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Short Communication

Retrospective evaluation of 99th percentile hCG results to adjust clinical decision points

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ABSTRACT

While accurate measurement of chorionic gonadotropin (hCG) is necessary, so are appropriate clinical decision points (CDPs) for patients of all ages. The CDP for hCG is intended to identify early pregnancy in patients of child bearing age; non-pregnant patients who are older frequently yield hCG results > 5 IU/L, making the use of a low hCG CDP problematic for these patients. Using a retrospective review of all hCG results generated over a 32-month period, 8507 hCG results from non-pregnant females of all ages were analyzed. Patients < 40 years of age comprised 74% of hCG measurements, and produced hCG results ≥ 5 IU/L 1% of the time, but this frequency increased in patients 40–49 (17% of hCG results; 4% ≥5 IU/L) and ≥50 (9% of hCG results; 20% ≥ 5 IU/L). While only 3% of hCG results were ≥5 IU/L in the overall data set, all (24/24) of hCG results 10–14 IU/L came from patients ≥ 40 years of age and all (3/3) hCG results ≥ 15 IU/L came from patients ≥ 50 years of age. The 99th percentile hCG results in the population were 3 IU/L in patients < 40, 7 IU/L in patients 40–49, and 13 IU/L in patients ≥ 50 years of age. These findings demonstrate a progressive increase in measurable hCG correlating to patient age and demonstrate a proof-of-concept that institutions could assess 99th percentile hCG results to assign more appropriate method-dependent CDPs to different age groups.

1. Introduction

Though a relatively infrequent finding, "equivocal" (eg, > 5 IU/L but < 20 IU/L) chorionic gonadotropin (hCG) results can delay needed imaging studies, drug administration, and other interventions in female patients. Emergency and Radiology Departments are particularly susceptible to delays in care delivery when these findings arise, but delays can also occur in facility pharmacies, pre-surgery and chemotherapy units, and in other clinical service settings. While most equivocal hCG results are associated with known fetal demise, miscarriage, postpartum hormone declines, and ectopic pregnancy cases, a subset is found in non-pregnant patients.

It is now well-known and widely accepted that menopausal females demonstrate low-level pituitary release of hCG that surpasses concentrations noted in non-pregnant females of childbearing age [1,2]. In recent years, updated reference intervals, and the pairing of hCG and FSH measurements [3], have been proposed for assessing hCG results in menopausal patients to account for this change; in particular, the primary group proposing these changes in the United States has suggested that a cutoff of 14 IU/L be used for patients ≥ 55 years of age, and confirmed this figure from a local data set including 798 women in this age group [4].

Due to inquiries from the WVU Medicine Emergency Department leaders at the JW Ruby Hospital (WVU Hospital, WVUH) regarding ways to better handle equivocal hCG results, a retrospective analysis was performed using local consecutive data in an expanded population set, to determine if similar adjustments to CDPs could be made at WVUH.

2. Methods

Retrospective analysis of all hCG results generated at WVUH in a 32-month period was performed to assess hCG results in patients of all ages, to determine if updating hCG CDPs by age was a feasible approach. Every quantitative hCG result generated at the WVUH from 7/9/2016 (go-live of Epic Beaker) to 3/14/2019 (day of the report) was pulled in a workbench report from Epic Beaker (2018 Edition; Epic Systems Corporation, Verona, WI USA). Tests performed on males were immediately excluded, leaving 13,255 hCG results on female patients. Data were sorted by medical record number and date to group hCG results to patients. Ordering locations consistent with Obstetrics & Gynecology or Oncology, single hCG results > 100 IU/L, and results with no associated clinical notes were excluded. Remaining hCG results > 5 IU/L prompted chart review to determine the reason for the testing and if there was a known OB/Gyn or oncological purpose (eg, monitoring pregnancy, decline, or intervention, or diagnosing and

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monitoring chorionic and other hCG-secreting tumors); such cases were excluded. After data culling, 4847 results were excluded as "true-positive" (35%) and 8507 presumed true-negative hCG results remained on female patients of all ages.

