Current Practices When Reporting Quantitative Human Chorionic Gonadotropin Test Results

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David G. Grenache.
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Guest: Dr. David Grenache is the chief scientific officer and medical director of the chemistry, immunology, and esoteric analytic chemistry labs at TriCore Reference Laboratories in Albuquerque, New Mexico, and a clinical professor of pathology at the University of New Mexico.

Randye Kaye: Hello and welcome to this edition of JALM Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Human chorionic gonadotropin, or hCG, has long been the biomarker of choice for determining pregnancy status. Despite hCG's widespread availability and use, there are no clear standards or best practice recommendations to guide clinical laboratories in reporting hCG results. Labs may use different reference intervals and different clinical interpretation criteria. Further, they may or may not have different reporting parameters for hCG results reported in males such as for the purposes of monitoring hCG as a tumor marker.

An article in the September 2020 issue of JALM analyzes survey responses from over 3500 laboratories regarding their practices for offering and reporting quantitative hCG testing. The author of the article is Dr. David Grenache. Dr. Grenache is the chief scientific officer and medical director of the chemistry, immunology, and esoteric analytic chemistry labs at TriCore Reference Laboratories in Albuquerque, New Mexico. He is also a clinical professor of pathology at the University of New Mexico. Dr. Grenache is currently serving as AACC's 2020-2021 President and we're excited to welcome him back as our guest for this podcast. Welcome back Dr. Grenache. Why were you interested in comparing the hCG reference intervals used by laboratories when reporting quantitative hCG results?

David Grenache: Well, for many years, hCG has been a subject of my research interests including analytical issues and its clinical applications. And something that became clear to me a really long time ago was that there was wide variation across laboratories when they reported hCG test results and I thought that was interesting. There are also no clear standards or best practice recommendations to guide clinical labs when reporting these results and understanding current practice is the first step to developing some sort of guidance recommendations, and I'd like to pursue that next.

Randye Kaye: All right. What surprised you most about the results of the survey?

David Grenache: Oh, there are a lot of things that surprised me. First, although I knew anecdotally that reporting practices were very varied, it was the wide variation that the survey revealed that was unexpected. As an example, among labs that used a single reference cutoff for identifying elevated hCG, there were 17 different cutoffs that were reported, and they range from anywhere from a low of 0.9 to an upper limit of 50. I was also surprised that the majority of labs, 69%, report results with more than one cutoff and apply an interpretive comment like positive, negative, or indeterminate and I just don't see the value of interpretive comments for hCG test results. I think they're unnecessary and outdated. And I am sure that they are in reference to a woman's pregnancy status, but hCG is not just used for determining a woman's pregnancy status. The use of the word "indeterminate" I think is particularly outdated. It's my opinion that an indeterminate interpretation is not clinically useful when hCG is used as a biomarker of pregnancy.

In the healthcare setting, it's the detection of any possible pregnancy that matters, and saying that an hCG result is indeterminate suggests that there's some uncertainty in the measurement that's just not supported by evidence. Another unexpected result was that 60% of labs reported gestational age-based reference intervals. And now that might sound like a good idea, but in reality, these gestational age-based reference intervals are so wide, you can drive a truck through them.

In addition, there are far more reliable estimates of gestational age that are based upon things like the date of the last menstrual period or an ultrasound assessment of the fetus. So, I just don't see a lot of value in these gestational age-based reference intervals. And the last thing that surprised me and actually, it wasn't much of a surprise at all, I think it's unfortunate that a minority of labs, only 25%, report male specific hCG reference intervals. hCG has well-established clinical value as a tumor marker in some testicular cancers and studies have clearly demonstrated that different hCG cutoffs are needed for men although even there, there remains some disagreement about what those cutoffs should be.

Randye Kaye: All right. Thank you. So, you've already spoken about the wide variation in reporting practices, gestational age-based reference intervals and then that a majority of labs don't report the reference intervals for males. So, I just want to ask you if you have any idea why you think these varieties,

these variations exist? Let's talk about the wide variation in reporting practices with the test results first.

