Human Chorionic Gonadotrophin (hCG) Trigger-Mediated Ovulation Induction in Infertility Management in South Indian Women Undergoing IVF/ICSI Regimens: A Pilot Sexual Medicine Study with Public Health Perspective

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Abstract

Introduction: Infertility is a global public health problem; cost-effective patient-friendly treatment modalities along with psychosexual intervention strategies are essential for infertility control/prevention/management among ethnically disparate populations.

Objectives: This study aimed to assess differential in vitro fertilization (IVF) success trends among infertile women of South Indian ethnicity.

Materials and Methods: Prospective, observational study designed in a hospital-based setting with active enrollment of infertile women undergoing IVF/intracytoplasmic sperm injection (ICSI) at Indira IVF Center, Chennai, Tamil Nadu, India (April-September 2019); inclusion criteria: age >35 years, South Indian ethnicity, married >1 year, absence of full-term clinical pregnancy, endometrial thickness <6 mm/thin endometrium; exclusion criteria: prior ≥2 IVF failures, fibroids/adenomyosis/cervical cancer/endometriosis. IVF success was determined by evaluating total frozen embryos transferred/month, average oocyte yield/donor, oocyte quality, M-II oocytes, biochemical/clinical pregnancy (beta-human chorionic gonadotropin positivity/fetal cardiac activity). Mycobacterium tuberculosis positivity was assessed by GeneXpert polymerase chain reaction-based technology, and psychosexual intervention-incorporated marital relationship counseling sessions/therapy, referrals for psychiatric assessments (cognitive impairment/schizophrenia/depression). Written informed consent of participants was taken and study was approved by Institutional Review Board.

Results: Mean age and endometrial thickness of study participants were 33.3 years (SD ±1.9) and 8.7 mm (SD ±0.5), respectively; average Body Mass Index (BMI) and anti-müllerian hormone (AMH) levels were 28.4 kg/m² and 4.7 ng/mL, respectively. Embryos transferred/month: 7 in April/13 in May/24 in June/36 in July/24 in August/30 in September, and pregnancies: 4/8/17/26/20/22 for the months of April, May, June, July, August, and September 2019, respectively. Subgroup stratification demonstrated M-II vs total oocytes retrieved were 76%, 73%, 60%, 71%, 77%, and 77%. Overall IVF success rates were 57% in April/62% in May/71% in June/72% in July/83% in August/73% in September; frozen embryo transfer success was 0 in April-May/67% in June/73% in July/89% in August/100% in September 2019. English/Tamil-speaking infertile women self-reported treatment-related satisfaction rates of 80% to 100%.

Conclusion: M-II oocytes’ yield, sociodemographics of infertile women, and increasing age/aberrant AMH/BMI profiles/endometrial receptivity/diminished ovarian reserve are promising predictors of IVF/ICSI success in genetically distinct patient population subset(s). Future multicentric gene epidemiology studies with larger sample size and precision-based psychiatric assessments/interventions are warranted for development of predictive biomarkers in infertility management.

Keywords

Biomarker, human chorionic gonadotrophin, infertility, M-II oocytes, South Indian

