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Atypicality index as an add-on to combined first-trimester screening for chromosomal aberrations

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Objective

To assess the clinical utility of an atypicality index as an adjunct to combined first-trimester screening for chromosomal aberrations.

Methods

From Central Denmark Region databases, we identified all pregnant women seen for cFTS between January 2008 and December 2018. All pregnancies with a cytogenetic or molecular analysis obtained prenatally, following pregnancy loss or termination of pregnancy, or postnatally were identified. An atypicality index was computed from nuchal translucency thickness, maternal serum free β-human chorionic gonadotropin, and pregnancy-associated plasma protein-A. An atypicality index quantifies how unusual an individual set of measurements are relative to a multivariate reference distribution for unaffected pregnancies, with increasing values reflecting a more atypical measurement profile.

Results

We retrieved data on 146,076 singleton pregnancies of which 9,856 (6.7%) were genetically examined. Overall, 1 in 122 of all pregnancies seen for cFTS (n=1,198, 0.82%) was affected by a fetal chromosomal aberration (12.2% of the pregnancies tested). In screen-negative pregnancies (cFTS T21 risk <1 in 100 and/or T18/13 risk <1 in 50), the risk of chromosomal aberrations increased with higher atypicality index (AcFTS). The risk of a chromosomal aberration increased from 0.28% [95% CI 0.25-0.31%] in pregnancies with the most typical measurement profile (AcFTS<80%) to 0.49% [95% CI 0.38-0.62%], 1.5% [95% CI 1.3-1.8%], and 5.1% [3.4-7.5%] in those with AcFTS of (80-90%], (90-99%], and >99%, respectively. Compared to the background risk in screen-negative pregnancies, the relative risk increased from 0.67 [95% CI 0.59-0.77] in the most typical group (AcFTS<80%) to 1.2 [95% CI 0.9-1.5], 3.6 [95% CI 3.1-4.3], and 11.9 [95% CI 8.1-17.5] in the highly atypical group (AcFTS>99%).

Conclusion

The atypicality index can be used as a tool for clinicians to optimize the interpretation of preexisting prenatal screening profiles. In pregnancies considered at low risk of chromosomal aberrations from cFTS, an atypicality index from NT, PAPP-A, and β-hCG MoM, identifies a subgroup of women with highly unusual measurement profiles where the risk of a chromosomal aberration is substantially increased, and further testing should be considered.