Human Chorionic Gonadotropin (hCG) Testing in Specimens of Tumor and Myometrial Tissues During Surgical Treatment of Gestational Trophoblastic Tumors

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Abstract: *Background*: Gestational trophoblastic tumors originate from trophoblastic tissues and secrete human chorionic gonadotrophin (hCG). Surgical treatment may be a line of treatment of chemoresistant cases.

Objective: To evaluate the accuracy of hCG dipsticks in detection of hCG in tissues of trophoblastic tumors and healthy myometrium during surgery of trophoblastic tumors.

Methods: We included 19 samples of tumor and apparently healthy myometrial tissues during surgical treatment of 5 cases of gestational trophoblastic tumors. The hCG dipstick was immersed in a solution containing 1x1 cm of tumor or myometrial tissues. The results of the tests were compared to the histopathological results.

Results: The mean age of patients were 38.8 years, the mean parity was 3.4. The mean serum B-hCG level was 101,745.6 mu/ml. Except for one specimen in case 5, all results of the hCG dipsticks were concordant with final histopathologic analysis of the specimens. Sensitivity of hCG test was 100% and specificity was 90%.

Conclusion: Intraoperative detection of hCG in different tissues and suspicious masses can be considered as simple, rapid, inexpensive, and reliable test. It can be used to detect the trophoblastic nature of tissues if frozen section is not available as some low resource setting countries. We recommend further larger prospective studies to compare the accuracy and reliability of this novel technique and frozen section analysis.

Keywords: Trophoblatic tumors, surgery, hCG test.

INTRODUCTION

Gestational trophoblastic diseases (GTD) defines a heterogeneous group of interrelated lesions arising from the trophoblastic epithelium of the placenta.They include hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumors [1]. There is worldwide geographic variation in incidence of GTD. The incidence of molar pregnancy in southeast Asia was reported to be 1-12 per 1000 pregnancies which is 7-10 times higher than that in Europe or North America where it was reported to be 0.5-1 per 1000 pregnancies [2-4]. In Africa, Moodley and colleagues reported that the incidence of GTN was 0.5 /1000 deliveries in South Africa [5].

All forms of GTD are characterized by a distinct tumor marker, the beta subunit of human chorionic gonadotropin (hCG) [6]. HCG has 3 independent molecules with different functions, regular hCG, hyperglycosylated hCG and hyperglycosylated free β hCG [7]. In 1967 the hCG radioimmunoassay was introduced and led to the development of commercial hCG tests. Serum and urine hCG testing became a part of the evaluation of every pregnancy nowdays [8]. In 1973 the hCG β-subunit radioimmunoassay was introduced, detecting hCG through its specific β-subunit [9].

Frozen section analysis of uterine tumors and myometrial tissues was mentioned by many authors [10,11] who reported its reliability to predict final histopathological results. Turan *et al.* [12], reported that myometrial invasion was assessed accurately by frozen section in 78.5% of patients with no myometrial invasion and in 90.5% and 95.3% of patients with myometrial invasion <1/2 and ≥1/2, respectively. The agreement of intraoperative frozen section and postoperative determination of myometrial invasion in cases of endometrial carcinoma was found in 85.4% of patients. However their study did not include cases of gestational trophoblastic neoplasia.

However, in some low resource setting countries, frozen section may be not available due to limited resources. So, we conducted this prospective study to compare the accuracy of myometrial hCG testing in relation to the final histopathological results of the

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cases of gestational trophoblastic tumors. To the best of our knowledge; there are no published articles to study this technique.

PATIENTS AND METHODS

The study was performed in the department of Obstetrics and Gynecology and department of Pathology during the period January, 2014 to end of December, 2014.We included 19 samples of tumor and apparently healthy myometrial tissues during surgical treatment of 5 cases of gestational trophoblastic tumors, four cases underwent hysterectomy and one case requested to preserve her fertility with local myometrial resection. The decision of performing surgical treatment was issued by the tumor board after counselling with the patients and their husbands.

