GENOME-WIDE NON-INVASIVE PRENATAL TESTING FOR RARE CHROMOSOMAL ABNORMALITIES: DIAGNOSTIC ACCURACY, DISCORDANT RESULTS AND CLINICAL IMPLICATIONS

Ph.D. Thesis Booklet

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1 INTRODUCTION

1.1 Overview of the topic

1.1.1 What is the topic?

Genome-wide non-invasive prenatal testing (GW-NIPT) is based on the analysis of circulating cell-free DNA (cfDNA) fragments present in maternal plasma. These cfDNA molecules originate predominantly from placental trophoblasts and represent a mixture of maternal and fetal genetic material. Advances in massively parallel sequencing technologies and bioinformatic modelling have enabled genome-wide interrogation of cfDNA, extending the scope of non-invasive prenatal testing beyond common trisomies to rare autosomal trisomies (RATs) and large subchromosomal copy number variations.

As a result, GW-NIPT has transformed prenatal screening by providing unprecedented genomic breadth. However, this expanded analytical scope has introduced new biological and clinical interpretative challenges related to the placental origin of cfDNA.

1.1.2 What is the problem to solve?

Although GW-NIPT is increasingly implemented in routine prenatal care, its clinical interpretation is inherently constrained by biological and technical factors. Because cfDNA primarily reflects placental rather than fetal genomic composition, abnormal GW-NIPT findings may be discordant with confirmatory invasive diagnostic results.

Furthermore, genome-wide analysis increases the likelihood of detecting signals unrelated to fetal chromosomal status, including confined placental mosaicism and maternal genomic abnormalities. These findings complicate genetic counselling and clinical decision-making, particularly in the absence of robust, chromosome-specific outcome data.

1.1.3 What is the importance of the topic?

Reframing certain discordant GW-NIPT results as indicators of placental pathology rather than simple analytical errors provides a biologically grounded explanation for these discrepancies. Importantly, accumulating evidence suggests that such findings may have prognostic relevance, as placental mosaicism is associated with adverse pregnancy outcomes including fetal growth restriction, pre-eclampsia, and preterm birth.

Accurate interpretation of GW-NIPT results is therefore critical for appropriate risk stratification, counselling, and prenatal surveillance.

1.1.4 What would be the impact of our research results?

The results of this research aim to support evidence-based interpretation of GW-NIPT findings by providing chromosome-specific risk estimates and outcome-based data. This has the potential to reduce unnecessary parental anxiety, improve counselling accuracy, and enable tailored prenatal management in pregnancies identified as high risk.

2 OBJECTIVES

This doctoral research aimed to evaluate the clinical performance, biological interpretation, and clinical implications of genome-wide non-invasive prenatal testing (GW-NIPT) for rare chromosomal abnormalities. Specifically, the thesis aimed to:

1. To evaluate the diagnostic performance of GW-NIPT for rare chromosomal abnormalities, a systematic review and meta-analytical approach was employed.
2. We also aimed to characterise discordant GW-NIPT findings by distinguishing between signals of fetal and placental origin and quantifying the chromosome-specific risk of adverse pregnancy outcomes.
3. We also aimed to assess the association between complex, multi-chromosomal GW-NIPT profiles and maternal malignancy.
4. The aim is to develop an evidence-based framework to support genetic counselling and clinical decision-making.

3 METHODS

3.1 Search Strategy

Comprehensive literature searches were conducted in MEDLINE, Embase, Cochrane Library, Scopus, and Web of Science databases using predefined search terms related to GW-NIPT, rare chromosomal abnormalities, adverse pregnancy outcomes, and maternal malignancies.

3.2 Eligibility Criteria

3.2.1 Study I

Study I included original research articles reporting GW-NIPT results for rare chromosomal abnormalities confirmed by invasive prenatal diagnostics, postnatal testing, or documented pregnancy outcomes.

3.2.2 Study II

Study II included studies reporting discordant GW-NIPT findings and associated pregnancy outcomes or maternal conditions, including malignancies.

3.3 Study Selection and Data Extraction

Two independent reviewers performed study selection and data extraction according to predefined criteria. Discrepancies were resolved by consensus or third-party adjudication.

3.4 Quality Assessment

Risk of bias and quality of evidence were assessed using validated tools appropriate for diagnostic accuracy and prognostic studies.

