

Tobacco as a significant predictor of infertility: A public health perspective in an Indian scenario

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Abstract

Introduction: Infertility is a major public health problem worldwide, including India. Tobacco consumption (smoking/chewing) is a significant predictor of metabolic perturbations in reproductive physiology, including infertility. The early identification of risk factors associated with infertility susceptibility in ethnically disparate population subsets is an attractive cost-effective strategy in infertility control, prevention, and management.

Materials and Methods: A comprehensive literature search using PubMed and Medline scientific database (s) (last accessed November 4, 2017) was performed by the authors for the inclusion of most relevant articles in this review. Public health research studies for developing cost-effective infertility risk-assessment protocols in low-resource settings targeting couples who are infertile in India are ongoing for reducing the increasing burden of reproductive disorders and addressing the psychological/financial distress associated with the exorbitant cost of infertility treatment procedures, namely *in-vitro* fertilization.

Results: With our clinical research experience in reproductive medicine/infertility, we strongly advocate the implementation of cost-effective community-based tobacco-cessation infertility management guidelines with robust public health research models in the specific population subsets of varying genetic landscapes and socioeconomic strata. Anti-tobacco public awareness campaigns should be organized for efficiently addressing health risks associated with tobacco consumption/cigarette smoking.

Conclusion: The authors speculate that oxidative stress caused by tobacco in the physiological milieu may be diminished by therapeutically targeting specific metabolic/biochemical signaling pathways associated with cellular stress/death, immunomodulation, and inflammation. Biomarker development/validation for the stringent management of tobacco-mediated infertility will certainly provide spectacular gains in our current understanding of the pathophysiological basis of tobacco-related reproductive aberrations/disorders, primarily infertility, in the 21st century.


Keywords: Awareness, biomarker, Indian, infertility, public health, tobacco

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INTRODUCTION

Clinical infertility is emerging as a major public health problem worldwide, including India.^[1] Recent years have witnessed an

upsurge of interest among the scientific/medical research community actively involved in the reproductive medicine/infertility field to unravel the complexities associated with aberrant reproductive physiology in the ethnically disparate

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patient population subsets(s) of varying genetic landscapes, cultural exposures, and socioeconomic strata. Tobacco usage, either smoking or chewing, is a significant predictor of metabolic perturbations/aberrant physiologic milieu in asymptomatic and symptomatic women and men of reproductive age presenting with infertility.^[2,3] “Infertility” is defined as the inability to conceive following 12 months of regular unprotected sexual intercourse.^[4] The early assessment/identification of risk factors associated with infertility susceptibility is a must. This is performed by designing robust, patient-centric clinical research management study protocols utilizing the available resources for conducting successful, timeline-based, collaborative meaningful gene–epidemiological, pharmacogenetic/genomic, observational, interventional, cross-sectional, cohort-based studies with statistically significant sample size. This method of study is an attractive therapeutic strategy in the long-term prevention/control of infertility globally.

SEARCH CRITERIA FOR THE SELECTION, EXTRACTION, AND SYNTHESIS OF DATA USING SCIENTIFIC DATABASE(S)

A comprehensive literature search using PubMed and Medline scientific database(s) (last accessed November 4, 2017) was performed by the authors for the inclusion of most relevant articles in this review. Initial brainstorming sessions followed by extensive clinical research discussions with team members and medical advisors in infertility–healthcare marketing/management were conducted and relevant suggestions incorporated for the selection, extraction, assimilation, and synthesis of most relevant scientific data suitable for this review in the reproductive medicine field. The rapid exchange of emerging scientific concepts in tobacco-mediated reproductive disorders, primarily infertility susceptibility among the Indian population, led the authors to finally include 21 most relevant articles in this review article. Our stringent search criteria for the selection of the cited articles in this manuscript highlights our meticulous planning, timeline-based clinical research efforts, and active interest in contributing meaningfully to the welfare of our Indian society by addressing “tobacco-mediated infertility,” which is an emerging public health challenge and global concern. Moreover, each of these 21 articles (original research articles, reviews, commentaries, letters to the editor, perspectives, and clinical trials) was thoroughly reviewed. Thereafter, the clinically relevant findings were amalgamated for inclusion in this review. The final selection of enlightening articles for inclusion in the review was based on the novelty of clinical research studies, scientific rationale, a thorough assessment of

well-defined aims/objectives, stringent research methodologies including adherence to good practice research/informed consent, infertility clinic/laboratory data, research outcomes/primary endpoint(s), and broad-spectral translational and public health impact in a clinical research setting in an Indian scenario.