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Introduction

Clinical infertility has emerged as a significant public health problem in both the Western world, including United States of America and Asia Pacific region, particularly the Indian subcontinent. “Infertility” is defined as the inability to conceive following 12 months of regular unprotected sexual intercourse. The etiopathogenesis of reproductive disorders, primarily female infertility, is indeed complex and intriguing. The clinical sequelae from initiation and/or manifestation of aberrant/altered reproductive physiology, including hormonal imbalances, endometrial receptivity, and/or diminished ovarian reserve, are well-represented in diverse human populations of varying genetic profiles. However, the underlying cellular and molecular mechanisms associated with infertility susceptibility in women of childbearing with differential sociodemographic/cultural exposures and genetic profiles have to be fully elucidated for significantly reducing the increasing burden of infertility among population subsets of diverse ethnicities. In this context, the genetically distinct Indian population of women is not completely homogeneous, and the diverse Indian population, in actuality, is an admixture of population subsets of women of varying cultural exposures, lifestyles, dietary patterns, and genetic profiles; this rather interesting Indian heterogeneous population pool with differential disease susceptibility patterns from North India to South India, including altered susceptibility to infertility and gynecologic malignancies, therefore provides an excellent sample set of a diverse array of genetically distinct subsets of women of childbearing age(s) for reproductive medicine research that may eventually provide spectacular gains in our current understanding of the pathophysiological and/or genetic basis of female infertility worldwide. Cost-effective strategies are essential for infertility control/prevention/management among ethnic populations of varying genetic landscapes; patient satisfaction at infertility medical centers/hospitals would certainly increase with the implementation of high-quality patient-centric clinical research focusing on early identification of risk factors of clinical infertility, precision-based clinical interventions viz in vitro fertilization (IVF), intracytoplasmic sperm injections (ICSIs), and/or psychosocial interventions. It is interesting to note that ethnicity is recently emerging as a strong predictor of infertility in both men and women worldwide; biomedical researchers are constantly endeavoring to dissect the molecular regulatory networks in infertility, and considerable time, efforts, and healthcare resources are being invested in health disparities’ related epidemiological research in the ever-expanding reproductive medicine field. Furthermore, stringent management of expensive assisted reproductive technology (ART) procedures/IVF-related adverse clinical outcomes, including unsuccessful embryo transfer rates, decreased implantation rates, multiple pregnancies, fetal malignancies, stillbirths, and so on, is essential so as to significantly enhance the overall IVF success trends among asymptomatic and symptomatic infertile women of South Indian ethnicity.

Cost-effective community-level public health-oriented health disparities research studies focusing on fertility preservation and infertility prevention among South Indian population subset(s) residing in different states of southern India (e.g. Tamil Nadu, Karnataka, Kerala, Andhra Pradesh) with varying regional dialects, demography, lifestyles, nutrient intakes, and socioeconomic backgrounds, yet overlapping/intermixed cultural exposures and genetic profiles, for developing cost-effective infertility management and risk-assessment protocols in low-resource settings, are ongoing at reputed medical center(s) with continued efforts of diminishing the prevalence of female infertility in reproductive-aged women.

The present exploratory public health-oriented research study aimed to assess differential IVF success trends among infertile women of South Indian ethnicity.

Materials and Methods

Study Design and Setting

The exploratory prospective research study was conducted in a clinical/hospital-based setting at Indira IVF Center, Chennai, Tamil Nadu, India enrolling clinically infertile women of South Indian ethnicity presenting with altered/aberrant endometrial receptivity and diminished ovarian reserve; this cohort-based study was conducted during a 6-month timeline from April to September 2019.

Selection of Study Subjects

Infertile women of South Indian ethnicity undergoing infertility treatment and IVF/ICSI workup/regimen(s) at Indira IVF Center at Chennai in Tamil Nadu, India, presenting with childlessness/failure to conceive and/or diminished ovarian reserve and thin endometrium; the author and expert panel members at Indira IVF, Udaipur and Lucknow, India defined stringent inclusion criteria: age ≥35 years, South Indian ethnicity, married for >1 year, absence of clinical full-term pregnancy, endometrial thickness <6 mm/thin endometrium, premenopausal, and exclusion criteria: prior ≥2 IVF failures, fibroids/adenomyosis/cervical cancer/ endometriosis, and menopausal/postmenopausal, ethnicity other than South Indian. A total of 134 infertile women residing in Chennai and adjoining geographical regions/cities/villages in Tamil Nadu were enrolled after brief counseling sessions. The study adhered to core tenets of good practice research with written informed consent of eligible participants at time of initial enrollment. Further, a majority of the selected study subjects (N = 134) had undergone pre-IVF awareness lecture and a subsequent patient-friendly one-to-one/facetoface infertility counseling session of approximately 10-minute duration in a senior consultant’s
chamber; occasionally, infertile women were counseled about infertility together with their partners/husbands, psychosexual disorders, marital-relationship discords/psychosocial distress/ stigma owing to childlessness, so as to explicitly understand the overall psychosocial determinants of clinical infertility with emphasis on timely psychosexual interventions (clinical fertility workshops, hormonal treatments, psychiatric treatments for enhancing coping skills while dealing with infertility) and overall cost of IVF treatment in Indian currency (INR).