In the culled data set, age bins (in years) were initially established in 5-year intervals. For each bin, percentile hCG results were calculated: 2.5th, median/50th, 97.5th, and 99th. Counts of hCG results from " < 1" to " > 20" were counted for analysis of result frequency and distribution by age, with binning for results " < 1", < 5, 5–9, 10–14, 15–19, and ≥20 IU/L; the ≥20 IU/L bin was eliminated, as no results were found in the data set after culling. For counting purposes and percentile calculations, results " < 1" were assigned a result of "0". Given low numbers for many of the age groups with the 5-year binning approach, age bins were subsequently collapsed to < 40, 40–49, and ≥50 years to allow for ample bin sizes with comparable percentile results. Variance and FTEST calculations guided configuration of student's t-tests for comparisons; the < 40 age bin was compared to the 40–49 and ≥50 age bins, and the 40–49 age bin was compared to the ≥50 age bin. *P*-values < 0.05 were considered significant. The data set, calculations, and all plots generated from the set have been provided as Supplemental Data.

Microsoft Excel Redmond, WA, USA was used for all data analysis and figure generation. The research qualified as quality assurance review employing summative data upon reporting, and as such, was exempt from IRB review. The measuring method for hCG was the Abbott (Abbott Diagnostics Corp., Abbott Park, IL, USA) ARCHITECT i2000 total β-hCG test. This reagent recognizes intact hCG and β-subunit, as well as nicked forms of hCG and β-subunit, but does not recognize the β-subunit core fragment [5].

3. Results

As shown in the Table 1, 6270 (74%) of the 8507 hCG results in the culled data set came from patients < 40 years of age, 1464 (17%) from patients 40–49, and 773 (9%) from patients ≥ 50. Results < 5 IU/L composed 97% (8253/8507) of the overall data set. In patients < 40 years of age, results < 5 IU/L composed 99% of results (6234/6270); in patients 40–49, 96% (1402/1464); and in patients ≥ 50, 80% (617/773). Equivocal (≥5 IU/L) results composed 3% (254/8507) of the overall data set. In patients < 40 years of age, equivocal results composed 1% of results (36/6270); 40–49, 4% (64/1464); and ≥ 50, 20% (156/773).

Also shown in the Table 1, hCG results " < 1" IU/L (ie, undetectably low) composed 87% (7410/8507) of the overall data set. In patients < 40 years of age, " < 1" IU/L results composed 97% (6074/6270) of hCG results; 40–49, 76% (1117/1464); and ≥50, 28% (219/773). Results 5–9 IU/L were unevenly distributed, with 16% (36/227) in patients < 40 years of age, 26% (59/227) in patients 40–49 years of age, and 58% (132/227) in patients ≥ 50 years of age. All (24/24) results 10–14 IU/L came from patients ≥ 40 years of age, and all (3/3) results ≥ 15 IU/L came from patients ≥ 50 years of age.

Table 1

hCG Result Bin, IU/L	COUNT (%)	COUNT (% of age bin) *% of hCG bin*		
	ALL	< 40 years	40–49 years	≥50 years
< 5	8253 (97)	6234 (99) *76*	1402 (96) *17*	617 (80) *7*
≥5	254 (3)	36 (1) *14*	62 (4) *24.5*	156 (20) *61.5*
" < 1"	7410 (87)	6074 (97) *82*	1117 (76) *15*	219 (28) *3*
1–4	843 (10)	160 (2.5) *19*	285 (19) *34*	398 (51) *47*
5–9	227 (2.6)	36 (< 1) *16*	59 (4) *26*	132 (17) *58*
10–14	24 (0.3)	0 (0) *0*	3 (< 1) *12.5*	21 (2.7) *87.5*
15–19	3 (< 0.1)	0 (0) *0*	0 (0) *0*	3 (< 1) *100*
Total	8507 (100)	6270 (74)	1464 (17)	773 (9)

