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THE EFFECT OF EXTERNAL ENVIRONMENT ON REPRODUCTIVE HEALTH

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Abstract. Environmental health is broadly defined as the aspects of human health determined by physical, chemical, biological and social factors in the environment and encompasses the assessment and control of those factors. The exogenous and endogenous environmental health determinants include all that surround us, and environmental impact includes not only physical, chemical and biological factors, but also hormones, diet and lifestyle. As most humans develop in a predictable fashion, growing from a fertilized egg to fetus, newborn, toddler, child, adolescent, and adult, there is little doubt that environment is a powerful modifier of the human reproduction and development. Starting 20 years ago, there has been a steady growth in the number of laboratories involved in the investigation on environmental impact on molecular reprogramming during the most critical windows of development, such as pre-conception, pre-implantation, the fetal period, and early childhood. And considerable evidence demonstrates that the gene-environmental regulation of gene expression is crucial, besides change in the DNA sequence.

Key words: environmental, human health, chemical and biological factors, reproductive, plasminogen, metabolically, menopause.

Introduction. The epigenetic information is often stored as chemical modifications falling into two main categories: 1- DNA methylation and 2- changes to the histone proteins that package the genome. By regulating DNA accessibility and chromatin structure, these chemical alterations influence how the genome is translated across diverse developmental stages. Untangling all the components of gene-environmental regulation might be problematic in conventional human setting. In this broadest sense, if contributions of multiple factors are substantial and likely to increase susceptibility to reproductive ailments, the effects of these should be apparent in the “normal” tissue prior to the development of disease. A differentiating tissue that is actively proliferating to generate additional cells will respond differently to an insult as compared to a tissue than a fully differentiated tissue that has already generated many of the required cells after molecular reprogramming. Evidence from both epidemiological and mechanistic studies has not only established a potential link of environmental pollutants with impaired human fertility, but also shown that they possess the ability to alter placental function and hamper fetal development. While some of these pollutants act as an endocrine disruptor, others activate a cascade of events which significantly disturbs the intact reproductive system. A wide range of female reproductive tract disorders like polycystic ovarian syndrome, placental abnormalities and aneuploidy are reported to be closely associated with the environmental chemicals results. Available reports also indicate that exposure of pregnant women to air pollutants results in increased risk of different abnormalities specifically related to heart, brain and lungs. Air pollution affects the normal developmental mechanisms of fetal brain and is related to the different diseases of the central nervous system.

Much of the excitement surrounding biomarkers today relates to identification of an ongoing change (genetic/epigenetic) and early disease diagnosis. For example, measuring appropriate biomarker in paternal blood and semen samples may provide early clues for well-timed and proper intervention. As significant amount of maternal chemical burden is shared with the developing fetus and infants, sampling of maternal blood or urine samples at different times of pregnancy allows an evaluation of the exposure of the fetus at different times of development, elucidating the chemicals that cross the placenta. A biomarker in clinical reproductive medicine may be useful to better understand and predict ovarian reserve, gamete quality, embryo viability

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and euploidy, as well as endometrial receptivity and pregnancy outcome, including miscarriage, ectopic pregnancy and obstetric complications, e.g. preeclampsia or preterm labor. Also, for effective management of in vitro fertilization (IVF) protocols, specific biomarkers could be used to discriminate between suitable and unsuitable embryos to be transferred. Some of the widely assessed biomarkers like serum progesterone, hCG and estrogen not only help to identify viable pregnancies but also provide crucial functional information about the disorders that affect testes, ovaries or adrenal glands. Similarly inhibin A is suggested to be beneficial in identification of ectopic pregnancies. Other proteins like CRP, placenta growth factor, fms-like tyrosine kinase-1(s-1FLT), leptin, transforming growth factor-a1 and plasminogen activator inhibitor may act as predictive biomarkers for different disorders including pre-eclampsia. Yet, these biomarkers have limited clinical exploitation due to poor sensitivity and specificity of the available methods for their detection.

Several thousands of environmental contaminants penetrate daily into our environment and exert various kinds of stress response on reproductive health. Included in the mixture of exposures are the billions of naturally occurring and man-made chemicals (e.g., heavy metals, persistent organic pollutants, etc.); physical agents such as noise, vibration, temperature, etc.; macro level factors like population density, sanitation, etc.; and a spectrum of lifestyle factors that includes diet, physical activity and sleep. Assessment of cumulative risks for any given biological end-point will involve analysis, characterization, and possible quantification of the combined risks from multiple environmental stressors. When a pollutant enters our body, it either accumulates, or is processed metabolically and excreted. For real-time monitoring, it could be the concentration of the parental compound, its metabolite or conjugated derivative with endogenous molecules via enzymatically catalyzed transformations which can be studied using mass spectroscopy techniques. On the other hand, for understanding the molecular repercussion of the exposure the mainstay of research will have to be on a combined “omics-based approach” involving bio-molecules such as DNA, RNA, proteins, and metabolites. Large scale quantification of genes coding for proteins, regulatory elements and non-coding sequences (genomics), RNA and gene expression (transcriptomics), protein expression (proteomics), metabolites and metabolic pathways (metabolomics) will enable the identification of important genes, pathways, and protein expression signatures in suitable biological matrix of sizeable cohorts of men and women.

