Screening strategies for the detection of all fetal karyotype abnormalities

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Objective

Cell-free DNA (cfDNA) and traditional serum±ultrasound screening (TSS) are screening tests for T21,T18,T13. For these targets, cfDNA tests have a higher detection rate (DR) and a much lower false positive rate (FPR). The higher FPR is often considered a limitation of TSS when compared with the highly specific, albeit more expensive, cfDNA test. However, the authors have identified a distinct advantage with TSS due to nuchal translucency's (NT) ability to pick up additional abnormalities in addition to the higher reflex invasive testing rate. As a result, rare, unexpected 'off-target' chromosome abnormalities may be discovered using TSS. The aim of this study is to compare the detection rates of all fetal karyotype abnormalities (target and off-target) at birth by cfDNA and TSS.

Methods

Using a model derived from our laboratory data, we predicted the DR of all karyotype anomalies for seven screening strategies, including different TSSs, cfDNA tests (±SCAs) and contingent or sequential approaches with first-tier combined first trimester screening and second-tier cfDNA in different risk groups. Three representative maternal ages (MA) - 25, 35 and 45 years- were considered. Predicted frequencies of any karyotype anomaly in pregnancies with no risk factors other than MA including previously published fetal loss rates for T13,18,21 were used to determine a-priori risk for each karyotype anomaly at birth (Ferreira et al, 2016). The DR and FPR for target anomalies were abstracted from several published studies. DRs for off-targets are 5%, 0.35% and 0.72%, corresponding to the FPR for T21 of TSSs and cfDNA tests, respectively. The DR for all target+off-target abnormalities using cfDNA was adjusted downwards as 1% of 'no result' cases by cfDNA are actually undetected karyotype abnormalities.

Results

CfDNA testing for T21,18,13+SCA (cfDNA-TXY) has the highest DR for all karyotype abnormalities at all MAs. In young women, cfDNA for T21,18,13 only (cfDNA-T) has a lower DR than any TSS as the higher 5% TSS FPR results in the identification of a greater proportion of off-target abnormalities, which dominate the overall chromosomal anomaly risk in young women; cfDNA-T equals contingent or combined first trimester screening at a MA of 38y, when trisomies dominate the risk.

Conclusion

As the distribution of the chromosome abnormalities is different at different MA, and although the two strategies may show approximately the same overall DR, TSSs favour the detection of a broader spectrum of other chromosomal abnormalities. On the other hand, universal cfDNA tests selectively and efficiently detect common aneuploidies with a limited view of the off-target abnormalities. These results are useful for the development of screening models and financial strategies for public health authorities .