Clinical Interventions/Planning for Ovulation Induction and IVF

Infertile women were assigned to undergo an array of biochemical tests/procedures, including assay-based hormonal assessments for anti-müllerian hormone (AMH), serum prolactin, luteinizing hormone, estrogen, follicle stimulating hormone (FSH); the titers/cutoffs were evaluated as per standard reference ranges. Endometrial thickness was assessed using the precision-based, high-throughput, sophisticated color Doppler imaging modality; Mycobacterium tuberculosis positivity was assessed by GeneXpert polymerase chain reaction (PCR)-based technology, and psychosexual intervention-incorporated marital relationship counseling sessions/therapy, referrals for psychiatric assessments (cognitive impairment/schizophrenia/depression). Recombinant FSH started at a dose of 300 IU or a combination therapy in an antagonist protocol on day 2 and antagonist (0.25 mg) started when lead follicle size was 12 mm. Human chorionic gonadotropin (hCG) trigger (250 µg) was administered when major cohort of follicles were 16 to 19 mm in size. Embryo freezing was done on day 3/5 using vitrification, and subsequent frozen thaw embryo transfer was performed during subsequent hormone replacement cycles. Embryo and oocyte quality were carefully assessed, and sterilized, contamination-free laboratory culture condition(s/environemnt was strictly maintained during the entire transfer procedures and overall IVF regimen(s) so as to avoid any technical errors and potential failures at critical steps viz oocyte retrieval, embryo transfer, and so on Clinically relevant determinants of IVF success rates among infertile women residing in Tamil Nadu included successful frozen embryo transfers, quality of oocytes, oocytes’ retrieval, M-II oocytes’ yield, implantation rate, biochemical pregnancy/ beta-hCG positivity, and ultrasound-based pregnancy confirmation with live birth per IVF/ART procedure, safety assessments including adverse drug reactions, either local or systemic, and ovarian hyperstimulation syndrome (OHSS).

Data Analysis

Clinical data with relevant parameters/variables were carefully reviewed, and robust data entries were meticulously amalgamated using Microsoft Excel program. Categorical data were summarized by number (N) and percentage (%) in each category, where N represents the total number of participants/eligible study subjects. Descriptive statistics for continuous variables were given as mean with standard deviation (SD) while those for categorical data were given as frequency distribution.

Results

Infertile women (N = 134) were counseled about infertility/ IVF regimens; one-to-one counseling sessions were conducted and also the entire cost of infertility treatment that would be incurred in INR, from the time of initial registration at Chennai-based IVF Center, IVF workup/regimen(s), clinical diagnostic assay-based hormonal/reproductive endocrinology-related tests, patient’s stay at the medical center during surgical interventions/IVF regimens, including embryo transfers, oocyte retrievals, pregnancy/live birth, post-IVF patient-centric quality care, medications, and so on, was explained keeping in mind the socioeconomic status of the study cohort seeking infertility treatment. Patient-centric interactions were explicitly conducted in either English and/or regional dialect (Tamil) to make study participants completely aware of their infertility history and treatment-related expenses; psychosocial counseling-based intervention(s): marital-relationship counseling/therapy, timely referrals for psychiatric treatments, primarily cognitive impairment, schizophrenia, and/or clinical depression, further ensured overall psychological well-being of patients, thereby significantly reducing anxiety, distress, depression, social stigma, restlessness, and so on. Core tenets of good practice research, including written informed consent of study participants at time of initial enrollment, were followed.

A careful and thorough assessment of the promising clinical research data highlighted that monthly frequency distribution of infertile cases during the 6-month study timeline, that is, April to September 2019 was 7, 13, 24, 36, 24, and 30 cases, respectively. Mean age and endometrial thickness of eligible participants were 33.3 years (SD ±1.9) and 8.7 mm (SD ±0.5), respectively; average Body Mass Index (BMI) and AMH levels were 28.4 kg/m² and 4.7 ng/mL, respectively. A very small fraction of the study population (<5%) tested positive for M. tb, as assessed by the precision-based GeneXpert PCR-based technology; M. tb is a known etiological factor of genital tuberculosis that is quite prevalent in infertile women of diverse ethnicities, including South Indian cohort of the Asia Pacific region. Interestingly, total embryos transferred per month were 7 in April, 13 in May, 24 in June, 36 in July, 24 in August, and 30 in September; frozen embryo transfer success was 0% in April and May, 67% in June, 73% in July, 89% in August, and 100% in September 2019.

