

“Background” Human Chorionic Gonadotropin in Healthy, Nonpregnant Women

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The report by Snyder et al. (1) in this issue of *Clinical Chemistry* solidifies at long last the use of 5 IU/L human chorionic gonadotropin (hCG) as a cutoff for detection of pregnancy. Although this cutoff has been widely used for many years, the studies to support it have included only limited numbers of nonpregnant women (2–5). This new study (1), for the first time, includes a large number of nonpregnant women ($n = 240$) of peak child-bearing age (18–40 years). Although the 97.5th percentile for this group was 2.5 IU/L and one woman had an hCG of 4.6 IU/L, the bulk of the cases had undetectable hCG, <2 IU/L. Clearly, to make a close to absolute detection of pregnancy in women 18–40 years of age, the serum hCG must be >5 IU/L to exceed the “background” hCG concentrations that are present in serum of healthy, nonpregnant women.

Some applications for hCG testing, such as monitoring gestational trophoblastic diseases, require more sensitive hCG detection (6). These are applications looking for recurrence or persistence of disease in women with a demonstrated history of gestational trophoblastic disease. With this consideration, many manufacturers’ hCG tests report results as low as 1 IU/L. Considering these important findings, it is critical that all reported hCG results note that use of cutoffs <5 IU/L to diagnose pregnancy produces a large number of false-positive results.

This timely publication (1) also examines in large groups ($n = 240$) the increased hCG in perimenopausal (41–55 years) and postmenopausal (>55 years) women. The authors (1) report hCG results as high as 7.7 IU/L in the perimenopausal group and 13.1 IU/L in the postmenopausal groups. The 97.5th centiles for the younger, peri-, and postmenopause groups were 2.5, 4.8, and 7.7 IU/L, respectively. It is appropriately suggested that, when such hCG concentrations are detected in perimenopausal women, follicle-stimulating hormone (FSH) testing be performed to determine whether the patient is in menopause.

A fundamental question is the nature and source of the hCG measured in the serum or plasma of healthy, nonpregnant women and why it is increased with the onset of menopause. To explore this issue, it is useful to review the physiology of the pituitary–gonadal axis. The gonadotrope cells of the pituitary produce luteinizing hormone (LH) and FSH under the control of hypothalamic gonadotropin-releasing hormone (GnRH). GnRH production is decreased by ovarian steroids. Starting in the perimenopausal period and intensifying in menopause, the ovarian steroid production decreases, thus limiting progesterone and estrogen feedback control of GnRH secretion. As a result, continuous GnRH stimulation of gonadotrope cells occurs, leading to increased LH and FSH production. Under this hyperstimulation, the pituitary may secrete an hCG-like molecule (7–9). Pituitary hCG is the cause of increased serum hCG results in nonpregnant women,

most notably in the peri- and postmenopausal periods (4–9). Not surprisingly, pituitary hCG is suppressed by estrogen/progestagen contraceptive pills (4, 6, 7, 9).

Pituitary hCG was first reported 30 years ago by Chen et al. (10); these findings were confirmed in 1983 by Hartree et al. (11). In 1987, Odel and Griffin (3) found that pituitary hCG production, like the pituitary’s production of LH and FSH, was pulsatile. In that same year, Stenman et al. (4) showed that pituitary hCG production, like production of LH and FSH, was modulated by GnRH and sex steroids. It was not until 1996 that Birken et al. (8) showed that pituitary hCG had N-linked sugar side chains resembling those of LH rather than those of pregnancy hCG; thus the wording “hCG-like molecule” has been used. It has taken almost 30 years to elaborate on the clinical significance of basic science discoveries.

Snyder et al. (1) point out that care is needed in interpreting a positive hCG result in peri- and postmenopausal women. Realistically, for pregnancy to be considered likely, hCG results need to exceed concentrations of at least 20 IU/L (1, 6). For a successful term pregnancy, hCG should then at least double every 2 days until 8 weeks of gestation (12). In cases in which persistently low hCG results are detected, malignancies may be considered (6). Trophoblastic malignancies make intact hCG dimer, whereas other malignancies primarily produce the free β -subunit of hCG (6, 13, 14). Both are detected by modern intact hCG assays. Pituitary production of hCG, or extreme cases of background hCG, always must be considered (1, 6), particularly in women who are peri- or postmenopausal. Pituitary hCG production can easily be excluded by showing that hCG production is suppressed by treatment for 3 weeks with a high-progesterone oral contraceptive pill (4, 6).

Among the cases we see each year of hCG concentrations that do not correspond with clinical observations (6), ~ 5 –6 are explained by the presence of pituitary hCG (6). Among 19 cases that we have diagnosed as pituitary hCG, 3 had undergone prior therapy for assumed cancer and 2 had been treated for suspected recurrence of gestational trophoblastic disease. In each of the 19 cases, suppression by treatment with a high-progesterone oral contraceptive pill was recommended. Among 11 cases for which feedback was received, the pill completely suppressed hCG in 10 cases and partially suppressed it in the other. Of the 19 women, 11 were considered to be perimenopausal and 8 postmenopausal based on the age criteria used by Snyder et al. (1) in this issue. In the perimenopausal group, hCG ranged from 1.2 to 11.4 IU/L, and in the postmenopausal group, it ranged from 3.5 to 16 IU/L. It is inferred that most of these cases came within the extremes or 95th centile of the ranges reported here by Snyder et al. (1).

The findings published in this issue by Snyder et al. (1) are landmark in finally confirming the 5 IU/L cutoff for

pregnancy. Importantly, they restrict their conclusion to women 18–40 years of age. As demonstrated by Snyder et al. (1) and as seen in our experience, it is important for laboratorians and physicians to recognize that background hCG from the pituitary increases in peri- and postmenopausal women. Pituitary hCG needs to be excluded before women are inadvertently treated for malignancy. Ideally, test reports should warn of the potential for error of using hCG cutoffs <5 IU/L as indicators of pregnancy and should indicate that higher hCG may be observed in women >40 years of age. Laboratory directors need to be able to advise clinicians on the interpretation of positive hCG results.

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