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Easy fix for clinical laboratories for the false-positive defect with the Abbott AxSym total β-hCG test

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Abstract

Background: False-positive hCG results can lead to erroneous diagnoses and needless chemotherapy and surgery. In the last 2 years, eight publications described cases involving false-positive hCG tests; all eight involved the AxSym test. We investigated the source of this abundance of cases and a simple fix that may be used by clinical laboratories.

Methods: False-positive hCG was primarily identified by absence of hCG in urine and varying or negative hCG results in alternative tests.

Seventeen false-positive serum samples in the AxSym test were evaluated undiluted and at twofold dilution with diluent containing excess goat serum or immunoglobulin.

Results: We identified 58 patients with false-positive hCG, 47 of 58 due to the Abbott AxSym total hCGβ test (81%). Sixteen of 17 of these "false-positive" results (mean 100 mIU/ml) became undetectable when tested again after twofold dilution.

Conclusions: A simple twofold dilution with this diluent containing excess goat serum or immunoglobulin completely protected 16 of 17 samples from patients having false-positive results. It is recommended that laboratories using this test use twofold dilution as a minimum to prevent false-positive results.

Keywords: hCG; Human chorionic gonadotropin; False-positive; Abbott AxSym; Interference; Heterophilic antibodies

Introduction

hCG is produced in pregnancy, in gestational trophoblastic diseases (GTD) and gestational trophoblastic neoplasms (GTN), and in men with testicular germ cell malignancies. hCG is a perfect tumor marker for GTD and GTN with 100% sensitivity and specificity [1–6]. GTN can be extremely invasive but is very responsive to chemotherapy. A GTN can be dispersed and therefore may not necessarily be detected by imaging methods. Thus, standard practice is to treat women with chemotherapy solely based on persistent elevated hCG results. When this therapy fails to suppress hCG, the hCG result may be questioned. False-positive hCG results have led to needless therapy [7–17], not just for GTN [7–11,17], but for recurrent testicular malignancy [12], for persistent hydatidiform mole [13], and for ectopic pregnancy [15]. They have also led to the erroneous identification of pregnancy [16].

Multiple reports now show that false-positive hCG tests are due to human heterophilic antibodies interfering with the multiple animal antibody mechanisms of hCG tests and of other assays [14,16,18–21]. This is a particular problem because hCG is one of very few antigens that is either wholly present (as in pregnancy and GTD) or wholly absent (no pregnancy or neoplastic disease).

We found 11 reports of false-positive hCG cases (Medline 1996–2003 and Google 2003) published in 2001–2003, all of which involved false-positive results and needless therapy due to the Abbott AxSym total hCGβ test [1,8–17]. According to the CAP, this test is the most commonly used technology and is instituted in 28% of laboratories participating in their survey [21,22]. We investigate here the source for the apparent disproportionate incidence of false-positive

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Table 1
Tests used by physicians to monitor 58 patients with false-positive hCG results, referred to the USA hCG Reference Service, 1998–2003