After performing hysterectomy (the first 4 cases), the uterus was bisected and 4 specimens were taken; 2 specimens of tumor tissues 1x1 cm each and 2 specimens of the apparently healthy myometrium were immersed in 10 ml saline for 2 minutes and shacked well. A commercially available urine dipstick pregnancy test (B.B HCG check strip, manufactured by Nantong Egens Biotechnology Co. Ltd, China) was inserted in the solution. According to the product instructions; the test was considered positive when both test and control marks appear on the dipstick and negative when only the control mark appears. The test can detect hCG concentration of 25 mu/ml or more of a fluid.

During surgery of the case of local myometrial resection, the test was done on an immersed specimen of tumor tissue then was repeated 4 times using myometrial tissues from the margin of the lesion; the test was gradually fainted. We excised more myometrial tissues till the test turned negative all over the specimens from the margin. All specimens from tumor and myometrial tissues as well as the whole uterus were marked and sent for histopathological examination as a gold standard.

RESULTS

The patients preoperative data were concluded in Table **1**, as can be seen from the table; the mean age of patients were 38.8 years (range: 29-47 years), the mean parity was 3.4 (range: 1-6). The mean serum B-hCG level was 101,745.6 mu/ml (range: 1328-480,000).

Two cases underwent hysterectomy after failure of first line (Methotrxate) and second lines of chemotherapy (EMA/CO protocol). One case had metastatic GTN to the liver, and was adviced by the tumor board to receive combination chemotherapy together with performing hysterectomy.The fourth case diagnosed as choriocarcinoma through uterine biopsy and the tumor was limited to uterus. The last case had also chemoresistant GTN with a local myometrial lesion; the patient requested to preserve her fertility and local myometrial resection was performed.

The results of the intraoperative tissue hCG tests were compared to the final histopathological examination in Table **2** and Figures **1-3**. Except for one specimen in case 5, all results of the hCG dipsticks were concordant with final histopathologic analysis of the specimens.The accuracy of dipstick hCG test in relation to the final histopathology test was demonstrated in Table **3**. As can be seen from the table; sensitivity of hCG test was 100% and specificity was 90%.

DISCUSSION

Most of cases of choriocarcinoma occur in patients aged below 35 years and difficult to diagnose in women above reproductive age due to its very low incidence [13]. The detection of trophoblastic nature of the tissues help the surgeon to take the proper decision during surgery especially for determination of the safety margin during local resection of GTN lesion for uterine or extrauterine lesions.

Table 1: Preoperative Data of the Studied Cases

	Age	Parity	Indication	Uterine lesion	Pre-hCG*
Case 1	43 years	5	Metastatic GTN	Intramyometrial mass 4x3 cm	11,200
Case 2	44 years	6	Chemoresistant GTN	2 masses, fundal 3x3cm and cervical 2x1cm	1,328
Case 3	31 years	1	Chemoresistant GTN, invasive mole	fundal mass 4x2cm	4,600
Case 4	47 years	4	Choriocarcinoma	6x5 cm mass in cavity of uterus	480,000
Case 5	29 years	1	Chemoresistant GTN	fundal mass 4x2cm	11,600

Pre-hCG*: pre-operative hCG (mu/ml).

Table 2: Concordance between Tissue hCG Test and Histopathological Results

	Surgical interference	Site of specimen	Tissue hCG test	Histopathology
Case 1	TAH,BSO*			
Specimen 1		Tumor	Positive	Choriocarcinoma
Specimen 2		Tumor	Positive	Choriocarcinoma
Specimen 3		Myometrium	Negative	Myometrium
Specimen 4		Myometrium	Negative	Myometrium
Case 2	TAH,BSO*			
Specimen 1		Tumor	Positive	Choriocarcinoma
Specimen 2		Tumor	Positive	Choriocarcinoma
Specimen 3		Myometrium	Negative	Myometrium
Specimen 4		Myometrium	Negative	Myometrium
Case 3	TAH,BSO*			
Specimen 1		Tumor	Positive	Invasive mole
Specimen 2		Tumor	Positive	Invasive mole
Specimen 3		Myometrium	Negative	Myometrium
Specimen 4		Myometrium	Negative	Myometrium
Case 4	TAH,BSO*			
Specimen 1		Tumor	Positive	Choriocarcinoma
Specimen 2		Myometrium	Negative	Myometrium
Case 5	Local uterine resection			
Specimen 1		Tumor	Positive	Choriocarcinoma
Specimen 2		Margin(1/2cm)	Positive	Choriocarcinoma
Specimen 3		Margin(1cm)	Positive#	Myometrium
Specimen 4		Margin (1cm)	Negative	Myometrium
Specimen 5		Margin (2cm)	Negative	Myometrium

TAH,BSO*: Total abdominal hysterectomy and bilateral salpingo-oophorectomy.
Positive#: the test was weak positive.

