Clinical Chemistry / Serum Pregnancy Tests

Should the Qualitative Serum Pregnancy Test Be Considered Obsolete?

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Key Words: Pregnancy test; Human chorionic gonadotropin; Turnaround time; Qualitative test; Quantitative test

Abstract

Qualitative and quantitative serum human chorionic gonadotropin (hCG) tests are used to diagnose pregnancy. We assessed physicians’ perceptions and compared turnaround times (TATs) and performance characteristics of both tests.

We surveyed 1,058 physicians about their perceptions of hCG tests. Seven months of TAT data were analyzed. hCG was measured in all qualitative samples. Pregnancy status was determined by chart review.

Of the physicians surveyed, 183 responded. Forty-nine percent preferred qualitative over quantitative serum tests for determining pregnancy status. Physicians were willing to wait 45 minutes for results from either test. Qualitative tests are performed faster than quantitative tests, but TATs were not significantly different when sample transport time was considered.

The negative predictive value of both tests was 99.9%.

Qualitative serum hCG testing could be replaced by quantitative hCG tests, but there is no clear advantage to doing so.

Rapid testing for the qualitative detection of human chorionic gonadotropin (hCG) in urine or serum using point-of-care (POC) test devices is frequently performed in health care settings to identify a possible pregnancy. Qualitative urine hCG tests are attractive because the urine sample requires no special processing and the tests are granted waived status by the Clinical Laboratory Improvement Amendments (CLIA). As such, testing can truly be performed at the POC by any health care provider. In contrast, qualitative serum hCG tests are categorized by CLIA as moderately complex because they require the collection of a whole blood specimen that must be centrifuged before testing to obtain the serum sample.

The need to perform qualitative hCG testing in serum has been questioned for several reasons.1 First, owing to the sample type, testing cannot be performed at the POC. Second, clinical laboratories are often able to perform quantitative serum hCG tests that have relatively short analytic times (10-20 minutes). Third, quantitative hCG tests can measure hCG at a concentration lower than the detection thresholds claimed by qualitative tests (~1 vs 10-25 IU/L, respectively). Fourth, because the only clinical use of a qualitative serum hCG test is to detect (or rule out) a possible pregnancy, it can be argued that the most analytically sensitive test available (ie, quantitative) should be used.

The limited clinical application of qualitative serum hCG tests, their relatively low claimed analytic sensitivity, and their inapplicability at the POC led us to question the need for these tests when quantitative serum hCG tests are readily available. Our hypothesis was that clinicians order qualitative serum hCG tests based on their perception that these tests have a shorter turnaround time (TAT) than quantitative tests.
and their limited understanding of the analytic performance of both types of serum hCG tests.

The objectives of this study were to compare the TAT and performance characteristics of both types of tests with clinician’s perceptions. These data would then be used to determine if the qualitative serum hCG test could be replaced with a quantitative test and still fulfill clinicians’ expectations.

Materials and Methods

Physician Survey

We invited, via e-mail, 1,058 physicians across all clinical departments at the University of Utah Health Sciences Center, Salt Lake City, to take a Web-based survey about their perceptions of and expectations for hCG tests. Partially completed surveys were not included in data analysis. Approval to administer the survey was provided by the University of Utah Institutional Review Board. The Fisher exact test or the Mann-Whitney test were used to identify associations between physicians’ preferences for qualitative or quantitative serum hCG tests and their impressions about the accuracy of results from both types of tests.

Study Samples

Serum samples sent to the University of Utah Health Sciences Center laboratory for physician-ordered qualitative serum hCG testing between March 25 and October 31, 2010, were used for this study. Aliquots of these samples obtained from women 18 years or older were stored at −20°C for up to 4 weeks before quantitative hCG testing. Samples were excluded if they were obtained from men of any age or from women younger than 18 years, if they lacked sufficient volume to perform a quantitative hCG test, or if they were hemolyzed, lipemic, or icteric.

