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Association of maternal serum beta human chorionic gonadotropin (β-hCG) level with intrauterine growth restriction: a case control study

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ABSTRACT

Introduction: Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality. The human chorionic gonadotropin (β-hCG) is suggested to be released in large amounts into the maternal circulation due to placental dysfunction. Studies have shown that raised levels of β-hCG was associated with IUGR in the first and second trimesters. However, no study was done during the third trimester. Therefore, the objective of the study was to determine the association of β-hCG level with IUGR during third trimester. **Methods:** A case-control one year-period study completed in the Department of Obstetrics and Gynaecology, BSMMU, Bangladesh. Pregnant mothers diagnosed with IUGR were taken as case (*n*=55) and mothers without IUGR as control (*n*=55). Serum β-hCG levels of these two groups were measured. The data was analysed with SPSS-16 software. Chi-square test was used for analysis. **Results:** The mean estimated fetal weight (EFW) of case was significantly less as compared to control ($p<0.001$). Out of 55 pregnancies with IUGR, 14 (25.5%) had raised level of β-hCG as compared to only 4(7.3%) of control had raised B-hCG level. The odds ratio (OR) of developing IUGR in pregnant women with raised β-hCG level was found to be 4.4 fold (95% CI: 1.331- 14.237) higher than the pregnant women with normal level of β-hCG. **Conclusions:** The study concluded a significant association between the raised levels of β-hCG with IUGR.

Keywords: IUGR; Perinatal morbidity and mortality; β-hCG.

INTRODUCTION

Fetus that has not attained its growth potential due to pathological restriction is termed as IUGR[1,2]. It is classified as early onset or symmetrical, late onset or asymmetrical and mixed type[3,4]. Early onset IUGR accounts for 20-30% of the cases and late onset IUGR for 70-80%[4,5]. Prevalence of IUGR is about 8-10% for general population and the incidence is six times higher in developing countries as compared to developed countries[4]. The incidence of IUGR in Bangladesh is 21%. IUGR is the end result of maternal, fetal, placental, genetic factors or can present in combination of any of these factors. All these factors contribute to a common pathway that results in uteroplacental insufficiency, causing fetal growth restriction 47. However, definite cause is unknown in 40% of cases". IUGR fetuses are more prone to develop complications during intrauterine, perinatal period and adulthood. IUGR fetuses account for 8 - 10% of intrauterine fetal death and 24.4% of perinatal complications[8,9]. There is a 2 fold increased risk of recurrence in future pregnancies.

Diagnosis of IUGR is made by a combination of assessment for risk factors from the history, serial clinical assessment for symphysio-fundal height and serial ultrasonography for fetal biometry. The accurate dating of pregnancy from the last menstrual period corroborated by early ultrasonography is essential for detection of IUGR[1,10]. However, fetal biometry and Doppler flow studies are the mainstay for the diagnosis of IUGR[11-13]. Abnormal uterine artery Doppler in combination with abnormal level of maternal serum marker analyte, β-hCG give better prediction for the development of IUGR fetus[14,15]. Some studies have shown associations between raised β-hCG level and IUGR[16-18]. In contrary, some studies have shown no association whereas other have revealed lower level of β-hCG were associated with IUGR[20,21]. Therefore, the use of serum analytes for the diagnosis of IUGR remains a subject of study. Several previous publications were based on the serum analytes measured during first or second trimesters. The current study was developed to report the relationship between serum β-hCG level during the thrid trimester and IUGR.

METHODS

Study design: Case-control study.
Place of study: Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University, BSMMU, Dhaka.

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Duration of study: One year (1st May 2016 to 30th April 2017).

Study population: Singleton pregnant women attending antenatal clinic and those admitted in the Department of Obstetrics and Gynaecology, BSMMU at their 29-40 weeks of pregnancy were enrolled for the study and divided into two groups:

a) Case: Singleton pregnant women with diagnosed intrauterine growth restriction of the fetus in third trimester (29-40 weeks) of pregnancy.
b) Control: Singleton healthy pregnant women without any medical disorders and has no intrauterine growth restriction of fetus in 3rd trimester (29-40 weeks) of pregnancy. These two groups were matched for maternal age, gravidity, period of gestation and BMI.