Biochemical pregnancies were assessed in terms of β-hCG positivity (Table 1); data sets revealed a total of 4, 8, 17, 26, 20, and 22 positive biochemical pregnancies for the months of April, May, June, July, August, and September.
Table 1. Biochemical Pregnancy in South Indian Infertile Women at Chennai, Tamil Nadu, India-Based Fertility Center/Hospital (N = 134 Women)

| Timeline            | Infertile Cases of South Indian Ethnicity (N = 134) | Biochemical Pregnancy (Beta-Human Chorionic Gonadotropin Positivity) (µg/mL) |
|---------------------|-----------------------------------------------------|--------------------------------------------------------------------------------|
| April 2019          | 7                                                   | 984.6                                                                           |
| May 2019            | 13                                                  | 1504.11                                                                         |
| June 2019           | 24                                                  | 2437.82                                                                         |
| July 2019           | 36                                                  | 1493.76                                                                         |
| August 2019         | 24                                                  | 1832.83                                                                         |
| September 2019      | 50                                                  | 1601.2                                                                           |

Source: Indira IVF Center/Hospital, Chennai, Tamil Nadu, India.

2019, respectively. Further subgroup stratification in the study population subsets demonstrated that M-II vs total oocytes retrieval rates per month (April-September 2019/6-months timeline) were 76%, 73%, 60%, 71%, 77%, and 77%. Overall, IVF success rates observed in the infertile cohort of South Indian women were 57% in April, 62% in May, 71% in June, 72% in July, 83% in August, and 73% in September 2019.

Discussion

Infertility is a significant public health concern in ethnically disparate cohorts worldwide. The pathophysiology of reproductive disorders, primarily infertility, remains debated in contemporary times; reproductive medicine researchers globally are constantly endeavoring to unravel the interplay between interrelated cell signaling cascades in developmental biology, embryonic induction, human reproduction, reproductive physiology, and reproductive pathophysiology.

