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LETTERS

Role of estrogens in immunoendocrine regulations of male reproduction

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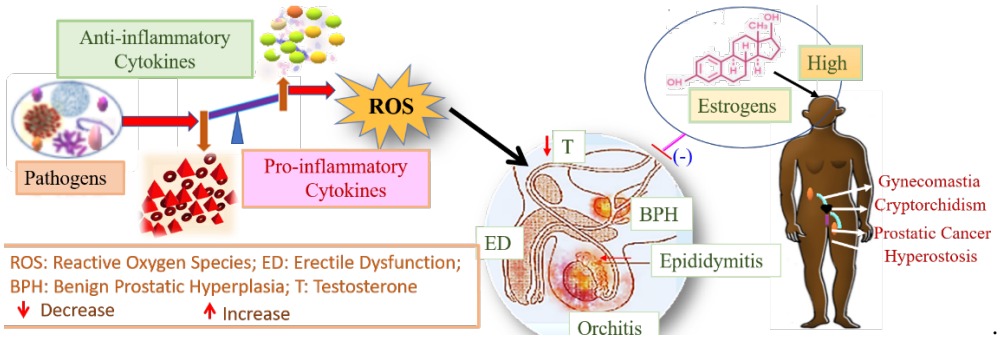
Review Article

ABSTRACT



Male infertility is a multifactorial disorder. A diverge array of autocrine and paracrine factors, genetic and epigenetic factors, pathogenic perturbations, testicular dysfunctions and oxidative stress, all together may contribute to male infertility. Interactions between different cellular components of testis, other accessory sex organs and hormones within the system's milieu act in a synchronized manner to help in normal reproductive function. In addition, immune cells and hormonal interplay may also assist such mechanisms. Androgens and estrogens are known to act as antagonizing hormones. They act via multiple receptors mediated signaling, producing such effects. Nevertheless, recent cropping up evidences in support of the role of hormones in managing testicular function indicate a vital role of estrogenic influences. Dietary or occupational exposure to artificial or natural estrogen may act as teratogen and a factor for some secular diseases of male reproductive tract leading to immune endocrine disbalances contributing to male infertility. The key role of estrogen in immune modulation related to immune dysfunction and inflammatory conditions in male germ cell signaling, Sertoli cell integrity and expression of altered immune responses are of a matter of great concern. Suppression of autoreactive immune cells, alterations of regulatory T cells (T_{Reg}), Th1 and Th2 ratio, Th17 cell responses, manipulation of inflammatory and autoimmune response confirms the essential role of estrogen in promoting protection against inflammatory conditions. Nevertheless, evidence based extensive research is essential to overrule the possibility of adverse outcomes of this sex steroid and sustain its beneficial action of estrogen in males.

Keywords: Estrogen, Hypogonadism, Infertility, Immune modulation, Male reproductive tract infection

INTRODUCTION

Besides reproductive actions, sex hormones have a considerable influence on the development and functions of the immune system.[1] Not only innate and adaptive immunity but also immune tolerance, autoimmunity, and other immune responses involving both humoral and cell- mediated immunity are dependent on the sex hormones.[2] Immune dimorphism of both testosterone and estrogen has been reported.[3] Though testosterone has immune-suppressive action making the testis an immune-privileged organ, estrogen has immune-modulatory action in the sense that it enhances immune responses.[4] The historical prospects of estrogens on male reproduction generate a preview that estrogen and phytoestrogens or any compound have structural mimicry to estrogen-an environmental toxicant may subside normal male gonadal function.[5] Since 1930, fetal exposure to a high dose of estrogen is known to be responsible for malformation of the male reproductive tract.[6] Customarily, estrogens are considered as female hormones, their roles in male reproduction cannot be overruled as supported by the recent literature.[6,7] In addition, estrogen receptors have been recognized in males since development till adulthood.[8] Studies reveal the presence of estrogen receptors in testis, epididymis, and seminal plasma of rats and other mammals.[9] In fact, a fine-tuning between testosterone and estrogen is of utmost necessity in all mammals for maintaining a healthy reproductive vitality.[9] Indeed, multiple paracrine and endocrine factors contribute to such functional

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balance between these two hormones.[9] Further sizeable amounts of this hormone have been characterized in the male brain.[10] Despite its anti-androgenic effects, this hormone is responsible for the generation of immune system hyperactivation, many auto-immune disorders like multiple sclerosis, Systemic lupus erythematosus (SLE), rheumatoid arthritis, loss of bone density, autoimmune renal damage, etc. with a higher prevalence in females much more than males.[11] Males deprived of estrogen as required in varying ages may suffer infertility suggesting the putative role of estrogen in male reproductive function.[7] It is quite common that, male infertility is not only caused by Hypothalamus Pituitary Gonadal (HPG) axis dysfunction, but many other inflammatory conditions augmented by multiple pathogens and other toxicants. These factors may reassign the normal immune-suppressive environment in testis, male accessory sex gland infection (MAGI), testicular and seminal ROS, NOs production resulting in poor semen quality and male infertility.