Inclusion criteria
1. Singleton pregnant women diagnosed with intrauterine fetal growth restriction at their third trimester (29-40 weeks) of pregnancy.

Exclusion criteria
1. Multiple pregnancies.
2. Mistaken dates.
3. Pregnancies with fetal chromosomal or structural anomalies.
4. Pregnant women diagnosed with choriocarcinoma.
5. Molar pregnancy.
6. Intrauterine fetal death.
7. Fetal congenital infections (TORCH and malarial infections).
8. Pregnancy with uterine anomalies.
9. Pregnancy with uterine fibroid.
10. Pregnant mother on medications (viz. Warfarin, cyclosporine, azathioprine, corticosteroids, beta blockers).
11. Pregnant women who have not given consent to participate in the study.

Sampling Size
The sample size was calculated using formula for hypothesis testing of single proportion (Hoque, 2016, p.157):

$$n = \frac{\left[Z_{\alpha}\sqrt{2p(100-p)} + Z_{\beta}\sqrt{p_1(100-p1) + p_2(100-p_2)} \right]^2}{(p_1 - p_2)^2}$$

Z_a=1.96 at 5% level and Z_β=0.85 at 80% power[22]. The other values were obtained from the Lepage et al., 2003 study conducted at Mt Sinai Hospital, University of Toronto. The margin of error was taken as 10. Using the standard formula and the baseline data, the sample size was 110, out of which 55 were taken as case and 55 as control.

Sampling technique
It was a purposive sampling.

Procedure
This case control study was conducted in the Department of Obstetrics and Gynecology, BSMMU, Dhaka from 1st May 2016 to 30th April 2017. After obtaining a written informed consent, a total of 110 pregnant mothers in their third trimester of pregnancy were enrolled in the study. Study population was divided into two groups; a case group (*n*=55) consisting of pregnant mothers diagnosed with IUGR and a control group (*n*=55) comprising of healthy pregnant mothers without IUGR. For recruitment, detailed history was taken and review of antenatal medical records was done regarding last menstrual period (LMP), expected date of delivery (EDD) and early scan to confirm the period of gestation. Relevant clinical examination was conducted to record the height, weight, BMI and symphysio-fundal height measurement in particular. IUGR was suspected clinically when symphysio-fundal height was less than the period of gestation and further confirmed by ultrasonography measurement of EFW. IUGR was diagnosed when the EFW was less than 10th percentile for that gestational age.

A pretested interviewer administered questionnaire was used for data collection.

Three ml of venous blood sample was collected from left antecubital vein in a plain test tube from the study subjects to estimate serum β-hCG level. The β-hCG was measured using Chemiluminescent Microparticle Immunoassay (CMIA) method with Automated Analyzer: Architech Plus ci8200, in the Department of Biochemistry and Molecular Biology, BSMMU. The gestation specific reference value of β-hCG was used. For 29 – 41 weeks of gestation, β-hCG level of >60000 IU/L was considered raised and level of 940 - 60000 IU/L as normal.

Data Management and Analyses

The collected data was analysed using SPSS version 16. Descriptive statistics such as frequency, percentage, mean, median, confidence interval and standard deviation were used to describe the study variables. In comparison of the baseline characteristics and outcomes between the two groups, t-test was used for continuous variables, chi-square test for categorical variables and Pearson's correlation test was done for two quantitative variables. Bar graph, line graph and scatter plot were used for the presentation of the results. Odds Ratio (OR) and 95% confidence interval were also estimated for the outcome. *p*-value <0.05 was considered statistically significant.

Ethical approval

The study proposal was developed as per the guidelines of the Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh. The research ethics approval was accorded vide Institutional Review Board (IRB) Approval Letter No. BSMMU/2016/3998 dated 12th April 2016.

