NON-INVASIVE CELL-FREE DNA-BASED APPROACH FOR THE EVALUATION OF CLINICAL MISCARRIAGE

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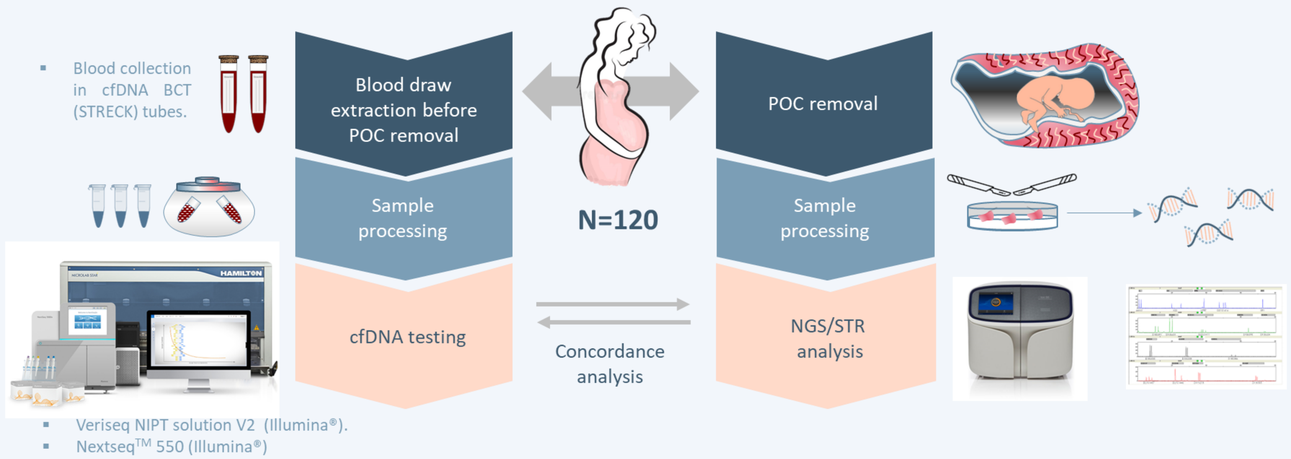
INTRODUCTION

It is well established that 50-70% of clinical miscarriages are caused by aneuploidies, mostly trisomies. To date, conventional cytogenetic and advanced molecular techniques are used for the analysis of Products of Conception (POC) to identify the genetic cause of miscarriage, providing valuable information for genetic counselling. However, both approaches are based on the direct analysis of the abortive tissue, which entails several limitations and risks including culture failure and/or maternal cell contamination (MCC), and surgical complications. Maternal cfDNA testing emerges as a promising tissue-independent alternative.

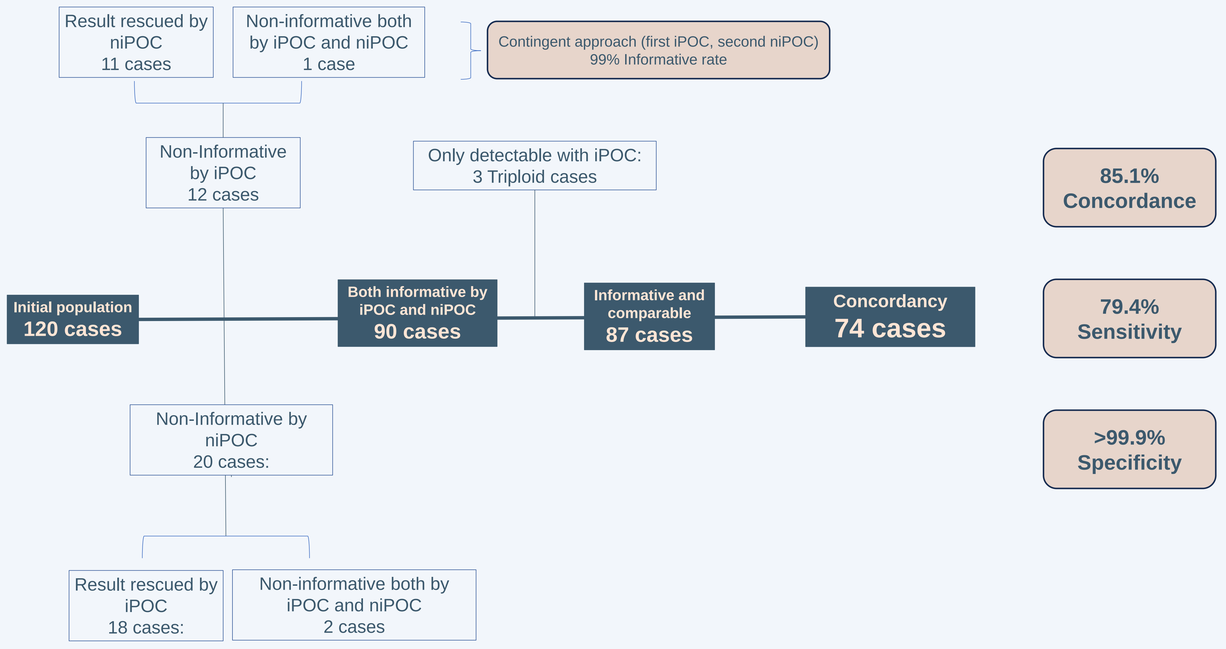


MATERIALS and METHODS

This is a retrospective study conducted in our laboratory from January 2021 to December 2022. A blood sample from 120 women was drawn to evaluate aneuploidies by cfDNA testing (niPOC). For this purpose, paired-end sequencing data were aligned to the reference genome (hg19), and VeriSeq NIPT Solution V2 algorithm was used for aneuploidy calling. Traditional genetic testing for POC in fetal remains (iPOC) was done using an NGS technology (Thermo Fisher Scientific, USA) for 24 chromosome aneuploidy screening. Short-tandem repeat (STR) analysis allowed us to detect or rule out maternal cell contamination (MCC) and identify some types of polyploidies in the traditional POC analysis (iPOC). Results derived from both studies were compared to assess the percentage of concordance and the cases of non-informativity (NIR) (fetal fraction (FF) <2%, or MCC).

RESULTS

We found no significant differences in the NIR between iPOC and niPOC analysis [10.0% (12/120) vs. 16.7% (20/120)]. Out of 120 samples, 90 provided an informative result on fetal tissue in iPOC and niPOC groups (75%). Excluding triploidy (not tested by niPOC) cfDNA analysis correctly identified 74/87 (85.1%) samples. Sensitivity and specificity were 79.4% and 100%, respectively; all discordant cases were female.



CONCLUSIONS

Genome-wide cfDNA-based screening provides a simple, non-invasive approach to determine whether fetal aneuploidy explains the loss in early pregnancy loss or recurrent pregnancy loss (RPL) patients. Given the simplicity and accuracy of niPOC, clinicians will be able to perform genetic testing in a group of patients where it was not previously feasible.

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