ESTROGENS AND MALE REPRODUCTVE PHYSIOLOGY

Expression of the aromatase in male reproductive tissues

Aromatase is the key enzyme complex responsible for the conversion of androgens to estrogens in both reproductive organs and also in other tissues.[12] This protein is a complex of a ubiquitous NADPH cytochrome P450 reductase and a cytochrome P450 aromatase which contains the haem and the steroid-binding pocket. The latter is a translational product of a single gene located in the q21.2 (cyp19A1) of human chromosome number 15. [13] Almost all tissues including male reproductive tissue express this gene to produce a fairly detectable amount of estrogen.[13]

In vivo and *in vitro* experiments with rat male reproductive tissue and isolated Leydig cells culture, revealed the compartmentalization of this gene expression citing an age-dependent fluctuation in the cellular distribution of aromatase activity. Carreau *et al.* reported the expression of this gene in Sertoli cells of immature animals, Leydig cells of adult animals respectively, and in the epididymis as well.[14] Analysis of aromatase gene expression also supported a comparable expression of this gene activity in germ cells and Leydig cells.[15] Carreau *et al* also substantiated that estrogen is expressed in adult murine pachytene spermatocytes, Golgi apparatus of round spermatids, and across the cytoplasm of elongated and late spermatids including spermatozoon.[14] Surprisingly, the amount of P_{450} aromatase mRNA declines as the germ cells progress towards maturation. Usually, preleptotene spermatocytes and spermatogonia express aromatase genes whereas the peritubular cells are devoid of this gene. Moreover, it has been claimed that half of the testicular aromatase activity is confined to the testicular germ cells but not in myoid cells.[14]

Human spermatogonia have the capability of converting pregnenolone to estrogen.[16] Critical analysis of the presence of the human aromatase gene transcripts in male semen by multiple throughputs like RT-PCR verified the expression of this gene in released ejaculated seminal spermatozoa, germ cell populations of spermatocytes and spermatids.[17,18] Besides, density gradient purification of motile and nonmotile fractions of spermatozoa in healthy adult human semen revealed the presence of human aromatase gene transcripts at a maximum concentration in the motile spermatozoa.[19] Carpino *et al.* have immunolocalized aromatase in the epithelial cells of human efferent ducts and to the proximal caput epididymis, indicative of another source of estrogen in the male reproductive tract.[20]

Expression of the aromatase in the hypothalamus

Local estrogen is commonly known to influence brain development and behaviour.[21] Aromatase, the key enzyme responsible for the conversion of androgens to estrogen in the brain has a profound role in organizing neuroendocrine function and social and reproductive behaviour as well.[22] Using *in-situ* hybridization techniques, high levels of aromatase activity have been mapped in different regions of the hypothalamus, preoptic area, sexually dimorphic nucleus, bed nucleus of the stria terminalis, hippocampus, and cerebellum.[23] Hypothalamic aromatase activity in perinatal animal models showed a sex-specific effect and in cyproterone acetate-treated mice, there seems to be a decrease in the expression of the aromatase genes in the hypothalamus. Further, detailed reports of such experiments supported those brain androgens are responsible for a higher levels of aromatase gene expression and estrogen synthesis in perinatal and in post-natal day 15 of these experimental animals.[24]

Estrogen receptors in male germ cells, and brain-gonadal axis

Estrogen receptors (ERs) are found throughout the spermatozoon and localized intensely within mitochondria, an organelle found in the mid-piece of spermatozoa that provides the energy source for flagellar movement in the female reproductive tract. In addition, aromatase and ER mRNA transcripts could be relevant markers for assessing infertility in men and may serve also as diagnostic tools for clinicians to evaluate sperm quality. Substantive advances in molecular technology (RTPCR), radiolabelling, knock-out animal studies revealed that there are 3 types of estrogen receptors ER1 (Erα), ER2 (Erβ) - gene products of ER1 and ER2 respectively and G protein-coupled estrogen receptors (GPER). ER1 and ER2 contain 530 and 549 amino acids respectively[16]. The subtypes of ERs, have more or less a fair conserved structure with five distinct functional domains[17]. The N-terminal domain is having only a 20% amino acid identity that may be accountable for the difference between the ER1 and ER2 action. This domain is responsible for ligand-independent promotor binding and cell-specific binding of activation factor (AF1). However, the C terminal domain is having 95% amino acid homology and is responsible for DNA binding (DBD), dimerization of receptors, and formation of homo or heterodimers. The D domain is the flexible hinge between the DBD and the ligand-binding domain (LDB). This domain, which is not well conserved between ER1 and ER2 (only 30% amino acid identity), is vital for nuclear translocation. Finally, the ligand-binding domain is partially conservative containing about 55% amino acid identity.

