The Association of Raised Mid-trimester Serum Human Chorionic Gonadotrophin (hCG) and Alpha-Fetoprotein with adverse Pregnancy Outcome

Marwa Hamood Jabir[1], Taghreed Salah Alquzwini[2]

[1]M.B.ch.B/Women and Children General Hospital / Al-Dewaniya Health Bureau / Ministry of Health
[2]Alqadissiya University /Iraq

Abstract

Background: Placenta is a temporary endocrine organ formed during pregnancy, which produces hormones important in the maintenance of a healthy pregnancy. hCG is the first one of these hormone that is measured in pregnancy test and used in the follow up of adverse pregnancy outcome, Alpha fetoprotein is a major plasma protein produced by the yolk sac and the fetal liver during fetal development.**Aim of study** :to study relationship between gestational complications and levels of maternal serum HCG and AFP and determine whether the semarkers are effective predictors adverse pregnancy outcomes. **Patients & Methods**:Prospective cohorts study in AlDiwaniyah maternity and pediatrics teaching hospital.We enrolled a total of 230 women at 14-23 gestational weeks and measurement of maternal serum HCG & AFP were done, of those with normal HCG & AFP formed (group l), group 2 involved women with elevated AFP , group 3 with elevated HCG & group 4 involved women with elevated both HCG & AFP.Follow up weekly of the patients for the development of adversepregnancy outcome.**Results**: A significant relationship between adverse pregnancy outcomes and abnormal elevation of HCG & AFP levels in the second trimester. In group 2 the patients developed higher rate of preterm labour & pre-eclampsia compared with the group 1. In group 3 with raised HCG the rate of pre-eclampsia & IUGR development were higher than group 1. In group 4 with elevated both HCG & AFP higher incidence of pre-eclampsia & placental abruption , with a specificity($p<0.001$). **Conclusion**: In the second trimester unexplained high AFP and HCG rates related to adverse maternal and perinatal outcomes.

Keywords: *Mid-trimester; Serum Human Chorionic Gonadotrophin(hCG);Alpha-Fetoprotein; adversePregnancy Outcome*

Introduction

Is a marker of glycoprotein hormone family (human chorionic gonadotrophin , follicular stimulating hormone FSH , luteinizing hormone LH, thyroid stimulating

hormone TSH).All of them are dimers consisting of a common alpha subunit and distinct beta subunit that are associated non-covalently.The distinct beta subunits confer biological activity and display various degrees of homology. In adult human chorionic gonorionic gonadotrophin expression is often associated with pregnancy, however human chorionic gonadotrophin can be found in another conditions such as gestational trophoblastic disease and non-germinomatous germ cell tumors [(1)] .

Human chorionic gonadotrophin is produced almost exclusively by the syncytiotrophoblast of the placenta . However it is synthesized by the fetal kidney und fetal liver Most of the human chorionic gonadotrophin in circulation is metabolized by the liver. Also 20% of the circulating human chorionic gonadotrophinis excreted by thekidney[(2)].Human chorionicgonadotropin interacts with the LHCG receptor of the ovary and promotes the maintenance of corpus luteum during beginning of

Corresponding author :
Dr. Marwa Hamood Jabir
E-mail: drnihadkhalawe@gmail.com

pregnancy. This allows the corpus luteum to secrete the hormone progesterone during the firsttrimester ,Because of its similarity to LH , hcG can be used clinicallyto induce ovulation in the ovaries as well as testosterone production in the testes. human chorionic gonadotropin also plays a role in the cellular differentiation. proliferation and may activate apoptosis [3] .