Public health research studies focusing on fertility preservation and tobacco-mediated infertility prevention among Indian population subset(s) residing in different states (e.g., Rajasthan, Maharashtra, Uttar Pradesh, West Bengal, Tamil Nadu, Karnataka, Orissa, etc.) with varying cultural exposures, dialects, demography, lifestyles and socioeconomic backgrounds were conducted. This was performed for developing cost-effective infertility risk-assessment protocols in low-resource settings targeting Indian couples who are infertile and are undergoing treatment at our reputed medical center(s). These protocols would help to reduce the increasing burden of infertility in the Indian society. Furthermore, psychological and financial distress associated with the exorbitant cost of infertility treatment procedures, namely *in-vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), etc., should be addressed by organizing monthly or quarterly and/or annual public awareness campaigns, anti-tobacco signature drives/campaigns, tobacco cessation and infertility awareness lectures/talks, free consultations, medical check-ups, counseling sessions, quality time investment with patients who are infertile, follow-ups of patients undergoing Assisted Reproductive Technology procedures, IVF/ICSI, etc. This was performed for evaluating the overall IVF success trends by assessing clinically relevant parameters such as the total number of embryo transfers (ETs, fresh or frozen), oocytes retrieved, oocyte quality, semen quality, sperm counts/morphology/motility, endometrial thickness, anti-Mullerian hormone levels, implantation rates, beta-human chorionic gonadotropin positivity/biochemical pregnancy, and live birth rates among the patients who are infertile and belong to the diverse states of India.

ENVIRONMENTAL TOBACCO-MEDIATED REPRODUCTIVE HEALTH RISKS: AN OVERVIEW

Environmental tobacco is significantly associated with the initiation, progression, and development of a spectrum of human diseases, including cervical/breast/prostate/esophageal cancers as well as clinical infertility in ethnically disparate populations worldwide.^[5-7] Intriguingly, the clinical sequelae associated with the initial exposure to environmental tobacco and the subsequent manifestation of clinical symptoms are indeed complex. Therefore, future clinical research studies in oncofertility, oncology, and infertility

should successfully investigate the reproductive health risks associated with tobacco consumption, either smoking (cigarette smoking; active vs passive smoking) or chewing (Indian betel/paan and “gutka”), so as to identify susceptible “at-risk” individuals in well-defined, specific patient population subsets of varying genetic profiles, lifestyles, cultural exposures, and socioeconomic strata.

Tobacco is a known environmental carcinogen. Recent studies have strongly implicated the emerging role of tobacco as a potential risk factor in reproductive disorders, including clinical infertility. Tobacco smoke contains several chemical constituents, including nicotine, tar, carbonic monoxide, polycyclic aromatic hydrocarbons, and heavy metals (e.g., cadmium and lead). Interestingly, tobacco metabolite cotinine, a byproduct of nicotine breakdown, is metabolized and detected in both human saliva and urine.^[8,9] Recently, the sale and consumption of electronic cigarettes has increased in the Western world. E-cigarettes have a liquid-filled container with a humectant (i.e., propylene glycol, vegetable glycerin, and/or polyethylene glycol 400), concentrated flavors, and variable concentrations of nicotine.^[10]

