

**Article:**

Vilte E Barakauskas, Samantha Pauer, Wee-Shian Chan, Benjamin P Jung.
Unmet Clinical Needs and Remaining Challenges of Pregnancy Reference Intervals.
Clin Chem 2026; 72(1): 47-60. <https://doi.org/10.1093/clinchem/hvaf150>

Guests: Dr. Wee Shian Chan from the Department of Medicine at BC Women's Hospital and Dr. Vilte Barakauskas from the Pathology Department at BC Children's Hospital in Vancouver, Canada.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Accurately measuring the concentration of an analyte is a core function of clinical laboratories. But without reference intervals that indicate what's normal, these highly accurate values are next to useless. A standalone number can't guide clinical management decisions—it needs to be accompanied by a reference interval that puts the patient's value in context.

This is true in all patient scenarios but becomes particularly challenging during pregnancy. The concentrations of many clinically relevant analytes change dramatically over the course of pregnancy, with "normal" values at one stage of pregnancy that are distinctly different from another stage of pregnancy and the pre-pregnancy state. It becomes clear that use of non-pregnant reference intervals during pregnancy greatly increases the risk of result misinterpretation and patient mismanagement.

The solution to this problem seems obvious. We should generate pregnancy-specific intervals and use them to interpret values in pregnant women. Unfortunately, as is often the case, effectively implementing this vision is far from straightforward. A new review article in the January 2026 issue of *Clinical Chemistry* makes the case for pregnancy-specific reference intervals and identifies the challenges preventing their widespread adoption.

Today, we are joined by two of the authors. Dr. Wee-Shian Chan is Head, Department of Medicine at BC Women's Hospital and lead in Obstetric Medicine. Dr. Vilte Barakauskas is a Clinical Biochemist and Division Head in Biochemistry in the Pathology Department at BC Children's Hospital in Vancouver, Canada. And Dr. Barakauskas, let's start with you. The importance of accurate and reliable reference intervals is well accepted in laboratory medicine. Why is there still a gap in our knowledge of normal laboratory ranges during pregnancy?

Vilte Barakauskas: Well, thank you for starting with that question. There are a lot of reasons for the persistent gap in pregnancy reference

intervals. These are related I think to the complexity of pregnancy itself as well as the resources that we need to characterize lab values during pregnancy. Lab values during pregnancy are dynamic, changing every trimester, even every week. So if you want to do a prospective study in the best way possible, that being a prospective, longitudinal study, you'll need 120 pregnant people for each week of gestation or whichever other partition you might need, and frankly, you might not always be clear about what partitions to use at the outset of your study.

Then you need to enroll people from the beginning of pregnancy, support their ongoing study participation, and then assess the pregnancy course and outcome to determine if they were a healthy pregnancy and that you could include their data in a reference interval calculation. Now, if you want to try and elaborate retrospective approaches to reference interval derivation that are actually being used quite a lot in non-pregnant cohorts nowadays, instead you'll need a source of lots of ideally unbiased lab values obtained during pregnancy.

And the problem with that is that routine lab testing during pregnancy isn't very extensive. In North America, for example, we see some lab testing during the first trimester, to screen for anemia or thyroid function and again in second trimester, for gestational diabetes screening. So little bit of prenatal screening that happens, but really comprehensive lab testing isn't part of routine healthy pregnancy care. Also, clinical labs often don't know the pregnancy status or gestational age of the person that presents to the lab, nor is this routinely stored in the lab information system.

And so the lab's ability to easily derive pregnancy reference intervals retrospectively is also somewhat limited. So those are examples of why we still have gaps in our knowledge. It's just hard to do these studies during pregnancy.

Bob Barrett: Well, thank you for that, but what impact does a lack of pregnancy reference intervals have on clinical care and what about other aspects of pregnancy? Dr. Chan?

Wee-Shian Chan: Thank you for the question. Thank you for having me here today as well. As clinicians, we use these lab values to manage pregnant people in our day-to-day care. And clinicians may not be aware that the reference intervals that often accompany these results are often reference intervals derived from non-pregnant people. So for a clinician who is not familiar with how these values can be affected by pregnancy physiology, they may unduly worry that their patients and perform more testing when the test is flagged abnormal or conversely not undertaking appropriate action when the lab value is not flagged abnormal in pregnancy.

Some examples of this will include your WBC, which is a white cell count, which can increase in pregnancy and often exceeds the reference intervals that accompanies it, or creatinine, which usually drops during pregnancy compared to the reference intervals that accompanies it.

