

Chromosome abnormalities investigated by non-invasive prenatal screening only account for approximately 50% of fetal chromosomal abnormalities associated with a relevant clinical phenotype

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During the past 20 years, non-invasive screening tests have been increasingly applied in the practice of prenatal diagnosis (PD). Considerable effort has been exerted by multicentric consortia to evaluate the performance of invasive screening tests in detecting women with an increased risk of having a pregnancy affected by trisomies 21, 18, and 13, monosomy X, and triploidies. However, an evaluation addressing how much of this group of abnormal karyotypes accounts for the total number of phenotypically-relevant fetal chromosomopathies has not been conducted. Herein we report an attempt aimed to quantify this proportion.

We undertook a retrospective analysis of a homogeneous survey of 115,128 invasive PD (84,470 amniotic fluid samples and 30,658 chorionic villi samples). All cases were classified according to the indication for invasive PD. We focussed on results from 96,416 karyotype analyses from pregnant women in which the advanced maternal age (≥ 35 y) and the gestational anxiety (< 35 y) were the sole indications for invasive sampling since they usually are the beneficiaries of non-invasive screening tests. The cumulative amount of fetal chromosomopathies with a significant phenotypic effect that might be detected by prenatal screenings was calculated subtracting from the observed amounts of T21, T18, T13, 45,X, and triploidies the portion that would be undetected due to the specific detection rate of the screening test. Finally, this value was related to the total chromosomopathies associated with a clinically abnormal phenotype ranging from moderate-to-severe. Our findings indicate that the chromosomal abnormalities investigated by screening tests represented $< 50\%$ of the fetal chromosomopathies associated with a high-intermediate risk of an abnormal outcome in women < 35 y (45.79% and 39.61% in the 1st and 2nd trimesters, respectively), and a sensitivity $> 50\%$ in women ≥ 35 y (65.10% and 61.78%, respectively). In conclusion, approximately 50% of the phenotypically-relevant abnormal karyotypes cannot be investigated by non-invasive prenatal screening tests.