Medical chart review was performed to determine pregnancy status on all patients with samples that were reported as qualitatively positive and patients with an hCG concentration of more than 5 IU/L regardless of the result of the qualitative test. Qualitative results that were reported as negative in conjunction with an hCG concentration ≤5 IU/L were recorded as 0.9 IU/L for data analysis.

To evaluate concordance across different brands of qualitative devices, qualitative serum hCG tests were repeated on a subset of 50 samples that included 36 that were reported as positive (34 with an hCG concentration >5 IU/L and 2 with an hCG concentration ≤5 IU/L) and 14 that were reported as negative (8 with an hCG concentration >5 IU/L and 6 with an hCG concentration ≤5 IU/L). These tests were performed by one of us (L.V.F. or D.G.G.) blinded to the reported qualitative test result and the hCG concentration. With the exceptions noted subsequently, each of these samples was tested with the following devices: the Icon 25 hCG test (Beckman Coulter; claimed detection threshold, 25 IU/L); the OSOM hCG Combo Test (Genzyme Diagnostics, Framingham, MA; claimed detection threshold, 10 IU/L); the SP Brand Rapid Test hCG Combo (Cardinal Health, McGraw Park, IL; claimed detection threshold, 10 IU/L); and the Sure-Vue Serum/Urine hCG-STAT test (Fisher HealthCare, Houston, TX; claimed detection threshold, 10 IU/L). These devices detect all clinically important serum hCG variants.2

In the laboratory, and the time the qualitative hCG result was reported. The same data were obtained for all quantitative serum hCG tests performed in the laboratory from March 25 to October 31, 2010.

The total TAT (TATtotal) was defined as the interval between sample collection and result reporting. The laboratory TAT (TATlab) was defined as the interval between the sample being received in the laboratory and result reporting.

Qualitative test TAT data were excluded for samples with a TATlab that was less than 5 minutes because that is the minimum time required to perform the test. Similarly, quantitative test TAT data were excluded for samples with a TATlab that was less than 20 minutes. TAT data were also excluded for either type of test if the TATlab or TATtotal exceeded 24 hours or if either test was added on to a previously obtained sample.

The Mann-Whitney test was used to compare the TAT distributions.

hCG Assays

Qualitative serum hCG tests were performed with the QuickVue One-Step hCG Combo test (Quidel, San Diego, CA). This test has an hCG detection threshold of 25 IU/L (manufacturer’s claim) and detects all clinically important serum hCG variants.2 Quantitative serum hCG testing was performed with the Total βhCG assay on a UniCel DxI 800 instrument (Beckman Coulter, Fullerton, CA), which also detects all clinically important serum hCG variants.3 Our laboratory has determined the analytic sensitivity of this assay to be 1.0 IU/L. Results reported by the instrument as less than 1.0 IU/L were recorded as 0.9 IU/L for data analysis.

To evaluate concordance across different brands of qualitative devices, qualitative serum hCG tests were repeated on a subset of 50 samples that included 36 that were reported as positive (34 with an hCG concentration >5 IU/L and 2 with an hCG concentration ≤5 IU/L) and 14 that were reported as negative (8 with an hCG concentration >5 IU/L and 6 with an hCG concentration ≤5 IU/L). These tests were performed by one of us (L.V.F. or D.G.G.) blinded to the reported qualitative test result and the hCG concentration. With the exceptions noted subsequently, each of these samples was tested with the following devices: the Icon 25 hCG test (Beckman Coulter; claimed detection threshold, 25 IU/L); the OSOM hCG Combo Test (Genzyme Diagnostics, Framingham, MA; claimed detection threshold, 10 IU/L); the SP Brand Rapid Test hCG Combo (Cardinal Health, McGraw Park, IL; claimed detection threshold, 10 IU/L); and the Sure-Vue Serum/Urine hCG-STAT test (Fisher HealthCare, Houston, TX; claimed detection threshold, 10 IU/L). These devices detect all clinically important serum hCG variants.2

Five samples had sufficient volume for repeat testing with 3 of the 4 different devices, and 1 sample had enough volume for repeat testing with only 2 different devices.
Results

Physician Survey

Of the 1,058 physicians invited to take the survey, 231 completed it (21.8% response rate). Of the 231 physicians, 48 indicated that they did not order hCG tests in clinical practice, and their responses were excluded, leaving 183 (17.3%) from whom responses were analyzed.