A dot-plot result distribution of hCG by age bins is shown in the Fig. 1. While no hCG results > 9 IU/L were found in patients < 40 years of age, results up to 11 IU/L were found in patients 40–49 years of age, and results up to 17 IU/L were found in patients ≥ 50 years of age. Population-based 99th-percentile hCG result in IU/L [95th percentile interval, IU/L; maximum result, IU/L] in non-pregnant females < 40 years of age was 3 [0–1; 9]; for patients 40–49, 7 [0–5; 11]; and for patients ≥ 50, 13 [0–10; 17]. Variance in hCG results by age bin differed significantly – 0.414 IU/L in patients < 40 years, 2.319 IU/L in patients 40–49 years ($P < 0.001$ vs < 40), and 7.785 IU/L in patients ≥ 50 years ($P < 0.001$, vs < 40 and vs 40–49).

4. Discussion

While hCG tests yield clear negative (< 5 IU/L) results in the majority of patients in this retrospective review (Table 1) and in the literature [3,4], equivocal results do arise in patients (Table 1 and Fig. 1), and this study demonstrates that equivocal results occur with increasing frequency as age increases. This tendency can delay care delivery when the decision to proceed with intervention hinges on hCG results and abnormality is defined by a single, low CDP (eg, 5 IU/L). For example, despite the ≥50 year age group comprising the smallest bin (773/8507, 9%) of hCG results, these patients contributed 58% (132/227) of results 5–9 IU/L, 87.5% (21/24) of results 10–14 IU/L, and 100% (3/3) of results 15–19 IU/L. Additionally, patients 40–49 years of age yielded intermediate proportions of results in each hCG result bin when compared to the older and younger bins (Table 1 and Fig. 1). Thus, despite the numbers of specimens with equivocal results being relatively low (254/8507, 3%) overall, these situations arise disproportionately in patients that would be considered perimenopausal or menopausal. These findings represent a need for age-appropriate CDPs to enable rapid clinical decision making if universal hCG testing is institutional protocol, and suggest that an intervention to reduce testing altogether in patients > 50 years of age is feasible.

The analysis provided in this study provided three important findings. First, the study demonstrates a similar 99th percentile hCG result in the WVUH population ≥ 50 years of age (13 IU/L) compared to the upper limit derived in the study conducted by Patel et al. [4]. When the local data set was binned to an age group ≥ 55 years of age (287 patients; Supplemental Data) to match the age binning in the referenced study, the 99th percentile hCG result at WVUH was 12 IU/L, with maximum hCG result of 16 IU/L, which is also highly comparable. Second, this analysis proposes a new intermediate clinical decision point for patients that could be considered perimenopausal, owing to their age (40–49 years) and the 99th percentile result of 7 IU/L. Third, the finding of a 99th percentile hCG result of 3 IU/L in patients < 40 years of age prompts new questions about whether there is a critical/statistical difference between the 99th percentile result derived from our data set, and the CDP given in the package insert (5 IU/L) for the reagent used; deeper statistical analysis, and potentially more data, are indicated to determine if the current in-house CDP requires adjustment.

The use of 99th percentile results rather than 95th percentile intervals in this study was rooted in the predominance of unmeasurably low results in a large portion of patients across age bins. This finding for hCG results mirrors markers like cardiac troponin, which are typically very low or absent in non-diseased individuals, and for which the guidance of using a single CDP representing 99th percentile results for clinical decision-making is given [6]. These findings in the data, and similarity in distribution to markers already defined by their upper