RESULTS

Raised level of β-hCG in the third trimester of pregnancy was found to be associated with IUGR. More than 60% of the study subjects were in the age range of 20-29 years with comparable mean age (USD). Majority of the study subjects for both the groups were house wives. More than 50% of the study subjects were overweight and the mean BM (USD) is similar in both the groups (p=0.910). The distribution of study subjects by obstetrical characteristics (parity, gravidity and gestational age) were comparable. Out of 55 IUGR fetuses, around 90% were detected after 32 weeks of gestation as compared to 10.9% being detected before 32 weeks of gestation (Table 1). Nearly 45.5% of the pregnant mothers with IUGR fetuses had hypertensive disorders followed by thyroid disorders (23.6%) (Table 2).

In the case group, 28(50.9%) had EFW in between 2000-2499g. In contrary, 31(56.4%) of the control group had EFW > 2500g. The mean EFW (ESD) of case (1874.96+442.89 g) was significantly lesser than the mean EFW (ESD) of control (2414.8736642.97g) with the p=<0.001 (Table 3). Out of 55 IUGR fetus, more than 90% was moderate IUGR while only 9% had severe IUGR (Figure 1).

The mothers with IUGR fetus had raised level of β-hCG in 14 (25.5%) as compared to 4 (7.3%) in mothers without IUGR fetus with raised level of β-hCG. The Odd Ratio (OR) of developing IUGR in pregnant women with raised level of β-hCG (>60000 IU/L) in their third trimester (29 – 40 weeks) of pregnancy was found to be 4.4 times (95% CI: 1.33-14.24) higher than that in women with normal level of β-hCG (p=0.010) (Table 4).

Table 1. Demographic characteristics of women with IUGR and maternal β-hCG levels in Bangladesh, 2016

	Groups		
Variables	**Case (n=55)**	**Control (n=55)**	***p*-value**
Age (years)			
<20	7 (12.7%)	4 (7.3%)	
20 – 29	35 (63.6%)	37 (67.3%)	
30-39	12 (21.8%)	13 (23.6%)	
≥40	1 (1.8%)	1 (1.8%)	0.822*
Mean age (±SD)	26.7±4.79	27.1±4.66	0.616**
Education			
Primary	6 (10.9%)	2 (3.6%)	
Secondary	17 (30.9%)	12 (21.8%)	0.216*
Higher secondary	23 (41.8%)	30 (54.5%)	
Graduate and above	9 (16.4%)	11 (20.0%)	
BMI (kg/m2)			
Underweight	1 (1.8%)	0 (0.0%)	
Normal	19 (34.5%)	21 (38.2%)	0.743*
Over weight	32 (58.2%)	31 (56.4%)	
Obese	3 (5.5%)	3 (5.5%)	
Mean BMI (±SD)	25.94±2.47	25.88±2.55	0.910**
Gravidity			
Primi gravida	16 (29.1%)	19 (34.5%)	
Multigravida	39 (70.9%)	36 (65.5%)	0.539*
Mean gravidity(±SD)	2.14±1.14	2.12±1.07	0.932**
Parity			
Nulliparity	33 (60.0%)	28 (58.9%)	0.627*
Multiparity	22 (40.0%)	27 (49.1%)	
Mean parity(±SD)	1.50±0.69	1.65±0.77	0.621**
Period of gestation (weeks)			
29-32	6 (10.9%)	14 (25.5%)	
33-36	23 (41.8%)	18 (32.7%)	0.136*
37-40	26 (47.3%)	23 (41.8%)	
Mean gestation age(±SD)	35.72±2.49	34.83±3.01	0.098**

**Chi-square test done for significance*
***student t-test done for significance*

Table 2. Distribution of women by medical disorders in the case group (*n*=55)

Medical disorders	Frequency	Percentage
Hypertensive disorders	25	45.5
Thyroid disorders	13	23.6
Heart disease	2	3.6
Renal disease	1	1.8
Hemoglobinopathies	2	3.6
Hepatitis	3	5.4
SLE	3	5.4
APS	2	3.6
No disorders	9	16.3
Total	**55**	**100**