David Grenache: Yeah. It's a really interesting phenomenon and at first glance, it does seem strange. After all, reference intervals and cutoffs are commonly determined from "normal" or reference populations. And it seems like we could do the same thing for non-pregnant women and for males. And actually, there are several studies that have done just that. However, those results from those different studies have also been very different and that is likely due to the analytical differences that we know exist across different hCG test platforms. hCG is a really complicated hormone and there are several variants of hCG that have been characterized. And it's that molecular heterogeneity, that's one reason why hCG assays are not harmonized. That means, different hCG assays will yield different results when the same sample is analyzed. But that is not the only reason for the variation in reporting practices that the survey revealed. I think another contributor is the different clinical uses of hCG tests. They're mostly used to determine a woman's pregnancy status, but testing for pregnancy is not limited only to women in their reproductive years and I've seen hCG test being used to identify possible pregnancies, in women who are well into their 60s and even their 90s. And it has been well documented that hCG can be increased in these older women, not due to pregnancy, and that necessitates the use of age-based reference intervals.

Studies evaluating appropriate hCG cutoffs in men have also not been uniform in their conclusions. And lastly, my survey showed that nearly 50% of labs utilize reference intervals or cutoffs that were provided in the manufacturer's product insert and those too show wide variation. So, taken together, it's not surprising that there is so much variation in hCG reporting practices.

Randye Kaye: So, the only thing we haven't really spoken about in terms of what causes it is the reference intervals for males where there is clinical value. What do you think is the cause of these inconsistencies?

David Grenache: I think hCG reference intervals for males is really important and I think that they're not widely used because in the manufacturer's package insert where they state the intended use of the hCG test, they only indicate the detection of pregnancy. There is no hCG assay that's commercially available in the United States that has received approval from the FDA for clinical use as a tumor marker. And because of that, labs are very likely to consider that an hCG test use in males, that it would be an off-label application. And then they would consider that off-

label application to be a modification of the test which means it would meet the definition of a laboratory developed test, which is something many labs are hesitant to offer because of increased regulatory requirements. However, in my opinion, that reasoning is incorrect.

The FDA defines a lab developed test as "an in vitro diagnostic that is intended for clinical use and designed, manufactured, and used within a single laboratory." And I note that this definition does not include a statement about intended use. Likewise, the clinical laboratory improvement amendments require laboratories to verify or establish analytical performance specifications of a test, but not clinical utility. And further, the College of American Pathologists requires that laboratories that it accredits, to validate clinical claims that are not included in the manufacturer's instructions, but only when the test result is accompanied by a clinical claim, such as diagnostic sensitivity or specificity, and a reference interval or a cutoff is not a clinical claim.

Randye Kaye: So, if you could wave a magic wand and change hCG reporting practices for everybody, what would be the outcome?

David Grenache: Oh, if only I could wield such power.

Randye Kaye: We would all like a magic wand.

David Grenache: Well first, I would harmonize hCG assays so that they would return the same numeric value for the same sample. Second, I would establish a single reference cutoff for hCG in males and chronological age-based specific cutoffs in non-pregnant females. That would also result in the removal of misleading interpretive comments like negative and indeterminate and positive from being attached to hCG results. And third, I would include a statement about hCG's clinical utility as a tumor marker in the intended use section of hCG assay product inserts.

Randye Kaye: All right. Very interesting. Thank you so much for joining us again today.

David Grenache: Oh, my pleasure Randye. Thank you very much.

Randye Kaye: That was Dr. David Grenache from TriCore Reference Laboratories, describing the JALM article, "Current Practices When Reporting Quantitative Human Chorionic Gonadotropin Test Results." Thanks for tuning in to this episode of "JALM Talk." See you next time and don't forget to submit something for us to talk about.