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Diagnostic and prognostic significance of serum beta hCG level in various gestational trophoblastic diseases

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Abstract
Introduction: Gestational Trophoblastic Disease (GTD) is a term used for a group of pregnancy-related tumours. These consist of various tumours and tumour like lesions characterized by proliferation of trophoblastic tissue. Amongst GTD, hydatidiform moles are the most common form. These lesions sometimes may develop into invasive moles, or, in rare cases, into choriocarcinoma. Risk factors of GTD include extreme of reproductive age, multiparity, smoking, alcohol consumption, lower socioeconomic class etc.
Materials and Methods: The present study was descriptive, observational, analytical type done in Department of Pathology at M.P. Shah Medical College Jamnagar.
All cases clinically suspected of GTD were included and its correlation with serum beta hCG was studied. The cases of GTD were classified according to WHO classification. Estimation of serum beta hCG level was done by using Indirect Sandwich Enzyme Linked Immunosorbent Assay (ELISA).
Results: During study period of 1 year from October 2019 to September 2020, 150 sample received out of which 16 cases were diagnosed as GTD. Most of the cases were of hydatidiform moles, few cases of choriocarcinoma and Placental Site Trophoblastic Tumour (PSTT). The common clinical presentation was per vaginal bleeding and amenorrhea. In majority of cases beta hCG levels were between 50,000 to 100000 mIU/ml. The correlation between beta hCG level and GTD was done.
Conclusion: Pregnant females clinically presenting with abnormal vaginal bleeding must be evaluated for GTD. Histopathological examination and serum beta hCG level are helpful for confirmatory diagnosis. Follow up beta hCG level is very useful indicator to detect these lesions and its recurrences.

Keywords: Beta hCG, GTD, PSTT, choriocarcinoma

Introduction
Human chorionic (hCG) is a glycoprotein hormone, produced during pregnancy that is made by the developing embryo after conception and later by the syncytiotrophoblast (part of the placenta) [1, 2]. Some tumors produce this hormone; measurement of its elevated levels when the patient is not pregnant can lead to diagnosis of cancer. However, it is not known whether this production is a contributing cause or an effect of tumorigenesis. The pituitary analog of hCG, known as luteinizing hormone (LH), is produced in the pituitary gland of males and females of all ages [1, 3]. Since the mid-20th century, hCG has been promoted as a supplement to promote weight loss, though there has been no proof that it is effective or safe. Human chorionic gonadotropin is a glycoprotein composed of 244 amino acids with a molecular mass of 36.7 kDa [4]. It is heterodimeric, with an a (alpha) subunit identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid - stimulating hormone (TSH), and (beta) subunit that is unique to hCG. The alpha subunit is 92 amino acids long. The human a -subunit is encoded by a single gene localized on chromosome 6ql2.21. The sequence of the alpha unit can be found on UniProtKB with ID:P01215. The beta-subunit of hCG gonadotropin contains 145 amino acids, encoded by six highly-homologous genes that are arranged in tandem and inverted pairs on chromosome 19ql3.3 - CGB. The sequence of the beta unit can be found on UniProtKB with ID: P01233.GTD is a tumor of placenta, these placental cells make lot of B-hCG protein. B-hCG is secreted by syncytiotrophoblast cells of placenta and appear in patients serum. The hCG exert its activity by binding to distinct cell surface receptors and activating adenyl cyclase [5]. hCG stimulates decidualization of uterine stromal cells and prevents their premature apoptosis [6].

hCG acts on the uterine wall to maintain a receptive environment for implantation and development. The uterus contains high concentrations of LH/hCG receptors [8]. hCG prevents the expulsion of both the uterine lining and the developing offspring during the implantation process and decreases muscle contractility until the completion of the pregnancy [9]. The number of LH/hCG receptors in the myomerrium changes during the course of a pregnancy. The level of LH/hCG receptors declines during both term and pre-term labor, indicating that the myomerrium's reduced sensitivity to hCG is a major contributing factor to uterine contractions during labor [7]. hCG levels are linked to the severity of morning sickness in pregnant women [10]. hCG also plays a role in cellular differentiation and proliferation and may activate apoptosis [11]. GTD includes Hydatidiform mole (H. mole) which includes complete mole and Partial mole, Invasive H. mole, Gestational choriocarcinoma, Placental site trophoblastic tumour. Complete molar pregnancy is well recognized to have a risk of developing persistent gestational trophoblastic neoplasia (PTN). In our institute we receive patient's sample from gynecology and radiotherapy department and we do B–hCG of these patients. So, it is a non-invasive procedure and we can correlate it with other radiological and clinical findings.