The complex molecular regulatory networks and biochemical signaling cross talk mechanisms at the maternal-fetal interface are indeed intriguing; a precise understanding of the signaling mechanisms coupled with the overwhelming and diverse array of transmembrane receptors, ion channels, intermediary kinases, transcriptional factors, and target genes and proteins, is essential for successfully elucidating the pharmacological and pathophysiological basis of infertility. Moreover, ethnicity and sociodemographic/lifestyle-related factors and the role of genetic variants and epigenetics are being emphasized in infertility susceptibility in reproductive-aged women of diverse patient population subset(s); the genetic basis of clinical infertility is still to be unraveled for a clear picture of the cellular and molecular regulatory networks involved in the early identification of “at risk” asymptomatic cohort and clinically confirmed symptomatic infertile symptomatic patient-population(s)/cohort. This single-center exploratory study strongly implicates the differential IVF/ICSI success trends among infertile women of South Indian ethnicity. The findings of the present study provide valuable insights in cost-effective infertility management; differential IVF success trends with primary and secondary outcomes/measures in a study timeline of 6 months viz April to September 2019, added to the study strengths. Another study strength was the timeline-based bias-free accurate, safe, and sophisticated study protocol with well-defined patient population subsets of same geographical region, that is, Tamil Nadu, India; therefore, possibility of population admixture and selection bias in terms of ethnicity was ruled out by incorporating clinically infertile married women of South Indian ethnicity residing in and around Chennai region, and therefore this patient population subset had similar sociodemographics and/or cultural exposures with a well-defined genetic profile and/or lineage. Interestingly, English and/or Tamil-speaking infertile women self-reported a patient satisfaction rate of 80% to 100% at the local IVF center; this response rate was elicited during one-to-one initial patient interactions, and relatively high patient satisfaction indices of 80% to 100% tremendously increased the overall quality of the exploratory study, thereby showcasing the clinical research endeavors and meaningful public health impact of the study. Bioethics, scientific integrity, and good practice research are core tenets of high-quality biomedical research; the author of this study with earned academic credits in bioethics from graduate schools of biomedical sciences at premier medical universities at Texas and Nebraska, USA and clinical observerships/patient-centric research exposures/interactions at prestigious medical college(s)/hospitals and laboratory at New York, USA, strictly ensured that study participants’ electronic medical records were accurately extracted and reviewed from the hospital-based registry. In case of missing details, the case number from the medical records was not included in the sample set for further review and analysis. After rigorous rounds of initial brainstorming sessions, the author and selection panel experts defined a stringent inclusion and exclusion criteria with careful review of adverse drug reactions and/or local/systemic events during IVF regimens. The findings of the preliminary study were promising and highlighted M-II oocytes’ yield, sociodemographics of study cohort along with increasing age/aberrant AMH/BMI profiles/endometrial receptivity/diminished ovarian reserve are meaningful predictors of IVF success in patient population subset(s). The author wishes to...
specify few study weaknesses/limitations so as to give a transparent, accurate, and bias-free report of the single-center infertility study conducted in specific population subset; limitations included a relatively small sample size (N = 134), lack of caffeine/tobacco usage/cigarette smoking/chewing history, live birth rate assessments post-IVF regimens, and paucity of patient-centric data pertaining to precision-based, stringent diagnostic criteria-based psychiatric assessments/evaluations. The inadequacy in sample size may lead to subsequent differential trends in IVF success in the study cohort over a study timeline of 6 months. The author speculates that more meaningful interpretation of data would be possible with a relatively large sample size in the patient subset(s). Moreover, maintaining homogeneity in sample numbers in the IVF-related data for the months April, May, June, July, August, and September in the year 2019, would have reduced any selection bias and/or possibility of ambiguity in terms of data interpretation. An ideal experimental clinical research study approach would have been to incorporate a larger sample size of South Indian women presenting with clinical infertility, and assigning an equal number of patients for the IVF workup/regimens in the 6-month study timeline, with a control group of age-matched women without infertility and of same ethnicity, that is, South Indian; a more stringent, well-designed, logical case-control epidemiological study protocol with relevant adjustments of potential confounders and stratification of study sample set(s) in both arms, viz infertile cases and healthy, fertile, age-matched, same ethnicity (South Indian) controls from random population(s) of Tamil Nadu, India, would have provided more critical insights in observed IVF/ICSI success trends among South Indian population. Apart from this study limitation, another weakness of this prospective exploratory study was lack of documentation of local/systemic adverse outcomes post-IVF/ICSI viz stillbirth, miscarriages, multiple pregnancies, intrauterine growth restriction, neural development defects/aberrant notochord oogenesis/neural tube activity, congenital fetal malignancies in newborn babies, and precision-based psychiatric assessment(s) of infertile couples with underlying mental-health disorders, primarily cognitive impairment, schizophrenia, and/or clinical depression. The author wishes to draw the attention of colleagues actively engaged in the ever-expanding infertility community health psychosexual research to the promising results corroborating the IVF/ICSI success trends by careful assessment of several clinically relevant parameters, including increasing age, BMI, endometrial thickness, ovarian reserve, AMH, beta-HCG levels, adverse local/systemic reactions/events including OHSS, fresh embryo transfer rates, M-II oocytes yield, and so on. It may be worthwhile to divert financial resources/funds for future multicentric sexual medicine research studies for comprehensively addressing the marital-relationship/spouse-compatibility issues, psychological factors, psychiatric disorders in infertile couples and perceived financial distress/hardships owing to exorbitant cost of infertility treatment coupled with referrals to psychiatric/sexual medicine clinics for an overall holistic-healing care with eventual long-term efficacy-based psychosexual outcomes in terms of successfully fulfilling the long-cherished dream of having a family with the inherent satisfaction of nurturing a baby. The cost of IVF and ART procedures in INR and/or USD is exorbitantly high; keeping in mind the relatively low socioeconomic status of the South Indian patient population subset enrolled in this study, the cost of IVF regimen(s) was considerably waived and/or tapered so as to ensure minimal loss of patients to clinical follow-ups during the entire course of treatment. In special circumstances wherein the clinically infertile women were psychologically distressed and/or in dearth of financial resources for treatment, counseling sessions coupled with motivational, awareness-based talks were conducted and their partners/husbands and families were provided complementary consultation/marital-relationship counseling to emotionally and financially support the treatment-seeking wife during the entire treatment regimen so as to ensure a relatively high pregnancy rate with successful biochemical pregnancy/beta-HCG positivity and clinical pregnancy/ultrasound-diagnosed gestational sac with fetal cardiac activity, eventually leading to successful live birth with the fulfillment of the cherished dream of motherhood.