The clinical departments with a 5% or greater response rate were family medicine (5%), radiology (5%), psychiatry (7%), obstetrics and gynecology (9%), anesthesiology (10%), internal medicine (13%), and pediatrics (23%). These 7 departments accounted for 72% of the responses.

When asked what sample type they most often used to determine the pregnancy status of a patient, 75% and 25% indicated urine and serum, respectively. When using a serum sample for that same purpose, 49% indicated they preferred to order a qualitative hCG test, while 31% preferred a quantitative test. Of respondents who were able to rate the accuracy of both types of tests (n = 148), 98% and 99% indicated that qualitative and quantitative serum hCG tests, respectively, had good to excellent accuracy for determining pregnancy status (P = 1.0). However, 59% of physicians considered quantitative hCG tests to have excellent accuracy, which was significantly (P < .0001) lower than the approximately 80% who rated quantitative serum hCG tests the same way. Forty-nine percent considered qualitative urine hCG tests to have excellent accuracy.

If pregnancy status needed to be known with a high degree of certainty, 59% and 25% of physicians would order a quantitative and qualitative serum hCG test, respectively (P < .0001). Sixteen percent would order a qualitative urine hCG test.

It was the perception of physicians that results of quantitative serum hCG tests took longer than qualitative serum test results to be received. Seventy-six percent and 48% reported waiting more than 60 minutes to receive the results of quantitative and qualitative serum hCG tests, respectively (P = .001).

Physicians were asked the maximum amount of time that they were willing to wait for the results of an hCG test after ordering to determine pregnancy status. Responses revealed no significant differences in wait times between qualitative and quantitative tests at up to 15 minutes (~100% vs ~100%; P = 1.0), 30 minutes (~97% vs ~92%; P = .06), or 45 minutes (~88% vs ~80%; P = .05). There were significant differences in maximum wait times between qualitative and quantitative tests at up to 60 minutes (~79% vs ~68%; P = .03) and 90 minutes (~58% vs ~45%; P = .02).

Comparison of Analytic Sensitivities

Of the 740 samples with qualitative hCG results, 698 (94.3%) were reported with a result of “negative” and 41 (5.5%) as “positive.” One sample was reported as “inconclusive” and was excluded from further analysis.

Medical chart review was performed to determine pregnancy status in 52 patients with a positive qualitative result or with an hCG concentration of more than 5 IU/L. Pregnancy status could not be determined in 8. Of the remaining 44 patients, 13 were not pregnant at the time of sample collection.
and 31 were pregnant or had a recent miscarriage, abortion, or resolving ectopic pregnancy. Chart review was not performed for 687 patients with a negative qualitative result and an hCG concentration of 5 IU/L or less.

The mean (SD) hCG concentration of the qualitatively negative samples was 1.1 (1.5) IU/L, with a range of 0.9 to 31 IU/L. The mean (SD) hCG concentration of the qualitatively positive samples was 8,796 (23,963) IU/L, with a range of 4 to 139,155 IU/L. Figure 1. The performance characteristics of the QuickVue One-Step hCG Combo qualitative test as measured against several criteria are shown in Table 3. When assessed against pregnancy status, the positive predictive value (PPV) was 90.9% and the negative predictive value (NPV) was 99.9%. One sample, obtained from a 32-year-old subject with an hCG concentration of 12 IU/L, produced a negative qualitative result. Medical chart review located a note that was dated 5.8 weeks after the qualitative test was performed that indicated she was 10.3 weeks pregnant. Assuming accurate dating, that means she was 4.5 weeks pregnant at the time the qualitative test was performed.