Aims and Objectives

- To study diagnostic and prognostic significance of serum beta hCG level in different forms of gestational trophoblastic disease.
- To study incidence and prevalence of GTD.
- To establish correlation between the values of B- hCG and histopathological diagnosis.
- To study changes in the value of B-hCG after treatment and to study effectiveness of treatment.
- To use B-hCG values to study recurrence.

Methodology

Patient's serum was taken as sample. Estimation of serum beta hCG is done by using ELISA method which is Enzyme immunoassay for the quantitative determination of serum beta hCG.

Calbiotech–ELISA kit was used. Robonik wash well and read well- ELISA instrument were used. Study was done by Indirect Sandwich ELISA method.

Assay procedure

Take out contents in ELISA kit on to the suitable work table inside a temperature controlled room or lab. The given test sample under analysis is taken. A fixed volume of the test sample is drawn into micropipette and loaded into the wells of ELISA plate.

Samples are loaded into wells in such a way to accommodate a blank, standard, (if available) and test sample in wells of ELISA plates. Then incubation time is given. Then wash is given. This step removes unbound part of sample from wells that is only antigen remain fixed on walls of well in ELISA plates. Then fixed volume of enzyme linked antibody is placed into washed wells and allowed to stay for specified amount of time. This lets firm binding of enzyme linked antibodies with antigen if any fixed to the walls of the wells. Again rinse the wells with washing buffer to remove any unbound enzyme linked antibodies. Now load the washed wells with a specified amount of ELISA substrate and incubate for specified time for the reaction to proceed and generate colour. In the mean-time switch on the ELISA instrument or ELISA plate reader and set the defined wave length filter. Mark the sample locations on the plate wells on the computer screen that is blanks, standards and test samples position to avoid latter confusion. After the time of incubation, immediately place the plate into the socket of ELISA instrument, close the socket door and take the reading after detection. The reading can be had in a printout. Then used plate is discarded.

Study duration

Oct 2019-September 2020

Sample size

Total 150 samples of B-hCG were received out of which 17 cases were clinically diagnosed as GTD.

Results

Table 1: B hCG in various GTD

Value	<10,000 mIU/ml	10,000-100,000 mIU/ml	>100,000 mIU/ml
Complete H. mole	0	1 (11%)	8 (88%)
Partial H mole	0	6 (85%)	1 (15%)
Placental site nodule	-	-	-
Invasive mole	-	-	-
Choriocarcinoma	-	-	1 (100%)

Table 2: Parity and age in relation to trophoblastic disease

Parity	Age group (Years)	Complete mole	Partial mole	Chorio-carcinoma	Placental site nodule
Primipara	Less than 20	1	1	-	-
Para 2	21-22	1	1	-	-
Para 3	23-28	2	2	-	-
Para 4	29-32	3	2	1	-
Para 5	>33	2	1	-	-

Table 3: Symptomology of patient with GTD

Types of GTD	Bleeding per vagina	Amenorrhea in trimesters			Pain	Hyper emesis gravidum	Toxemia of pregnancy
		1st	2nd	3rd			
Complete H. mole	9	9	2	0	6	2	1
Partial H. mole	7	6	3	0	3	0	0
Placental site nodule	-	-	-	-	-	-	-
Invasive mole	-	-	-	-	-	-	-
Choriocarcinoma	1	1	1	-	-	1	-

Table 4: Height of uterus in relation to gestational age in case of H-mole

Height of uterus	Complete mole	Partial mole
Larger for the period of gestation	7 (77%)	1 (14.4%)
Corresponding to period of gestation	1 (11%)	3 (42.8%)
Smaller for the period of gestation	1 (11%)	3 (42.8%)

