

PhD Viva Voce

Project Title: Idiopathic Recurrent Pregnancy Loss: Possible Association of paternal exposure to endocrine disruptors and epigenetic modifications in sperm

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ABSTRACT

Recurrent pregnancy loss (RPL) is the loss of two or more consecutive pregnancies before the 20th week of gestation and is a distressing problem for couples with a desire to have children. 1-2% women experience RPL of which ~50% cases are idiopathic (iRPL). Aside from female factors, the male factors could also play a role in disease etiology. Spermatogenesis and epigenetic regulation are hormone sensitive processes and can be very susceptible to environmental chemicals which act like endocrine disruptor chemicals (EDCs) such as phthalates (used as plasticizers) which are ubiquitously present in the environment. Though, these chemicals are rapidly eliminated from the human body, some unmetabolized levels remain in circulation or are deposited in the adipose tissue due to their lipophilic nature. In recent years, much has been studied regarding EDCs exposure and their plausible effects on epigenetic mechanisms in spermatogenesis; however, its ability to influence embryonic and placental development leading to RPL remains elusive. Therefore, one arm of our study aimed to estimate Phthalate exposure levels in the iRPL and fertile study populations to check for any association with iRPL and the sperm epigenome. Specific phthalates were found to be associated with iRPL with either the male or female partners.

Furthermore, the sperm epigenome itself can be a crucial contributor to the regulation and expression of early embryogenesis genes. Recent studies have shown that ~20% of the DNA

methylome escapes epigenetic reprogramming during embryogenesis. The human sperm also retains 5-15% of the nucleosomes which are enriched on loci of developmental importance and a fraction of it, too, escapes epigenetic reprogramming. These marks have been assigned to instruct timely embryo and placenta developmental regulation. Therefore, this study further aimed to investigate the whole genome methylation landscape and histone/modified histone profiles of the sperm genome in iRPL. We observed an altered sperm DNA methylome with promising epimutation biomarkers associated with iRPL. Also, altered levels of modified histone H3K4me3 were observed in the iRPL group as compared to the fertile population. Further, correlation analysis was done to check whether higher serum phthalate levels in the study population were associated with alterations in the sperm epigenome. All the results will be discussed in detail during the presentation.