Use of the claimed hCG detection threshold of 25 IU/L produced a PPV and an NPV of 78.0% and 99.9%, respectively. A single serum sample collected from a 37-year-old woman with pancreatitis and an hCG concentration of 31 IU/L was negative by the qualitative test. Medical chart review did not reveal any indication of a possible pregnancy.

When an hCG cutoff of 5 IU/L was used as the evaluation criterion, the NPV decreased to 98.4% owing to 11 patients with an hCG concentration more than 5 IU/L and a negative qualitative result. All but 1 of these patients (the...
The aforementioned 32-year-old) was not pregnant. At this cutoff, the PPV was increased to 95.1% as only 2 samples produced a positive qualitative result when the hCG concentration was 5 IU/L or less.

Age-specific hCG cutoffs have been proposed to be 5, 8, and 14 IU/L for persons 40 years or younger, 41 to 55 years, and older than 55 years, respectively. Use of these cutoffs produced a PPV and an NPV of 95.1% and 99.3%, respectively. Five women had an hCG concentration of more than their age-specific cutoff in conjunction with a negative qualitative result, and only 1 was pregnant (the aforementioned 32-year-old). Two had a positive qualitative result at an hCG concentration less than their age-specific cutoff. One patient was a 30-year-old woman with a recent miscarriage and the other was a nonpregnant 48-year-old with multiple myeloma.

By comparison, the PPV and NPV of the quantitative serum hCG test as assessed against pregnancy status using age-specific cutoffs to indicate the absence of pregnancy were 83.3% and 99.9%, respectively (Table 3). One sample was obtained from a 30-year-old patient with severe pelvic adhesive disease and an hCG concentration of 4 IU/L who was believed to have an ectopic pregnancy 10 days before the qualitative test was performed. The hCG concentration at that earlier date was 513 IU/L. An ectopic pregnancy was not confirmed, and she was diagnosed as having a spontaneous miscarriage.

Qualitative results from the 50 samples retested with 4 different brands of test devices were concordant across all brands tested. In contrast, 3 of 36 samples originally reported as positive were negative on repeat testing. Two of these had an hCG concentration of 4 IU/L, and the third had an hCG concentration of 13 IU/L. Similarly, 1 of 14 samples originally reported as negative was weakly positive on repeat testing and had an hCG concentration of 12 IU/L.

Table 3 shows the number of samples that gave discrepant results when evaluated against the detection threshold of each brand of qualitative hCG test. Overall, the qualitative hCG tests performed as expected and produced appropriately

![Figure 1](https://example.com/f1.png) Concentration of serum human chorionic gonadotropin (hCG) and pregnancy status by the qualitative result obtained from the QuickVue One-Step hCG Combo test (detection threshold, 25 IU/L). The dashed horizontal lines represent hCG concentrations of 25 and 5 IU/L. Of the negative samples, 646 had an hCG concentration <1.0 IU/L and appear as a broad dark line. hCG values are in Système International units; conventional units are mIU/mL, and the conversion factor is 1.0.

Table 3.
Performance Characteristics of the QuickVue One-Step hCG Combo Qualitative Test* as Measured Against Several Criteria†

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Qualitative Test Negative (n)</th>
<th>Qualitative Test Positive (n)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not pregnant</td>
<td>697† 3</td>
<td>96.8 (83.3-99.9)</td>
<td>99.6 (98.8-99.9)</td>
<td>90.9 (75.7-98.1)</td>
<td>99.9 (99.2-100)</td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>1</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG concentration (IU/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>697 9</td>
<td>97.0 (84.2-99.9)</td>
<td>98.7 (97.6-99.4)</td>
<td>78.0 (62.4-89.4)</td>
<td>99.9 (99.2-100)</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>1</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>687 2</td>
<td>78.0 (64.0-88.5)</td>
<td>99.7 (99.0-100)</td>
<td>95.1 (83.5-99.4)</td>
<td>98.4 (97.2-99.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>11</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Age-specific hCG cutoff</td>
<td>683 2</td>
<td>88.6 (75.4-96.2)</td>
<td>99.7 (99.0-100)</td>
<td>95.1 (83.5-99.4)</td>
<td>99.3 (98.3-99.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; Age-specific hCG cutoff</td>
<td>5</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Age-specific hCG cutoff</td>
<td>694‖ 1</td>
<td>96.8 (83.3-99.9)</td>
<td>99.1 (98.1-99.7)</td>
<td>83.3 (67.2-93.6)</td>
<td>99.9 (99.2-100)</td>
<td></td>
</tr>
<tr>
<td>&gt; Age-specific hCG cutoff</td>
<td>6</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

hCG, human chorionic gonadotropin.