Table 5: B-hCG level – Post treatment follow up (n = 17)

Condition	Decrease	No significant decrease
Complete H. mole	9	2 (22%)
Partial H. mole	7	0
Choriocarcinoma	1	0

Discussion

Table 6: Comparative analysis of the age incidence of GTD

Age in years	Chhabra S *et al.* (1998) [12]	Paul MN *et al.* (1983) [13]	Sajjanshety *et al.* [14]	Present study
Less than 20	22.7%	-	22.35%	12%
20-30	64.0%	80.0%	52.94%	64%
30 and above	13.3%	20.0%	24.69%	24%

Table 7: Comparative analysis of gravida and GTD

Parity	Kalyani Kutty P and Nalini (1970) [15]	Sajjanshetty *et al.* (2005) [14]	Present study
Primi	29.33%	11.11%	15%
Para-2	20.78%	44.44%	15%
Para-3	20.77%	3.70%	24%
Para-4	16.92%	22.22%	30%
More than 4	12.32%	18.52%	16%

Table 8: Comparative study of symptomatology of patients with GTD

Symptomatology	Chhabra S *et al.* (1988) [12]	Sajjanshety *et al.* (2005) [14]	Present study
Bleeding per vagina	97.78%	100%	100%
Amenorrhea	84.44%	97.6%	88%
Pain abdomen	91.11%	69.4%	52%
Hyperemesis Gravidarum	17.78%	18.82%	17%
Toxemia of Pregnancy	6.67%	10.58%	6%

Table 9: Comparative analysis of the heights of uterus in complete H. mole

Height of the uterus	PGI Chandigarh (1989)	KGH Madras (1993)	Sajjanshetty *et al.* (2005) [14]	Present study
Larger for period of amenorrhea	68.8%	53.84%	62.5%	77%
Corresponding to the period of amenorrhea	14.6%	27.7%	31.2%	11%
Smaller for period of amenorrhea	16.6%	18.46%	6.2%	11%

Table 10: Comparative analysis of the heights of uterus in partial H. mole

Height of the uterus	Szulman AE, U (1982) [16]	Sajjanshetty *et al.* (2005) [14]	Present study
Larger for period of amenorrhea	11.00%	9.00%	14.4%
Corresponding to the period of amenorrhea	24.00%	36.30%	42.8%
Smaller for period of amenorrhea	65.00%	54.5%	42.8%

Table 11: Comparative analysis of incidence of B-hCG level in H. mole

Various workers	H. mole	<1,00,000	>1,00,000
Ross S Berkowitz (2000)	Complete	54%	46%
	Partial	94%	6%
Mongkol Benjapibal *et al.* (2000)	Complete	59%	41%
	Partial	-	-
Present study	Complete	11%	88%
	Partial	85%	15%

Summary

Findings suggest that elevation of B-hCG value is more and marked in complete mole than partial mole. Most common complain was bleeding per vagina followed by amennorrhoea and pain in abdomen. Most common age group of presentation was 20-30 yrs. In complete mole height of uterus was found to be larger than period of gestation while in partial mole it was either corresponding or smaller than period of gestation. All cases showed decrease in value in post treatment follow up except 2 which was diagnosed as having persistent trophoblastic disease.

Conclusion

Normal values in adult are < 5mIU/ml, value > 5mIU/ml is considered elevated.

B-hCG value although has definitive diagnostic value, it is not to be used as sole diagnostic measure and supportive measure and supportive investigations like clinical presentation, radiological investigations and other laboratory tests should be used in conjunction with B-hCG value to avoid wrong diagnosis. ELISA is rapid, sensitive, reliable and cost effective test for measurement of B-hCG. Pre and post therapeutic level is useful in monitoring of GTD. Persistence or elevation after treatment indicates residual disease or recurrence or dissemination. Thus we can say that serum B-hCG is a diagnostic and prognostic measure for GTD while histopathological findings remains the confirmative diagnostic modality. H. Mole is commenest GTD.

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