Recent years have witnessed a growing interest in cohort-based reproductive medicine research studies, cross-sectional, observational, gene-epidemiology, and/or interventional, addressing fertility preservation and infertility prevention in susceptible women of diverse ethnicities; in this context, well-designed prospective exploratory single-center and large multicentric clinical research epidemiological studies with pooled patient-population subsets of clinically infertile women are enhancing the overall quality of patient care in both low-resource and high-resource settings with an overwhelming mix of patients of different socioeconomic strata, awareness, and/or satisfaction quotients and genetic profiles. Embryo-related research studies are generating tremendous support from the clinical research community and funding bodies so as to dissect the embryo morphokinetics, spatiotemporal patterning and cleavage events, embryonic transfers (fresh and/or frozen), vitrification, cryopreservation, and so on. Time-lapse microscopy is a precision-based novel noninvasive assessment tool with significant potential for enhancing embryo selection during infertility treatment for predicting embryo development and implantation potential; static phenomena are occasionally overlooked using conventional incubators, viz irregular divisions, blastocyst disintegration/collapse and re-expansion, timing of blastocoeals appearance, and formation and internalization of fragments. AMH is a significant predictor of ovarian reserve in polycystic ovary syndrome (PCOS) in females of
diverse ethnicities; 2 isoforms proAMH (inactive precursor) and AMHN-C (receptor-competent) have been reported to be efficacious and therapeutically relevant in PCOS. The ideal method of oocyte and embryo selection would be noninvasive, inexpensive, and able to be incorporated into embryology workflow with minimal disruption. The biomechanical properties of oocytes and embryos are indeed interesting to study; maintaining contamination-free embryology laboratory culture conditions is essential for dynamic and time-specific cellular-level transformation and/or maturation of oocytes and embryos through blastocyst formation. Further, the growing relevance of gene-editing tools such as clustered interspaced short palindromic repeats in embryonic screenings has been highlighted.

Psychological burden of infertility among childless women may be an underlying cause of depressive traits, anxiety, anger, restlessness, and marital discords/family problems; therefore, adequate counseling and motivational talks may be supportive in building an overall positive outlook during the course of IVF treatment. The findings of the present cohort-based study focusing on differential IVF/ICSI success trends in South Indian women with clinical infertility, certainly appear promising and may be utilized for future design and planning of personalized tailor-made individual-specific ovulation induction and IVF treatment regimen(s)/protocol(s); moreover, the author selected a specific ethnic patient population group viz South Indian, for elucidating the precise infertility-related clinical assessments, including primary and/or secondary outcomes of IVF so as to clearly understand the basis of differential IVF success rates in Indian women of distinct geographical region(s) at the state level(s). The findings suggest that the same and/or slightly tapered and/or modified ovulation induction and IVF regimen may yield differential oocyte yields, embryo transfer success rates, biochemical and clinical pregnancy rates, and IVF success rates in specific subset(s) of infertile women; the root cause and scientific basis of this skewed trend of IVF success rates across Indian women of South or North or East or West India may be demystified by further exploring the genetic basis of migrant Indian populations residing in specific geographical regions yet reporting a common ancestry/descent or genetic background. Thus, ethnicity-specific genetic profile-based and anthropological studies utilizing a pooled sample cohort of South Indian and North Indian infertile women, with a mixed cocktail of BMI-adjusted dosages of ovulation induction and/or IVF-treatment related drugs, so as to have optimal (nearly 100%) success rate of IVF, may be designed prospectively in the coming years; state-specific nodal IVF centers catering to specific subsets of infertile couples would be instrumental in long-term strategic fertility preservation and infertility prevention/management protocols. Enlightening clinical research perspectives with snapshots of emerging trends in IVF success rates at the ethnicity level may provide key insights in molecular medicine and future directions for advanced level reproductive immunology and embryology-related clinical research in the postgenomic era. Study limitations included small sample size (N = 134), lack of caffeine/tobacco usage/cigarette smoking/chewing history, live birth rate assessments post-IVF/ICSI regimens.