* Claimed detection threshold, 25 IU/L.

† The performance characteristics of the quantitative serum hCG test as measured against pregnancy status are also shown for comparison. Sensitivity, specificity, positive predictive value, and negative predictive value are given as percentage (95% confidence interval). Age-specific cutoffs are 5, 8, and 14 IU/L for people aged ≤40, 41-55, and >55 years, respectively. hCG values are in Système International units; conventional units are mIU/mL, and the conversion factor is 1.0.

‖ 687 were assumed to be not pregnant owing to a negative qualitative test result and an hCG concentration ≤5 IU/L; chart review not performed.
positive or negative test results relative to their claimed detection thresholds. Qualitative tests produced negative results when the hCG level was greater than the claimed detection threshold in about 3.0% of samples. In these samples, the measured hCG concentration was within 3 to 6 IU/L of the devices’ hCG detection thresholds. However, qualitative tests tended to have greater analytic sensitivity than claimed and produced a positive result at an hCG concentration 3 to 21 IU/L lower than their stated limit of detection.

The hCG concentrations of the 700 nonpregnant patients ranged from 0.9 to 31 IU/L. The qualitative hCG test result was reported as negative in 697 (99.6%) and positive in 3 (0.4%). In the 31 pregnant patients, hCG concentrations ranged from 4 to 139,155 IU/L with 30 (96.8%) being reported as qualitatively positive. The results for 1 pregnant patient were reported as qualitatively negative, and she had an hCG result of 12 IU/L. Table 5 shows relevant clinical and laboratory data for all patients with qualitative hCG results that were discrepant with pregnancy status or between the hCG concentration and the detection threshold of any device tested.

**Discussion**

This is the first study to compare the TAT of qualitative and quantitative serum hCG tests and to assess physicians’ perceptions of their clinical performance. Although there are no published data to demonstrate that the qualitative detection of hCG using POC devices improves patient outcomes, such tests are commonly performed in health care settings. The need to perform qualitative hCG testing in serum has been questioned. Arguments in favor of discontinuing the use of these tests include their inapplicability at the POC, their lower analytic sensitivity compared with quantitative hCG tests, and the logic that, when detection of a possible pregnancy is of high importance, the most analytically sensitive test available should be used.

We hypothesized that clinicians order qualitative serum hCG tests based on the perception that they are more likely to receive the test results more quickly compared with results from quantitative hCG tests. This was supported by the finding that fewer physicians (48%) perceived waiting more than 60 minutes for results from qualitative tests compared with the 76% who perceived that it took that long to receive results from quantitative tests. This likely explains why physicians prefer using qualitative urine hCG tests, which can be done at the POC, to determine pregnancy status rather than using a serum test, which must be performed in the laboratory.

**Table 4**

| Number of Samples That Gave Discrepant Results When Evaluated Against the Claimed Detection Threshold of Each Brand of Qualitative hCG Test* |
|-----------------|----------|--------|--------|--------|--------|
|                  | QuickVue| Icon 25| OSOM   | SP Brand| Sure-Vue|
| Claimed hCG detection threshold (IU/L) | 25       | 25     | 10     | 10     | 10     |
| Negative result when hCG < detection threshold | 697/706 (98.7) | 16/23 (69.6) | 15/18 (83.3) | 15/18 (83.3) | 14/16 (87.5) |
| Negative result when hCG ≥ detection threshold | 1/33 (3.3) [31] | 0/27 (0) [—] | 1/31 (3.2) [13] | 1/32 (3.1) [13] | 0/28 (0) [—] |
| Positive result when hCG < detection threshold | 32/33 (97.0) | 27/27 (100) | 30/31 (96.8) | 31/32 (96.9) | 28/28 (100) |
| Positive result when hCG ≥ detection threshold | 9/706 (1.3) [4-20] | 7/23 (30.4) [7-20] | 3/18 (16.7) [7-9] | 3/18 (16.7) [7-9] | 2/16 (12.5) [7-9] |