As per the estimates of the World Health Organization, ~8% of couples globally and 10–15% of couples in industrialized countries experience clinical infertility.^[11] Clinical infertility is a prevalent public health problem with considerable psychosocial and financial costs. Therefore, a comprehensive evaluation of the tobacco-usage status of married couples presenting for infertility treatment is essential so as to provide personalized infertility treatment options along with counseling, motivation, and timely advice to quit tobacco usage especially when trying to conceive. Moreover, urinary cotinine level is a cost-effective and noninvasive method to assess tobacco exposure and, accordingly, stratify tobacco users from nonusers for designing strategic public health research models in infertility management. Reproductive medicine experts should constantly endeavor to address patients’ concerns and discuss their infertility management regimen(s). In addition, these experts must spend one-to-one quality time with them, thereby encouraging to quit tobacco so as to lead a healthy, disease-free lifestyle by reducing tobacco-associated risk(s). Such inexpensive patient-centric interventions would certainly ensure an increased level of infertility treatment adherence and fewer complications and/or risks related to tobacco usage.

An interesting tobacco awareness study among the Indian population to reduce the overall consumption of tobacco in

the community highlighted the urgent need of community-based tobacco-cessation programs for creating awareness about the ill-effects of smokeless tobacco usage on reproductive health. The study strongly suggested the implementation of monitoring and surveillance for the complete eradication of tobacco-mediated adverse effects on human health.^[12] Cost-effective tobacco-cessation infertility management protocols with robust community-based public health research models incorporating a large sample size of infertile cohorts of diverse ethnicities, including the Indian cohort, are warranted for early risk assessment. Awareness campaigns and motivational talks, pharmacogenetic/genomic studies, and psychosocial interventions should be effectively conducted for fertility preservation and infertility prevention.

EFFECT OF TOBACCO ON MALE AND FEMALE INFERTILITY: PUBLIC HEALTH IMPACT

Tobacco-mediated infertility among ethnically disparate cohorts is a major public health concern in contemporary times in both the Western world and the Asian Pacific region, including India. The socioeconomic impact of infertility, along with the high cost of assisted reproduction technology (ART)/IVF procedures (in USD and INR) for fulfilling an infertile couple’s cherished dream of having a baby, is tremendously increasing. In this context, reproductive medicine experts actively engaged in contributing meaningfully to the welfare of society are constantly streamlining their concerted efforts and quality time in enhancing the overall patient satisfaction by providing sophisticated, high-quality treatment options and modalities for the early identification of the cause(s) of clinical infertility (male factor or female factor or male and female factor or unknown etiology). The causes of clinical infertility include diminished semen quality, altered/low sperm count/morphology/motility, azoospermia, oligospermia, asthenozoospermia, teratozoospermia, diminished ovarian reserve, aberrant folliculogenesis, thin endometrium, polycystic ovary syndrome, a lower number and/or quality of oocytes, and altered endometrial receptivity. Moreover, the timely cost-effective management of expensive ART procedures/IVF-related adverse clinical outcomes, both primary and secondary endpoints, including unsuccessful ET rates (both fresh and frozen ETs), decreased implantation rates, multiple pregnancies, fetal malignancies, and stillbirths, is essential so as to significantly enhance the overall IVF success trends among the infertile couples of varying ethnicities, cultural exposures, lifestyles, and socioeconomic strata. Tobacco-cessation and awareness-based psychosocial interventions are being initiated at our Udaipur, Rajasthan-based IVF center catering to the Indian infertile cohort(s) so

as to educate the Indian “at-risk” susceptible individuals about the adverse health effects associated with cigarette smoking and tobacco chewing. Effective follow-ups and the regular monitoring of infertile couples during the tobacco-cessation campaign is indeed critical for evaluating the effect (s) of tobacco usage on reproductive health and any perceived withdrawal symptoms while quitting tobacco usage. Public health experts and policymakers should initiate strategic and successful partnerships for the eventual eradication of tobacco-mediated infertility in the Indian population subset(s) and, thereby, endeavor to reduce the incidence of tobacco-mediated infertility among ethnically diverse populations worldwide. The authors are strongly of the opinion that substantial financial support by federal, government, state/regional, and local funding bodies as well as the pharmaceutical/biotechnology healthcare corporates is urgently required for the successful management of clinical infertility. Financial resources should be strategically and responsibly diverted toward reproductive health promotion and infertility prevention on a large scale by adhering to stringent good practice research guidelines. The subsequent utilization of healthcare resources and financial grants for global promotions and the cost-effective management of infertility are warranted to provide a satisfactory, significant, meaningful, and long-term solution to the ever-expanding problem of tobacco-mediated infertility worldwide.

