Should the first-trimester aneuploidy screen be maternal age adjusted? Screening by absolute risk versus risk adjusted to maternal age

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Objective To compare the absolute risk (AR) screening approach to the current approach of risk adjusted to maternal age in patients undergoing first-trimester screening (FTS).

Material and Methods Three-stage retrospective analysis of 3073 pregnancies that had FTS during 2006–2007. (1) Distribution analysis of AR as defined by (final FTS risk)/(risk by age). (2) Analysis of the screen-positive group by the AR method. (3) Analysis of the screen-positive advanced maternal age (AMA) patients.

Results (1) AR > 1 was found in 151 (4.9%) patients, and AR >1.2, 2 and 3 was found in 4, 3.1 and 2%, respectively. (2) 145 (4.7%) of the 3073 patients screened positive. Twelve were diagnosed with chromosomal abnormalities and 3 with major anomalies. All had AR >1.2. Of the 145 (55.8%) screen positives, 81 had AR >1.2. AR was significantly higher in the chromosomally abnormal as compared to normal gestations (t-test, p < 0.01). (3) Of the 145 screen positives, 103 were AMA. Only 39 (28%) had an AR >1.2.

Conclusions The AR screening approach, using AR >1.2 as a cut-off, captured all abnormal pregnancies diagnosed by the current screening method. This method offers lower false positive (FP) rates to AMA women and has the potential for higher detection rates in younger women. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: first-trimester screen; nuchal translucency; advanced maternal age; foetal ultrasound; foetal imaging; maternal serum screening; genetic counselling

INTRODUCTION

Prenatal diagnosis of chromosomal abnormalities has been available for almost half a century. Historically, invasive testing has been offered routinely only to pregnant patients over the age of 35 (Kupperman et al., 1999), even though half of aneuploid foetuses are born to younger women (Resta, 2005).

Non-invasive screening tests for Down syndrome in pregnancy commenced 24 years ago with the pioneering observation by Merkatz et al. (1984), of the association between decreased second-trimester maternal serum levels of alpha-fetoprotein and foetal trisomy 21. Over the following two and a half decades, screening underwent major transformations with the elucidation of additional second-trimester biochemical markers, and most recently by the combination of ultrasonography with maternal serum markers in the first trimester (Snijders et al., 1998). Despite improvements in detection and the addition of foetal specific markers such as the nuchal translucency (NT) measurement, the algorithm remains a risk adjustment to background risk by maternal age.

Invasive testing is now offered to all pregnant women regardless of maternal age (ACOG Committee on Practice Bulletins, 2007) and most advanced maternal age (AMA) patients opt for screening prior to making their decision (Zoppi et al., 2001). For the growing group of AMA patients, it appears that the risk adjustment method might be inappropriate in view of their extremely high false positive (FP) rates (Wapner et al., 2003). Elimination of maternal age from the equation will result in a real, or absolute, risk analysis. The aim of this study was to evaluate the absolute risk (AR) method as a screening approach as compared to the currently used method in patients undergoing first-trimester screening (FTS) at our institution.

MATERIAL AND METHODS

We performed a three-stage retrospective analysis of 3073 patients that had the FTS at our nuchal translucency quality review (NTQR) credentialed institution from 1 January 2006 to 31 December 2007.

FTS was performed in accordance with the customary criteria of the Foetal Medicine Foundation. Maternal serum markers were analysed by Genzyme (2432 samples) and by NTD-Perkin Elmer (641 samples).

In stage 1, we calculated the normal distribution of AR as defined by final FTS risk/risk by age. In stage 2, we used the AR method to determine risk for patients who had been found screen positive by the current method. Additionally, AR was compared between chromosomally normal and abnormal gestations. Foetal and newborn
chromosomal and structural outcomes in the screen-positive group were validated through karyotype or postnatal physical examination. In stage 3, we analysed the screen-positive AMA patients. The student \( t \)-test was used for statistical analysis. \( p < 0.01 \) was considered statistically significant.

**RESULTS**

In stage 1, 145 (4.7%) of the 3073 patients that underwent FTS in the study period screened positive by the current method (Figure 1). Overall, AR > 1 was found in 151 (4.9%) patients, and AR > 1.2, 2 and 3 were found in 123 (4%), 96 (3.1%) and 61 (1.98%), respectively.