Table (1): Human chorionic gonadotrophin levels in weeks from the last normal menstrual period[4]:

LMP in weeks	levels of hCG
3 weeks LMP	5-50
4 weeks LMP	5-426 mIU/ml
5 weeks LMP	18-7,340 mIU/ml
6 weeks LMP	1,080- 56,500 mIU/ml
9-12 weeks LMP	25,700-288,000 mIU/ml
13-16 weeks LMP	13,300-254,000 mIU/ml
17-24 weeks LMP	4,060-165,400 mIU/ml
25-40 weeks LMP	3,640-117,000 mIU/ml
Women who are not pregnant	<5.0 mIU/ml
Women after menopause	9.5 mIU/ml

Maternal serum alpha-fetoprotein(AFP) is a glycoprotein of 591 aminoacids and it's a member of the albuminoid gene family [alpha- fetoprotein (AFP), albumin(ALB), alpha albumin (a-ALB), vitamin D binding protein (DBP)] . In adults AFP expression is often associated with atocellular cancer, non-germinomatous germ call tumors andgastrointestinal cancer , however AFP can be found in non-neoplastic conditions such as : hepatitis, cirrhosis and pregnancy [5].

Alpha-fetoprotein is normally produced in early pregnancy primarily by the fetal liver and yolk sac . It is also produced to a lesser extent by the fetal gastrointestinal tract as the yolk sac involutes at the 9th week of gestation, the fetal liver is the principal source of alpha-fetoprotein during development [6;7].

Measurement of alpha fetoprotein is generally used in two clinical contexts. First, its measured in the pregnant women through the analysis of maternal blood or amniotic fluid as a screening test for certain developmental abnormalities such as aneuploidy. Second ,serum level of AFP elevated in people with certain tumors , and so used as biomarker to follow these diseases [8].

There is association between elevated of human chorionic gonadotropin , alpha fetoprotein and some obstetrical conditions , like: Preeclampsia; Reduced fetal growth ;Preterm birth and Intrauterine death (still birth) .

Aim of study: To investigate the maternal serum determine whethote the relationship between gestational complications and high levels of serum human chorionic gonadotrophin and alpha- fetoprotein and to whether these markers are effective predictors to adverse pregnancyoutcomes.

Patients and Methods

Between 25 Janwomen who att Maternity and Pedi weeks were enroll and consent fourteen 25 January 2017-15 December 2017, a total of 230 pregnantattended obstetrics and gynecology department, AL-Diwaniyah . Materially andPediatrics Teaching Hospital, with a gestational weeks between 14-23enrolled in this study. All cases were informed about the screening test ant forms were obtained. The study protocol was approved

by the localethical committee.

The inclusion criteria were stated as follows:

1. Single live pregnancy.

2. Gestational age between 14-23 weeks and dating was based according to thelast menstrual period or early sonogram.

3. Regular antenatal follow-up.

The exclusion criteria were:

1. Discordant gestational age according to first trimester

2. Multiple pregnancy

3. Lack of antenatal follow-up

4. Feto-placental or congenital anomaly

5. Diabetes mellitus

6. Molar pregnancy

7. History of chronic hypertension, chronic renal disease, autoimmune disorder,thrombophilia, cardiovascular diseases and liver diseases or malignancies.

8. History of preeclampsia, IUGR, preterm labour.

After taking detailed history, general and obstetrical examination were done. Routine investigations, liver function tests, renal function tests and determination of maternal serum HCG (mIU/ml) and AFP (ng/ml), the samples are collected from patients.

Each patents draw about 2 cc blood sample and put it in 360 Automatedthese patients were followimmunoassay Analyzer (TOSOH AIA) for 20 minute and record the results. Allmis Were followed up till puerperium and the fetal outcome was reported.

The study was started with 230 pregnant, and 17 patients were excluded from the study, as 14 patients were lost to follow up, one patient developed gestational labetes mellitus, one patient had a fetus with congenital abnormality as vmphalocele) and one patient had given birth to a baby with Down's syndrome.

Statistical Analysis

Data analysis was carried out using SPSS (Statistical Program ofout using SPSS (Statistical Program of Social Sciences) ver. 32.0 SPSS. Continuous variables were expressedjous variables were expressed as mean and standard deviation, whereas percentages and frequencies werepercentages and frequencies were used for categorical variables. Groups were controlled in terms of conformity to normal distribution by graphical check and Shapiro Wilk test. Kruskall-Wallis variance analysis was performed for not normally distributing continuous variables and ANOVA was used for normally distributed continuous variables. Intergroup differences for categorical values were assessed with chi square test. Sensitivity, specificity, positive predictive value and negative predictive value were calculated together with risk estimation using Odds ratio. A p-value <0.05 was considered statistically significant.