Significant clinical research efforts in the field of tobacco-mediated reproductive disorders, including infertility, have been made in recent years. However, the pathophysiological basis of tobacco-mediated reproductive risks, including male and female infertility, is yet not fully deciphered. Reproductive medicine scientists and physicians worldwide, including in India, are constantly devoting their quality time and sincere efforts in unraveling the underlying cellular/molecular mechanisms and/or complexities associated with tobacco usage in infertility. Interestingly, the scientific literature databases are providing up-to-date clinically relevant information related to the adverse reproductive health effects of tobacco consumption, both in the form of tobacco chewing and smoking. However, available research data provide conflicting findings, thereby warranting the design and implementation of more robust, statistically significant studies using a large sample size in a well-defined infertility patient population subset(s) and/or healthy, disease-free controls belonging to same ethnicity. In fact, ethnicity is recently emerging as a strong predictor of infertility in both men and women. Therefore, multicentric and/or multinational cohort-based research studies with pooled clinical specimens of ethnically disparate

populations are warranted in the near future with a common theme. These studies must have the objective of reducing the overall incidence of male and female infertility in susceptible populations. The effect of tobacco smoking on semen quality among men in Ghana has been reported; 140 participants, comprising 95 smokers and 45 nonsmokers, were enrolled as per stringent inclusion/exclusion criteria. A subgroup stratification of the tobacco smokers into mild, moderate, and heavy smokers demonstrated that semen quality (sperm concentration, motility, viability, and morphology as per the criteria of the World Health Organization) in smokers was significantly low ($P < 0.05$) in comparison with nonsmokers.^[13] Further, smokers were observed to be at a higher risk of developing oligospermia, asthenozoospermia, and teratozoospermia [odds ratio (OR) = 3.1, 4.2 and 4.7; $P < 0.05$] than nonsmokers. The impact of cigarette smoking on male infertility has been well-reported. Tobacco-mediated reproductive risk assessments have been conducted in different countries, and the emerging trends in male infertility in a global scenario, including the Indian setting, are indeed overwhelming, with a majority of tobacco smokers presenting with diminished semen quality and altered/aberrant sperm kinetics, morphology, and quality.^[14,15] A meta-analysis incorporating twenty studies with 5865 participants demonstrated that exposure to cigarette smoking was associated with reduced sperm count [mean difference (MD): -9.72×10^6 /ml; 95% confidence interval (CI): -13.32 to -6.12], motility (MD: -3.48% ; 95%CI: -5.53 to -1.44), and morphology (MD: -1.37% ; 95%CI: -2.63 to -0.11), thereby suggesting that cigarette smoking had an overall negative effect on semen parameters, and the deterioration of semen quality is more pronounced in moderate and heavy smokers.^[14] Emerging genetic/epigenetic data highlight the adverse effects of smoking on semen parameters. Smoking increased the presence of reactive oxygen species. This resulted in oxidative stress that considerably damaged semen quality, including sperm viability/morphology, and impaired sperm function, eventually reducing male fertility.^[15] Elevated oxidative stress, Deoxy Ribonucleic Acid (DNA) damage, and cell apoptosis have been linked with tobacco smoking, thereby impacting male fertility.^[16] It is indeed challenging to draw definitive conclusions from the enormous dataset(s) extracted from the retrospective and prospective clinical research studies due to the diversity of the study population subsets, mixed, conflicting results, or a lack of conclusive evidence. However, a careful assessment of the study’s strengths and limitations, including the stringent selection criteria of eligible participants, sample size, and the sophisticated statistical methodologies yielding bias-free, accurate results, provided insights into the meaningful interpretation of data and/or the extrapolation of study

