

## Enigmatic Array of Toll-Like Receptors and Tissue-Inhibitor-of-Matrix-Metallo-Proteinase-2 as “Inflammatory Physiological Triggers” of Clomiphene Citrate/Letrozole/Cisplatin-Induced Ovarian Damage in Tobacco-Mediated Polycystic-Ovarian-Syndrome, Mycobacterium tuberculi-Positivity and Clinical Infertility in Genetically Susceptible Cohorts of Heterogeneous Population-Pools of Asian Indian/American/British/African/Australian women in the Covid-19 Vaccine Era: Emerging trends in Predictive Biomarkers for Infertility Management

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Received: September 29, 2022; Published: October 04, 2022

Targeting toll-like receptors and tissue-inhibitor-of-matrix-metalloproteinase-2 inflammatory and immunogenic cell-death-signaling-networks in demystifying the genetic/cellular/molecular basis of clomiphene citrate/letrozole/cisplatin-induced ovarian damage in tobacco-mediated polycystic-ovarian-syndrome, *Mycobacterium tuberculi*-positivity and clinical infertility in genetically susceptible cohorts of Asian-Indian women in the Covid-19 Vaccine Era offers fascinating immunotherapeutic evidence-based, pragmatic and patient-friendly public health-oriented avenues in innovative design of pharmacological scaffolds and predictive biomarkers in risk-stratification of asymptomatic vs symptomatic cohorts of ethnically disparate population-pools of infertile women of child-bearing age.

“Infertility” is defined as the inability to conceive following 12 months of regular unprotected sexual intercourse; moreover, the psychosocial and psychosexual distress coupled with stigma, depression and “blame game: for childlessness in dysfunctional marital relationships warrants urgent attention for addressing the overwhelming problem of infertility in the ongoing unpredictable Covid-19/Omicron pandemic era. With the advent of high-throughput precision-based medicine, Toll-like receptors (TLRs), a family of evolutionarily conserved pathogen recognition receptors, are emerging as pivotal players in the pathophysiology of a spectrum of inflammatory human diseases, including tobacco-mediated clinical infertility; inflammation in the urogenital tract leading to sexually transmitted diseases with recurrent bacterial/viral infections in the female reproductive tract are common causes of infertility globally; TLR immune surveillance initiates inflammatory responses to foreign pathogens by intricate cross-talks at the transmembrane and intracellular cell-cell junctions of maternal-fetal interfaces. The genetically distinct Asian-Indian population of women is not completely homogeneous, and the geographically diverse Indian population, in actuality, is an admixture of population-subsets of women of varying cultural exposures, lifestyles, dietary patterns, and genetic profiles with differential disease susceptibility patterns from Asia-Pacific region(s) spanning North India to South India, including altered genetic susceptibility to infertility and gynecologic malignancies, therefore providing an excellent statistically-powered sample set of a diverse array of genetically distinct subset of women of childbearing age(s) for reproductive medicine research on a global platform that may eventually provide spectacular gains in our current understanding of the pathophysiological and/or genetic basis of female infertility worldwide; interestingly, replicative prospective studies focusing on *Chlamydia*-positivity, erectile dysfunction and tobacco-mediated male infertility would certainly pave the road ahead for creating a blueprint for reproductive disorders primarily infertility amongst psychosexually-distressed couples/married partners worldwide. Prospective case-control (1:1)

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# Enigmatic Array of Toll-Like Receptors and Tissue-Inhibitor-of-Matrix-Metallo-Proteinase-2 as “Inflammatory Physiological Triggers” of Clomiphene Citrate/Letrozole/Cisplatin-Induced Ovarian Damage in Tobacco-Mediated Polycystic-Ovarian-Syndrome, Mycobacterium tuberculi-Positivity and Clinical Infertility in Genetically Susceptible Cohorts of Heterogeneous Population-Pools of Asian Indian/American/British/African/Australian women in the Covid-19 Vaccine Era: Emerging trends in Predictive Biomarkers for Infertility Management

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age-/ethnicity-matched hospital-based cross-sectional epidemiology/association studies with statistically powered sample-sets of Asian-Indian *Mycobacterium tuberculi*-positive infertility patients with PCOS/>35 years and unrelated age-/ethnicity-matched *M. tb.*- negative married (parity:2-4) controls (sample-size-calculation: Quanto software) would prove immensely beneficial in predictive biomarker-development by targeting the array of TLRs and TIMPs in the aberrant inflammatory physiologic milieu at the complex maternal-fetal interface in asymptomatic vs symptomatic infertile women of varying genetic landscapes.

With my proven excellence and expertise in clinical research and translational medicine spanning States of Texas, New York, Nebraska in United States of America and home country India (Lucknow/New Delhi/Udaipur cities), I would like to add that fertility-reproductive medicine-oncofertility, one of my clinical research areas of special interest, certainly warrants relatively more stringent data-sharing/data-management protocols involving multicentric-multiethnic pooled population subsets with asymptomatic-borderline-symptomatic infertility, either *Mycobacterium tuberculi*-mediated female infertility, tobacco-mediated male/female infertility; scientifically sound, robust and ethical clinically impactful research involving eligible human subjects should adhere to core tenets of bioethics with written informed consent of study-participants. Moreover, international collaborations viz. pooled clinical samples-American+Asian Indian (North vs South Indian)+British+African+Australian, etc. subsets of infertility cases and controls, should be stringently monitored for compliance issues, international study-site specific medical research ethics/approval mandates, by a special surveillance/medical research vigilance team laying emphasis on financially transparent, ethical, competent and unparalleled scientific excellence-driven leadership in the ever-expanding reproductive medicine field. The future of fertility science and clinical research appears indeed enlightening and fascinating with competitive evidence-based innovative timeline-driven targets for cost-effective biomarker development by amalgamating the sophisticated and enigmatic biochemical signaling “inflammatory physiological triggers”: TLRs-TIMPs immunogenic intersections in global infertility management in genetically susceptible cohorts in the Covid-19 vaccination era [1-4].

## Acknowledgement

Dr. Pandey acknowledges her 1-1 dynamic clinical research discussions in molecular medicine focusing on Toll-like Receptors-TIMPs-COX-2-Wnt-Autophagy biochemical/metabolic inflammatory signaling cascades in immunomodulation of inflammatory diseases at University of Texas-MD Anderson Cancer Center, Houston, Texas, USA, Watson School of Biological Sciences, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA and Department of Urology, New York Presbyterian-Weill Cornell Medical College, New York, NY, USA.

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**Volume 5 Issue 10 October 2022**

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