Now, in other aspects of pregnancy life which can be affected by not having pregnancy-specific reference intervals, would be life insurance purposes. Often people, pregnant people when they're in the process of family planning or right into family planning and pregnancy would often think about getting life insurance policies. And often, the most infamous one is the lipids. Lipids are abnormally increased, abnormal as compared to the non-pregnancy reference intervals. And this is part of normal pregnancy physiology and this lipids would appear very, very abnormal when they're done during pregnancy, to an insurance company.

Bob Barrett: So what do care providers currently do, given that labs generally don't provide pregnancy-specific reference intervals?

Wee-Shian Chan: Well, care providers who are not familiar with the care of pregnant patients would defer these patients often to the obstetricians, or to physicians such as myself who specialize in the area of pregnancy complications when they obtain an abnormal flagged result, and often is our job to try and refocus or to organize appropriate testing if needed. But unfortunately, we still encounter many pregnant people who unfortunately were not appropriately managed because abnormal results were not recognized when they were performed.

Bob Barrett: What have been some of the more challenging aspects of deriving pregnancy reference intervals?

Wee-Shian Chan: Having worked on an actual study with Dr. Vilte in which we attempted to define pregnancy reference intervals at only one time point during pregnancy, I can attest that recruiting adequate numbers of altruistic pregnant people who will allow us to draw their blood at frequent intervals throughout their pregnancies for nine months and a bit would be very challenging. Despite the fact that pregnant people often have multiple appointments to keep, scheduling their blood draws will be difficult, even if we try to be opportunistic. We have to also track the pregnancy health course for complications and any medications and especially vitamins which they are taking during pregnancy.

Our own experience with a study that we spoke about, referred to earlier, has taught us that attrition rate can be as high as 50% from missed sampling, pregnancy complications,

or other exclusion criteria that arose only after initial study enrollment. So it's particularly challenging. Furthermore, if we have to consider other cohort characteristics like age, parity, and so forth, this really adds complexity to study recruitment. Our research team not only has to be well funded but also dedicated, persuasive, and highly compassionate for this.

Bob Barrett: So what strategies can help overcome these challenges?

Vilte Barakauskas: I'll take this one. I think one of the ways to facilitate recruitment and retention, some of the challenges that Dr. Chan has shared that we've experienced ourselves, could be to build in participation opportunities with every visit that a pregnant person has to a lab or health organization, obviously, with appropriate consents and ethics board approvals in place and things like that. Things I've had to think mostly we're providing an opportunity for all comers to the institution, or to the lab to enroll, and for labs to be able to save samples or draw samples from pregnant patients for reference interval use on a routine basis.

Other things that might make it more successful is to offer sample collection, for example in people's homes or in maternity care clinic so that the sample collection is more convenient and less of a burden on patients. Other thoughts I've had about strategies that would reduce barriers to deriving pregnancy reference intervals might be to record pregnancy status and gestational age for all blood collections and clinical labs to facilitate retrospective studies.

Then again you know, our own foray into pregnancy reference intervals has greatly benefited from Dr. Chan's collaboration and I think that bridging the lab and maternity fields together, in particular to define and agree upon standard definitions of pregnancy reference interval populations, what characteristics of both the population and the methods that we're using should, that we should routinely report in published studies. I think that in and of itself would reduce some of the challenges that Dr. Chan mentioned and would also help ensure that future pregnancy reference interval data is more readily comparable between studies and more easier for labs to adopt for their own use.

Bob Barrett: So finally, in your review, you outlined ways to improve lab testing during pregnancy. For each of your own practice settings, what actions do you feel are most achievable or perhaps most impactful?

Vilte Barakauskas: We need to strive for solid multicenter and multinational collaborations to collect samples during pregnancy. As I mentioned before, hopefully using standardized cohort definitions so that labs can adopt well circumscribed reference

intervals applicable to their local settings. What is probably more achievable in the short term is for us to have a set of go-to literature that is locally vetted so that we are confident that it's reliable for our own lab and patient context, and to have this out ready or summarized for easy access by practitioners, both clinicians as well as laboratorians.

Wee-Shian Chan: And I have to add that on the clinical front, until all these issues are addressed, I think there has to be greater awareness by clinicians of their current limitations using reference intervals that were not derived in pregnant people, and perhaps education and outreach through podcasts like this should be encouraged. And pregnant patients will continue to receive great care.

Bob Barrett: That was Dr. Wee-Shian Chan from BC Women's Hospital and Dr. Vilte Barakauskas from BC Children's Hospital, both in Vancouver, Canada. They wrote a review article in the January 2026 issue of *Clinical Chemistry*, describing strategies to generate pregnancy-specific reference intervals and they have been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.