findings for the future design of molecular-biology-based genetics–epidemiological as well as translational research studies so as to effectively evaluate the tobacco-related risks in susceptible males with infertility belonging to diverse ethnic cohorts. An elegant cross-sectional study with a statistically significant large sample size demonstrated an inverse dose-based association between tobacco smoking and semen volume, total sperm count, and the percentage of motile spermatozoa. Interestingly, the sperm concentration of heavy smokers was considerably lower than that of nonsmokers.^[17] Another interesting study exploring the role of tobacco in susceptible men revealed that smokers had relatively lower acrosin enzymatic activity than nonsmokers despite presenting with normal semen parameters.^[18] Moreover, the impact of oxidative stress on spermatozoa, semen quality, and male infertility, in general, has been well documented. There is adequate clinical research data on the biological roles of reactive oxygen species in male reproductive physiology.^[15,19]

Tobacco-mediated infertility among susceptible “at-risk” women has been a hot topic of research in reproductive medicine/infertility research in recent times. One of the frequently encountered study limitations in tobacco-mediated female infertility research in an Indian setting is the difficulty in eliciting a true bias-free response from Indian women, including both clinically infertile study participants and donors scheduled for infertility treatment/follow-up workups prior to undergoing the expensive and time-consuming ART procedures, primarily IVF. During one-to-one structured questionnaire-based interviews for tobacco-related risk assessments and quality time investments during the interactions of patients belonging to Indian ethnicity, the authors became aware of the limitations of a potential study bias related to lower and/or false response rate(s) regarding the actual history of tobacco usage, both cigarette smoking and/or tobacco chewing. With years of proven experience and expertise interacting with Indian women at hospital-based settings, the authors attributed the lower response rates regarding lifestyle, tobacco usage, and socioeconomic status to psychological distress and perceived family-based problems/issues encountered by a majority of Indian women with infertility. Motivational talks, constant encouragement, and prenatal/antenatal care coupled with well-implemented infertility management counseling sessions dealing with holistic healing, tobacco cessation, and the reduction of infertility-related psychological stress, anxiety, restlessness, and/or stigma should be routinely organized at leading reproductive medicine centers and IVF hospitals so as to educate the Indian women, both

infertile and healthy, pregnant women, about the overall reproductive hazards associated with tobacco-related toxins. To further substantiate the association of unhealthy lifestyle behavior(s), for example, daily tobacco smoking, weekly alcohol consumption, body mass index (BMI) ≥ 25 , and regular physical exercise < 2 h/week, with psychological distress, a recent study has emphasized the ill effects of tobacco and other modifiable risk factors with anxiety [prevalence ratio (PR): 1.24; 95%CI: 1.09–1.40] and depressive symptoms (PR: 1.25; 95%CI: 1.04–1.49).^[20] A recent study evaluated the prevalence of smoking in Korean women with infertility. This study on Korean women exhaustively collected details regarding smoking status, education, occupation, personal lifestyle behavioral habits, current/past medical history, stress quotient(s), and menstrual characteristics/irregularities from self-report questionnaires. The study included 785 women of age < 42 years and demonstrated that the prevalence of current, secondhand, past, and never smokers was 12.7, 45.7, 0.9, and 40.6%, respectively.^[21] Furthermore, primary infertility was more frequent in secondhand smokers. Interestingly, the underlying causes of infertility were similar among current, secondhand, and never smokers. The prevalence of diabetes mellitus (4.0%) was significantly higher in current smokers than in secondhand smokers ($P=0.002$) or never smokers ($P=0.031$). The self-reported prevalence of depression were similar among women with differing smoking statuses. Hyland *et al.*^[2] investigated the association between lifetime tobacco exposure–active smoking/secondhand smoke (SHS) and infertility as well as natural menopause (before age 50). Their findings demonstrated that active-ever smokers had overall ORs of 1.14 (95%CI: 1.03–1.26) for infertility and 1.26 (95%CI: 1.16–1.35) for earlier menopause than women who never smoked. Further stratification suggested that women who never smoked with the highest levels of lifetime SHS exposure had adjusted ORs of 1.18 (95%CI: 1.02–1.35) for infertility and 1.18 (95%CI: 1.06–1.31) for earlier menopause. These tobacco-mediated reproductive risk-related findings were really impressive, and it was worthwhile to observe that active-ever smokers reached menopause 21.7 months earlier than the mean age of 49.4 years for never smokers who were unexposed to SHS. Conversely, women exposed to the highest SHS level(s) reached menopause 13.0 months earlier. Future public health research studies dissecting the intricacies of tobacco smoke related reproductive risks, including infertility in Indian women, are warranted to provide more critical clinical research insights in successful infertility management using a cost-effective patient-friendly protocol with well-designed timeline-based outcomes.