hCG, human chorionic gonadotropin.
* Data are given as number with specified result/total tested (percentage) unless otherwise indicated. hCG values are Système International units; conventional units are mIU/mL, and the conversion factor is 1.0.
As might be expected, the majority of physicians prefer to use serum rather than urine hCG tests when pregnancy status is to be known with as much certainty as a laboratory test can provide. However, of the physicians who would use serum over urine for this purpose, 25% would order a qualitative hCG test over a quantitative test. From a clinical perspective, a false-negative qualitative hCG test result is more concerning than a false-positive one. A pregnant patient who is incorrectly classified as not pregnant risks undergoing interventions that are potentially harmful.

Because qualitative and quantitative serum hCG tests are performed in the laboratory, our initial premise was that the use of a qualitative test could be discontinued when a quantitative test was readily available. This premise is defensible when considered in the light of the TAT data. While the TAT lab was significantly shorter (15.3 minutes on average) for qualitative tests relative to quantitative tests, there was no significant difference in the TAT total between the test types. This is not surprising because it is the preanalytic components such as specimen collection and transport or postanalytic components such as result reporting that contribute the most to delays in the total testing process.6,7

The difference between TAT_{total} and TAT_{lab} can be considered an estimate of the time required to transport the sample to the laboratory. In this regard, the median difference for qualitative tests was 76.4 minutes and was 40.9 minutes for quantitative tests (Table 1), suggesting that qualitative test samples had longer transport times. It is possible that the physical distances between the patient care areas influenced these data; however, our hospital uses a pneumatic tube system for sample transport that is available at all clinic locations. We did not receive any samples from external locations. Qualitative serum hCG tests seem to have lower hCG detection thresholds than claimed by the manufacturers. The 2 devices with claimed detection limits of 25 IU/L (QuickVue and Icon 25) produced positive results using samples with hCG concentrations as low as 4 and 7 IU/L, respectively. Similarly, positive results were obtained from samples with an hCG concentration between 7 and 9 IU/L using the devices with claimed detection thresholds of 10 IU/L (OSOM, SP Brand, and Sure-Vue). A study that investigated the analytic sensitivity of POC and over-the-counter qualitative urine hCG devices reported similar findings.8 In that report, the devices tested showed considerable differences in the lowest hCG concentration they were capable of detecting. Many samples produced positive results close to the claimed detection limit of 25 IU/L, but some samples produced a positive result at an hCG concentration several fold lower than claimed.8

As suggested, we chose to evaluate the diagnostic performance of the QuickVue qualitative serum hCG test against several criteria. From a clinical perspective, a false-negative qualitative hCG test result is more concerning than a false-positive one. A pregnant patient who is incorrectly classified as not pregnant risks undergoing interventions that are potentially harmful.

### Table 5
Clinical and Laboratory Data for 11 Patients With Qualitative hCG Results That Were Discrepant With Pregnancy Status or Between the hCG Concentration and the Detection Threshold of Any Device Tested