SLE-systemic lupus erythematosus
APS-anti-phospholipid syndrome

Table 3. Distribution of women in study groups by EFW (*n*=110)

	Group		
EFW (gram)	Case	Control	*p*-value
<1000	1 (1.8%)	0 (0.0%)	
1000-1499	12 (21.8%)	4 (7.3%)	
1500-1999	14 (25.5%)	13 (23.6%)	<0.001*
2000-2499	28 (50.9%)	7 (12.7%)	
≥2500	0 (0.0%)	31 (56.4%)	
Total	**55 (100%)**	**55 (100%)**	
Mean EFW (±SD)	1874.96±442.89	2414.873±642.97	<0.001**

**Chi-square test done for significance*
***student t-test done for significance*

Table 4. Association of β-hCG level with IUGR fetus (*n*=110)

	Group		OR	
β-hCG level (IU/L)	Case (*n*=55)	Control (*n*=55)	(95% CI)	*p*-value
>60000	14 (25.5%)	4 (7.3%)	4.4 (1.33-14.24)	0.010*
940-60000	41 (74.5%)	51 (92.7%)		

**Chi-square test done for significance*
NB:β-hCG level>60000IU/L considered raised and 940-60000IU/L as normal

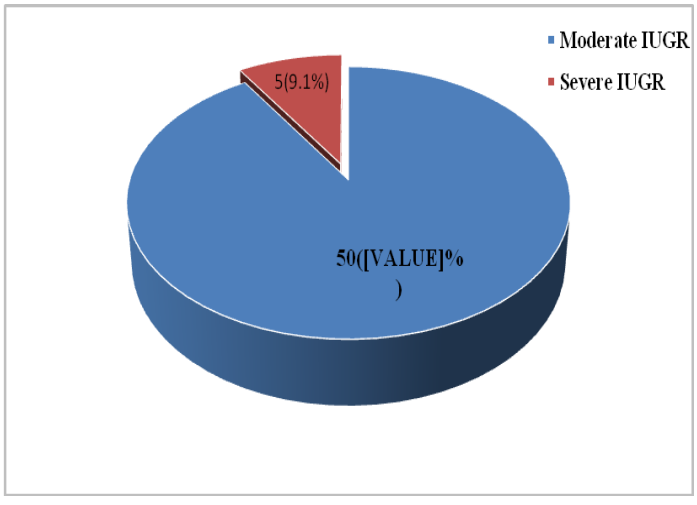

Figure 1. Pie chart showing distribution by types of IUGR

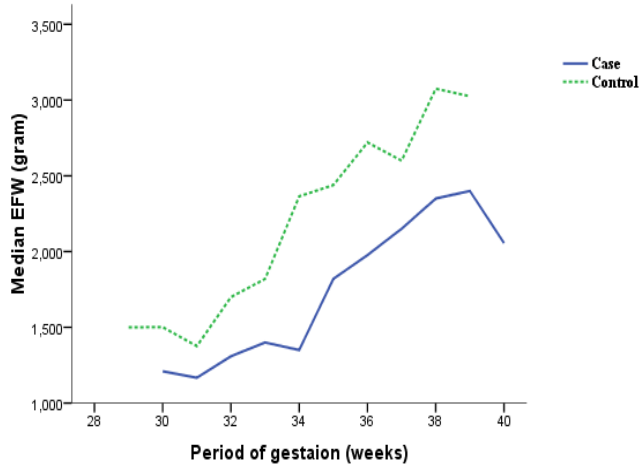

Figure 2. Line graph showing the variations of estimated fetal weight (EFW) with the period of gestations in the study groups, Bangladesh in 2016

Table 5. Association between severity of IUGR and serum β-hCG levels (*n*=55)