Findings

Table (2): Demographic characteristics of the study groups.

Characteristic	Group 1 n = 172	Group 2 n = 19	Group 3 n =16	Group 4 n = 6	P
Age(years) mean±SD	27.80 ±6.09	26.16 ±7.17	25.69 ±3.74	31.50 ±6.98	0.154
Gestational age (weeks) mean±SD	19.05 ±2.88	17.11 ±3.36	19.38 ±2.33	20.17 ±3.06	0.027

Table (3): Laboratory data of the study groups.

Characteristic	Group 1 n = 172	Group 2 n = 19	Group 3 n =16	Group 4 n = 6	P
AFP(ng⁄ml)	28.82 ±11.92	91.53 ±15.72	47.50 ±18.38	100.83 ±9.17	<0.001
Beta-HCG(mIU⁄ml)	25.60 ±11.54	44.84 ±15.36	83.75 ±8.42	82.50 ±6.12	<0.001

Table (4): Multiple of the median expressed as mean and standard deviation for AFP and β-HCG

Characteristic	Group 1 n = 172	Group 2 n = 19	Group 3 n = 16	Group 4 n = 6	P
AFP	0.76 ±0.32	2.34 ±0.54	1.26 ±0.49	2.67 ±0.24	<0.001
BHCG	0.77 ±0.35	1.30 ±0.49	2.51 ±0.25	2.48 ±0.18	<0.001

Group1: Women with AFP MoM <2 and β-HCG MoM <2; Group2: Women with AFP MoM ≥2 and β-HCG MoM <2; Group3: Women with AFP MoM <2 and β-HCG MoM ≥2; Group3: Women with AFP MoM ≥2 and β-HCG MoM ≥2

Table (5):Pregnancy –related complications of the study groups.

Complication	Group 1 n = 172 n (%)	Group 2 n = 19 n (%)	Group 3 n =16 n (%)	Group 4 n = 6 n (%)	Total
PET	2 (1.2)	3 (15.8)	9 (56.3)	4 (66.7)	18 (8.5)
IUD	2 (1.2)	0 (0.0)	2 (12.5)	0 (0.0)	4 (1.9)
IUGR	1 (0.6)	1 (5.3)	3 (18.8)	0 (0.0)	5 (2.3)
PTL	4 (2.3)	8 (42.1)	0 (0.0)	0 (0.0)	12 (5.6)
Abruption	0 (0.0)	1 (5.3)	1 (6.3)	2 (33.3)	4 (1.9)

Table (6): The sensitivity , specificity and predictive rates of AFP and HCG levels for predicting pregnancy complications.

	-	+	Sensitivity	Specificity	PPV	NPV	OR	P
Group 1	9	163						
Group 2	13	6	61.9	96.4	68.4	94.8	39.24	<0.001
Group 3	15	1	62.5	99.4	93.8	94.8	271.67	<0.001
Group 4	6	0	40.0	100.0	100.0	94.8	223.74	<0.001

Discussion

The results of our research showed that in the second trimester unexplained high AFP and hCG rates have been found related to adverse pregnancy outcomes. Pregnancies in which both AFP and hCG rates increasing together are being more complicated with adverse pregnancy complications in a more serious manner than pregnancies in which rates increase one by one[9].

In a prospective study conducted by Genc Z., et al study (2005), showed that in the second trimester increased hCG rate was in relation with increased antenatal complications [10] .

