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Role of maternal serum copeptin in correlation with umbilical cord copeptin and umbilical artery Doppler indices in differentiating IUGR from constitutional small and appropriate for gestational age fetuses

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Abstract

Background: Neonate have a wide range of birth weights. Our focus on fetuses and neonates who appear to be, or are, small for their gestational age. They may simply be small (constitutionally or genetically small), or are small for a pathological reason. The key issues are how to screen a low-risk population in order to identify these small fetuses and, once identified, how best to identify those that are at increased risk in utero or in labour.

Study design: A prospective case-control study .

Patients and Methods: seventy-five pregnant women between 16_40 years old with singleton pregnancies were seen in Al-Yarmook and AL-Kadhymia Teaching hospitals from April 2016 to March 2017. The patients were divided (according to estimated fetal weight and umbilical artery Doppler indices) into 3 group .,Control group: included 25 pregnant women with appropriate for gestational age fetuses and normal umbilical artery Doppler indices .Group one (SGA): included 25 pregnant women with small for gestational age fetuses and normal umbilical artery Doppler indices .Group two (IUGR): included 25 pregnant women with small for gestational age fetuses and abnormal umbilical artery Doppler indices .In all groups, we measured maternal serum copeptin level at gestational age between 26-36weeks and umbilical cord copeptin immediately after delivery along with recording Apgar score and neonatal birth weight.

Results: Maternal serum copeptin level in intrauterine growth restriction group was significantly higher (1.95 ± 0.38) ng/ml than constitutionally small (0.94±0.31)ng/ml and control group (0.39 ± 0.08) ng/ml with p-value (<0.001). It had excellent ability to differentiate intrauterine growth restriction from constitutional small, with cut off value 1.39 ng/ml for predicting IUGR From constitutional small having 100% specificity and 92% sensitivity .Umbilical cord copeptin level in the intrauterine growth restriction was higher (3.70 ± 1.33) than constitutional small (2.07± 0.72) and control (0.37 ± 0.11) with cut off value >2.09 ng/ml for predicting IUGR from constitutional small and it have 95.83% specificity and 72% sensitivity .Inverse relationship between maternal serum copeptin and PI and RI only in the group two (p value 0.018), while in control group and group one the relationship was not significant(0.201, 0.644) respectively .

Conclusions: Maternal Serum copeptin had excellent ability to differentiate Intrauterine growth restriction from constitutionally small and control but still Inferior to umbilical artery Doppler ultrasound as it is elevated in both Constitutional small and intrauterine growth restriction although it is higher in Intrauterine growth restriction .

Key words: IUGR, constitutional small, umbilical artery Doppler, Copeptin.

INTRODUCTION

Intrauterine growth restriction (IUGR) denotes a pathological process in which a fetus does not achieve its biologically determined growth potential and it is not equivalent with small for gestational age (SGA) while SGA refer to an infant who had been born with estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th centile on ultrasound(1).Appropriate for gestational age (AGA) is demarcated as birth weight ranging between (10th and 90th percentile) for infant's gestationl age (2). Approximately 70% of fetuses with EFW below the 10th percentile are merely constitutionally small; so that, the term IUGR is inaccurate for many fetuses. Differentiating between normal and pathologic growth can be difficult, but a fetus with normal anatomy, amniotic fluid volume and growth pattern over time will generally be considered constitutional small rather than pathological small(3). IUGR can complicate 10-15% of all pregnancies but the incidence can varies depending on population, geographical location and standard growth curves used as reference(4). The regulation of fetal growth is complex and is based upon maternal, placental and fetal interactions.IUGR pregnancy is associated with neumerous maternal,fetal ,neonatal and even long term complication (3)

The aim of antenatal diagnosis is early detection of IUGR so that antenatal management can be optimized for better neonatal outcome. Diagnosis is based on accurate estimation of GA, history, physical examination and investigation(1).

