OBSTETRICS

Routine measurement of amniotic fluid alpha-fetoprotein and acetylcholinesterase: the need for a reevaluation

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OBJECTIVE: The objective of the study was to evaluate whether the current screening regimen of measuring amniotic fluid alpha-fetoprotein (AF-AFP) at the time of amniocentesis and reflex acetylcholinesterase testing vs ultrasound alone to detect neural tube and ventral wall defects offers improved diagnostic accuracy and cost benefit.

STUDY DESIGN: A retrospective chart review on all patients who had amniocentesis performed at 1 center over the past 11 years was performed. Those with an elevated AF-AFP were compared with those whose AF-AFP was within normal limits. Ultrasound findings and outcomes were reviewed in all cases to assess whether neural tube defects (NTDs) or ventral wall defects (VWDs) were missed by AF-AFP or ultrasound screening. A cost-benefit analysis was then performed.

RESULTS: Of 6232 women who underwent amniocentesis between January 2002 and December 2012, 81 had an elevated AF-AFP with or without a positive acetylcholinesterase (AChE). Of these 81 women, 13 had NTDs and 5 had VWDs. The sensitivity of the detailed ultrasound was 100% in detecting NTDs and VWDs, whereas that of the AF-AFP ranged from 22% to 77%, with the inclusion of AChE. The total expenditure for AF-AFP in our sample set (n = 6232 amniocentesis at $76.00 per AF-AFP) was $473,632, and all NTDs and VWDs were detected by ultrasound. Translated to a national laboratory (>42,447 samples/year), the cost savings in 2011 alone would be $3,225,972.

CONCLUSION: Given the accuracy of high-resolution ultrasound in the detection of both NTDs and VWDs, measuring AF-AFP and AChE as a reflex-screening test is not a cost-effective approach.

Key words: amniocentesis, amniotic alpha-fetoprotein, neural tube defects, ultrasound, ventral wall defects

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Measurement of amniotic fluid alpha-fetoprotein (AF-AFP) for all genetic amniocentesis is a well-established protocol. Although its greatest value is in cases in whom the maternal serum alpha-fetoprotein (MSAFP) is elevated, the routine measurement of AF-AFP remains the laboratory and community standard. Although this dogma has been challenged, there has not been a universal adaptation of a new scheme.

Using maternal serum alpha-fetoprotein levels (MSAFP) has played a vital role in the screening and detection of open neural tube defects (NTDs) and ventral wall defects (VWDs). The standard evaluation for elevated MSAFP (≥2.5 multiples of the median [MOM]) includes diagnostic ultrasound and invasive testing via amniocentesis to determine AF-AFP levels.

Acetylcholinesterase (AChE) levels are measured if AF-AFP levels are abnormally high (≥2.0 MOM). Over the last 3 decades, this approach has remained essentially unchanged despite major improvements in imaging modalities and evidence that the diagnostic accuracy for ultrasound diagnoses of NTDs and VWDs is very high.[1-3]

At the onset of ultrasound screening for congenital anomalies, there was early consensus that recognition of NTDs was difficult. The use of both MSAFP and AF-AFP levels improved the detection and led to the screening approaches that have continued to this day.[4] In spite of substantial improvements in ultrasound producing definable and diagnostic images for NTDs and VWDs,[5-7] MSAFP and AF-AFP guidelines as outlined at the Third Scarborough Conference in 1980[8] continue to be utilized for the diagnosis of these disorders, and these analytes are obtained routinely at amniocentesis, irrespective of the indications for the procedure.

The diagnostic accuracy of AF-AFP has been established. Levels of AF-AFP correlate with the likelihood of an NTD, especially for those in the higher range (≥5 MOM) and associated with a positive AChE.[3,9-13] However, the presence of a detectable abnormality if the AF-AFP is positive (≥2 or ≤10 MOM) with a negative AChE is less than 50%.[14,15]

This study set forth the null hypothesis that the measurement of AF-AFP was not a useful adjunct to amniocenteses, regardless of indication. Data were collected in an active prenatal diagnostic center over an 11 year period in which

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TABLE 1
Maternal characteristics

Characteristic	Value
Maternal age, y	39 (17-50)
Maternal ethnicity	White: 62% Asian: 11.5% Black: 2.1% Middle Eastern: 12.5% Hispanic: 4.7% Other: 7.2%
Maternal weight at time of amniocentesis (average)	142 (90-278) lbs

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the laboratory standard of practice was to obtain AF-AFP at the time of amniocentesis. We evaluated all cases undergoing second-trimester amniocentesis and reviewed MSAFP and AF-AFP (AChE) levels, ultrasound findings, and all pregnancy outcomes. The overall costs of the AF-AFP and AChE were estimated and were compared with the use of ultrasound alone in the detection of NTDs and VWDs.

