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Abstract Title:- Comprehensive approach involving cfDNA and metabolites in embryo selection for ART treatment

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Aims:-Assisted reproductive technologies (ART) have revolutionized the field of infertility treatment, yet the selection of high-quality embryos resulting to healthy fetus remains a challenge. Significant progress has taken place in selection of embryo by scanning genome for chromosomal or segmental aneuploidy, yet its also known fact that all euploids don't transform to healthy fetus. So, it is necessary to evaluate more markers to identify problems related to implantation and development of healthy fetus during ART treatment. As embryo grow, it exchanges many metabolites with culture media along with presence of cell-free DNA (cfDNA) in media. Recent advancements in the fields of metabolomics and cfDNA analysis, it have opened new possibilities for non-invasive Preimplantation Genetic Testing for Aneuploidy (niPGT-A). This innovative approach combines LC-MS-based metabolomics in spent culture medium with cfDNA aneuploidy testing to offer a comprehensive and non-invasive strategy for embryo selection in infertility treatment. The main objective of this study is to identify potential metabolite markers in association with the aneuploidy identified in the spent culture medium of the embryos that can be use to predict embryo quality non-invasively.

Methods:- Total 204 spent culture medium (SCM) samples were analyzed using Whole Genome Amplification of cfDNA for aneuploidy screening and Liquid Chromatography-Mass Spectrometry (LC-MS) for metabolite profiling including amino acids, lipids, and small molecules.

Results:- During the analysis of cfDNA, the low DNA concentration was observed in 6.4% (n=13) and hence, they were excluded from this study. After analyzing remaining cfDNA released by embryos into the culture medium, it was postulated that 42.15% (n=86) samples showed normal chromosome complements. The abnormal chromosome complements i.e. presence of aneuploidies in 24.5% (n=50) samples and mosaicism observed in 26.95% (n=55). Our metabolomics analysis with LC-MS demonstrated the high sensitivity distinct metabolomic profiles of varying quality in correlation with respect to the euploidy and aneuploidies observed i.e. monosomy as well as trisomy of chromosome 16, 19, 21 and 22 in highest count, whereas, aneuploidies in chromosome 1, 5 and 6 with the lowest count. There are certain key metabolites such as lactate, pyruvate, glutamine, and specific amino acids exhibit significant differences between high-quality and low-quality embryos.

Conclusions:- This novel approach has unique key advantages, including non-invasiveness and the ability to evaluate both metabolic activity and chromosomal integrity. By combining metabolomics and cfDNA aneuploidy testing, infertility specialists can make more informed decisions regarding embryo selection for In-Vitro Fertilization (IVF), ultimately leading to improved success rates and healthier pregnancies for

individuals and couples navigating infertility. The application of this dual-method approach underscores that metabolomics in embryo assessment represents a promising advancement in the field of reproductive medicine. Nevertheless, further validation and prospective clinical studies will pave the way in the field of embryo selection for the infertility treatment.

Keywords:- ART, Cell-free DNA (cfDNA), LC-MS, Metabolite markers, Embryo selection.