Doppler velocimetry of fetal vessels provides further insight into the fetal response to altered growth, and has become part of the standard assessment of the fetus once IUGR is diagnosed. Doppler velocimetry has been shown to decrease the interferences and improve fetal consequence in pregnancies at risk for IUGR.(4) The normal Umbilical Artery (UA) circulation is a low-impedance circulation, with an increase in the volume of end-diastolic flow with progressing gestation. UA Doppler waveforms reveal the status of the placental circulation, and the increase in end-diastolic flow that is seen with advancing gestation is a result of an increase in the sum of tertiary stem villi that takes place with placental maturation(5).At least a 50 % reduction of terminal placental vessels is required before the pulsality index (PI) becomes abnormal. An increasing resistance index (RI) is powerfully linked with poorer fetal outcome. When UA Doppler flow indices are abnormal therefore (PI >+2 standard deviations above mean for GAwwwqq and delivery is not indicated, surveillance is required twice per week if end-diastolic velocities remain present. Doppler abnormalities are significantly associated with suboptimal fetal outcome and daily Doppler indices are required unless delivery is imminent(1).

Arginine Vasopressin (AVP) is a stress hormone working as a potent synergistic factor with corticotrophin releasing hormone to stimulate the release of adrenocorticotrophic hormone and cortisol. AVP stimulate chromaffin cells in the adrenal medulla to synthesize more epinephrine, thus predisposing to hyperglycemia by enhancing glycogenolysis in the liver (6). Cortisol reduce the action of insulin in encouraging glucose uptake by cells, inspiring

glucagon secretion and glycogenolysis, and finally cause elevation of plasma glucose levels. The combined effect of these mechanism may be essential to maintain a higher maternal–fetal glucose gradient to guarantee adequate fetal glucose metabolism under chronic stressful conditions; thus the process may be adaptive in nature(7). Owing to preanalytical difficulties, circulating AVP is cumbersome to measure. However, AVP is cleaved off a precursor molecule and secreted stoichiometrically, with three other peptides, among them copeptin(8). Copeptin is more stable in the circulation and easy for measurement than AVP. In addition, Copeptin had been shown to be more finely reflects the individual stress level compared to cortisol. Due to the positive association of copeptin with the severity of illness and outcome, copeptin has been proposed as a prognostic marker in acute illness.(9)

PATIENTS AND METHODS

This is a prospective case control study, It was carried out at AL-Yarmouk & AL-Kadhmiya teaching hospitals, department of obstetrics and gynecology in Baghdad city during the period from first of April 2016 to the first of march 2017 after approval by the supervising committee of Arab Board Obstetrics and Gynaecology and informed consent from all of the pregnant women was taken. Seventy-five pregnant women were selected during their attendance to the antenatal care unit age between 16 - 40 years, singletone pregnancy, Parity 0-8 & Gestational age between 26weeks – 36weeks(the gestational age was confirmed by last menstrual period and early first trimester ultrasound) were included . women in labor, chorioamnitis, multiple pregnancy, uncertain gestational age, medical disease (cardiovascular disease, hypertension, diabetes) & fetal congenital anomaly, all were excluded. Detailed history was taken from all participant including current and past obstetric history, medical, surgical, family, medication use, occupation and socioeconomic state history. Normal Pregnant women, appropriate for gestational age (AGA) fetuses in whom the fundal height measurement is in line with gestational age were taken as a control group (25 women), where as those more than 2cm below the expected gestational age where sent for ultrasound fetal biometry and amniotic fluid index measurement. Those with AC below the 10th percentile for gestational age where sent for Doppler ultrasound inside the hospital outpatient ultrasound clinic to measure umbilical arterial Doppler indices,pulsality index (PI) and Resistance index RI), by using transabdominal curvilinear transducers of 3.5 MHz. According to Doppler indices, the SGA group were divided into, Group one: constitutional SGA include 25 pregnant women with normal umbilical artery Doppler indices (normal PI and RI). Group two: pathological SGA (IUGR) include 25 pregnant women with abnormal umbilical artery Doppler indices (RI >95% for gestation and PI >2 SD above the mean for gestational age). A five milliliter of venous blood was taken from each participant pregnant women after the initial assessment and Doppler ultrasound examination. All women with suspected IUGR were admitted to the ward, where they subjected to increased fetal surveillance including nonstress test, biophysical profile and Doppler ultrasound with individualized frequency, whereas those with normal umbilical artery Doppler indices either constitutional SGA or control discharged and continued with their regular antenatal care till the time of confinement. Two to four milliliter of mixed cord blood was taken immediately after delivery along with assessment of Apgar score at the first and fifth minute and weighing of the newborn. Diagnosis of IUGR was confirmed after delivery as they weighing less than 2500 gram and have characteristics features: anxious, hyperalert infant with large head, wide anterior fontanel, absence of buccal fat (old man), long finger nails, loose dry easy peel able skin, poor breast bud formation, small scaphoid abdomen, thin umbilical cord, small placenta.