Medical treatment incurred because of false-positive hCG results	False-positive concentration at time or closest time to referral to USA hCG Reference Service
(a) Abbott AxSym total βhCG test, used by 28% of laboratories [21,22]	47 cases (81% of total), mean 111 IU/l
D&C, Lap, Mtx, AcD, HYS, EMACO, THO	220 IU/l
D&C, Lap, Mtx, HYS, EMACO, Coma	68 IU/l
D&C, Lap, Mtx, Mtx, AcD, HYS	142 IU/l
D&C, Lap, Mtx, HYS	17 IU/l
D&C, Lap, HYS, BSO	150 IU/l
D&C, Lap, Mtx, BSO	145 IU/l
D&C, Lap, Mtx, HYS, BSO	81 IU/l
D&C, Lap, Mtx, AcD, EMACO	558 IU/l
D&C, Lap, Mtx, EMACO	80 IU/l
D&C, Lap, Mtx, AcD	22 IU/l
D&C, Lap, Mtx, AcD	21 IU/l
D&C, Lap, Mtx, AcD	110 IU/l
D&C, Lap, Mtx, AcD	114 IU/l
History of hydatidiform mole, Mtx, AcD	115 IU/l
D&C, Mtx, D&C, Lap, Mtx	20 IU/l
D&C, Lap, Mtx, Mtx	97 IU/l
D&C, D&C, Lap, Mtx	122 IU/l
D&C, Mtx, AcD	14 IU/l
D&C, Lap, Mtx	60 IU/l
D&C, Lap, Mtx	139 IU/l
D&C, Lap, Mtx	402 IU/l
D&C, Lap, Mtx	37 IU/l
D&C, Lap, Mtx	607 IU/l
D&C, Lap, Mtx	300 IU/l
D&C, Lap, Mtx	21 IU/l
D&C, Mtx	202 IU/l
D&C, Mtx	18 IU/l
D&C, Mtx	81 IU/l
D&C, Mtx	170 IU/l
D&C, Mtx	124 IU/l
D&C, Mtx	70 IU/l
D&C, Mtx	21 IU/l
History of hydatidiform mole, Mtx	17 IU/l
History of hydatidiform mole, Mtx	8 IU/l
D&C, Lap	14 IU/l
D&C, Lap	23 IU/l
D&C, Lap	24 IU/l
D&C	32 IU/l
D&C	93 IU/l
D&C	143 IU/l
GTN considered, no therapy	53 IU/l
GTN considered, no therapy	174 IU/l
GTN considered, no therapy	25 IU/l
GTN considered, no therapy	224 IU/l
GTN considered, no therapy	20 IU/l
Male patient, recurrence of TGCM considered, no therapy	15 IU/l
Male patient, TGCM considered, no therapy	38 IU/l
(b) Dade Dimension RXT intact hCG test, used by 21% of laboratories [21,22]	2 cases (3.4% of total), mean 53 IU/l
D&C, Mtx	84 IU/l
D&C, Mtx	23 IU/l
(c) Beckman Access-2 total βhCG test, used by 15% of laboratories [21,22]	0 cases
(d) Bayer ADVIA Centaur total hCG test, used by 7.5% of laboratories [21,22]	3 cases (5.2% of total), mean 19 IU/l
D&C, Mtx	20 IU/l
GTN considered, no therapy	18 IU/l
GTN considered, no therapy	18 IU/l
(e) Ortho Vitros ECi total hCG test, used by 6.1% of laboratories [21,22]	2 cases (3.4% of total), mean 48 IU/l
GTN considered, no therapy	55 IU/l
History of hydatidiform mole, Mtx, AcD	41 IU/l
(f) DPC Immulite/Immulite 2000 hCG test, used by 4.1% of laboratories [21,22]	0 cases
(g) Roche Elecsys E170 intact hCG test, used by 3.6% of laboratories [21,22]	0 cases
(h) Bayer ACS180 total hCG test, used by 3.3% of laboratories [21,22]	2 cases (3.4% of total), mean 39 IU/l
History of hydatidiform mole, no therapy	65 IU/l
Mtx, AcD	20 IU/l
(i) All other assays (one case with Tosoh Nexia, one with Bayer Immuno-1)	2 cases (3.4% of total), mean 30 IU/l
D&C, Lap	53 IU/l (Immuno 1)
GTN considered, no therapy	7 IU/l (Nexia)

The table shows test used and false-positive results reported to physician at or closest to the time of referral to the USA hCG Reference Service. The table also summarizes the medical treatment incurred by the patient because of the continuous false-positive hCG test result. D&C is dilation and curettage; Lap is laparoscopy; Mtx is methotrexate chemotherapy; AcD is actinomycin D chemotherapy; EMACO is five agent cytotoxic chemotherapy (Etoposide, Mtx, AcD, alternating with cyclophosphamide and vincristine); HYS is hysterectomy; BSO is bilateral salpingo-oophorectomy; THO is thoracotomy; and Coma is diabetic coma due to destruction of Islet cells by chemotherapy. TGCM is testicular germ cell malignancy and GTN is gestational trophoblastic neoplasm. Data are presented in order of proportion of laboratories using a test where the tests are the first most common, second, third, fourth, fifth, sixth, and seventh most commonly used hCG tests in North America [21,22].
In a t test comparing the mean false-positive result in the Abbott AxSym with the mean result in all other tests $P < 0.05$.

results with this assay and describe simple methods for laboratories using the Abbott AxSym total hCGβ to identify and avoid false-positive results.

Methods

Serum samples were accumulated as part of the ongoing practice of the USA hCG Reference Service. After obtain-

ing approval from the University of New Mexico Health Sciences Center Human Research Review Committee (HRRC #02-548), we disclose USA hCG Reference Service Results and hCG results reported at each referring center.