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>hCG (IU/L)</th>
<th>QuickVue</th>
<th>Icon 25</th>
<th>OSOM</th>
<th>SP Brand</th>
<th>Sure-Vue</th>
<th>Pregnancy Status</th>
<th>Relevant Clinical Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>QNS</td>
<td>Pregnant</td>
<td>Vaginal bleeding; hCG concentration increased to 45 IU/L 4 d later, then decreased to 29 IU/L 3 d later; probable biochemical pregnancy</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>QNS</td>
<td>Pregnant</td>
<td>Mitral valve regurgitation and hypertension; 8 d beyond day of expected menses; hCG not detected in subsequent testing; clinical assessment; biochemical pregnancy</td>
</tr>
<tr>
<td>28</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>QNS</td>
<td>Pregnant</td>
<td>Vaginal bleeding</td>
</tr>
<tr>
<td>29</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>QNS</td>
<td>Pregnant</td>
<td>Vaginal bleeding; hCG &gt;300 IU/L 6 d later</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Pregnant</td>
<td>Severe pelvic adhesive disease; hCG 10 d earlier was 513 IU/L; presumed spontaneous miscarriage</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Pregnant</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>32</td>
<td>12</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Pregnant</td>
<td>Determined to be 10.3 wk pregnant 5.8 wk after sample collection</td>
</tr>
<tr>
<td>37</td>
<td>31</td>
<td>–</td>
<td>QNS</td>
<td>QNS</td>
<td>QNS</td>
<td>QNS</td>
<td>Not pregnant</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not pregnant</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>53</td>
<td>13</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>QNS</td>
<td>Not pregnant</td>
<td>Depression; likely pituitary hCG</td>
</tr>
<tr>
<td>69</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Not pregnant</td>
<td>Multiple myeloma; likely pituitary hCG</td>
</tr>
</tbody>
</table>

hCG, human chorionic gonadotropin; QNS, quantity not sufficient; +, positive; –, negative.

* hCG values are in Système International units; conventional units are mIU/mL, and the conversion factor is 1.0.
to a fetus. Conversely, while a nonpregnant patient who is incorrectly classified as pregnant may undergo additional studies to confirm pregnancy, the potential for harm is usually less. Notably, there are reports of considerable patient harm occurring owing to the detection of hCG in the absence of pregnancy. Therefore, focus is appropriately placed on the diagnostic sensitivity and NPV of a qualitative hCG test.

In our cohort, these were greatest when evaluated against actual pregnancy status or the claimed hCG detection threshold of 25 IU/L (Table 3). As compared against both criteria, only a single sample was identified as a false-negative. As compared against pregnancy status, 1 sample was truly false-negative as it was obtained from a patient in early pregnancy. It is interesting that when this sample was retested using each of the 4 other brands of qualitative hCG tests, all results were interpreted as positive, suggesting that the original result may have been performed, interpreted, or reported incorrectly. If that were the case, the NPV would have been calculated to be 100%. As compared against the 25 IU/L detection threshold, 1 sample was a technical false-negative in the sense that the negative result was obtained from a sample with an hCG concentration above the cutoff. The person from whom the sample was obtained was not pregnant.

The diagnostic sensitivity and NPV of the qualitative test were lowest (78% and 98.4%, respectively) when evaluated against an hCG cutoff of 5 IU/L, the cutoff commonly used for quantitative serum hCG tests. Because serum concentrations of hCG are known to increase with age, likely due to hCG synthesis by the pituitary gland, we also evaluated qualitative test performance against the upper hCG reference limits for nonpregnant women. This resulted in a diagnostic sensitivity and an NPV of 88.6% and 99.3%, respectively.

By comparison, the diagnostic sensitivity and NPV of the quantitative serum hCG test using age-specific hCG cutoffs were identical to the qualitative test (96.8% and 99.9%, respectively). Therefore, a negative result from a qualitative or a quantitative serum hCG test confidently excluded pregnancy. The PPV of the quantitative test using age-specific hCG cutoffs was slightly less (83.3%) than for the qualitative test (90.9%) owing to some nonpregnant patients with hCG concentrations that exceeded the cutoff but were interpreted as qualitatively negative.