SUMMARY/CONCLUSION

To summarize, we emphasize that tobacco-mediated infertility is a major public health problem in recent times. Tobacco risk assessment is essential for unraveling the pathophysiology of a spectrum of human diseases (e.g., cervical/breast/prostate/esophageal cancers), including infertility. With the advent of high-throughput, sophisticated precision-based molecular diagnostic technologies and/or immunodiagnostic imaging modalities/techniques for infertility diagnosis and research, significant clinical and translational research developments have been made in India. IVF-ET technology is extensively utilized in the stringent management of tobacco-mediated infertility in Indian women and men of reproductive age, both tobacco users (chewers/smokers; active and/or passive smokers) and nonusers. However, demystifying the cellular and/or molecular mechanisms in the pathophysiology of tobacco-mediated male and female infertility is indeed essential in contemporary times for effectively addressing the ever-expanding public health problem of clinical infertility among susceptible population subset(s). Moreover, IVF success rates (primary endpoint(s): clinical pregnancy/live-birth rates) remain relatively low, primarily because of implantation failure. There are conflicting reports regarding the IVF success trends and live birth rates among the infertile cohorts belonging to diverse ethnicities. With our scientific and clinical experience/expertise in biomedical research at premier medical centers in the United States of America, including Texas, New York, and Nebraska, and quality interactions with Indian patients at our medical center in Udaipur, Rajasthan, which is streamlining collaborative efforts in reproductive medicine/infertility, we strongly advocate the timely implementation of cost-effective community-based tobacco-cessation infertility management guidelines with robust public health research models in the specific population subsets of varying genetic landscapes and socioeconomic strata. Tobacco-cessation awareness-based motivational talks/lectures coupled with anti-tobacco public awareness campaigns should be organized for efficiently addressing the potential reproductive health risks associated with tobacco consumption/cigarette smoking.

The authors speculate that oxidative stress caused by tobacco in the physiological milieu may be diminished by therapeutically targeting specific metabolic/biochemical signaling pathways associated with cellular stress/death, immunomodulation, and inflammation. In