The presence of false-positive hCG was identified by the USA hCG Reference Service as described previously [1,7]. Briefly, false-positive results were demonstrated by at least three of four observations: (a) presence of hCG or related molecule immunoreactivity in serum but not urine; (b) results varying more than fivefold in multiple different hCG assays or immunoreactivity not detected in hCG Reference Service assays, the DPC Immulite hCG and free β assay (DPC, Los Angeles CA), or the "in-house" microtiter plate 2 monoclonal antibody intact hCG and β-core fragment assays, as described previously [1,7]; (c) hCG immunoreactivity suppressed by heterophilic antibody blocking agent HBT (Scantibodies Inc., San Diego, CA) using either the DPC Immulite hCG or free β assay or the "in-house" microtiter plate 2 monoclonal antibody intact hCG assay; and (d) the finding of elevated urine β-core fragment in serum but not urine using the "in-house" microtiter plate 2 monoclonal antibody assay as described previously [1,7].

In six cases of false-positive hCG, serum samples were also analyzed on the Abbott AxSym total hCGβ test at the referring center, both undiluted and twofold diluted with Abbott AxSym diluent. This includes the two cases identified by Giannopoulos et al. [16]. One case was run on the AxSym, undiluted and at twofold dilution at the initiative of the laboratory. A further 10 serum samples, demonstrated as false-positive by the four criterion described in the previous paragraph in the Abbott AxSym total hCGβ test (Table 2), were tested undiluted and at twofold dilution.

Data on the numbers of laboratories using a specific professional laboratory hCG test were obtained from the combination of three College of American Pathologists surveys, the Excel survey 2002 and 2003 [21], and the K/KN-A Ligand (General) survey [22]. Data are the most recent available, from the C-15 [21] and K-05 [22] surveys involving 4554 testing laboratories.

In all cases, the specific hCG test used by the referring physician to test the patient, and the most recent false-positive result, was confirmed with the referring center's laboratory. All statistics were determined in the Microsoft Excel spreadsheet, including means and Student's *t* test.

Results

Table 1 summarizes the 5-year experience of the USA hCG Reference Service with cases with false-positive hCG results. It also summarizes medical treatment resulting solely from the false finding of elevated hCG results. As shown, in order of test use according to CAP surveys [21,22], 47 cases with false-positive results (81%) were from centers using the Abbott AxSym total hCGβ test; 2 false-positive cases (3.4%) involved the Dade Dimension RXT intact hCG test; no false-positive results were recorded with the Beckman Access-2 total βhCG test; 3 false-positive cases (5.2%) involved the Bayer ADVIA Centaur total hCG test; 2 false-positive cases (3.4%) involved the Ortho Vitros Eci assay; no false-positive results were recorded with the DPC Immulite/Immulite 2000 or the Roche Elecsys E170 Intact hCG test; and 2 false-positive cases (3.4%) involved the Bayer ACS180 total hCG test. The remaining two false-positive cases came from centers using the Tosoh Nexia and Bayer Immuno-1 total hCG tests. No false-positive results were recorded with Abbott's new hCG test, the Abbott Architect hCG test, a newly designed immunometric assay, or with any other manufacturer's assay. It should be noted, however, that while the Abbott AxSym and most of the other tests have been available for the 5 years duration of this study, one of assays, the Roche Elecsys E170, has been in use for less than 5 years. It is not possible, however, to project the Roche result since one cannot amplify zero (0 false-positives).

We considered the relationship between the proportion of false-positive results due to a specific test and the proportion of laboratories using a specific test: Abbott AxSym total hCGβ test (ratio is 81% *H* 28% or 2.9*X*, where *X* is the multiplicand of the share of the market); Bayer ACS180 total hCG test (ratio 0.94*X*); Bayer ADVIA Centaur total hCG test (ratio 0.69*X*); Ortho Vitros ECi total hCG test (0.56*X*); Dade Dimension RXT intact hCG (0.16*X*); Beckman Access-2 total βhCG test (0*X*); DPC Immulite hCG (0*X*); and Roche Elecsys E170 intact hCG (0*X*). The Abbott AxSym total hCGβ test accounts for a high number of false-positive hCG cases, clearly disproportionate to its share of the market. In addition, the average false-positive result in the Abbott AxSym total hCGβ test (mean 111 mIU/ml) is significantly higher than of all other test false-positive results combined (*t* test, $P < 0.05$). Of the 47 cases with false-positive results in the Abbott AxSym total hCGβ test, 40 (85%) needlessly received surgery or chemotherapy. Of the 11 other false-positive test cases, only six (55%) received needless therapy.

