Evidence Map

Management of Positive Human Chorionic Gonadotropin Test Results in Nonpregnant Patients without Gynecologic Malignancy

Elevated hCG Tests

RECOMMENDATION STATEMENT

- Health care professionals should have an understanding of the various etiologies for elevated hCG in nonpregnant individuals without gynecologic malignancy.
- Health care professionals should follow a systematic approach to retesting and evaluating test results that considers patient history, outcomes from previous tests and assays, and patient risk for other underlying causes of a positive hCG test.
- Health care professionals should be aware of alternative retesting methods to identify heterophilic antibodies that would result in false-positive hCG tests.

Supporting Literature

Category I	Category II	Category III
	Observational Studies Azimi 2021: In summary, our study is the largest of its kind and demonstrates an association between mildly increased hCG and degree of renal dysfunction in women ≥41 years of age, and suggests that a cutoff of ≤22 IU/L may be more informative in excluding pregnancy in these patients. Conversely, no association between reduced renal function and mildly increased hCG was found in women ≤40 years of age. Thus, age appears to be the dominant driver of mild increases in hCG concentrations in patients with CKD. Cole 2004: Quiescent gestational trophoblastic disease (GTD) was identified in 121 cases by the absence of invasive trophoblast antigen and nonresponse to chemotherapy (64	*Narrative Reviews* Braunstein 2002: The false-positive human chorionic gonadotropin measurements are characterized by serum levels that are generally <1000 mIU/mL, the absence of human chorionic gonadotropin in the urine, nonparallelism of the human chorionic gonadotropin levels in serial dilutions of the serum with the human chorionic gonadotropin standard, results that are not consistent with the clinical or operative findings, the absence of a substantial change in the serum levels over time or after therapy, and the finding of a negative result when an alternative type of human chorionic gonadotropin assay is used. An algorithm is presented to aid in the recognition of false-positive human chorionic gonadotropin results in patients.

cases with a history of hydatidiform mole or gestational trophoblastic neoplasia (GTN) and 57 cases following antecedent pregnancy). Another 61 Reference Service cases had false positive hCG, and we observed 7 cases with low levels of hCG of pituitary origin (hCG subsequently suppressed by estrogen-progesterone medication). Most disturbing is that the majority of these cases (68%) received needless therapy for assumed GTN/choriocarcinoma/placental site trophoblastic tumor before consultation with the Reference Service.

Gehin 2021: The aim of the study was to assess RF cross-reactivity to animal antibodies used in immunoassays, and to test if selected commercial immunoassays are vulnerable to interference from RF, causing false test results. We found considerably stronger reactivity toward animal antibodies, particularly mouse IgG1 (73% vs. 12%) and rabbit IgG (81% vs. 6%), in sera from RF-positive RA-patients compared to controls ($p < 0.001$).

Knight 2005: Patients were seen at Mount Sinai Medical Center and included 54 patients (ages 1-80 years, 32 females, 22 males) with IgA deficiency. Thirty percent of 54 IgA deficient patient sera yielded positive pregnancy tests by one or more of the three betahCG assays, however, none of the patients were pregnant. In comparison to sera of normal controls, 39% of the patient sera contained significant amounts of anti-goat antibody and 18% contained significant amounts of anti-mouse antibody. While heterophile antibodies are common in IgA deficient serum, false positive assays for betahCG in IgA deficient serum have not been previously reported. The possibility of false positive test results should be considered prior to invasive procedures in IgA deficient patients.

Rotmensch 2000: All 12 women met both criteria for false-positive hCG, and all had corroborating findings. In all 12 cases, a false diagnosis had been made, and most of the women had been subjected to needless surgery or chemotherapy. Assay kinetics indicated that heterophilic antibodies were responsible for the false-positive results. As a result of our findings all further therapy was stopped.

Vasquez 2022: Fifty pediatric patients were enrolled, including 20 with augmentation enterocystoplasty, 20 age- and sex-matched controls, and 10 with Mitrofanoff appendicovesicostomy only. Among the 20 patients who had undergone augmentation cystoplasty, 15 (75.0%) had positive pregnancy test results on OTC Test A, including 11/13 (84.6%) females and 4/7 (57.1%) males. No control patients or patients with Mitrofanoff appendicovesicostomy only had a positive test. No patients had positive pregnancy test results on OTC Test B or the POC test. While patients with augmentation enterocystoplasty were significantly more likely to test positive

El Hage 2021: In postmenopausal patients with elevated FSH and stable low levels of hCG (>14 IU/L), it is most likely that the hCG detected is produced by the pituitary. If FSH is in a menopausal range (>40 IU/L), no further testing is required

Oyatogun 2021: The term "phantom hCG" refers to persistently positive hCG levels on diagnostic testing in a nonpregnant patient and such results often lead to a false diagnosis of malignancy and subsequent inappropriate treatment with chemotherapy or hysterectomy. There remains a need for a consistent and rational diagnostic approach to the "phantom hCG." This article aims to review the different etiologies of positive serum hCG testing in nonpregnant subjects and concludes with a practical, stepwise diagnostic approach to assist clinicians encountering this clinical dilemma.

Stenman 2004: Elevated hCG has been described in many tumor types including, but not limited to: breast, gastrointestinal, genitourinary, lung, squamous cell cancers, and renal tumors

Case Reports & Case Series

Bidot 2021: Human chorionic glycoproteins (hCG) is a generic term for a heterogenous mixture of structurally related molecules, among which 2 play a critical role in pregnancy (hCG and hyperglycosylated hCG), one is produced by the pituitary gland (sulfated hCG), and the remaining 2 (bhCG and hyperglycosylated bhCG) are mainly produced by non germ cell tumor malignancies. Perimenopausal nonpregnant women and postmenopausal women might have mildly elevated serum hCG secondary to increased pituitary hCG secretion (loss of negative feedback from ovarian steroids) Immunoassay interference might stem from the presence of anti-animal heterophilic antibodies in some patients' sera, resulting in false positive hCG. Decreased hCG clearance in nonpregnant women with end-stage kidney disease might result in mild and persistent elevation of hCG <100 IU/L.

Schmid 2013: Human chorionic gonadotropin (hCG) is useful in evaluating and monitoring early pregnancy as well as trophoblastic disease. Here we describe the management of women with elevated serum human chorionic gonadotropin in a case of a 51-year-old female who was unsuccessfully treated for ectopic pregnancy. She was subsequently diagnosed with pituitary hCG production, which should be considered as differential diagnosis before treatment is initiated.

Yadav 2022: We present a highly sensitized prospective kidney transplant recipient with a positive pregnancy test with low levels of serum human chorionic gonadotrophin. She underwent additional preoperative testing after which we proceeded with the kidney transplant. Herein, we discuss the management of

	for blood ($p = 0.01$), nitrate ($p = 0.03$), and leukocytes ($p < 0.0001$), these factors were not significantly associated with false positive pregnancy results. No patient factors or UA results were associated with increased likelihood of false positive OTC pregnancy test results.	patients who have an unexpected positive pregnancy test before transplant.

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