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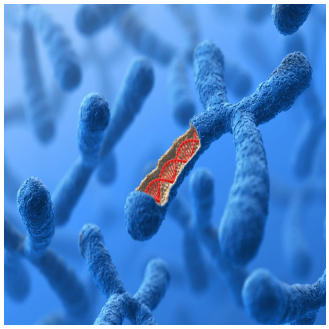
Identifying Atypical Chromosomal Aberrations in the First Trimester



Chromosomal abnormalities during pregnancy can lead to various developmental issues in the foetus. Prenatal screening has been instrumental in identifying risks for common trisomies, such as trisomies 21, 18, and 13. However, standard non-invasive prenatal testing (NIPT) might not effectively detect other atypical chromosomal aberrations. The Danish nationwide study sheds light on the efficacy of combined first-trimester screening (cFTS) and invasive diagnostics like chromosomal microarray analysis (CMA) in identifying these atypical aberrations. A recent article published in Obstetrics & Gynaecology focusses on how cFTS and invasive testing detect these conditions, the benefits and limitations of each approach, and their potential implications for prenatal care.

Performance of cFTS in Identifying Chromosomal Aberrations

The combined first-trimester screening (cFTS) has proven to be effective in detecting common trisomies by analysing maternal age, nuchal translucency (NT) thickness, and serum biomarkers such as β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A). Risk estimates for trisomies 21, 18, and 13 are generated through this process. However, alongside these common trisomies, cFTS also identifies other atypical chromosomal aberrations, including pathogenic copy-number variants (pCNVs), sex-chromosome aberrations (SCAs), and rare autosomal trisomies (RATs). The study found that while cFTS is particularly effective in detecting common trisomies and triploidy, its sensitivity decreases when screening for submicroscopic atypical aberrations like pCNVs.

Comparing Invasive Testing with cFTS and NIPT

In Denmark, following a high-risk result from cFTS, invasive testing is typically offered, which may include chorionic villus sampling (CVS) or amniocentesis analysed through CMA. The introduction of CMA has allowed for the detection of a broader range of submicroscopic aberrations compared to conventional karyotyping. In contrast, NIPT focuses on screening for specific chromosomal abnormalities, predominantly common trisomies. Despite the emergence of genome-wide NIPT, which has broader coverage, its resolution is often insufficient for detecting smaller aberrations, especially those less than 5–7 Mb. The study found that 79% of pCNVs diagnosed in their national cohort were smaller than 5 Mb, making them undetectable through standard NIPT platforms. Thus, cFTS, followed by invasive testing with CMA, significantly enhances the detection of these smaller pathogenic aberrations.

Implications of Replacing Invasive Testing with NIPT

The study raises important considerations regarding the potential impact of replacing invasive testing with NIPT for pregnancies identified as high-risk by cFTS. While NIPT offers a non-invasive alternative for aneuploidy screening, its limitations in detecting atypical chromosomal aberrations highlight a substantial trade-off. According to the study's findings, if NIPT were to replace invasive testing, many pathogenic chromosomal anomalies could be missed. Specifically, 1 in 26 high-risk pregnancies would still carry a chromosomal aberration not identified by conventional NIPT. This highlights the crucial role of invasive testing in ensuring comprehensive prenatal diagnosis and raises the need for better screening methods or an advancement in NIPT technology to match the resolution capabilities of CMA.

The study underscores the importance of using a combined approach for prenatal screening to effectively identify a range of chromosomal aberrations. While cFTS is a valuable initial screening tool for common trisomies and some atypical aberrations, invasive diagnostics such as CMA provide critical insights, especially for detecting pCNVs and other submicroscopic anomalies. The limitations of NIPT, particularly its reduced sensitivity for smaller aberrations, emphasise the need for invasive testing in high-risk cases or the development of more advanced non-invasive techniques. Ensuring accurate prenatal diagnosis is vital for informed decision-making and appropriate clinical management during pregnancy.

Source: **Obstetrics & Gynaecology**

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