Reconsidering Race Adjustment in Prenatal Alpha-Fetoprotein Screening

Nicholas R. Burns, MD, Teodora Kolarova, MD, Ronit Katz, DPhil, Kimberly Ma, MD, and Shani Delaney, MD

OBJECTIVE: Black racial designation is the only race for which adjustment is recommended for maternal prenatal serum alpha-fetoprotein (AFP) screening. The objective of this study is to reevaluate the relationship between maternal race and maternal serum AFP values in prenatal analyte screening.

METHODS: This was a single-center retrospective analysis of patients who underwent prenatal analyte screening between January 2007 and December 2020. Nomograms for raw maternal serum AFP values by gestational age were created and compared between patients identified as “Black” and “non-Black” on the laboratory requisition. Multivariable linear regression models were created to evaluate the relationship among gestational age, maternal weight, and maternal race on maternal serum AFP levels. The new models were compared with the laboratory-derived calculations, which used historically determined race adjustments.

RESULTS: A total of 43,997 patients underwent analyte screening, and 27,710 patients had complete data for analysis. Of these, 6% were identified as Black. Black patients had laboratory blood draws at a mean gestational age of 123 days, compared with 120 days in non-Black patients (P<.001), and had higher maternal weight (mean 170 vs 161 lbs, P<.001). Nomograms for raw maternal serum AFP values did not differ between Black and non-Black patients (P=.065). When adjusted for gestational age and maternal weight, no difference in maternal serum AFP values was identified between Black and non-Black individuals (P=.81).

CONCLUSION: No difference in maternal serum AFP values was identified between Black and non-Black pregnant individuals when adjusted by maternal weight and gestational age at blood draw. These findings suggest that routine race-based adjustment of maternal serum AFP screening should be discontinued.

(Redact Gynecol 2023;00:1–7)
DOI: 10.1097/AOG.0000000000005045

Race adjustments in maternal serum prenatal screening are common practices in current obstetric care. The inclusion of race into prenatal algorithms is based on studies performed 20–50 years ago, without clarity on how race was originally defined and without acknowledgement of race as a social construct with tremendous bias and influence on health outcomes and inequities. Alpha-fetoprotein (AFP) was discovered in 1956 and was found to measurably cross the placenta into maternal serum.1 By the 1970s, maternal serum AFP measurements became the pioneering test in the new field of prenatal screening and diagnosis, given its association with open neural tube defects.2 With uptake of the test clinically, studies demonstrated that several clinical and demographic factors might alter maternal serum AFP values for a given gestational age. Some of these include maternal weight,3–5 smoking status,6 diabetes,7,8 chronic hypertension,9 and racial or ethnic origin.10–13

Some of these adjustments have been deemed inconsequential and are not in routine use in current practice.14–16 However, the adjustment for maternal Black race has persisted for the past 50 years and remains an advised practice by the American College of Medical Genetics in their 2019 Technical Bulletin.
on maternal serum AFP screening. Additionally, in their 2021 Master Checklist, the College of American Pathologists, which provides accreditation for most laboratories in the United States, requires laboratories that perform maternal prenatal serum screening to solicit race to perform race-specific adjustments for maternal serum AFP and other prenatal serum analytes; however, the Black racial designation is the only race for which an adjustment is recommended. Laboratory directors may choose whether to adjust for other factors such as other racial categories, diabetes, in vitro fertilization, and tobacco cigarette smoking, based on their screening population.

Race is increasingly recognized as a social construct that should not be used as a surrogate for biology, geographic ancestry, or genetics. Consequently, clinical screening practices in several medical specialties have been adjusted, such as in the calculation of glomerular filtration rate, or the vaginal birth after cesarean success calculator. The inclusion of race in medical calculators has been shown to perpetuate, and potentially exacerbate, inequities in health care. This study, therefore, aims to reappraise the relationship between race and maternal serum AFP values in a modern general obstetric population, hypothesizing that there is no difference in maternal serum AFP values between Black and non-Black individuals when adjusted for maternal weight and gestational age.

METHODS

This was a retrospective cohort study of all patients who underwent prenatal analyte screening at the University of Washington Medical Center (Seattle, Washington) between January 2007 and December 2020. Pregnancy data were abstracted automatically from the laboratory requisition in the electronic medical record, including patient weight, race (Black or non-Black), and gestational age at blood draw. Raw maternal serum AFP levels and race-adjusted multiples of the median (MoM) were extracted. During the study period, all MoM calculations were race-adjusted by the laboratory. Unadjusted MoM values were unavailable in the electronic medical record. Patients were excluded from analysis if their laboratory requisition indicated maternal diabetes mellitus, a prior history of a pregnancy affected by an open neural tube defect, multiple gestation, or missing data. No other prenatal or clinical outcomes information was abstracted beyond this information available in the standard laboratory requisition.

