Quantitative Urine hCG and Urine Pregnancy Test in Gestational Trophoblastic Disease Patients with Low hCG Titer

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Objective: To study the correlation between serum and urine hCG levels in gestational trophoblastic disease (GTD) patients with low hCG level. The correlation between serum hCG and results from urine pregnancy tests are evaluated along with quantitative measurement.

Material and Method: In this prospective study, 86 cases of gestational trophoblastic disease patients with positive and low level of serum hCG (<100 mIU/ml) were recruited. Quantitative serum hCG, urine hCG and urine pregnancy test were performed. The correlation coefficients between serum and urine hCG were then analyzed by SPSS 16.0. Furthermore, the levels of serum hCG were compared to the results of the urine pregnancy test.

Results: From February 2006 to June 2008, 86 cases were recruited for this study. The correlation coefficient between serum and urine hCG levels in all cases was 0.44 (using Pearson correlation), p = 0.01. In subgroup analysis, the correlation coefficient between serum and urine hCG levels in chemosensitive gestational trophoblastic neoplasia (GTN) patients (n = 27) was 0.73, p<0.01. The correlation coefficient in chemoresistant GTN patients (n = 38) was 0.29, p = 0.07; and the correlation coefficient in hydatidiform mole patients (n = 21) was 0.47, p = 0.03. A urine pregnancy test was positive only in 10 of 86 specimens.

Conclusion: The correlation coefficient between serum and urine hCG in GTD patients with low hCG level showed significant correlation. However, patients with chemoresistance had less correlation than those with chemosensitivity and hydatidiform mole. Urine pregnancy test had low correlation with urine hCG and was not useful in this group of patients.

Keywords: Gestational trophoblastic disease, Urine hCG, Human chorionic gonadotropin

Gestational trophoblastic disease (GTD) is a group of diseases caused by abnormal proliferation of trophoblastic cells. This group of diseases can express either benign or malignant manifestations. The incidence of this disease varies worldwide, and seems to be higher in Asian countries. The incidence of hydatidiform mole is 1 in 450 delivery cases at King Chulalongkorn Memorial Hospital, Bangkok, Thailand[1]. Approximately 15-20% of hydatidiform mole cases will turn into a malignant manifestation, which is defined as postmolar gestational trophoblastic neoplasia (postmolar GTN)[2-5]. Gestational trophoblastic neoplasia (GTN) is a fatal disease that can occur following any form of pregnancy. However, it is a highly chemosensitive cancer for which the remission rate is over 80% even in distant metastasis cases[6].

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced from the trophoblast. This hormone plays a major role in the management of GTD. In hydatidiform mole, after evacuation of the molar tissue, serial hCG titer is crucial for monitoring the occurrence of post molar GTN. The diagnosis of this condition is based on FIGO 2000 criteria, according to serial hCG levels[2]. Furthermore, the diagnosis of GTN is made by clinical findings along with the hCG titer. This malignant condition is an exceptional cancer, in that the diagnosis can be made without histologic confirmation. Therefore, the hCG test is an important tool in the management of GTD. The quality of the hCG test needs to be highly sensitive and specific for this
tumor.

In clinical practice, serial hCG levels in GTD patients are obtained from serum. However, many studies have shown that serum hCG and urine hCG are correlated in linear fashion\(^9\)-\(^{10}\); therefore, some trophoblastic centers use urine hCG titer for follow-up of GTD cases because urine is easier to collect. Furthermore, some rural areas in Thailand have no hCG testing available, even in the hospital. Urine pregnancy tests or point-of-care hCG devices are only used in some hospitals. The authors questioned whether the urine hCG level or urine pregnancy test is useful in GTD patients, especially in neoplasia cases.

**Objective**

The present study aimed to determine the correlation between the levels of serum and urine hCG in low titers, which represent the follow-up patients, and to investigate the results of urine pregnancy tests in the same situation.

**Material and Method**

This prospective study was conducted from February 2006 to June 2008. Gestational trophoblastic disease patients at King Chulalongkorn Memorial Hospital with serum hCG level >5 but <100 mIU/ml were enrolled in the study. Patients with renal disease or urinary tract infection were excluded. Serum hCG was routinely followed-up every two weeks for monitoring after treatment of hydatidiform mole or GTN. After giving informed consent, urine specimens were collected at the time that blood was drawn. A urine pregnancy test was done and interpreted by the investigator, then both serum and urine specimens were sent for hCG quantitative assay. The present study used Roche Elecsys® hCG+β for automated total hCG quantitative assay and WH Accu Test (WHPM Bioresearch & Technology Co, Ltd) as a qualitative point-of-care device or home urine pregnancy test. Correlation coefficients of hCG levels in the serum and urine were analyzed by Pearson’s correlation coefficient. The results from urine pregnancy tests were compared to the hCG level in the urine specimens. Other clinical data were analyzed by using descriptive statistics. Statistical analysis was performed by SPSS software for Windows version 16.0 (SPSS Inc., Chicago, IL), and statistical significance was set at \(p\)-values of less than 0.01.

**Results**

After IRB approval, 86 paired specimens from patients with gestational trophoblastic disease and positive serum hCG titer but less than 100 mIU/ml were recruited. Twenty-one of these paired specimens were classified as hydatidiform mole. Sixty-five paired samples were classified as gestational trophoblastic neoplasia; of these, 38 pairs of the samples were from patients who responded well to treatment with chemotherapy (chemosensitive) and 27 from patients with disease refractory to chemotherapy (chemoresistant). The hCG data in each groups are shown in Table 1.