Sexual medicine research has seen a reasonable growth in the last 7 decades; however, psychological and cultural factors associated with the development of various sexual dysfunctions have not received considerable attention for evaluating indigenously designed psychosexual interventions/strategies for cost-effective, public health-oriented management of female as well as male sexual disorders in infertile couples of varying genetic landscapes worldwide. A well-structured questionnaire comprising marital-relationship assessment, psychoeducation, and cognitive behavioral interventions should prove beneficial in addressing the psychosexual problems encountered in infertile couples’ marital-relationship/interactions; infertile women and their partners/husbands should receive comprehensive, patient-friendly care from providers (urologists, gynecologists, infertility specialists, psychiatrists) with timely referrals to psychiatry outpatient services and sexual medicine clinics. Recent studies in the nascent sexual medicine research field have demonstrated that erectile dysfunction, premature ejaculation, and Dhat syndrome are the most common psychosexual dysfunctions observed in psychiatry outpatients; moreover, promising data sets are now available from patient-centric studies in Indian population(s) focusing on the psychosexual side effects associated with psychotropic medications viz antipsychotics, antidepressants, and mood stabilizers, primarily lithium. The public health impact of infertility with emphasis on female and male sexual dysfunction along with compatibility issues in healthy, distress-free marital/spouse-relationship have been highlighted, thereby paving the road for future meaningful collaborative research globally. Furthermore, critical pharmacoeconomic assessments may aid in developing a globally acceptable cost-effective public health research model in clinical infertility management with eventual patient-friendly outcomes leading to relatively higher interpersonal satisfaction indices in compatible marital relationships with minimal need for aggressive psychosexual interventions/psychiatric referrals, and so on. A sexual medicine public health research model with well-defined tiers (3-tier model system) comprising tier 1: research, tier 2: teaching and training, and tier 3: awareness and prevention, has been elegantly suggested by leading experts in the psychosexual medicine area, thereby emphasizing the urgency of allocating funds/financial support for propelling this field in the coming years. Early identification of prevalence of female and male sexual disorders in infertile couples with mental disorders is essential for successful interventions with maximal efficacy, feasibility, and acceptability by patients subjected to pharmacological, nonpharmacological, and combinatorial drugs' treatments.
Conclusions

Overall, key take-home messages include: (a) infertility is a major public health problem in both United States of America as well as India with considerable psychosocial distress in healthy, mutually compatible marital relationship; differential IVF/ICSI success trends among infertile women of South Indian ethnicity warrant the urgency of developing feasible, cost-effective, patient-friendly, public health-oriented awareness-based treatment modalities for efficacious infertility management protocols/strategies for reproductive-aged infertile women of varying genetic landscapes and socioeconomic strata with asymptomatic and/or symptomatic psychiatric disorders. (b) Embryo-quality assessments and oocytes’ yields, including M-II oocytes turnovers, endometrial thickness, increasing age, altered AMH profiles, and dietary/lifestyle-related patterns including caffeine/tobacco usage, are meaningful predictors of overall IVF success in precision-based sophisticated assisted reproduction technology laboratories and IVF centers globally; quality assurance and quality control in IVF is essential for enhancing pregnancy rates, including live birth rates, with well-justified utilization of healthcare resources. (c) Public health research models incorporating large sample size of infertile cohorts of specific patient population subsets residing in different geographical regions are warranted for early risk assessment and timely referrals to psychiatric outpatient clinics and/or sexual medicine clinics; sexual disorders/infertility-awareness campaigns, pharmacogenetic/genomic studies, and psychosexual interventions (marital-relationship counseling sessions/therapy, timely referrals for psychiatric assessments: cognitive impairment/schizophrenia/depression/stigma, pharmacological, and nonpharmacological treatment strategies) should be effectively designed for infertility prevention and successfully implemented for robust clinical management globally.

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