β-hCG level (IU/L)	Group		OR	*p*-value
	Severe IUGR (*n*=5)	Moderate IUGR (*n*=50)	(95% CI)	
>60000	4 (80.0%)	10 (20.0%)	16 (1.61-159.31)	0.003*
940-60000	1 (20.0%)	40 (80.0%)		

**Chi-square test done for significance*

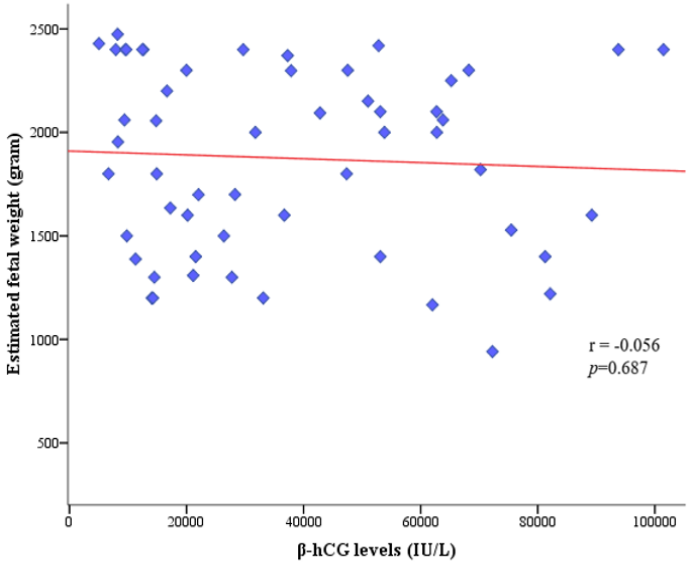

Figure 3. Correlation of β-hCG level with EFW in pregnant mothers with IUGR fetus (*n*=55), Bangladesh in 2016

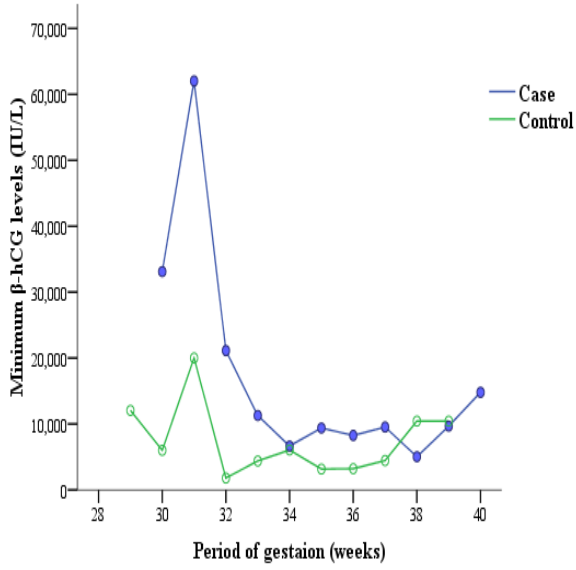

Figure 4. Line graph shows the variations of β-hCG level with the period of gestation in the study groups, Bangladesh in 2016

Out of 5 severe IUGR, 4 (80.0%) had raised level of β-hCG (>60000 IU/L) as compared to only 1 (20.0%) of the severe IUGR fetuses had B-hCG level between 940-60000 IU/L. The Odds ratio (OR) of having raised level of β-hCG in women with severe IUGR in their third trimester was estimated to be 16-fold (95% CI: 1.61-159.31) higher than that in women with moderate IUGR (*p*=0.003) (Table 5).

There was a wide variation of EFW with the period of gestation between the case and control groups. The EFW for the case was remarkably lesser than the control group (Figure 2). There was a weak negative correlation between EFW and the β-hCG level for pregnant mothers with IUGR fetus with *r*= -0.056 and *p*=0.687 (Figure 3).

The β-hCG levels were comparatively higher for pregnant mothers with IUGR as compared to healthy pregnant mothers without IUGR. However, after 37 weeks of gestation the β-hCG levels were comparable between case and control groups (Figure 4).