Our institution’s laboratory used the alpha software version 8 to calculate an expected maternal serum AFP value based on the patient’s characteristics and compare it with the original sample. The calculation for maternal serum AFP value in alpha adjusts for decimal gestational age, maternal weight, and maternal race. Our laboratory updated population medians monthly for non-Black patients and on a quarterly basis for Black patients.

Nomograms for raw AFP levels were created for Black and non-Black patients to describe the relationship between maternal serum AFP levels and gestational age. To evaluate the relationship between weight, gestational age, and race, multivariable linear regression models were created for Black and non-Black patients. The value of maternal serum AFP is known to fluctuate based on the gestational age at the time of blood draw, as well as with maternal weight. Thus, analyses were adjusted to a population median weight of 152 pounds. To evaluate the influence of race on maternal serum AFP MoM, population medians for maternal serum AFP values were calculated using the linear regression model using the entire cohort.

All analyses were performed with SPSS 26.0 and R 4.1.1 (https://www.R-project.org/). Descriptive statistics were calculated for all variables of interest using mean (SD) or medians (interquartile range) for continuous variables. Comparisons were made between means of Black and non-Black patients using the student t test. The nomogram was created from a scatter-plot of gestational age against maternal serum AFP values stratified by race. Interactions of race and gestational age were computed from a linear regression, with mean maternal serum AFP value as the outcome. We further used a linear regression model adjusted to median weight to visualize the association of maternal serum AFP value and gestational age by race. A two-sided P<.05 was considered statistically significant for all analyses.

The study was determined by the University of Washington IRB to not involve human subjects as defined by federal regulations and, therefore, did not require exempt status or further IRB consideration. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed throughout the study (www.strobe-statement.org).

RESULTS

A total of 43,997 patients underwent prenatal analyte screening during the study period. 27,710 patients had complete data for analysis; 26,050 (94.0%) were identified as non-Black, and 1,660 (6.0%) were identified as Black (Fig. 1). Black patients had laboratory
blood draws at a mean gestational age of 123 days, compared with 120 days in non-Black patients ($P<.001$), and had higher average maternal weight (170 lbs vs 161 lbs, $P<.001$) (Table 1).

Population nomograms for raw maternal serum AFP value by gestational age were similar for Black and non-Black groups (Fig. 2A; $P=.065$). Linear regression models were used to adjust for differences in weight and gestational age at blood draw. The models demonstrated no difference between Black and non-Black patients overall ($P=.59$, Table 2), nor when the mean maternal serum AFP value was analyzed continuously at the median population weight of 152 lbs (Fig. 2B; $P=.813$). Evaluating mean maternal serum AFP values at the average gestational age of the population (132.5 days), there was no difference between non-Black individuals (55.0 ng/mL, 95% CI 52.7–57.1) and Black individuals (58.8 ng/mL, 95% CI 56.5–60.1).

The differences between the laboratory-derived model and the regression model are summarized in Table 2. Median raw maternal serum AFP values without adjustment for weight or gestational age at blood draw were different between Black and non-Black patients (41.2 vs 37.4 ng/mL, $P<.001$). Laboratory-supplied maternal serum AFP MoM (adjusted for maternal weight, gestational age, and race with alpha software) was statistically different between Black and non-Black groups (1.02 vs 0.99, $P=.009$). Using the regression model to remove race adjustment, no difference was seen between Black and non-Black patients in median raw maternal serum AFP values (37.5 vs 37.3 ng/mL, $P=.59$), nor in the median maternal serum AFP MoM (1.00 vs 0.99, $P=.59$).

**DISCUSSION**

In this study of more than 27,000 patients who underwent prenatal analyte screening at a single academic center, no difference in maternal serum AFP values was identified between Black and non-Black pregnant individuals when adjusted by maternal weight and gestational age at blood draw. It is worth noting that the magnitude of the observed difference in adjusted laboratory-supplied maternal serum AFP MoM (1.02 vs 0.99, $P=.009$), although statistically significant, is likely clinically insignificant and underscores the potential problem with race-based adjustments.

These findings from a modern obstetric cohort stand in contrast to older literature. The American College of Medical Genetics and Genomics, the College of American Pathologists, and alpha software technical manuals point to two primary studies of maternal serum AFP values to justify the inclusion of race in prenatal analyte screening. The first study, published in 1983 by Crandall et al, was based on a pilot program for maternal serum screening in California, with samples collected between 1978 and 1980.10 Of 9,054 samples from patients with self-identified race (439 Black, 619 "Oriental," 695 Hispanic, and 6,544 White), Crandall et al identified that the maternal serum AFP value averaged 10.0% higher in pregnant Black patients compared with pregnant White patients after adjusting for median maternal weight (135 lbs) and eliminating any pregnancies that did not end in a live birth with a newborn weight greater than 2,500 g. Notably, this study did not collect information regarding other factors, such as diabetes mellitus, tobacco use, or history of prior neural tube defect, that today are known to affect maternal serum AFP values and interpretation.