3.5 Data Synthesis and Analysis

3.5.1 Study I

Random-effects meta-analyses were performed to estimate pooled prevalence and positive predictive values of rare chromosomal abnormalities detected by GW-NIPT.

3.5.2 Study II

Meta-analytical methods were applied to assess associations between discordant GW-NIPT results, adverse pregnancy outcomes, and maternal malignancies.

4 RESULTS

4.1 Study I

This systematic review and meta-analysis incorporated 17 studies involving 740,076 genome-wide non-invasive prenatal tests (GW-NIPTs). Together, rare autosomal trisomies (RATs) and structural chromosomal aberrations (StrCAs) affected approximately 0.2–0.3% of tests, and were infrequent.

The pooled proportion of RAT-positive results was 0.26%. Diagnostic performance was limited, with a pooled positive predictive value (PPV) of 7% when strict confirmation was used, rising to 13% when clinically relevant pregnancy outcomes were considered. Despite the low PPVs, discordant RAT results were consistently associated with placental pathology rather than random false positivity.

StrCAs were detected in around 0.16% of cases, demonstrating substantially higher diagnostic accuracy with pooled PPVs of 47–52%, as well as lower heterogeneity, compared to RATs.

Chromosome-specific analyses revealed significant variability. Although trisomy 7 was the most frequently detected, true fetal involvement was most strongly associated with trisomies 16, 22 and 15. Several chromosomes showed negligible detection rates and minimal fetal confirmation.

Overall, the large cumulative sample supports the chromosome-specific interpretation of rare GW-NIPT findings, despite considerable heterogeneity.

4.2 Study II

This systematic review and meta-analysis included 16 studies comprising 681,633 genome-wide non-invasive prenatal testing (GW-NIPT) analyses. The focus was on discordant GW-NIPT results for rare autosomal trisomies, examining their association with adverse pregnancy outcomes and maternal malignancies.

Discordant GW-NIPT results were consistently associated with placenta-related pregnancy complications. Compared with population controls, pregnancies with discordant rare trisomy findings were found to have significantly higher odds of intrauterine growth restriction, being small for gestational age, preterm birth and, to a lesser extent, pre-eclampsia and stillbirth. Although substantial heterogeneity was observed for some outcomes, the direction of effect remained stable across sensitivity analyses.

Chromosome-specific analyses revealed marked risk heterogeneity. Trisomy 16 showed the strongest overall

association with adverse pregnancy outcomes, followed by trisomies 4, 6, and 22. In contrast, common trisomies such as 7, 8, and 20 were associated with a lower risk. Elevated risks of uniparental disomy were particularly observed for chromosomes 15 and 16, far exceeding background population rates.

Furthermore, analysis of complex, multi-chromosomal discordant GW-NIPT profiles demonstrated a strong association with underlying maternal malignancy. Approximately 40% of these cases were linked to a confirmed cancer diagnosis, representing a several-hundred-fold increase compared with background incidence rates during pregnancy. The most frequently identified cancer types were breast cancer, lymphoma, and gastrointestinal malignancies.

Overall, these findings demonstrate that discordant GW-NIPT results frequently provide clinically actionable information reflecting placental dysfunction and, in complex cases, an increased likelihood of maternal malignancy.

5 CONCLUSIONS

The integration of genome-wide non-invasive prenatal testing (GW-NIPT) has broadened the scope of prenatal screening to encompass not only common aneuploidies, but also fetal, placental, and maternal genomic signals. This systematic review and meta-analysis shows that, while rare chromosomal abnormalities are uncommon individually, their detection is clinically significant. Although the overall positive predictive value is low, certain chromosomes — particularly chromosomes 16, 22 and 15 — are more frequently associated with true fetal involvement, especially when supported by ultrasound abnormalities.

Importantly, discordant GW-NIPT results should not simply be dismissed as false positives. These results often reflect confined placental mosaicism, which is strongly associated with placental dysfunction and adverse pregnancy outcomes, such as intrauterine growth restriction and pre-eclampsia. Furthermore, complex, multi-chromosomal GW-NIPT patterns may indicate underlying maternal malignancy, providing incidental, yet clinically relevant, information on maternal health.

Overall, these findings support the use of GW-NIPT as a multi-purpose screening tool. Chromosome-specific risk stratification, standardised counselling and enhanced obstetric surveillance are essential for managing rare and discordant results, highlighting the importance of integrated, multidisciplinary prenatal care.

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