Screening for Open Neural Tube Defects

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KEYWORDS

- Alpha fetoprotein • Maternal serum • Spina bifida • Anencephaly
- Adverse pregnancy outcome

KEY POINTS

- Biochemical prenatal screening was initiated with the use of maternal serum alpha fetoprotein to screen for open neural tube defects.
- Screening has evolved to include multiple marker and sequential screening protocols involving serum and ultrasound markers to screen for aneuploidy.
- Most recently cell-free DNA screening for aneuploidy has been initiated and whether or not it becomes the primary form of screening for aneuploidy it is not effective in identifying neural tube defects.
- Although ultrasound is highly effective in identifying neural tube defects in high-risk populations, in decentralized health systems where screening of the general population takes place maternal serum screening still plays a significant role.
- Abnormal maternal serum alpha fetoprotein alone or in combination with other markers may indicate adverse pregnancy outcome in the absence of open neural tube defects.

Maternal serum screening for fetal congenital anomalies began in the early 1970s with the advent of alpha fetoprotein (AFP) screening for neural tube defects.[1,2] It was from this screening protocol that the initial observation that AFP is low in Down syndrome–affected pregnancies was made.[3] Today, screening for Down syndrome is highly complex with protocols that include various combinations of serum, ultrasound, and cell-free DNA markers across the first and second trimesters of pregnancy. Although, cell-free DNA testing shows great promise in high-risk populations conventional maternal serum screening remains the most appropriate screening approach in low-risk populations.[4] For those women who undergo second trimester conventional

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screening, risk assessment for open neural tube defects is an integral part of the process. However, in those instances where patients have undergone aneuploidy screening (first trimester conventional or cell-free DNA screening) it is important to offer these women screening for open neural tube defects in the second trimester. The most common approach to such screening is evaluation of AFP in maternal serum.

Maternal serum AFP (MSAFP) screening is conducted between 15 and 21 weeks of gestation. Blood specimens may be collected as liquid whole blood or dried blood spots.[5] Median MSAFP levels increase steadily by about 15% per week from a concentration of approximately 25 IU/mL at 15 weeks of gestation to a level of approximately 60 IU/mL at 21 weeks of gestation. To account for this upward trend in normal levels throughout pregnancy, values of AFP are converted into multiples of the gestational age–specific median (MoMs) by dividing the patient's analytical AFP concentration by the median concentration for that gestational age. The MoM values are then typically corrected for demographic factors, such as maternal weight, ethnicity, and diabetic status.

Patients with higher maternal weight tend to have on average lower MSAFP levels than those with lower maternal weight.[6] As a result, the MoM values for patients with higher maternal weight are adjusted downward, whereas patients with lower maternal weight are adjusted upward (**Fig. 1**).

MSAFP levels have been demonstrated to vary by ethnicity. The most significant shift is observed in African American patients who tend to have MoM values that are on average 16% greater than in white patients after weight adjustment.

Insulin-dependent diabetes mellitus affects open neural tube defect screening in two ways. First, the incidence of open neural tube defects is three- to four-fold higher in patients with insulin-dependent diabetes mellitus.[7] Second, MSAFP levels are approximately 20% lower in patients with insulin-dependent diabetes mellitus compared with the general population.[8] Although recent publications have suggested that this adjustment factor may no longer be necessary,[9] guidelines still suggest including an adjustment.[10]

In cases of open spina bifida and anencephaly, openings in the spine or skull result in leakage of AFP into the amniotic fluid, which then diffuses into the maternal blood

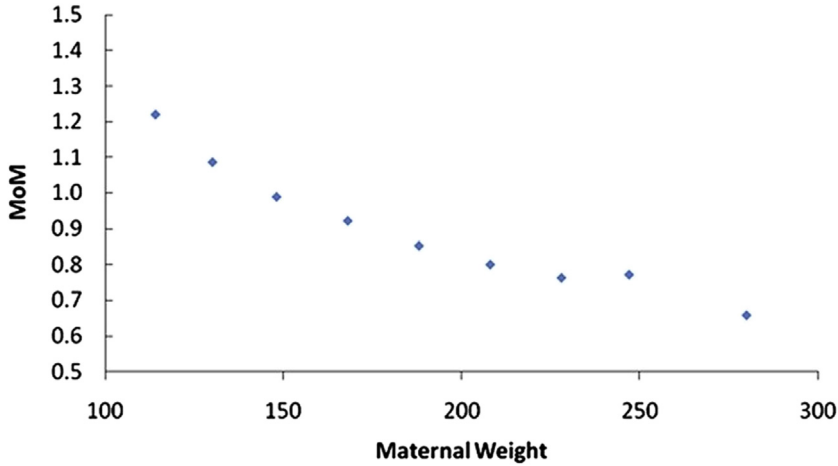

Fig. 1. Median AFP MoM versus median weight in 21,972 white patients.