DISCUSSION

More than one-fourth of the pregnant mothers with IUGR fetus are found to have raised level of β-hCG as compared to only 7.3% of mothers without IUGR had raised level of β-hCG. The possible explanation is IUGR develops due to uteroplacental insufficiency and there is hypoxia induced hyperplasia of trophoblastic cells in the placenta. So the increased number of trophoblastic cells produce larger amount of β-hCG into maternal circulation[23-25].

The raised level of β-hCG has been reported to be associated with the IUGR in several studies[16-18]. However, those studies were conducted at first or second trimester of pregnancy in conjunction with aneuploidy screening or most of the past studies were based on the comparison of pregnancy outcome with the level of biomarkers obtained during the aneuploidy screening. Those studies have found that with the raised level of β-hCG detected during the screening for aneuploidy were associated with poor pregnancy outcomes[20,26]. The present study revealed similar finding that the raised level of β-hCG was associated

with fetal growth restriction (Table 4); however, the study was conducted during the third trimester of the pregnancy. Therefore the present study lacks the data on β-hCG level during the first and second trimester as compared to past studies. So the present study fails to comment on the association between initial β-hCG levels with development of IUGR unlike other studies.

The serum ß-hCG level varies with the gestational age (Figure 4). The serum β-hCG levels were comparatively higher for the pregnant mothers with IUGR as compared to β-hCG level of mothers without IUGR. However, after 37 weeks of gestation, the β-hCG levels were comparable between the study groups. The possible explanation could be, due to persistent trophoblastic cellular hyperplasia induced by hypoxia initially giving rise to persistent rise in β-hCG level. The fall in β-hCG level after 37 weeks of gestation could be due to hypoxic induced destruction of the trophoblastic cells when it can no longer withstand the chronic hypoxic insult[27].

Around 90% of IUGR fetuses were detected after 32 weeks of gestation and 90% were moderate IUGR in the current study. The possible explanation for late detection (>32 weeks) could be because the study subjects were enrolled in their third trimesters for the study. However, the late detection of IUGR fetuses were in line with the existing literature which have reported that 80% of IUGR are of late onset IUGR (>32weeks) and only 20% are detected before 32 weeks of gestation (early onset)

LIMITATIONS

The potential error in the current study could have occurred while estimating fetal weight and labelling it as IUGR. Most of the mothers report wrong LMP. The initial CRL is often inappropriately estimated by adjusting the EDD to match with EDD of LMP. These would have led to wrongly labelling fetus as IUGR. This may explain lesser percentage of mothers with IUGR fetus is having raised level of β-hCG.

Other limitation was that the exclusion of constitutionally small fetus could not be differentiated from IUGR fetus with 100% accuracy due to the human and or the ultrasound machine error.

Another limiting factor was short duration of study period and the financial constraint. Due to time and financial constraint, this present study could enrol limited number of study subjects and also could not do β-hCG level during the first and second trimesters. This could have been appropriate to compare and contrast the trimester-wise β-hCG level in relation to development of IUGR.

CONCLUSIONS

The present study concluded that the raised level of serum β-hCG during third trimester of pregnancy was associated with IUGR. Therefore, the pregnant mothers with risk factors may use β-hCG estimation during the third trimester to screen for the development of IUGR. Although the usefulness of measuring β-hCG level during third trimester of pregnancy for the prediction of IUGR is narrow, the current study showed there is an association of raised β-hCG level during third trimester with IUGR. However, further researches are required to validate the finding before it is made available for clinical use. It will not be cost effective for all the pregnant mothers to routinely screen with β-hCG level during third trimester; however, it can be individualized and can be used as a part of follow up investigations for high risk mothers identified. This study was hospital based and done on a small sample size. Therefore, the finding cannot be generalized to the whole population. It invites more investigators to do more research in this regard, in order to come to a consensus which would help in planning strategies and allocating resources for the prevention and management IUGR in the future.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

YD: Concept, design, data collection and analysis, manuscript writing and review.

Author agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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