

# Emerging and Future Challenges of Hormonal Contraceptives

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## Hormonal Contraceptives

Oral Contraceptives (OC) are widely used to avoid pregnancy by suppression of ovulation. Today, conceptualization of Hormonal Contraceptives (HC) as a tool to reduce the risk of cancers such as colorectal, endometrial and ovarian [1] opened newer roads to understand its applications beyond the scope. The primary challenge for scientific community is to understand the lacunae and limitations of OC with respect to long term sustainable impacts at population levels.

It is well documented that sex differences play a key role in differential immune response (both innate and adaptive) thereby influencing outcome from diseases (infectious, autoimmune and cancer) and vaccination [2]. Hence, OC mediated immunological skewness must be addressed for better clinical management at individual level. A lower level of circulating Natural Killer (NK) cells and reduced cytotoxic activity of NK cells were observed among individuals with long term practices of OC. Exposure to ethinylestradiol was associated with lowered phagocytic and microbicidal activity of neutrophils [3]. Further, individuals under OC therapeutics displayed ramification of monocyte derived macrophage functions due to alteration in the levels of tumor necrosis factor -  $\alpha$  [4].

The alterations in immunological responses due to OC usage raised our interest to question the relationship between OC practices and diseases. A long term usage of OC (>5 year) was related with two fold higher risk for development of cervical cancer [5]. Further, exposure to OC conferred susceptibility for development of venous thromboembolism [6], arterial diseases [7], autism spectrum disorders, inflammatory bowel diseases [8], several autoimmune diseases and breast cancer [9]. Moreover, risk for development of childhood wheeze and few allergic outcomes in their progeny were related with the maternal OC exposure.

Our present knowledge on OC induced alteration on immunological responses at individual level is very limited. Findings from epidemiological studies provided indirect evidence for the presence of OC induced immunological skewness at individual level. These signatures suggested that occurrence of phenotypic changes at individual level is strongly driven by OC practices. Yet, localized OC induced changes on expression pattern of immune function associated proteins such as Human Leukocyte Antigen (HLA) and Killer cell Immunoglobulin like Receptor (KIR) remains unclear. It is well known that these factors possess a strong population and geographic specific pattern with greater degree of variability.

Genomic instability is strongly related with initiation and progression of wide range of cancer [10]. Of note, Naz et al. [11] reported a higher rate of DNA damage among individuals with long term exposure to OC and the degree of damage seems to relate with duration of OC exposure. The phenomena of differential DNA

methylation pattern with respect to age, gender and ethnicity among healthy individuals is often related with outcome of certain diseases [12]. Hypomethylation of total DNA isolated from peripheral lymphocytes of women treated with OCs provided direct suggestion for OC induced epigenetic alteration [4]. Further, variation in methylation of CpG site cg17124583 located in GATA3 gene conferred higher risk for asthma at puberty [13] was reported. All these findings collectively indicated that OC practices hold the ability to tamper human genetic makeup.

The observation of increased risk for twinning after discontinuation of OC practices [14] pointed out the possibility for long term impact at population level. However, available evidence inferred that the incidence of twin birth rates was small and without any specific orientation across the world. Interestingly, disruption of disassortative mate preferences among individuals with long term practice of OC indicated the possibility for development of limited genetic diversity [15]. Even though, human social mating system is not solely dependent on olfactory cues or hormone mediated selection as in case of most animals but consideration of such impact at long tenure seems logical [16]. Hence, it is time to accumulate knowledge on OC induced twinning's and associated environmental parameters to enhance our understanding on circulating genetic pool at population level across geographical boundaries.

Epigenetic modifications on genes that associated with immune functions (both in autosome and allosome) must be studied to address inter-individual variability in clinical outcome of various diseases. Further, sustainability of such changes for several generations is a bigger enigma. But, observation of OC induced twinning may provide such chances to pass on epigenetic modifications to next generations. Moreover, a continuous passage of a particular set of gene pool (without or oriented modification) for several generation opens the gate for a population to hold limited genetic dissimilarities. Hence, scientific measures must be developed to monitor such changes at population level across the globe. It is undeniable that the combination of genotypic (limited genetic dissimilarities, genomic instability and oriented epigenetic modifications) and phenotypic (skewed immunological response and varied gene expression) variability under the influence of environmental factors (existing and emerging diseases, carcinogens, teratogens etc) can force human population to face founder effects at distant point. Hence, deeper understanding on all aspects of contraceptives mediated challenges on human race is need of the hour.

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