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

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R. Nerenz and A. Gronowski.
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Guests:
Drs. Ann Gronowski and Robert Nerenz are from the Department of Pathology and Immunology at the Washington University School of Medicine in St. Louis.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Rapid urine pregnancy tests have been available for over 30 years. They can be performed in minutes and are used at home, in doctors' offices and in emergency rooms. Doctors in particular rely on these tests to rule out pregnancy in order to prevent fetal injury or death that could be caused by certain medical procedures or drugs.

For that reason, in healthcare settings incorrect results can have disastrous consequences. The March 2015 issue of *Clinical Chemistry* published an opinion paper by Dr. Ann Gronowski and Dr. Robert Nerenz at the Washington University School of Medicine in St. Louis, that discussed the problem of false pregnancy test results and issues that need to be addressed in order to reduce this problem.

On this podcast we have both Dr. Gronowski, who is Professor in the Departments of Pathology and Immunology and Obstetrics and Gynecology, who led this research study, and her co-author Dr. Nerenz, a fellow in the Department of Pathology and Immunology.

Dr. Gronowski, let's start with you, we have talked to you before about false negative results in point of care and home pregnancy devices. Just refresh our memory a bit, on what some of the causes are of false negative results?

Dr. Ann Gronowski: Sure! The most common causes of false negative urine pregnancy results are of course testing the patient too early in gestation. In other words, the concentrations of the pregnancy hormone hCG are too low to detect.

Second would be dilute urine. Unlike serum, urine will be affected by the amount of fluids that a person drinks. So the concentrations of hCG in the urine can be quite low if the patient has had a lot of fluid intake.

Third, is the so-called hook effect. This occurs in women with very, very high concentrations of hCG due to some pathological conditions such as gestational trophoblastic disease or hyperemesis gravidarum.

Even though the hCG concentrations are very high in these patients, a false negative test is observed. So these days this problem doesn't occur often because these pathological conditions are actually pretty rare and manufactures have modified their devices to accommodate very high concentrations of hCG.

And then finally, false negatives due to a form of hCG called hCG beta core fragment. This problem is dependent on the pregnancy device that's used, and it occurs in normal women with normal concentrations of total hCG.

So as you know, we have discussed this in several previous podcasts, and it occurs because certain pregnancy devices do not recognize hCG beta core fragment. After five weeks of pregnancy, some women make so much hCG beta core fragment that it prevents a positive signal, similar to that which is seen in the hook effect.

Bob Barrett: Now, Dr. Nerenz, over to you, the opinion piece discusses the causes of these false negative results, how did the idea for this article get started?

Dr. Robert Nerenz: Well, recently we published a paper that evaluated 11 of the most commonly used point of care pregnancy tests, which are the devices used in hospitals. And we were surprised to find that 9 of the 11 were susceptible to false negative results caused by hCG beta core fragment. So while that study highlighted the limitations of these devices in a research setting, it was unclear whether users actually experienced false negatives in clinical practice.

So, as one way to approach this question, we performed the search of the FDA's website, looking for “Manufacturer and User Facility Device Experience” or MAUDE reports, and these are reports of problems filed with the FDA from users of really any kind of medical device.

Bob Barrett: That's interesting! What did you end up finding?

Dr. Robert Nerenz: Well, using the search term “MAUDE pregnancy false negative” we found 707 reports between 2000 and 2014 that described false negative urine hCG results in women shown to be pregnant at the time of testing. 91 different point of care hCG devices were described from 14 different manufacturers, including 10 of the 11 devices that we evaluated in our initial screening study.

So then based on the description in the MAUDE report, we subdivided the false negatives by potential cause, and in 433 of these reports, the cause for the false negative result was unknown. In 132, the likely cause was that the hCG concentration was so low that it was below the limit of detection for the test device. Of these 132, 9 were associated with adverse events.

We also found that 142 reports were likely due to hCG beta core fragment hook effect, and 10 or 7% of these were associated with adverse events.

Bob Barrett: Doctor, you talked about adverse events right there; what kind of adverse events are you talking about, what did you find?

Dr. Robert Nerenz: Well, that's an excellent question! The adverse events in these pregnant women varied from either delayed prenatal care, radiology being performed, delayed treatment of ectopic pregnancy, and even surgery resulting in miscarriage.

I should point out that it's virtually certain that many more of these false negative test results have adversely affected patient management, but have gone unreported to the FDA.

Furthermore, these false negative results occurred using 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, and this is really what led us to write our opinion piece.

Bob Barrett: Okay. Dr. Gronowski, back to you, in your article you state that false negative pregnancy tests represent a public health issue that you feel must be addressed and you suggest a coordinated efforts between all of the actors involved. Let's talk about some of those actors. What should the manufacturers and the FDA do about this?

Dr. Ann Gronowski: Well, we feel that the FDA and device manufacturers need to market products with improved performance characteristics. So the current clinical practice at most institutions is to perform urine hCG testing on all women who present to the emergency room, regardless of their symptoms or their likelihood of advanced pregnancy.

So for this reason, point of care hCG devices must generate a positive signal in patients that are at all gestational ages, from very early, to very late in gestation.

It's our understanding that the FDA has acknowledged the need for devices that are not susceptible to false negatives due to hCG beta core fragment, and they require that all

new devices generate positive signal in the presence of high concentrations of beta core fragment.

Unfortunately, this requirement doesn't, to the best of our knowledge, apply to previously approved devices. This leaves manufacturers free to choose whether or not to modify the currently available products known to be negatively affected by hCG beta core fragment.

Bob Barrett: Let's talk now about the people who are really hands-on with these tests as they are being used, the clinicians and the laboratorians. What about your suggestions for them?

Dr. Ann Gronowski: Right! Well, clinicians can help by using urine pregnancy tests appropriately. Clinicians who advocate for the use of urine point of care hCG tests on the grounds that it speeds up patient care, they must understand the risks that are associated with making important clinical decisions based on qualitative urine hCG tests.

As I have said before, at most large institutions serum quantitative hCG measurement can be performed in a timeframe that really meets their clinical requirements. Therefore, when it's possible, serum quantitative hCG should be performed 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 the sensitivity of the test results.

And then we as laboratorians must also take steps to reduce the incidents of false negative results. Laboratory personnel should initiate a dialogue with clinicians and emphasize the need to modify the testing approach based on the patient's presenting symptoms. Serum quantitative testing should be encouraged, we feel, whenever possible.

It's our belief really that many of the currently available urine pregnancy devices present a risk to patients, and those risks can be mitigated in the short-term by correct usage that's enforced by clinicians and laboratory personnel. And as a long-term solution we hope that the FDA and device manufacturers choose to improve the performance of devices that are marketed in the United States.

Bob Barrett: Dr. Ann Gronowski is Professor in the Departments of Pathology and Immunology, and Obstetrics and Gynecology at the Washington University School of Medicine in St. Louis. And Dr. Robert Nerenz is a fellow in the Department of Pathology and Immunology, also with Washington University. They have been our guests in this podcast from *Clinical Chemistry* on rapid urine pregnancy tests.

I am Bob Barrett. Thanks for listening!