The second major study, published by Watt et al in 1996, evaluated 20,725 (9,462 White, 4,392 South Asian, 4,215 Black or "Afro-Caribbean," and 2,656 "other") pregnant patients who had serum screening through a single laboratory in London, United Kingdom.13 The authors observed an approximately 20.0% higher maternal serum AFP value for Black
patients than for White patients for a given gestational age and did not find a material difference after weight adjustment. The authors note that, “adjusting for ethnic group only had a small effect on screening performance: a maximum of about 0.5% extra detection at a 5.0% false-positive rate.” As in the 1983 Crandall et al article, this study did not evaluate the prevalence or effect of other biological factors that can alter maternal serum AFP values. A portion of this group provided updated data and recommendations for race adjustment in a 2013 research letter, based on pregnant patients who underwent serum screening between 1994 and 2011. That study similarly evaluated race as the primary difference for adjustment and did not evaluate other population-level differences in other factors that could affect maternal serum AFP values.

Race is fraught with problems of definition, both in how it is defined and by whom it is defined. As described above, historical studies of maternal serum AFP levels have used changing terms without precise definition: “Black,” “Afro-Caribbean,” and “African-American” are but a few. For many electronic medical record systems, it is unclear whether the entered race was designated by the patient or presumed by a clinician or laboratory technician without confirming the patient’s self-identified race. Even within this study, although our institution has embraced racial self-identification as standard practice, it is possible that some patients may have had racial categories assigned to them by clinicians or laboratory technicians.

There are several biological mechanisms that may account for historically identified differences in maternal serum AFP screening, but they have not been systematically or consistently evaluated for confounding effects in past literature. For instance, the recognition of the importance of folic acid and subsequent policy changes, such as fortification of wheat flour with folic acid in the United States in the 1990s, is estimated to have reduced open neural tube defect prevalence by about 30.0%. Rates of obesity have increased significantly in the United States, from a 22.9% prevalence in the 1990s to a 42.4% prevalence in 2018. Tobacco cigarette smoking amongst adults declined 68.0% overall from 1965 to 2018. Oral medications for diabetes, such as metformin and sulfonylureas, were introduced in the United States in the 1990s, changing the landscape and definitions of glycemic control that may be relevant to the historical observations of “insulin-dependent diabetes mellitus” in pregnancy. These are all significant changes that are worthy candidates for investigation but are not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Black (n=1,660)</th>
<th>Non-Black (n=26,050)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>28.4±5.7</td>
<td>29.9±5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal weight (lbs)</td>
<td>172±48</td>
<td>161±42</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age at MSAFP draw (d)</td>
<td>123±11</td>
<td>120±10</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

MSAFP, maternal serum alpha-fetoprotein. Data are mean±SD unless otherwise specified.

Fig. 2. Maternal serum alpha-fetoprotein by gestational age for Black and non-Black patients. A. Nomogram (P=.065). B. Predicted maternal serum alpha-fetoprotein from a linear regression model adjusted to population median weight of 152 pounds (P=.813). Race is specified on each graph as Black (black) and non-Black (red).

routineyanalysisconsideredincurrentscreeningpracticesat
callcenters,whereasrace–specifically,Blackcomparedd
tiwonon-Blackracialdesignation—remainsauniver-
sallyadvisedadjustmentintechicalbulletinsandscreeningalgorithms.17,18Using“non-Black,”asther
referenceraceinmaternalserumAFPscreeningincorrectlyimpliesthatthisgroupisamonolithand
perpetuatesracismbyimplyingthatBlackindividuals
areSIGNIFICANTLYdifferentsolelyduetoracialiden-
tification.Furthermore,referencepopulationsareprone
tobethebiasofbeing“normal,”potentiallyplacing
Blackindividualsinthecategoryof“abnormal”compare-
dithreferencerace.Thecontinuedinclu-
sionofBlackraceastheunderlyingdifferencein
maternalserumAFPvalues—ratherthanobesity,
tobaccouse,diabetes,consumingahealthydietforti-
fiedwithvitamins,orotherplausiblebiologicalrisk
factors—reflectsanotherinstanceofmisrepresentation
ofraceasa biologicalfactor,ratherthanasocial
construct, in medicine. This perpetuates longstanding
health inequities and fails to ignore the potential
adverse effect of continuing to adjust for Black racial
designations in prenatal AFP screening.