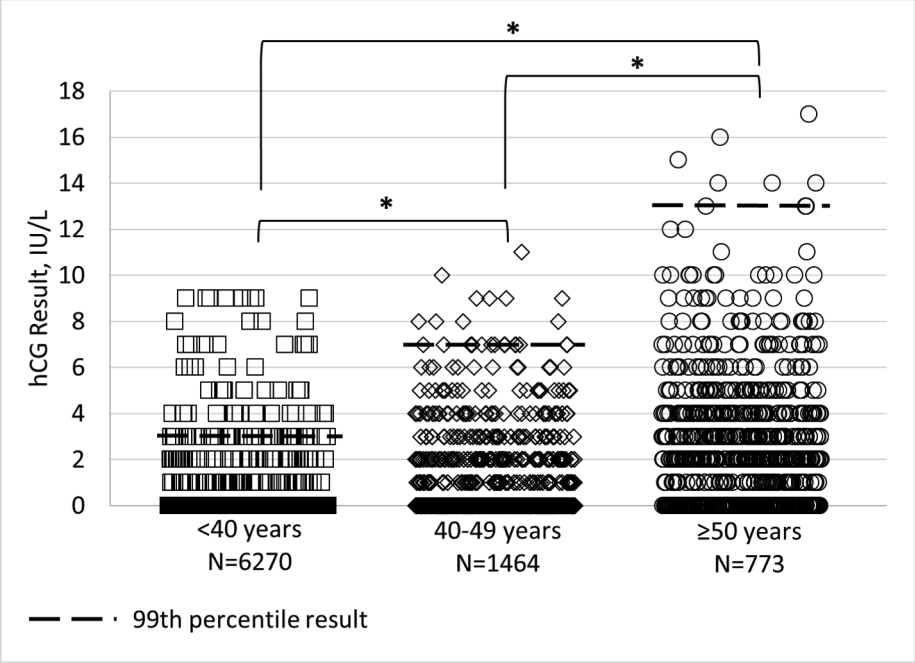

Fig. 1. Jittered dot plots of hCG results from patients by age bin. The number of patients in each group is given below the x-axis label. The 99th percentile hCG result for each age bin is indicated with a dashed line. *, $P < 0.001$ by one-tailed heteroscedastic students' *t*-test.

decision limits, imply that population-based reviews of hCG data can and likely should be used to inform tailored CDP-setting at or near a 99th percentile result limit, based on local reagents used and their recognition of β-hCG subunit [5].

The strengths of this retrospective review included extraction of continuous hCG results over a period of 32 months, with use of chart review and exclusion criteria intended to narrow the data set to hCG results representing non-pregnant patients of all ages; these data represent testing performed in ambulatory, emergency, and inpatient facility settings. From the 8507 records obtained after data culling, the inclusion of younger women of childbearing age was possible and provided a negative control group to check the general success of the data review/culling process and confirm that most results in this non-pregnant control group indeed fell below the current CDP of 5 IU/L. The continuous data set – both in terms of time and patient age – demonstrates that the reagent used and population tested were representative of actual prevalence among patients tested. These are important factors in making the consideration of assessing alternate CDPs for other age groups. A final strength of this study is that it confirms the findings of Patel et al. [4] in a separate, large, and geographically distinct patient group tested with the same analytic platform and reagent.

The limitations of this study include inability to efficiently assess actual menarchal status, medications and diagnostic associations that may suggest central stimulation of pituitary hCG release, and lacking parallel measurement of FSH because it is not a routine part of the clinical workup used. An additional limitation was that the analysis was method-specific, since only the Abbott ARCHITECT i2000 method was used in measuring hCG; all institutions seeking to replicate this analysis should consider the performance of the method used, given lacking standardization for hCG measuring assays. These limitations restrict the ability to determine the root cause of equivocal hCG results in a broader population of patients that are younger than the ones previously studied by Patel et al. [4]. While it is possible that medication-associated stimulation of pituitary hCG release underlies the increasing frequency of equivocal hCG results in non-pregnant patients – as has been noted for prolactin, TSH, and other hormones released by the pituitary [7–10] – significantly more study is necessary in this area.

From this study, recommendations have been sent to the WVUH Emergency Department and obstetrics groups, to confirm retention of the 5 IU/L clinical decision point for patients < 40 years of age until more analysis of this CDP can be completed, but also to consider new CDPs of 7 IU/L (for patients 40–49 years of age) and 13 IU/L (for patients ≥ 50 years of age). Given the high configurability of modern electronic health records and laboratory information systems, this stratified approach is easily attainable and should further reduce situations where hCG results delay healthcare delivery.

5. Conclusions

Using a retrospective, expanded review of historical hCG results, institutions can assess current and proposed clinical decision points for hCG to tailor local settings and prevent care delays, and should pay special attention to the clinical decision points used for patients ≥ 40 years of age.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2019.10.007.

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