Serum copeptin was measured using enzyme linked immunoassay (ELIZA) by using human copeptin ELIZA Kit, SHANGHAI YEHUA Biological technology co., Ltd. Cat. NO: YHBO830Hu) according to manufactures instruction. With assay range : 0.05ng/ml→20ng/ml and Sensitivity : 0.024ng/ml SPSS 20.0.0, Minitab 17.1.0, MedClac 14.8.1, GraphPad Prism 7.0 software package were used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05, chi square test, One-way ANOVA , Tukey's post hoc analysis was used to analyze the significant difference between each pair. Linear regression analysis was performed to assess the relationship between different variables. Scatter plot used to present the regression analysis, Receiver operator curve was used to see the validity of different parameters.

RESULT

In our study, we observed the level of copeptin in maternal serum and umbilical cord in the three groups (control with AGA fetuses, group one: constitutional small, group two: IUGR) and its role in diagnosis of IUGR and differentiating it from constitutionally small and AGA in correlation with umbilical artery Doppler indices In our study the age, BMI and parity were not significantly different among the three groups, as illustrated in table 1

Regarding neonatal characteristics :

Both GA at sampling and gender of the infant were not statistically significant among the three groups. While GA at delivery, Apgar score and birth weight were significantly different among the three groups as illustrated in table 2.

Table 3: shows copeptin level in maternal serum and umbilical cord in the three groups. We see that both maternal serum and umbilical cord copeptin were significantly higher in group two compared to both group one and control groups, while in group one was significantly higher than in control group as illustrated in table 3 and figure 1 .

Table 1: Maternal demographic characters.

		Control	Group one	Group two	P value
Number		25	25	25	-
Maternal age	Mean ± SD	27.1 ± 6.5	28.7 ± 5.6	26.1 ± 6.7	0.344
	Range	17 – 39	18 – 37	16 – 40	
BMI	Mean ± SD	22.8 ± 3.8	23.4 ± 2.9	21.7 ± 2.7	0.171
	Range	17 – 30	18 – 30	17 – 26	
Parity	Mean ± SD	2.8 ± 2.1	3.0 ± 1.9	2.3 ± 1.9	0.403
	Range	0 – 8	0 – 7	0 – 7	

Table 2: Neonatal characteristics

	Control	Group one	Group two	P value
Number	25	25	25	-
Gestational age at sampling	31.0 ± 2.1	31.6 ± 2.3	31.9 ± 2.5	0.410
Gestational age at delivery	37.8 ± 1.5	37.3 ± 1.0	34.2 ± 2.0	<0.001
APGAR	8.4 ± 1.0	8.5 ± 0.9	6.4 ± 1.8	<0.001
Birth weight	3.4 ± 0.5	2.5 ± 0.3	2.2 ± 0.7	<0.001
Gender				0.948
Female	14 (56%)	14 (56%)	13 (52%)	
Male	11 (44%)	11 (44%)	12 (48%)	

Table 3: Maternal serum and umbilical cord copeptin (ng/ml) in study group

	Control	Group one	Group two	P value
Number	25	25	25	-
Maternal Serum copeptin (mean ±SD)	0.39 ± 0.08	0.94 ± 0.31	1.95 ± 0.38	<0.001
Umbilical cord copeptin(mean±SD)	0.37 ± 0.11	2.07 ± 0.72	3.70 ± 1.33	<0.001