The optimal analytic sensitivity of a qualitative hCG test has been debated. A detection limit of 25 IU/L has been advocated owing to the low positive concentrations that can be observed in nonpregnant women and perimenopausal and postmenopausal women. Also, a very sensitive pregnancy test increases the likelihood of detecting a biochemical pregnancy, a pregnancy that is spontaneously lost very early after conception. In our study population, 2 patients seem to have had this type of pregnancy (Table 5). Others have argued for a detection threshold of 5 IU/L for qualitative hCG tests to maximize diagnostic sensitivity and minimize the potential for false-negative results. Based on pregnancy status, our data would seem to support the use of a detection limit of 5 IU/L (Figure 1), a threshold that is already achieved by the 5 different qualitative devices included in this study. All but 1 of the 31 known pregnancies produced a positive result when the hCG concentration was 4 IU/L or more, 6 of which were less than 25 IU/L (Figure 1). If the detection limit of the qualitative test was truly 25 IU/L, the 6 pregnancies would have been undetected. The fact that at least 2 of these were biochemical pregnancies is of little importance. In a health care setting, the detection of any possible pregnancy is what matters, and it cannot be known whether a pregnancy is viable based on a single qualitative or quantitative hCG test result. All detected pregnancies must be assumed to be viable and appropriate medical decision making guided by that assumption until a nonviable pregnancy declares itself.

Test TAT is used by many clinicians to judge the quality of the laboratory and often drives a physician’s preference for a test when different test options for the same analyte are available. One of the objectives of this study was to determine if the qualitative serum hCG test could be replaced with a qualitative test and still fulfill clinicians’ expectations. Our data indicate that the total TAT is similar for both types of tests and that both tests have similar analytic sensitivity. Therefore, while a quantitative hCG test could be substituted for a qualitative test, there seems to be no clear advantage to make the substitution.

There are several limitations to our study. First, the physician survey and analysis of TATs were performed at 1 university medical center. Physician opinions and use of hCG tests and the TAT data may not be representative of other health care delivery systems. Second, despite the large sample size, only 41 qualitatively positive samples were identified. A greater number of positive samples, especially samples with an hCG concentration between 5 and 25 IU/L, would have been desirable. Third, the use of medical chart review to confirm pregnancy status is challenging. Because qualitative tests are frequently used to rule out pregnancy, patients with negative results are assumed to be not pregnant. This is the primary reason we chose not to review charts for patients with negative results and an hCG concentration of 5 IU/L or less.

Physicians usually prefer to use qualitative serum hCG tests over quantitative tests but will use the latter when pregnancy status is needed to be known with high certainty. They are also willing to wait up to 45 minutes for results from either type of test. Because the TATs of qualitative and quantitative serum hCG tests are similar, the use of qualitative tests could be abandoned and still meet physicians’ expectations. However, because qualitative serum hCG tests have detection limits and performance characteristics similar...
to quantitative tests and are less expensive to perform, there
seems to be little need to do so.

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References

tests within the clinical pathology laboratory. Am J Manag
2. Sigel CS, Grenache DG. Detection of unexpected isoforms
of human chorionic gonadotropin by qualitative tests [letter].
analytical specificity of human chorionic gonadotropin assays
determined using WHO International Reference Reagents.
considerations in the measurement of human chorionic
gonadotropin in aging women. Clin Chem. 2003;51:1830-
1835.
5. Palmer OM, Grenache DG, Gronowski AM. The NACB
laboratory medicine practice guidelines for point-of-care
6. Steindel SJ, Novis DA. Using outlier events to monitor test
7. Steindel SJ, Howanitz PJ. Physician satisfaction and
emergency department laboratory test turnaround time. Arch
Qualitative point-of-care and over-the-counter urine hCG
devices differentially detect the hCG variants of early
9. Cole LA, Khanlian SA. Inappropriate management of
women with persistent low hCG results. J Reprod Med.
for a gonadotropin from nonpregnant subjects that has
physical, immunological, and biological similarities to
human chorionic gonadotropin. Proc Natl Acad Sci U S A.
11. Odell WD, Griffin J. Pulsatile secretion of human
1987;317:1688-1691.
12. Stenman UH, Alfthan H. Optimal sensitivity for pregnancy
13. Cole LA, Ladner DG. Background hCG in non-pregnant
individuals: need for more sensitive point-of-care and over-