Qualitative Point-of-Care Human Chorionic Gonadotropin Testing: Can We Defuse This Ticking Time Bomb?

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Qualitative point-of-care (POC) human chorionic gonadotropin (hCG) testing is routinely performed on urine samples obtained in the Emergency Department (ED) or before surgery to rule out pregnancy and prevent fetal injury or death. Because potentially harmful treatments are allowed to proceed on the basis of a negative hCG test result, false-negative results can have disastrous consequences.

We recently evaluated the performance of 11 common qualitative POC hCG devices and determined that 9 of the 11 devices were susceptible to false-negative results caused by hCG β core fragment (hCGβcf) (1). Although that study highlighted important limitations of these devices in a research laboratory setting, it was unclear whether users experience false negatives in clinical practice. We performed a search of the FDA’s Manufacturer and User Facility Device Experience (MAUDE) database using the search term “MAUDE pregnancy false negative” (2). Our findings are shown in Figure 1. Seven hundred seven reports described false-negative POC hCG results in women shown to be pregnant at the time of testing. Ninety-one different POC hCG devices were described from 14 manufacturers, including 10 of the 11 devices evaluated in our initial screening study.

On the basis of the descriptions in the MAUDE report, false negatives were subdivided by potential cause unknown, likely hCGβcf hook effect, and likely limit of detection. One hundred forty-two reports were likely due to hCGβcf hook effect, and 10 (7%) of those were associated with adverse outcomes. Although the exact cause of the false-negative results cannot be conclusively established, interference by high concentrations of hCGβcf potentially occurred in >200 patients.

It is virtually certain that many more false-negative test results have adversely affected patient management but have gone unreported. Furthermore, these false-negative results occurred with many of the currently available devices, indicating that this problem is not limited to a single manufacturer or a period of time in the past but represents a much larger public health issue that must be addressed. To reduce the frequency of false-negative POC hCG test results, coordinated efforts from multiple parties are required.

Manufacturers and the FDA

The FDA and device manufacturers should take steps to market products with improved performance characteristics. In defense of their products, manufacturers often point to the fact that their devices are intended for use in early pregnancy, when urine hCGβcf concentrations are not high enough to interfere with device performance (3). This may be the manufacturers’ recommendation, but it is no secret that the current clinical practice, at most institutions, is to perform urine hCG testing on all women who present to the ED, regardless of symptoms or likelihood of advanced pregnancy. Therefore, POC hCG devices are regularly used to guide clinical management of pregnant women with high concentrations of hCGβcf, and thus POC hCG devices must reliably generate a positive signal in this patient population.

It is our understanding that the FDA has acknowledged the need for POC hCG devices that are not susceptible to hCGβcf interference by requiring that all new devices generate positive signal in the presence of high concentrations of hCGβcf. Unfortunately, this requirement does not apply to previously approved devices, leaving manufacturers free to choose whether to modify currently available products known to be negatively affected by hCGβcf.

Collectively, the FDA and device manufacturers can make a significant positive contribution by ensuring that all POC hCG devices available for purchase generate positive results in all pregnant women, including those with high urine concentrations of hCGβcf.

Clinicians

Clinicians can also make meaningful contributions by implementing appropriate use of available testing methods. Extensive literature indicates that most currently
available POC hCG devices have inherent limitations, including false negatives due to dilute urine, early gestational age, or increased hCG or hCG/βcf (1, 4–9). Unfortunately, these same devices are often inappropriately used to make crucially important decisions in a vulnerable patient population. Clinicians who advocate for the use of urine POC hCG testing on the grounds that it speeds up patient management must first understand the risks associated with making important clinical decisions on the basis of qualitative POC urine hCG urine tests. In many cases, urine qualitative testing is performed on women who are known to be pregnant or present with vaginal bleeding and cramping or other symptoms that suggest abnormal pregnancy. In these women, a negative urine qualitative test result can delay proper treatment and may allow improper treatment that can result in fetal harm or death.

At most large institutions, serum quantitative hCG measurement can be performed in a time frame that meets clinical requirements. Serum quantitative measurement is preferred over urine qualitative testing because of the absence of hCG/βcf in serum, increased...
sensitivity of serum quantitative assays (5 IU/L) relative to urine qualitative devices (20 or 25 IU/L), higher hCG concentrations in serum relative to urine, and lack of sample dilution due to fluid volume status. We recommend that clinicians at large institutions perform serum quantitative hCG measurement in place of urine qualitative testing, with the understanding that any modest increases in testing turnaround time are offset by increases in the accuracy and sensitivity of the test result.

Ultimately, we urge clinicians to take each patient’s clinical symptoms into account when deciding how to assess pregnancy status. In women with a high clinical suspicion of pregnancy, serum quantitative measurement is the best testing option. In these women, urine qualitative testing is redundant at best and often dangerously misleading. By refraining from inappropriately performing urine qualitative POC hCG testing on women with a high clinical suspicion of pregnancy, clinicians can reduce the incidence of false-negative POC hCG test results.

Laboratorians

As the clinical group ultimately responsible for the accuracy of laboratory tests, laboratorians must also take steps to reduce the incidence of false-negative results. Laboratory personnel should initiate dialog with clinicians at their institutions and emphasize the need to modify the testing approach on the basis of the patient’s presenting symptoms. Additionally, the laboratory should encourage the use of serum quantitative testing whenever possible and work to minimize turnaround time to make serum quantitative testing performed in the central laboratory more appealing to their clinical colleagues. Turnaround time can be decreased by communicating a “positive above linearity” result to the ED for samples that generate an initial result greater than the assay’s analytical range. Subsequent dilution should be performed to generate a quantitative result. If qualitative testing must be performed, laboratorians need to thoroughly evaluate all available options and select the device that provides an optimal combination of sensitivity and lack of susceptibility to interference caused by increased concentrations of hCGβcf. Finally, laboratory personnel should be able to identify a false-negative result caused by high concentrations of hCGβcf by diluting the sample and observing stronger positive signal in the diluted sample relative to the original sample.

Conclusion

When presented with the potential consequences of false-negative POC hCG urine testing and the fact that little has been done to improve the performance of existing devices despite the initial report in 2008 (5) of false-negative results caused by increased hCGβcf and additional cases reported to the FDA every year, it is natural to inquire what will be required to bring about meaningful change. For manufacturers, a positive motivating factor might be the desire to gain increased market share by demonstrating superior performance of a device that is unaffected by hCGβcf. Because no movement in this direction has been observed to this point, it is more likely that loss of revenue and significant negative publicity caused by a high-profile lawsuit because of patient mismanagement caused by a false-negative result will force manufacturers to modify their devices. Unfortunately, it is likely that this same type of negative publicity caused by a false-negative result will be required to ultimately convince clinicians to give up urine qualitative POC testing performed in the ED in favor of quantitative serum testing performed in the central laboratory. As for the FDA, it is unlikely that improvement in currently available devices will be required until the FDA feels obligated to act to eliminate patient safety concerns. Because no studies have established the prevalence of false-negative results caused by hCGβcf, further work may be necessary to demonstrate the magnitude of this public health issue and convince the FDA to mandate changes to currently available devices.

We believe that many of the currently available POC hCG devices present a risk to patients that can be partially mitigated by correct usage enforced by clinicians and laboratory personnel. As a long-term solution, we hope that the FDA and device manufacturers choose to improve devices before a high-profile case of patient mismanagement forces their collective hand.

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