Earlier studies have also reported that the altered methylation of guanine nucleotide-binding protein G(s) subunit alpha isoforms short (GNASAS) and insulin (INS) is associated with the increased risk of developing coronary heart disease. Exposure to tobacco smoke was reported to be significantly associated with the increasing miR-223 levels in both maternal and cord blood which further co-related with the rising cotinine concentrations in maternal urine. Similarly, a significant down-regulation of miR-146a was observed after nicotine and benzopyrene exposure further signifying the utility of epigenetic profile in assessing exposure associated dysregulations. Converging lines of evidence support the possibility that epigenetics may be a causal link between the genotype and environment, and hence, between the phenotype and disease which further substantiates that the changes incurred during in utero development can be transmitted trans-generationally. Recent advances in high-throughput methylated DNA analysis through whole-genome bisulfite sequencing and RNA-Seq, epigenome-wide association studies, epigenome editing approaches are more likely to provide novel insights to developmental origins of adult diseases. Although the cost of these technologies might be substantially high for large-scale application at the moment, these techniques can be used for more niche questions on limited samples to gain biological insight for further exploration.

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While identifying and characterizing the significant consequences of these associated factors on human reproduction and development, two defined clusters of population might be the most affected: susceptible and; vulnerable populations. Whereas, “susceptibility” refers to inherent biological factors, “vulnerability” indicates population at higher risk due to personal factors. Population with both susceptibility and vulnerability may together be referred as “sensitive” population. How environmental exposures affect reproductive function and development, and how this knowledge can be translated to reduce associated morbidities and enhance quality of life is precisely warranted. Recently, a large number of environmental and host risk factors have been identified that are associated with reproductive health risk resulting in dramatic fold increase in number of biomarkers reaching for clinical validation. However, the translation of these for use in the population-level screening in such a way as to have a significant impact on clinical practice poses a major challenge. Often the use of a predictive biomarker has poorer test characteristics when it is validated in two separate populations. If validated in a low disease prevalence setting, the predictive value may be low; on the other hand, in high disease prevalence setting, the same biomarker could have enough potential clinical utility. Therefore, the process of identification and validation for clinical application among the large number of purported biomarkers associated with environmental illness is a critical step in the translation process.

In recent years, the global average age for menarche has been declining. Importantly, CECs could alter the age of menarche by disrupting food availability, nutritional factors, or through increased toxin/pollutant release. Perturbations in the timing of menarche may further affect mental health, fertility-related conditions, cardiovascular disease, and bone health. Moreover, an inverse association between mortality and the timing of menarche has been suggested. The significant amount of pollutants discharged into the environment due to increasing industrial and agricultural activities is a serious threat for human health. Moreover, several of these synthetic chemicals with long half-life times are classified as potential endocrine-disrupting chemicals (EDCs) and can affect women's reproductive health. In addition to the impact of CECs on diet and nutrition, exposure to EDCs has also been associated with early menarche. These reproductive toxicants in air pollution can also cause defects during gametogenesis leading to impaired fertility. Air pollution may further aggravate asthma, which is associated with difficulties in conception. EDCs may also adversely affect the ovarian reserve in women and high levels of EDCs have been linked to a decline in ovarian function, infertility, and earlier menopause.

In contrast with infant formula, which has a standardized composition, human milk composition changes dynamically throughout the day and throughout gestation. Importantly, human milk can contain environmental pollutants, and pollutants with lipophilic properties may have serious effects when absorbed in the neonate digestive track; the presence of heavy metals in human breast milk has been associated with abnormal immune function in the neonate and allergy, endocrine disorders, neurodevelopment delay, and neuropsychiatric disorders later in life. However, it is important to note that the American Academy of Pediatrics and World Health Organization still recommend breastfeeding for at least the first months of life. Breastfeeding is not only beneficial for the mother and neonate but also for the environment, minimizing the impact on the earth's resources.

Conclusion. The current climate crisis is threatening global health and disproportionally affects disadvantaged communities. The literature in this space is increasing and opportunities for novel research exist. Importantly, CECs not only negatively impact many stages of a woman's reproductive life but also impact the health of future generations. The impact of CECs

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on reproductive health can no longer be ignored. Interventions to mitigate CECs are critical to ensuring the future health of women and children worldwide.

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