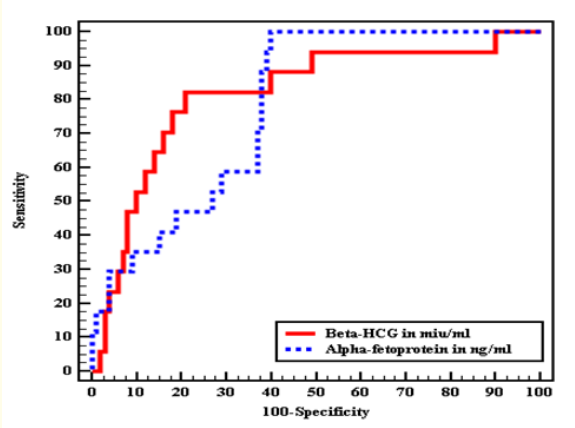

Figure 1: *ROC curve for Beta-HCG and Alpha-fetoprotein to diagnose IUGR from normal.*

Table 8 shows that Beta-HCG cut off value is > 88729 miu/ml, with sensitivity 35.29% and 92% specificity with 42.9% positive predictive value and 89.3% negative predictive value.

While Alpha-fetoprotein cut off value is > 208.8 ng/ml, with sensitivity 29.41% and 91% specificity with 35.7% positive predictive value and 88.3% negative predictive value.

	AUC	p	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Beta-HCG in miu/ml	0.817	< 0.001*	0.704	0.931	> 88729	35.29	92.0	42.9	89.3
Alpha-fetoprotein in ng/ml	0.779	< 0.001*	0.685	0.874	> 208.8	29.41	91.0	35.7	88.3

Table 8: *Agreement (sensitivity, specificity) for Beta-HCG and Alpha-fetoprotein to diagnose IUGR from normal.*

Discussion

In this study, out of 117 cases, patients with chronic hypertension were 22, with history of IUGR were 23, with history of preeclampsia were 64, SLE were 4 cases, chronic renal disease were 2 and with anti-phospholipid disease were 2.

Only (17) who suffered from IUGR, this group showed no significant difference from the other one in relation to Ductus venosus Doppler indices at delivery. But showed significant difference between umbilical artery, middle cerebral artery and uterine artery Doppler indices at delivery.

Investigators tried to improve the prediction of IUGR by combining Doppler indices with biochemical and clinical parameters due to the insufficient predictive value of each marker alone [20].

In this study, Umbilical artery and uterine artery Doppler in the IUGR group showed increase in Mean (± SD) of all Doppler indices. Middle cerebral artery Doppler in the IUGR group showed increase in Mean (± SD) PSV and decrease in Mean (± SD) S/D ratio, PI and RI from the other group and this results mostly due to head sparing phenomenon.

Gomez., *et al*. in 2006 showed that the sequence of changes in the uterine flow between the first and second trimester correlates with subsequent appearance of IUGR and the highest risk is held by women with persistent low vascular indices [23].

In this study, both groups showed significant difference in regard to Alpha-fetoprotein and Beta HCG but with low sensitivity and positive predictive value of both markers. Sensitivity of Beta-HCG to diagnose IUGR is 35.29 %, specificity is 92 % with PPV 42.9 % and NPV is 89.3 %. While Alpha-fetoprotein has 29.41 % sensitivity, 91 % specificity with 35.7 % PPV and 88.3 % NPV.

There is no significant difference in Beta-HCG, Alpha-fetoprotein in relation to the medical risk factor (medical history) of the patients in IUGR group.

In a prospective study conducted by Konachuk and friends, 35% of the pregnants with unexplained increased AFP level had at least one adverse perinatal outcome [24].

Enochian and friends has shown that among the women with unexplained AFP rate early and frequent follow-ups to increase antenatal survival did not improve outcomes. However these results contradicts with other studies conducted by performing biophysical profile and umbilical artery doppler as their basis in which they reported increased fetal survival [25].

Conclusion

- Combining Doppler indices with biochemical and clinical parameters improve the prediction of IUGR due to the insufficient predictive value of each marker alone.
- There is significant difference in regard to Alpha-fetoprotein and Beta HCG to diagnose IUGR in the high risk pregnancy patients with Sensitivity of Beta-HCG to diagnose IUGR is 35.29 %, specificity is 92 % with PPV 42.9 % and NPV is 89.3 %, While Alpha-fetoprotein has 29.41 % sensitivity, 91 % specificity with 35.7 % PPV and 88.3 % NPV.
- There is no significant difference in Beta-HCG, Alpha-fetoprotein in relation to the each medical risk factor (medical history) of the patients in IUGR group.

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