In our study, the specificity of high(≥ 2.0) MOM of AFP and HCG for the development of antepartum complications in group 4 was 100% and sensitivity was 40%, with positive predictive value of 100%. For group 3, the specificity of isolated high HCG MOM (≥≥2.0) for the development of antepartum complications was 99.4% with sensitivity of 62.5% with positive predictive value of 93.8% . While forgroup 2, the specificity of isolated high AFP MOM (≥≥2.0) in the development of antepartum complications 96.4%, sensitivity of 61.9% with positive predictive value of 68.4%. In the absence of fetal chromosomal or structural anomalies, mid trimester AFP levels (above 2.5) MOM were associated with a defect in placentation (placental abruption and abnormal placental adherence. They also associated with increased risk for pregnancy complications including fetal death [OR 10.1 (95% CI: 7.5-13.5)], gestational hypertension [OR 1.6 (95% CI:1.3-2.1)], preterm delivery [OR 1.8 (95% CI 1.5-2.3)], preeclampsia [OR 0.83(95% CI: 0.44-1.56)] and IUGR[OR 2.37[11].

Hui D *et al .,* study (2012), showed that elevated mid trimester HCG levels have been associated with congenital abnormalities, placental dysfunction and adverse pregnancy outcome . However, In the absence of fetal chromosomal or structural anomalies, mid-trimester HCG (2.5 MOM) associated with an increased risk for pregnancy complications including: fetal loss [OR 2.2(95% CI: 1.33.0)),gestational hypertension [OR 1.4 (95% CI: 1.1-1.8)],preeclampsia [OR 1.19(95% CI: 0.88-1.61)] , IUGR [OR 1.3(95% CI: 0.9-1.7)],preterm delivery [OR 1.7 (95% CI: 1.4-2.1)] [12]

Extremely high mid-trimester HCG (> 10 MOM) imply a poor pregnancy outcome as shown by Lepage N, et al study (2003) [13].

In our research, the relationship with high AFP and/ or HCG levels and maternal complications have been found statistically significant (p= 0.001) & our sensitivity and positive predictive value were high.

Conclusions

As a result of our research, in the second trimester unexplained high nester unexplained high AFP and hCGrates have been found related to adverse maternal and perinatal outcomes. Pregnancies in which both AFP and hCG rates increasing together are being more complicated with adverse pregnancy outcome, and in a

more serious manner than pregnancies in which rates increased one by one.

Conflict of Interest : None

Source of Funding : Self

Ethical Clearance : From patients and my college .

References

1. Cole LA . Biological functions of hCG and hCG-related molecules.Reproduction Biology Endocrinology 2010; 8 : 102 .
2. The practice committee of American Society for reproductive meBirmingham, Alabama .November 2008.
3. HcG diet products are Illegal. FDA,FTC act to remove homeopathic , HcGweight loss products from market . FDA.December 6, 2011.
4. Guideline to HCG level during pregnancy. American pregnancy association.22August 2017.
5. Pucci P,Sicilino R, Malorni ,Marino G,Tecce mf ,Ceccarinic , Terrana B .May2001.
6. Jones EA, Clement-Jones M , James OF, et al. Differences between humanand mouse alpha-Fetoprotein expression during early development.. J Anat. 1 2001 ; 198(5): 555-559.
7. Ball D, Rose E, Alpert E, March 2002 AFP levels in normal adults.
8. Jassam N Jonescm ,Briscoe T ,Horner JH . July 2006.
9. Genc Z , Balta O, Eren S, etal .Elevated serum levels of human chorionicgonadotropin and alpha -fetoprotein predicting for development of severepreeclampsia. T kiln J gynecol. 2005; 4 : 305-310.
10. Dugoffl . first and second trimester maternal serum markers for aneuploidy andadverse obstetric outcome . Obstet. Gynecol. . 2010;115 (5):1052-1061.
11. Hui D, Okun N , Murphy K, etal. combinations of maternal serum markers topredict preeclampsia , small for gestational age and still birth. J obstet.
12. Robinson, GE (January 2014). " pregnancy loss". Best Practice and Research. Clinical obstetrics and gynecology. 28(1): 169-78.
13. Gynecol. 2012;34 (2):142-153. 59. Lepage N, chitayat D, kingdom J, etal. Association between second trimesterisolated high maternal serum hCG and obstetrical complications in singleton and twin pregnancies. Am J obstet. Gynecol. 2003; 188(5): 1354-1359.