Materials and Methods

An institutional review board approved a retrospective chart review, and it was performed at the Center for Fetal Medicine and Women's Ultrasound from January 2002 to December 2012. Computerized analysis identified all the cases of second-trimester amniocentesis performed during the study time period. Both singleton and multiple gestational pregnancies were included. For higher-order multiples, amniocenteses were performed on individual sacs unless the pregnancy was established to be monoamniotic/monochorionic. Within the cohort there were a total of 232 twin pregnancies including 6 monoamniotic/monochorionic gestations. One triplet gestation was also included as 3 separate amniocenteses.

Charts were reviewed and results recorded for maternal demographic information; indications for amniocentesis; laboratory results associated with the amniocentesis including MSAFP, AF-AFP, and AChE levels; karyotype; and array comparative genomic hybridization analyses. Ultrasound evaluations were performed by a combination of obstetrical sonographers or maternal-fetal medicine fellows and repeated by maternal-fetal medicine (MFM) specialists (in many cases the MFM specialist performed the ultrasound alone) using the GE Voluson 730 or E8 (GE Healthcare, Milwaukee, WI) and Phillips IU 22 (Phillips, Bothell, WA).

All amniotic fluid collections were obtained by the MFM specialists under direct ultrasound guidance and then were processed at Genzyme Genetics laboratories (Integrated Genetics; now Labcorp, Monrovia, CA). Follow-up of birth outcomes were obtained by contacting the delivering physician regarding the absence or presence of congenital abnormalities at the time of delivery.

In evaluating cases for AF-AFP, they were categorized into positive (>2 MOM) or negative (<2 MOM) and if positive, the presence or absence of AChE was documented. For all cases determined to be positive for AF-AFP levels, ultrasound evaluations stored on a digital system were reviewed. The efficacy of AF-AFP and AChE was determined by comparing the ultrasound findings prior to the amniocentesis with the biochemistry results and compared with birth outcomes (including terminations).

A cost assessment was done to evaluate the estimated economic cost of routine testing for AF-AFP and AChE (when AF-AFP was >2 MOM). The total cost of routinely measuring AF-AFP and AChE over the 11 year period, 2002-2012, was calculated. Costs for each test during study period were obtained from billing charges and then averaged for the 11 year period. This cost estimate was then multiplied by the total number of amniocenteses in which either AF-AFP or AF-AFP/AChE testing was obtained. The determined cost was then compared with the diagnostic value of these biochemical screening tests compared with a detailed ultrasound alone.

TABLE 2
Indications for amniocentesis

Variable	n (%)
Indications for amniocentesis	6232
Advanced maternal age	3708 (59.5)
Abnormal ultrasound finding	750 (12)
Maternal anxiety	131 (2.1)
Abnormal noninvasive screening evaluation	
First trimester	498 (8)
Second trimester	872 (14)
Positive family history for a genetic disorder	186 (3)
Potential exposure risk	62 (1)
Follow-up after inconclusive CVS	25 (0.4)

CVS, chorionic villus sampling.

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Results

The maternal characteristics for the amniocentesis cases are listed in Table 1. Indications for amniocentesis are listed in Table 2. A total of 6232 women underwent an amniocentesis between January 2002 and December 2012. There were 81 cases that had an elevated AF-AFP (1.3%) (Figure 1). AChE was positive in 18 cases and negative in 63 cases. Preamniocentesis MS-AFP levels were available in 37 of the 81 cases.

On review of cases with both available MSAFP and AF-AFP levels, 29 of 37 had MS-AFP levels less than 2.5 MOM, yet AF-AFP levels were 2.0 MOM or greater. Among the 81 cases with AF-AFP 2.0