ER1 is the most vital receptor in animal fertility and is dominant in both sexes.[18] Next, it is reported that GPER is most

abundant in males along with ER1 while females have a preponderance of ER2 with a comparatively low GPER. Indeed, observations from knockout studies with ER2 have been proved this receptor to be less productive in males. Although GPER expression is higher in males, gene deletion of GPER is proven to be useless in altering male fertility or the dynamics of the HPG axis.[19] However, conflicting data about ER1 are reported in the case of humans. Some have observed the presence of ER1 in Leydig cells and in human Leydig cell tumours, others reported the absence of ER1 in human testis, yet the presence of ER1 in rat and human spermatozoa has been reported (Table 1). On contrary, ER2 is expressed in Leydig cells, peritubular cells, germ and Sertoli cells of these mammals. In cultured Sertoli cells, estrogen bind to either ER1 or ER2 assisting Sertoli cell proliferation but not differentiation. Most interestingly ER2 is co-expressed with ER1 in tumoral seminoma cells to counter the tumour cell proliferation mediated by ER1.[22] Besides, the human ER2 isoform 2 has a negative impact on the spermatogenic population while other variants may have different role in spermatogenesis. Considering the overall literature, it may be perceived that estrogen may act in males by canonical genomic estrogen rectors and even by non-genomic GPERE. Both types of receptor signaling, may affect Sertoli cell function and maintenance.[18,19].

Table 1. Expression of subtypes of estrogen receptors in different cellular components of testis

Spermatogonia	Spermatocytes	Spermatids	Spermatozoon	Sertoli Cells	Leydig cells	Myoid cells
ER2	ER2	ER1	ER2	ER1	ER2	ER1

The efferent ductules is an abundant area of ER1 and ER2 expression and action. They are critical for reabsorbing testicular fluid for maintaining water and ionic homeostasis of the ductular milieu. Target disruption of ER genes and knock out experiments revealed that ER1 is essential for normal functioning and maintenance of efferent ductular function.[20,21] The epididymis has also been identified as an organ for estrogenic influence. P_{450} aromatase mRNA, estrogen E2 estrogen sulpho-transferases and sulphated conjugates of estrogen are expressed in bovine epididymis in cauda and caput regions ER1 and ER2 are expressed in all segments of epididymis in monkeys.[22,23] Indeed, different species have different patterns of estrogen subtypes expression. Treatment of mammals with anti-estrogens provided species specific array of response including, a reduction of aquaporin1, NHE3 expression, capping and vascularization of narrow cells in the initial segment of the epididymis, appearance of PAS positive granules, vesiculation, lysosomal particles, in cauda and caput portion, reduction of sperm concentration and motility.[24,25] Other studies on laboratory animals sustained the fact that estrogen are essential for maintenance of normal fertility, epididymal contraction during semen emission and maintenance of internal milieu quality for sperm function.[26] Real Time PCR has helped scientists to identification of ER1, ER2 and GPER in vas deferens in males of all ages. Anti estrogen supplementation, leads to stromal and epithelial cell abnormalities. Estrogen is thus essential at developmental stages for formation of a morphologically normal epithelia and stroma of vas deferens. [6,7] With advancement of immune reproductive techniques, estrogen has been reported to affect the prostatic functions by both ER1 and ER2. In adult males, stromal cells express ER1, however rodent prostate showed a decline in ER1 as age progresses which may be interpreted as ER is involved in prostatic development. Further studies in ER1 deficient mice showed that squamous cell metaplasia advances in estrogen type 1 receptor deficient animals showing its paracrine influences on prostatic epithelium.[18] Human stromal ER1 is reported to contribute to the development of benign prostatic hyperplasia (BPH) and cancer metastasis. Unlike, rodents ER2 is involved in morphogenesis and differentiation of the prostate in humans. Expression of ER2 in basal epithelial cells, with lower stromal expression, and high expression of ER2 in both basal and luminal epithelial cells of the adult human prostate has been reported by multiple scientists however with controversial approaches. ER is having a potential for checking prostatic anti-inflammatory and ant-proliferative activity.[26]

Recently ER2 isoform in male rodent brain and in human has been identified using immunocytochemical technique.[25,26] Direct effects of estrogen on male GnRH neurones through ER2 is involved with LHRH neurones.[19] Extensive studies on estrogen receptor expression pattern in pituitary may infer that probably testicular steroids mediate their hypothalamic-pituitary activity directly through AR or indirectly through aromatization and activation of either ER1 or ER2 signalling pathways. Yet strikingly, ER1 independent estrogen signalling possibly through GnRH receptor involving PKC and MAP kinase pathway is also evident that may draw attention on the involvement of GPER receptor pathway also. [19]