In stage 2, 12 (8.27%) of the 145 screen-positive patients were diagnosed with chromosomal abnormalities (2 × T21, 4 × 45, XO, 3 × T18, 2 × T13, and 1 × Marker 21), and 3 (2.06%) with major structural anomalies (Tetralogy of Fallot, duodenal atresia, brain malformations). Of the 145 patients that screened positive using the current method, 81 (55.8%) had AR > 1.2 (Figure 1). All the screen-positive patients diagnosed with aneuploidies or major structural anomalies were in this group. In addition, two patients who had second-trimester spontaneous miscarriages had AR > 1.2. A statistically significant difference was found in AR between chromosomally normal and abnormal gestations (see Figure 2; \( t \)-test, \( p < 0.01 \)). Two patients were diagnosed with chromosomal abnormalities in the screen-negative group. The first patient was 32 years old and had a negative screen with AR < 1. She was diagnosed at 18 weeks with trisomy 13 after multiple anomalies were noted on her anatomy scan. The second patient was a 26-year-old who had a negative screen, but with AR > 1.2. The patient delivered a full-term newborn with trisomy 21.

In stage 3, 103 of the 145 patients that screened positive by the current method were AMA. Using AR > 1.2 as a cut-off, only 39 (28%) of these patients would have been considered screen positive by the AR screening method. In fact, all 64 patients that screened positive by the age adjustment method with AR < 1.2 were AMA, and 56 (87.5%) of them had a completely negative AR.

**DISCUSSION**

The inclusion of maternal age background risk for aneuploidy in the currently used risk calculation method results in high FP rates in AMA patients, and may result in false negative results in younger patients. It is paradoxical to think that a 20-year-old with an NT of 3 mm, and thus, a significantly increased AR, can be screen negative, while a 40-year-old with completely average markers and a decrease in AR can be screen positive. The patient’s question: ‘Does my risk increase or decrease as a result of the screening test?’ is certainly not well answered with the current system. Our results indicate that eliminating background risk by maternal age from the equation and using the AR cut-off > 1.2 captured all abnormal pregnancies identified by the current screening method with a lower FP rate.

Our study is in agreement with Schmidt *et al.* (2007) who suggested that including maternal age in the screening algorithm is not beneficial, and furthermore, that eliminating maternal age results in comparable sensitivity with a lower FP rate. Combining the screening risk with the age-related background risk greatly increases the FP rate, which reaches 50% for a 40-year-old woman (Centini *et al.*, 2005). This leads one to question the point of FTS for older patients in general, when so many will screen positive and be faced with having to decide whether to have invasive testing anyway. In our population, only 28% of the AMA women who screened positive by the current method would have screened positive by the AR method. The latter method results in a low fixed FP rate for all women with a seemingly comparable detection rate. For the AMA group, a reduction
in the FP rate is particularly beneficial as their current pregnancy may be their last.

The maternal age risk adjustment method also increases the false negative rate for younger women. Wapner et al. (2003) reported only a 66.7% detection rate for trisomy 21 using FTS in women under 35 years old. In our study, two patients in the screen-negative group were known to be subsequently diagnosed with foetal aneuploidy, and both were under 35 years of age. One had an AR > 1.2 and would have been diagnosed prenatally by the AR method. Due to the retrospective nature of our study, however, adequate follow-up data by karyotype or by a geneticist’s physical exam was only available for the screen-positive patients. Therefore, we chose not to provide statistical analysis on the screen-negative group as their follow-up data might be incomplete and the calculation possibly misleading. Nonetheless, we do believe that the AR method has the potential to improve detection rates in younger women and that this important question can only be adequately studied in a prospective manner.

This study is limited by its retrospective nature and small population size. Nevertheless, the results certainly question the importance of including maternal age background risk in the screening algorithm. Eliminating age from the equation by using the AR approach has the potential to reduce the stress associated with FP results, particularly in AMA patients. We hope that this study would serve as a platform for a prospective, large-scale study to validate the AR screening method.

REFERENCES


