17th World Congress in Fetal Medicine

Cell-free DNA screening: positive predictive value for Turner syndrome is critically dependent on nuchal translucency measurement

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Objective

Laboratories report positive cell-free DNA test results in various ways, as either “aneuploidy detected” or “high risk” or “>99%”, which could be misleading. Neither of these reporting methods is as useful to obstetric providers and patients as a positive predictive value (PPV). Many medical societies (ACOG, SMFM) encourage laboratories to report individual VPP for each aneuploidy tested and the National Society of Genetic Counselors and the Perinatal Quality Foundation developed an online PPV calculator for cfDNA screening. PPV for Turner syndrome is reported to be about 30-40% but this includes a mixture of cases with and without typical ultrasound features. We aimed to investigate the influence of nuchal translucency (NT) measurement on the PPV on a cfDNA screening cohort of 2502 singleton pregnancies that included non-autosomal aneuploidies screening.

Methods

We reviewed our cfDNA screening outcome records in singleton pregnancies that included non-autosomal aneuploidy (NAA) screening from 29 July 2013 to 29 September 2017 at Fleury Medicina e Saude diagnostic center. All our tests screened positive for a NAA aneuploidy were recorded and first trimester NT measurement, when available, was recorded. Diagnosis was confirmed when prenatal or postnatal karyotype was concordant with cfDNA findings. Some cfDNA cases screened positive for Turner syndrome that resulted in fetal demise were also considered as true positives when ultrasound revealed exuberant characteristic findings. All true-positive (TP) and false-positive (FP) cases for Turner syndrome and for other NAA were recorded and the PPV was calculated for Turner syndrome cases with and without NT > 99th centile, and for other NAA. In the first 951 cases a targeted MPS (tMPS) technology was used, while the remainder 1551 cases were analysed using massive parallel shotgun sequencing (MPSS).

Results

There were 13 cases screened positive for 45X and 7 cases screened positive for other NAA (2 XXX and 5 XXY). Four cases screened positive for 45X presented a NT >99th centile and all were confirmed as true positives. Eight cases screened positive for 45X presented a nuchal translucency measurement below the 99th centile, and all but one were false positives. Among the false positives there was one patient that developed a lung malignancy and three fetuses that developed IUGR. The only true positive case that presented a normal NT was in fact a mosaic monosomy X, with no syndromic features at birth. There was one case screened positive for 45X that was lost to follow-up and NT measurement was not recorded. The positive predictive value for 45X in cases with NT <99th centile was 12. 5% (0. 3-52. 7%) and for cases with NT > 99th centile it was 100% (39. 8-100%). All cases screened positive for other NAA in which a karyotype was performed were confirmed as true positives (2 XXX and 3 XXY). Two patients screened positive for XXY declined prenatal or postnatal karyotype. The positive predictive value for other NCA was 100% (47. 8-100%).

Conclusion

Patients screened positive for 45X would be better counselled using a PPV based on NT findings. Despite being small, this series supports that the vast majority of cases screened positive for Turner syndrome presenting a normal NT are in fact false positives and might be managed expectantly, with close surveillance of fetal growth and maternal health.