Copeptin role as discriminator between pregnant women in the three groups Copeptin had excellent ability to differentiate group one and group two from control (using both serum and umbilical cord copeptin) as illustrated in table 4, table 5 show the optimal cut point: >0.5 ng/ml for serum copeptin and >0.67 ng/ml for umbilical cord that both had 99% sensitivity, specificity and accuracy for predicting constitutionally small and IUGR from control. Maternal Serum copeptin had excellent ability to differentiate group two from group one, while umbilical cord copeptin had good ability to differentiate group two from group one as illustrated in table 4, figure 2 shows the optimal cut point >1.39 ng/ml for predicting IUGR from constitutional small using serum copeptin and it have 100% specificity and 92% sensitivity, and >2.09 ng/ml for predicting IUGR from constitutional small using umbilical cord copeptin and it have 95.83% specificity and 72% sensitivity, this indicate that maternal serum copeptin is better than umbilical cord copeptin, as illustrated in table 4

Correlation between maternal serum and umbilical cord copeptin: In control group there was none significant direct correlation between umbilical and serum copeptin, this direct relationship remain in both group one and group two and also become statistically significant, in the group two the correlation was the strongest compared to the other groups, as illustrated in table 5.

Correlation between maternal serum copeptin levels with umbilical artery Doppler indices: There was Inverse relationship between maternal serum copeptin with PI and RI only in the group two, while in control group and group one the relationship was not significant as illustrated in table 6 and 7.

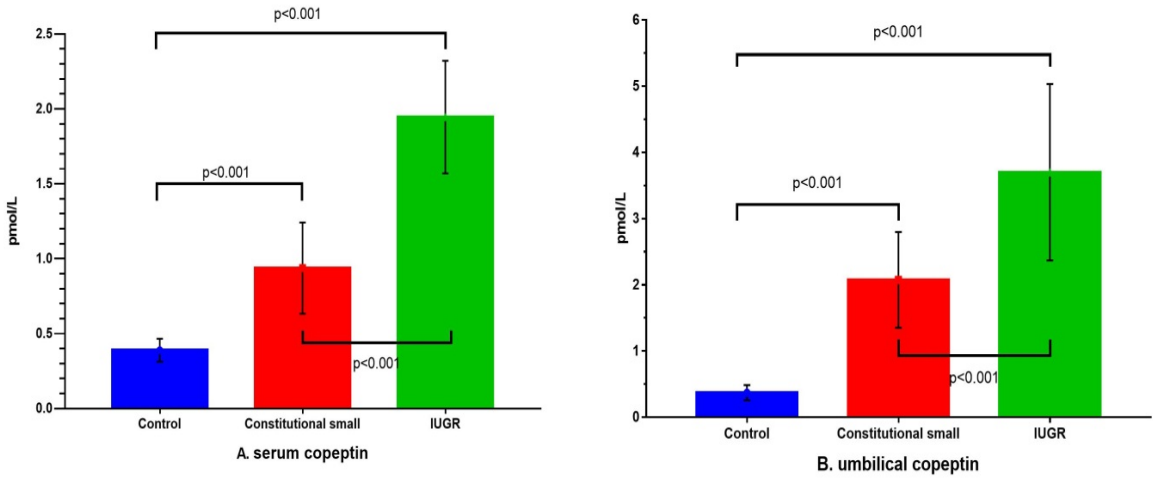

Figure 1: Copeptin (maternal serum and umbilical cord)

Table 4: validity of maternal serum copeptin in discrimination between the three groups.

	AUC (95%CI)	P value	Cut point	Sensitivity	specificity	Accuracy	PPV	NPV
Group one from control								
Maternal Serum copeptin	1.0 (0.929 – 1.0)	<0.001	≥0.5	99%	99%	99%	99%	99%
Umbilical cord copeptin	1.0 (0.929 – 1.0)	<0.001	≥0.67	99%	99%	99%	99%	99%
Group two from control								
Maternal Serum copeptin	1.0 (0.929 – 1.0)	<0.001	≥0.5	99%	99%	99%	99%	99%
Umbilical cord copeptin	1.0 (0.929 – 1.0)	<0.001	≥0.67	99%	99%	99%	99%	99%
Group two from group one								
Maternal Serum copeptin	0.979 (0.892 – 0.99)	<0.001	≥1.39	92%	100%	96%	100%	92.6%
Umbilical cord copeptin	0.888 (0.765 – 0.960)	<0.001	≥2.09	95.83%	72%	83.9%	76.7%	94.7%

Table 5: Relationship between maternal serum and umbilical cord copeptin in study groups.