We investigated the cause and potential remedies for false-positive results in the Abbott AxSym total hCGβ test. Seventeen serum samples from individuals with false-positive hCG results were tested in the Abbott AxSym total hCGβ test with no dilution and after twofold dilution with the supplied Abbott AxSym diluent (at both referring center laboratories, external laboratories under instruction of the USA hCG Reference Service, and as ordered by the USA hCG Reference Service). As shown in Table 2, 16 of the 17 serum samples, clearly positive for hCG when tested with no dilution (mean concentration 100 IU/l), became undetectable (sensitivity of Abbott AxSym total hCGβ test is 2 IU/l) after a twofold dilution. The remaining sample gave a result of 8.5 IU/l (versus 34 IU/l) when twofold diluted,

Table 2
Seventeen serum samples from patients with proven false-positive hCG result in the Abbott AxSym assay, tested undiluted and twofold diluted to illustrate false-positive hCG result

Sample	Abbott AxSym, no dilution (IU/l)	Abbott AxSym twofold dilution (IU/l)
1	607	Not detected
2	174	Not detected
3	224	Not detected
4	30	Not detected
5	17	Not detected
6	36	Not detected
7	17	Not detected
8	7	Not detected
9	16	Not detected
10	45	Not detected
11	34	8.5
12	55	Not detected
13	62	Not detected
14	110	Not detected
15	98	Not detected
16	87	Not detected
17	83	Not detected
Mean concentration	100	<5

Sample 1 is the data reported to the USA hCG Reference Service. Samples 2–11 were tested at request of the hCG Reference Service (Abbott AxSym results determined by an independent laboratory in Albuquerque). Samples 12–17 are communicated reports (USA hCG Reference Service suggests to external laboratory considering Abbott AxSym false-positive problems to repeat test with twofold dilution, results then communicated back to reference service).

indicating a multifold reduction of false-positive hCG results.

Discussion

In 1998, we described three false-positive cases, two of the three were from physicians using the Abbott AxSym test [23]. In 1999, we had data on six false-positive cases, five of six were monitored using the AxSym [17]. In 2000, we described 12 false-positive cases, 11 of the 12 false were due to the AxSym [7]. Now, in 2003, we report 58 patients, 47 of 58 due to the AxSym (81%). In the majority of cases (85%), patients had needless therapy because of the false-positive hCG values reported by clinical laboratories. Considering the use of this assay in the USA, 28% of laboratories [21,22], this seemed an extraordinary high incidence. In support of this 5-year observation by the USA hCG Reference Service, all recently published articles (11 of 11 article) describing false-positive hCG cases (between 2001 and 2003) involved patients tested falsely with the Abbott AxSym total hCGβ assay [1,8–17]. All of these findings clearly show that the Abbott AxSym total hCGβ test is responsible for a disproportionately large number of false-positive cases. Furthermore, the average false-positive result in the Abbott AxSym total hCGβ test was statistically higher than false-positive results in all other tests combined and led to a higher proportion of patients having needless surgery and chemotherapy than for all other tests combined. The Abbott AxSym total hCGβ test clearly causes an unacceptable high number of false-positive hCG tests.

The Abbott AxSym total β-hCG test instruction manual recommends no dilution for serum samples containing up to 1000 IU/l. This covers a major proportion of hCG determinations. The manual describes the three components in the reagent pack: (1) a monoclonal anti-βhCG coated on microparticles in Tris buffer with protein stabilizers and azide preservative; (2) a purified goat anti-βhCG conjugated to alkaline phosphatase in Tris buffer with protein stabilizers and azide preservative; and (3) a sample diluent containing bovine and goat serum and azide preservative. The animal serum or immunoglobulin, to protect from heterophilic antibody interference, is only described as present in the diluent. As such, undiluted samples would have no animal immunoglobulin protection against false-positive results. All of the false-positive samples described in Table 1 were <1000 IU/l, so were likely tested undiluted or without protection. In one false-positive case, for example, the AxSym test gave a result of 607 IU/l. When this serum sample was tested at twofold dilution, hCG immunoreactivity was undetectable (reported at <5 IU/l). A twofold dilution is the minimal practical dilution. Clearly, the addition of a minimal amount of diluent animal antibodies completely suppressed the false-positive result. As described, a simple twofold dilution with Abbott AxSym diluent blocked false-positive results completely in 16 of 17 cases and partially block results in one case. This confirms that the absence of diluent or nonspecific animal immunoglobulins leads to false-positive hCG results. The lack of protection of undiluted samples against false-positive results, by the addition of nonspecific animal immunoglobulin, is clearly a defect in the design of the Abbott AxSym total β-hCG test. This defect has been independently described by Pesce [13] and by Giannopoulos et al. [16].