**Correlation between serum and urine hCG titer**

The titers of serum hCG and urine hCG in each case were compared, and the distribution of the correlation shown. The correlation coefficients of all paired specimens were \(r = 0.44\) (\(p<0.01\)). After being classified into GTD subgroups, the correlation coefficient of the patients with hydatidiform mole was \(r = 0.47\) (\(p = 0.03\)). The correlation coefficients of patients with chemosensitive and chemoresistant were 0.73 (\(p<0.01\)) and 0.29 (\(p = 0.07\)), respectively. The scatter grams of correlation between the serum and urine hCG were demonstrated in Fig. 1-4.

**Correlations among serum hCG, urine hCG and urine pregnancy tests**

Among the 86-paired specimens, only 10 (11.6%) positive urine pregnancy tests were found. The levels of serum hCG in this group ranged from 20-78 mIU/ml. All 10 cases were classified as malignant GTN; eight of them were chemosensitive. The clinical data are shown in Table 2.

**Discussion**

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced from the trophoblast. Determination of hCG concentrations in the serum and urine is widely used to detect pregnancy and pregnancy related disorders. This hormone can be developed from trophoblastic tumors and some germ cell tumors\(^{11}\). In gestational trophoblastic disease, hCG measurement is utilized as sensitive tumor marker. Serial monitoring of hCG levels in this disease has been widely used for diagnosis of postmolar GTN as well as for determining the success after chemotherapy treatment in GTN patients\(^{2,12,14}\). Quantitative urine hCG may be preferable
Table 1. hCG data according to GTD subgroup classification

<table>
<thead>
<tr>
<th>GTD classification</th>
<th>Serum hCG titer (mIU/ml)</th>
<th>Urine hCG titer (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GTD (n = 86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>31.1</td>
<td>23.7</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>24.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Median</td>
<td>22.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Range</td>
<td>3.5-93.8</td>
<td>0-155.8</td>
</tr>
<tr>
<td>Hydatidiform mole (n = 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>33.1</td>
<td>21.7</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>26.1</td>
<td>26.8</td>
</tr>
<tr>
<td>Median</td>
<td>26.9</td>
<td>10.6</td>
</tr>
<tr>
<td>Range</td>
<td>3.5-93.8</td>
<td>0-102.8</td>
</tr>
<tr>
<td>Chemosensitive (n = 38)</td>
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</tr>
<tr>
<td>Mean</td>
<td>34.7</td>
<td>31.9</td>
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<tr>
<td>Standard deviation</td>
<td>23.9</td>
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<tr>
<td>Median</td>
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<td>Range</td>
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<td>Chemoresistant (n = 27)</td>
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<tr>
<td>Standard deviation</td>
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<td>15.7</td>
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<tr>
<td>Range</td>
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<td>0-68.8</td>
</tr>
</tbody>
</table>

Fig. 1 Correlation coefficients between serum and urine hCG in total 86 cases \( r = 0.44 \) \( (p<0.01) \).

Fig. 2 The correlation coefficient between serum and urine hCG in hydatidiform mole \( (n = 21) \) \( r = 0.47 \) \( (p = 0.03) \).

to serum hCG level because the collection of urine specimens is more convenient and non-invasive. Many studies have demonstrated the correlation between serum and urine hCG\(^7\text{--}10\text{,}15\). In the UK, the Gestational Trophoblastic Disease Centres use urine hCG for follow-up of patients with GTD, who mail the specimens by post\(^16\text{,}17\). In the present study, we found a significant correlation coefficient between the quantities of serum and urine hCG \( (r = 0.44, p<0.01) \). However, the correlation coefficient was less than that of a previous study\(^10\). The explanation for this finding is probably that we focused only on patients with low hCG levels.

However, hCG is produced in trophoblastic disease and appears in heterogeneous molecules\(^18\). Both serum and urine quantitative immunoassays differ in which fragments of hCG they detect and this may lead to different results\(^15\text{,}19\text{,}20\). It should be recognized
that commercial assays detect hCG in variable degrees; some with overestimation while others the opposite. In urine specimens, the hCG beta core, fragment subunit widely predominates\(^{(20-22)}\). The ability of an assay to detect hCG beta core fragment is necessary if urine hCG is analyzed\(^{(17)}\). From our results, low hCG level had a lower correlation coefficient compared to higher hCG levels in other studies\(^{(10)}\). The authors thereby recommend not to use quantitative urine hCG during treatment because the sensitivity in low hCG level may not be accurate; however, the urine hCG level may be applicable for monitoring in remission cases.

In the present study, urine pregnancy testing was done using WH Accu Test (WHPM Bioresearch & Technology Co, Ltd), which has been claimed to have a lower limit of hCG detection of 25 mIU/ml. However, our outcomes showed positive testing in some specimens in which hCG level was less than the lower limit of the test, and many negative test results from specimens in which hCG level was higher than 25 mIU/ml. Several reports showed that heterogeneous fragments of hCG in urine could lead to misinterpretation of the results\(^{(20,21,23-25)}\). In Thailand, especially in remote areas, hCG quantitative assays are not available; hence, urine pregnancy tests are occasionally used for monitoring GTD patients. Nonetheless, the results from our study confirmed that urine pregnancy testing is not appropriate for following-up this disease.

In conclusion, there was a significant correlation coefficient between serum and urine hCG in GTD patients with low hCG level; however, patients with chemoresistance had less correlation than those with chemosensitivity and hydatidiform mole. Urine pregnancy testing had a low correlation with urine hCG and was not useful in this group of patients.
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Potential conflicts of interest
None.

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