

***Chlamydia trachomatis*-Positivity and Tobacco-Smoking Status of Oligospermic/Azoospermic Male Partners as Predictors of Toll-Like Receptors-Mediated Erectile Dysfunction and Infertility amongst Asian-Indian and American Cohorts in the Covid-19 Global Pandemic Era: Emerging Trends in Reproductive Immunology and Urology in Asia-Pacific and United States of America**

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Immunotherapeutic targeting of the enigmatic array of Toll-like-receptors in precisely dissecting the cellular/molecular/genetic basis of microbiota-associated-infertility amongst American and Asian-Indian cohorts is an attractive strategy for cost-effective infertility management on a global platform in the overwhelming Covid-19 pandemic era. Innovative timeline-driven evidence-based clinical research studies evaluating the causal role of intracellular TLR-3 (c.1377C/T)/TLR-9 (G2848A) genetic variants in susceptibility to inflammatory occlusive-tubal-factor infertility amongst American and Asian-Indian women with *Chlamydia*-positive oligospermic/azoospermic tobacco-smoking male-partners symptomatic of erectile dysfunction are emerging as fascinating immunotherapeutic “road-maps” for winding through the complex “infertility maze” in ethnically disparate population-pools of at-risk reproductive-aged women and men with varying lifestyles.

In this context, prospective case-control (1:1) hospital-based-studies with large sample-size and considerable statistical power coupled with stringent inclusion and exclusion criteria of eligible study-subjects, viz. American/Asian-Indian *Mycobacterium tuberculi*-positive infertility patients, > 35 years of age, 200 - 250 unrelated, age-/ethnicity-matched *M. tb.*-negative/married (parity: 2 - 4) controls (sample-size calculation: Quanto) are an asset in demystifying the bottlenecks in reproductive disorders. Moreover, *M. tb.*-positivity as-

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assessment using Gene-Expert, TB-Gold-PCR-testing, endometrial-thickness determination using Granulocyte Colony Stimulating Factor (GCSF)-infusion/Color-Doppler-imaging, and male-partners' *Chlamydia* positivity/azoospermic/oligospermic-status investigation(s) by high-throughput andrology-assessments: semen/first-void-urine (FVU)-specimens from asymptomatic infertile men and symptomatic erectile dysfunction cases using in-house inhibitor-controlled polymerase-chain-reaction (PCR)-microtiter-plate-hybridization-assay are valuable immunodiagnostic modalities in risk-assessment and risk-stratification in clinical infertility management. It is indeed critical to develop a robust andrology infrastructure for semen-analysis following World-Health-Organization (WHO) guidelines; furthermore, nominal scale-variables/Mann-Whitney-test/Kruskal-Wallis-nonparametric analysis-of-variance-test for statistical analysis would yield convincing clinical end-points for efficiently managing the ever-expanding global challenge of tobacco-mediated male and female infertility. Data-sets and algorithm-based modeling demonstrating borderline-/positive-/negative- causal association between intracellular TLR-signaling involving TLR-3/TLR-9 gene-polymorphisms and risk of developing *M. tb.*-mediated infertility with marital partners/spouses symptomatic of erectile dysfunction utilizing stratified/case-only-analysis would impart considerable risk-conferring-effect of TLR-3/TLR-9 on *M. tb.*-positive infertile patients with thin endometrium < 6.0 mm; TLR-3/TLR-9 genetic variants'-mediated immunomodulation in aberrant reproductive physiological milieu may significantly modulate (upregulate/downregulate) the risk in *M. tb.*-positive infertile patients with *Chlamydia*-positive oligospermic/azoospermic male-partners, and multiple-comparisons in stratified subgroups with smaller sample-size comprising ethnically disparate population-subsets of > 50% - 75% tobacco-users: cigarettes/e-cigarettes smokers and/or chewers) with relatively higher concordance (> 95%/kappa > 0.9) in *Chlamydia*-positivity in semen/FVU-specimens) may confer borderline association amongst genetically susceptible cohorts of American (Caucasian/Hispanic/White/African-American) and Asian-Indian (Brahmin caste, etc.) descents/lineage as well as other diverse ethnic population-pools globally. In my expert opinion, highlighting the significance of TLR-3/TLR-9 signaling networks and cellular/molecular/genetic intersections in inflammatory occlusive-tubal-factor-infertility:mild/moderate/severe in *M. tb.*-positive American as well as Asian-Indian women with *Chlamydia*-positive/tobacco-smoking/oligospermic/azoospermic male-partners, would certainly offer spectacular avenues for development of novel pharmacological-scaffolds and predictive biomarkers in clinical infertility management worldwide.

It has been aptly assumed that time and tide wait for none, and contextually one may be even sceptical and/or in a psychosexual dilemma that the distressing yet emotionally weakening reproductive disorder manifesting as symptomatic erectile dysfunction and tobacco-mediated infertility amongst ethnically disparate population-pools of men and women of child-bearing age may be a life-long bane appearing incurable and leading to marital incompatibility and familial discords with rampant "blame-game for childlessness" amongst married couples coping with the "infertility stigma"; I strongly believe that just like the proverbial saying "every dark cloud has a silver lining", the distressing infertility-mediated psychosexual emotional stigma indeed has a curable "silver spoon" laced with patient-friendly "flavors" with the advent of TLR-3/TLR-9-based-immunotherapeutics and cost-effective predictive biomarkers for erectile dysfunction and tobacco-mediated infertility management in genetically susceptible cohorts/population-pools in the Covid-19/Omicron global pandemic and Covid-19 vaccination era [1-4].

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