Excess animal serum and immunoglobulins or heterophilic antibodies blocking agents should be a requisite component added to all samples, regardless of dilution, either in the capture or tracer (also called conjugate) antibody components. As published, the DPC Immulite/Immulite 2000 and Roche Elecsys E170 tests use false-positive blocking agents in all antibody mixtures [13]. Applicable technical staff informed us that the Dade Dimension RXT intact hCG assay, Ortho Vitros ECi, Beckman Access-2 total βhCG assay, and Bayer Diagnostics ADVIA Centaur and ACS180 assay all use blocking in either or both the capture and tracer component of the assay to avoid all false-positives at all dilutions. As such, in seven of the eight of the most commonly used hCG assay by laboratories in the United States and Canada, protection is present in a requisite component regardless of sample dilution. This is not the situation with the Abbott AxSym total β-hCG test in which the blocking agent (animal serum) is in the diluent. This leaves undiluted samples virtually unprotected. This is an irregular design, making the assay defective. Considering

the large number of people being hurt because of this assay defect, receiving needless surgery or chemotherapy (40 cases described here, others in the cited papers [8–17] and an unknown number not reported), Abbott should consider its ethical responsibility to the public and fix the assay or withdraw it.

Twenty years ago, competitive hCGβ radioimmunoassays were used. Using these assays, which use limiting antibody, lack of parallelism with dilution was an indicator of a cross-reacting antigen such as a heterophilic antibody [24–28]. The excess antibody design of modern immunometric assays makes parallelism with dilution less of an indicator. In our experience, most cases of false-positive results decrease parallel to dilution.

Giannopoulos et al. [16], concerned by the Abbott AxSym false-positive problem, started at the initiative of the USA hCG Reference Service to run the test both undiluted and at twofold dilution for a period of 14 months. During this time, 2 patients out of 2860 tested were identified by this means (twofold dilution result compared to undiluted result) as having false-positive results with no dilution yet not detected at twofold dilution). False-positive results were confirmed using urine samples and three other serum assays [16]. This indicates that approximately 1 in 1430 tests yield false-positive results. Considering that approximately 7 million women achieve pregnancy or each year in the United States and Canada [29], that the Abbott Axsym total β-hCG test is used in 28% of laboratories [21,22], and 1 in 1430 false-positive rate, then approximately 1371 women are likely to get erroneously identified with pregnancy or ectopic pregnancy each year due to the limitation of the Abbott AxSym test. This estimate does not include those incidentally checked for pregnancy before surgery or X-ray, the most common reason for initial hCG tests among the 58 false-positive cases described here. It also does not include the women with history of hydatidiform mole or other malignancy or men with testicular malignancy having hCG tests and falsely diagnosed with recurrence. As such, the true incidence of Abbott AxSym false-positive cases is likely to be significantly greater.

However, when one examines or analyzes these numbers, a large number of people are being erroneously diagnosed and treated because of a clear deficiency with one hCG test. This test can easily be fixed by Abbott Laboratories, by adding serum, nonspecific antibodies or other blocking agents to a requisite component (capture or conjugate antibody wells) of the test pack. As shown here, and confirmed in an abstract by Giannopoulos et al. [16], an easy fix for clinical laboratories that continue to run the Abbott AxSym total β-hCG test is either (1) running all samples undiluted and at twofold dilution to identify false-positives, or (2) limiting the test to twofold dilution avoiding undiluted samples and most false-positive results. The test currently has a sensitivity of 2 IU/l but recommends stating negative pregnancy results at <5 IU/l (Abbott Axsym total β-hCG test instruction manual). This detection level (5 mIU/ml) should not be affected by running the test at twofold dilution. The twofold dilution is not an automatic dilution programmed in this assays software. It needs to be performed manually and will take time. Laboratories, however, need to also take responsibility in avoiding the numerous false results that occur. They need to consider legal responsibilities and the possibility of being sued for false-positive hCG results.

In 2000, in response to the false-positive hCG test problem, Abbott Laboratories added warning and limitation notices to its instruction manual. Warning letters have also been sent by Abbott to all laboratories. It is noted in these warnings that this test should only be used for pregnancy and not for GTN. Most of the cases, however, started off with multiple false-positive pregnancy test results before pregnancy, and ectopic pregnancy was excluded and GTN was assumed. This warning will not prevent false-positive hCG results in GTN cases. In particular, it will not prevent false-positive pregnancies and assumptions of ectopic pregnancies.

Considering the data described here, limiting the test to twofold dilution, as the least dilution, will largely surmount the false-positive defect and greatly decrease the occurrence of false-positive hCG results. Alternatively, running samples undiluted and at twofold dilution would identify most false-positive cases.

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