There is a call to action underway across medi-
cinetosystematicallyreevaluatetheuseinracein
clinicalpractice.30,31 This work has already begun in
earnest; in obstetrics and gynecology, race has been
reevaluated in several tools for clinical decision-
making, such as in the vaginal birth after cesarean
calculator, in the definitions of anemia in pregnancy,
and in guidelines for low-dose aspirin prophylaxis in
pregnancy.22,32,33 Prenatal screening algorithms
would benefit from the same attention these clinical
guidelines and calculators have garnered. Although
maternal serum AFP level has obvious implications,
given its historical significance in identifying risk of
open neural tube defects and Down syndrome, race-
basedadjustmentsarealsoincludedaspartofcom-
mon laboratoryadjustmentsforallotherfirst-
andsecond-trimesterscreeninganalytes,aswellasinthe
Fetal Medicine Foundation’s preeclampsia risk calcu-
lator.24,34,35Theseadjustmentsmayaffecttheraw
valueofsomeanalytes,suchaspregnancy-associated
plasmaprotein A (PAPP-A), by as much as 50.0%.
Thus, there are other areas in prenatal geneticand
risk screening, beyond maternal serum AFP, that
require re-evaluation.

Ourfindingsarelimitedbythenatureofasingle-
institution study, serving a specific geographic region,
and ascertainment of race through laboratory requisi-
tions that may not have relied on patient self-
identification. Our retrospective study also lacked
pregnancy outcome data and other clinical correlates
for screen-positive results, limiting our ability to make
broaderconclusionsregardingthediagnosticsignifica-
tionsof screen-positive rates. However, other authors
have suggested that maternal serum AFP may not be
a useful screening tool in the era of modern ultrasonog-
raphyandcell-freedNAScreeningandthat,perhaps,
appropriate MoM cutoffs should be revisited.36 This
question is beyond the scope of our investigation.

In conclusion, our study found no difference in
maternal serum AFP values between Black and non-
Black pregnant individuals when adjusted by maternal
weight and gestational age at blood draw. These
findings suggest that routine race-based adjustment
ofmaternal serum AFP values for Black individuals
should be discontinued. Further research to confirm
these findings at other centers or large reference
laboratories should be considered, as well as research
to determine how the removal of race adjustment
might changetest performance characteristics and
subsequentratesofdiagnostictesting.Systematic
evaluation of how to include and adjust for truly
biological variables should also be a focus of future
research and implementation efforts.

Table 2. Maternal Serum Alpha-Fetoprotein Values by Laboratory-Derived Race-Adjusted Screening
Compared With the Modern Race-Free Model

<table>
<thead>
<tr>
<th>Racial Designation</th>
<th>Black (n=1,660)</th>
<th>Non-Black (n=26,050)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw MSAFP (ng/mL)</td>
<td>41.2 (30.8–89.1)</td>
<td>37.4 (28.7–76.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Regression model MSAFP (ng/mL)*</td>
<td>37.5 (32.3–66.7)</td>
<td>37.3 (33.0–60.5)</td>
<td>.589</td>
</tr>
<tr>
<td>Laboratory-calculated MSAFP (MoM)*</td>
<td>1.02 (0.82–1.88)</td>
<td>0.99 (0.80–1.74)</td>
<td>.009</td>
</tr>
<tr>
<td>Regression model MSAFP (MoM)*</td>
<td>1.00 (0.86–1.77)</td>
<td>0.99 (0.88–1.61)</td>
<td>.589</td>
</tr>
</tbody>
</table>

MSAFP, maternal serum alpha-fetoprotein; MoM, multiples of the median.
Data are median (interquartile range) unless otherwise specified.
* Adjusted for weight and gestational age at blood draw.
† Adjusted for weight, gestational age at blood draw, and maternal race (Black vs non-Black).
REFERENCES


Double-Blind Peer Review

*Obstetrics & Gynecology* uses double-blind peer review, which means that authors and reviewers do not know each other’s identities. The goal of double-blind peer review is to help minimize potential reviewer bias.

Based on feedback from authors and reviewers, the journal will be adjusting the current submission requirements in order to better balance the goals of double-blind peer review with a streamlined submission process. The journal is now requiring less action from authors to self-blind submissions. Below you will find an updated list of requirements necessary to comply with double-blind peer review.

Requirements include:

- Submitting a separate title page and manuscript
- Removing authors’ names and initials from the manuscript
- Avoiding disclosure of identity in files names, headers and footers, figures, tables, videos, supplemental digital content, and references to previously published studies

See the Instructions for Authors on our website for details.
Questions? Contact the Editorial Office at obgyn@greenjournal.org

rev 2/2022