Control		Group one		Group two	
Beta	P value	Beta	P value	Beta	P value
0.375	0.064	0.558	0.004	0.751	<0.001
Beta: person correlation coefficient					

Table 6: Correlation between maternal serum copeptin and pulsatility index.

Group	Beta	R^2	P value
Control	0.264	0.07	0.201
Group one	0.097	0.009	0.644
Group two	-0.470	0.211	0.018

. **Table 7: Correlation between maternal serum copeptin and resistance index.**

Group	Beta	R^2	P value
Control	-0.222	0.049	0.287
Group one	-0.242	0.059	0.243
Group two	-0.401	0.161	0.047 [Sig.]

DISCUSSION

Antenatal attention that the fetus is not growing well is an essential compartment of good maternity care(1). Fetuses that are labelled as SGA invariably fall into one of two categories: those who are growth-restricted due to pathological factors and those who are constitutionally small. Distinguishing between the two populations is important, since the former group is more likely to be associated with increased neonatal and long-term morbidity and mortality.(10) The aim of our study was to determine whether maternal serum copeptin and fetal umbilical cord copeptin concentration in AGA, constitutional SGA and IUGR in correlation with umbilical artery Doppler indices are different or comparable, so that we can differentiate between IUGR and constitutionally SGA and AGA .

Increased maternal serum copeptin concentration with fetal growth restriction may reflect a stress response, as the mother may be warry that she is pregnant with a SGA fetus and her fetus may be in a condition associated with poor outcome(6). In our study, we found that maternal Serum copeptin had excellent ability to differentiate IUGR from constitutional group with optimal cut point >1.39 ng/ml for predicting IUGR from constitutional group and it have 100% specificity and 92% sensitivity,this agree with Foda et al study in 2013(11) & Bulbul et al study(12) in 2014 who found maternal serum copeptin was significantly higher in pregnant women with fetal growth restriction than maternal serum copeptin in pregnant women with normal fetal growth($P < 0.01$) and constitutionally SGA ($P < 0.05$) (11). Our study disagree with Hansen et al in 2014 who conducted a study on maternal copeptin levels measured in GA 12 and 19 weeks and risk of SGA and found no difference in copeptin levels in cases compared to controls (12). In our study, we found that umbilical cord copeptin had good ability to differentiate IUGR from constitutional group, the optimal cut point >2.09 ng/ml for predicting IUGR from constitutional group and it have 95.83% specificity and 72% sensitivity. our study agree with Burkhardt et al in 2012(13) & Foda et al in 2013 (11) study who reported that umbilical cord copeptin levels were raised significantly in IUGR as compared with the constitutionally SGA newborns ($P < 0.001$) and with the newborns of AGA ($P < 0.001$). The umbilical cord copeptin level in constitutionally SGA newborns were not increased significantly ($P > 0.907$) as compared with the levels of AGA newborns(11). Finally our study also agree with Bulbul et al study in 2014 they reported that umbilical cord copeptin levels were higher in IUGR and significantly increased in neonates with adverse outcomes (12). Summanen et al in 2017 findings suggest that copeptin had high potential to become a routinely used as a biomarker for acute birth asphyxia and neonatal distress.(14) These findings further support the result of our study, we found that umbilical cord copeptin levels were higher in neonates with IUGR especially those with adverse outcomes(in the form of low APGAR score). Our study disagree with Briana et al in 2017 who showed that fetal copeptin concentrations were similar in IUGR cases and AGA controls however, in their study Cord blood copeptin concentrations were measured in well-defined, uncompromised, asymmetric IUGR and AGA full-term pregnancies, where as in our study both compromised and uncompromised IUGR and preterm fetuses where included(15). In addition, in our study, we found inverse relationship between serum copeptin and PI and RI of umbilical artery only in the IUGR, while in control and constitutionally small, the relationship was not significant. This result was in agreement with Bulbul et al in 2014 who found that maternal copeptin levels were inversely correlated with the uterine artery and umbilical artery indices and positively correlated with neonatal birth weight(12) . Maternal serum copeptin can't be considered as pathognomonic for IUGR, neither be a substitute for umbilical artery Doppler velocimetry as there may difference in its level with difference in the gestational age at delivery, markers being used to measure and socioeconomic state of the mother.

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