this context, tobacco-mediated DNA damage, altered/aberrant sperm morphology/motility, and diminished ovarian reserve/endometrial receptivity in both male and female clinical infertility may be studied extensively by creating “biorepositories” at designated medical centers in India, which are well-equipped with world-class facilities and robust clinical research infrastructure. Subsequently, stored patient clinical specimens, namely, blood, tissue, DNA, ribonucleic acid (RNA), sperms, embryos, and stem cells from the “biobanks,” may be strategically utilized for multicentric and/or multinational cohort-based pharmacogenetic/genomic studies for the eventual development of predictive biomarkers and/or therapeutic drugs for well-defined infertility patient-population subsets, including the tobacco-using subgroups of male and female patients with infertility and “at-risk” tobacco-consuming individuals susceptible to infertility from a random population(s) of varying genetic profiles.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pandey S. Dissecting toll-like receptor molecular regulatory network (s) in reproductive medicine, primarily infertility: A snapshot. *Fertil Sci Res* 2015;2:95-101.
2. Hyland A, Piazza K, Hovey KM, Tindle HA, Manson JE, Messina C, *et al.* Associations between lifetime tobacco exposure with infertility and age at natural menopause: The Women’s Health Initiative Observational Study. *Tob Control* 2016;25:706-14.
3. Asare-Anane H, Bannison SB, Ofori EK, Ateko RC, Bawah AT, Amanquah SD, *et al.* Tobacco smoking is associated with decreased semen quality. *Reprod Health* 2016;13:90.
4. Bojar I, Witczak M, Wdowiak A. Biological and environmental conditionings for a sperm DNA fragmentation. *Ann Agric Environ Med* 2013;20:865-8.
5. Pandey S, Mittal B, Srivastava M, Singh S, Srivastava K, Lal P, *et al.* Evaluation of Toll-like receptors 3 (c.1377C/T) and 9 (G2848A) gene polymorphisms in cervical cancer susceptibility. *Mol Biol Rep* 2011;38:4715-21.
6. Pandey S, Chandravati XX. Breast screening in north India: A cost-effective cancer prevention strategy. *Asian Pac J Cancer Prev* 2013;14:853-7.
7. Pandey S, Khanna A. Single cell analysis and circulating tumor cells in prostate cancer: Experience of an observership at Cold Spring Harbor Laboratory, CSH and New York Presbyterian Hospital (Cornell Campus), New York. *Asian Pac J Cancer Prev* 2015;16: 6173-4.
8. Florescu A, Ferrence R, Einarson T, Selby P, Soldin O, Koren G. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: Focus on developmental toxicology. *Ther Drug Monit* 2009;31:14-30.

9. Moyer TP, Charlson JR, Enger RJ, Dale LC, Ebbert JO, Schroeder DR, *et al.* Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloids in serum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. *Clin Chem* 2002;48:1460-71.
10. World Health Organization. Infections, pregnancies, and infertility: Perspectives on prevention. *Fertil Steril* 1987;47:964-8.
11. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, *et al.* Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014;23:133-9.
12. Nair S, Schensul JJ, Bilgi S, Kadam V, D'Mello S, Donta B. Local responses to the Maharashtra gutka and pan masala ban: A report from Mumbai. *Indian J Cancer* 2012;49:443-7.
13. Asare-Anane H, Bannison SB, Ofori EK, Ateko RO, Bawah AT, Amanquah SD. Tobacco smoking is associated with decreased semen quality. *Reprod Health* 2016;13:90.
14. Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: A new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. *Eur Urol* 2016;70:635-45.
15. Harlev A, Agarwal A, Gunes SO, Shetty A, du Plessis SS. Smoking and male infertility: An evidence-based review. *World J Mens Health* 2015;33:143-60.
16. Dai JB, Wang ZX, Qiao ZD. The hazardous effects of tobacco smoking on male fertility. *Asian J Androl* 2015;17:954-60.
17. Ramlau-Hansen CH, Thulstrup AM, Aggerholm AS, Jensen MS, Toft G, Bonde JP. Is smoking a risk factor for decreased semen quality? A cross-sectional analysis. *Hum Reprod* 2007;22:188-96.
18. Gerhard I, Fröhlich E, Eggert-Kruse W, Klinga K, Runnebaum B. Relationship of sperm acrosin activity to semen and clinical parameters in infertile patients. *Andrologia* 1989;21:146-54.
19. Agarwal A, Prabakaran SA. Mechanism, measurement, and prevention of oxidative stress in male reproductive physiology. *Indian J Exp Biol* 2005;43:963-74.
20. Salih Joelsson L, Tydén T, Wanggren K, Georgakis MK, Stern J, Berglund A, *et al.* Anxiety and depression symptoms among sub-fertile women, women pregnant after infertility treatment, and naturally pregnant women. *Eur Psychiatry* 2017;45:212-9.
21. Shin JJ, Jee BC, Kim H, Kim SH. Major disease prevalence and menstrual characteristics in infertile female Korean smokers. *J Korean Med Sci* 2017;32:321-8.