Figure 1: The hCG dipstick was inserted in saline containing small strips of the tumor tissues (sample 1, case 2) and the test is positive.

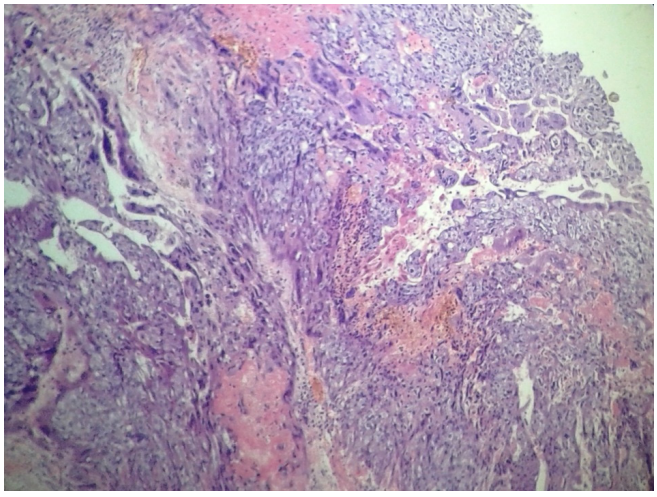

Figure 2: Histopathology of the previous tumor specimen of (sample 1, case 2) revealed choriocarcinoma. The slide was stained with H&E stain.

Gestational trophoblastic neoplasms are chemosensitive tumors [1] however, chemoresistance occur in 10-15% of cases [14]. Surgical treatment may be a line of treatment of such cases. Doll *et al.* and Huang *et al.* [15,16] recommended performing

hysterectomy after failure of chemotherapy. Local myometrial resection of a focal uterine lesion was suggested by some authors [17,18] for cases of chemoresistant GTN who requested to preserve their fertility.

Figure 3: The hCG dipstick was inserted in saline containing small strips of the myometrium (sample 3, case 2) and the test is negative.

Table 3: Sensitivity and Specificity of Dipstick hCG Test

	Histopathology positive	Histopathology negative	Total
Dipstick positive	9 (true positive)	1(false positive)	10
Dipstick negative	0 (false negative)	9 (true negative)	9
Total	9	10	19 specimens

Sensitivity: 100 %.
Specificity: 90 %.

The result of hCG dipsticks was comparable to the final histopathological results. Only one case; the specimen was taken from myometrium at 1 cm of tumor margin.The result of the test was weak positive while final histopathology showed normal myometrium. The explination may be due to diffusion of the secreted hCG by tumor to the surrounding myometrium without tissue invasion by the trophoblastic tumor.

The suggested test may be helpful in situations where the surgeon is confronted with a metastatic mass or masses suggestive to be trophoblastic in nature, while serum B-hCG was not done preoperatively. Mukherjee *et al.* [19] reported a case which documents an unusual site of skeletal metastasis of choriocarcinoma and advises caution during diagnosis and management of various anterior abdominal wall swellings.

To the best of our knowledge; detection of hCG in different tissues during surgery of GTN lesions was not mentioned in any previous publication. We have to clarify that the suggested test is not a substitute of frozen section; but may be used in a situation where frozen section is not available. The limitations of our study included limited number of cases and absence of comparison between results of frozen section analysis and results of hCG test in tissues.

CONCLUSION

Intraoperative detection of hCG in different tissues and suspicious masses can be considered as simple, rapid, inexpensive, and reliable test. It can be used to detect the trophoblastic nature of tissues if frozen section is not available as some low resource setting countries. We recommend further larger prospective studies to compare the accuracy and reliability of this novel technique and frozen section analysis.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interests with the contents of this manuscript.

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