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Use of Maternal Race and Weight Provides Equitable Performance in Serum Screening for Open Neural Tube Defects

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Guest: Dr. Glenn Palomaki has recently retired from Women & Infants Hospital of Rhode Island and is an Emeritus Professor of Pathology and Laboratory Medicine at Brown University.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Non-invasive screening for open neural tube defects [ONTD] was introduced in the 1970s and still remains an integral part of prenatal care. Briefly, alpha-fetoprotein, or AFP, is measured in a maternal serum sample during the second trimester of pregnancy to identify women at high risk who should be referred for definitive follow up testing. During the initial screening test, measured AFP values are normalized to the median value for that week of gestation, which generates a multiple of the median, or MoM. Previous work has shown that factors such as maternal weight, race, smoking status, and others can affect the MoM and recommend including these factors in the risk assessment to improve its accuracy.

Recently, the use of race in clinical laboratory results reporting has been discouraged, highlighted by the widespread implementation of a race-agnostic equation for the estimation of GFR. Should a similar approach be taken here? What is the expected impact on patient care if race-agnostic analysis were used for prenatal serum screening for open neural tube defects? A new research article appearing in the July 2024 issue of *Clinical Chemistry* asks exactly this question and extends its conclusions to other areas of prenatal screening. In this podcast, we are excited to speak with the article's senior author. Dr. Glenn Palomaki earned his PhD from Queen Mary University of London in Epidemiology and has recently retired from Women & Infants Hospital of Rhode Island. He is an Emeritus Professor of Pathology and Laboratory Medicine at Brown University, with interests in prenatal screening, laboratory medicine, and evidence reviews. Doctor, serum screening for open neural tube defects has been around for quite some time. So what prompted you to undertake this new study?

Glenn Palomaki: Well, there have been a number of changes since the 1970s and 1980s when using maternal serum AFP screening for open neural tube defects began. First of all, most pregnancies back then were dated by last menstrual period

and the gestational age was often off by a month, which makes the interpretation of the results inappropriate. Nowadays, most pregnancies have first trimester ultrasound dates. There are very few screen positives that are due to inaccurate dating. Prenatal screening for ONTD occurs between 15 and 20 weeks, early in the second trimester, and this is quite a bit earlier than what high resolution ultrasound occurs, which is later, 20 weeks or 24 weeks, which is quite late in pregnancy to identify defects and be able to do any sorts of follow up treatments. In addition, the field's become much more sophisticated, accounting for variables such as maternal weight, maternal smoking status, presence of diabetes, and maternal race, and recently there's a strong effort to review laboratory tests that use maternal race to determine whether their inclusion is justifiable.

Bob Barrett: Briefly, could you provide an overview of the findings and their implications for laboratories performing serum based screening?

Glenn Palomaki: Our aim was to mainly focus on the maternal race and weight adjustments in a large population of pregnancies screened in the correct time period of 15 to 21 completed weeks. We wanted all pregnancies to be dated via ultrasound so there were no bad dates, and collected over a relatively short time period, with four months, relatively recently, in late 2022 and early 2023. The entire population included 13,316 results in women with a singleton pregnancy. All had reported maternal race of White or Black. About three quarters reported White, and about one quarter reported Black. Other race and ethnicities and missing data were excluded. So it was a simple comparison. Using the standard statistical methodology that's been in use for decades for serum screening, we generated race-specific AFP medians and race-specific maternal weight adjustment factors. The AFP MoM levels in Black pregnancies were approximately 9% higher than in the White pregnancies, which is consistent with most other studies. The maternal weight in Black pregnancies was also 14 pounds heavier, 185 pounds versus 171. After applying these adjustments for both gestational age and race, the median MoM levels in the two groups were 0.99 in Blacks and 1.00, respectively. The overall screen positive rate at an AFP MoM of 2.5 or higher was 0.81, less than 1%, 0.81%. The screen positive rate was slightly higher in Blacks, 1.00 versus 0.74 in White pregnancies, but that difference was not statistically significant.

Then we did a race neutral analysis. That is, we ignored whether the pregnancy was classified as Black or White and created a single set of medians and a single weight adjustment. The overall screen positive rate was nearly identical, 0.86 versus 0.81, but the screen positive rate in the Black pregnancies was 2.4 times higher, 1.5 versus 0.63, and

this difference is highly significant. So when race was not accounted for, two and a half times more Black pregnancies would be considered screen positive than White pregnancies.

Bob Barrett: So, should maternal race and weight continue to be collected and used in the interpretation of AFP results?

Glenn Palomaki: Well, the short answer is yes, I believe so. A recent CDC follow up study of a quarter million pregnancies in the US found the rates of neural tube defects in various racial ethnic groups was quite similar. This suggests that the key to focus on is the screen positive rate. It should be similar in white and black pregnancies as the prevalence of the disorder is similar. We showed in this study that that can only occur when the maternal race and weight are accounted for.

A recent publication from Washington confirmed that the median AFP levels are higher in Black pregnancies and that their maternal weight is also higher. These findings are consistent with ours and the long historical record. However, that study did not examine the screen positive rate in the two groups.

Bob Barrett: Finally, doctor, given these findings, are there other screening tests in the pipeline that would also make use of self-reported maternal race and weight?

Glenn Palomaki: Well, in the field of prenatal screening, there's been a lot of data accumulating over the last 10 years or so that you can have a first trimester screening test that pregnancy is a risk of preterm preeclampsia. This is feasible, and there have been randomized trials that show that you do have the ability to reduce that risk considerably by taking baby aspirins nightly starting before 15 weeks gestation. So this would be a first trimester screening test with a treatment of aspirin, which can greatly reduce the risk of preterm preeclampsia.

Two of the markers are serum markers that have been identified. They are PAPP-A (pregnancy-associated plasma protein A), which many of you might be familiar with from first trimester screening for Down syndrome and PlGF (placental growth factor). Now, both of these markers are 40% to 50% higher in Black pregnancies compared to White. Remember, we found only about 9% for AFP. This is 40% to 50% higher, much more of an effect. In addition, PAPP-A is a very, very large molecule, bigger than any of the molecules we've used in screening before, and the molecular size is related to how strong a maternal weight effect there is. So there'll be a very strong maternal weight effect. So the differences in average weight in the two groups will become even more important.

So, in summary, maternal serum AFP for neural tube defects will continue to be an option in prenatal care. It's not going to be replaced by ultrasound. We don't believe first trimester ultrasounds for dating. It can't identify neural tube defects. The comprehensive ultrasound done at 20 weeks and 22 weeks, 24 weeks can certainly identify neural tube defects, but it's a little bit too late in pregnancy at that point. And the interpretation of screening results are improved when maternal race and weight are provided. As of now, I can think of no other alternative that could replace this query. So I'd like to thank my co-authors at Women & Infants and at Labcorp, and the de-identified raw data was provided by Labcorp.

Bob Barrett: That was Dr. Glenn Palomaki from Women & Infants Hospital in Providence, Rhode Island. He is the senior author of a research article on the use of maternal race and weight in serum screening for open neural tube defects in the July 2024 issue of *Clinical Chemistry*, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.