Usually, estrogen binds to ERα or ERβ in the cytoplasm is followed by receptor dimerization[34]. Next, this complex is translocated to the nucleus, and subsequent binding of chromatin at ERE sequences take place at specific enhancer sequences within or close to promoters, and/or 3'-untranlated regions of target genes.[27]

Non genomic or indirect effects

GPER may interact with all these various types of estrogenic ligands with the highest affinity for E2.[27] GPER activates a couple of downstream signaling cascade that exert diverse effects to modulate cell growth, migration and programmed cell death in different tissues. GPER acts via G-protein, followed by stimulation of Src-associated tyrosine kinase family and phosphorylation of the Shc adapter protein, leading to MMP expression. Estrogen action via GPER concerns both rapid non-genomic estrogen response and long-term regulation of gene transcription that concerns stimulation of adenyl cyclase, enhancement of PI3K signaling pathways, MAPK, mobilization of calcium ions from intracellular stores, as well as upregulation of genes such as FOS and CTGF.[28]

ESTROGENS AND IMMUNITY

The running literature about sex hormones and immune responses reports that estrogen and testosterone affect the cells of innate and adaptive immunity. In fact, gonadal hormones exert

specific effects on the male and female immunocompetence at both the cellular and the molecular level. Estrogen has large immune enhancing effects. The ERs are highly expressed in most immune cells of innate and adaptive immune systems. The immune plasticity in the male reproductive tract is performed by steroid hormone receptors like androgen receptors (AR) and estrogen receptors (ER). Though age and stage-dependent, ER are differentially expressed in lymphocyte precursors. mRNA expression and protein levels of ER are reported in activated CD4, CD8 T cells, NK cells, B cells, and antigen-presenting cells like dendritic cells and monocytes.[29-31] Estrogen regulates the differentiation and maturation of dendritic cells (DCs). Functional mature DCs population is augmented by E2. Alongside, E2 also increases the expression of cytokines and chemokines like IL-6, IL-10, CXCL8, and CCL2 in DCs. [32,33]

Besides, neutrophil and macrophages also express ER. It has been reported that estrogen regulates the number of neutrophils and their functional attributes like - chemotaxis, infiltration, production of ROS, induction of chemokines and cytokines. Estrogen can also modulate the functions of macrophages including chemotaxis, phagocytosis, production of cytokines, reactive nitrogen species and nitric oxide. Unlike testosterone, estrogen increases inflammatory cytokines at a certain physiological dose.[30] The inflammatory mediators like IFNγ, IL6, and tumor necrosis factor α are known to be produced more with physiological dose of estrogen,[33] but at higher doses estrogen is reported to suppress these mediators[34] and reduced inflammatory cytokine production suggesting a dual role of estrogen in infection, inflammation and immune responses.[35]

Observations regarding the role of estrogen in B cell-mediated humoral immune responses, both types of ERs are involved in B cell maturation and differentiation, assists BCR signaling and CD22 expression, but the alpha subtype ER mediates the decrease in B cell receptor signaling.[30]

Another immunogenic cell population related to adaptive immune responses is the T cell. The αβ-TCR expressing T cell subsets including CD4+ (Th1, Th2, Th17, and Treg cells) and CD8+ cells are influenced by E2. E2 upregulates Th-1 cells promoting higher expression of IFNγ. However, in males this subset of T lymphocytes is downregulated. Interestingly, the paradigm of Th1/Th2 responses is critical to promote cell-mediated or humoral immune responses. In general, INFγ, IL-2 cytokines promote cellular responses whereas Th2 cytokines, IL-4, IL-5, IL,9, IL-10 and IL-13 are optimal for humoral immune responses. Females produce higher Th2 response and antibodies optimizing better protection from infections but the hyperimmune response makes them susceptible to autoimmune diseases.[36] Males generate more Th17 responses and are less likely to develop autoimmunity. [37]

In addition, E2 suppresses TH1 and TH17 mediated immune responses. Suppression of IL-17 and TH17 differentiation by ER-α promotes neuroprotection and defends the development of inflammatory diseases in males. Estradiol treatment inhibits Th1, Th2 and Th17 differentiation. Estrogen also augments the number of T_{reg} cells providing immune tolerance.[38] A study conducted on a humanized model of a mouse model of inflammation showed that exogenous supply of estradiol and castration in male mice modulates functions of B cells and

Table 2. Beneficial effects of estrogen in combatting testicular immune disruption in some diseased conditions

Disease	Mechanism of infection in males	Estrogen Receptor modulators	Mechanism of action
SARS -Cov2 infection	Metalloproteinase domain 17(ADAM 17), ACE2 and TMPRSS2 may promote IL6 production	Tamoxifen Quercetin Quinestrol Raloxifene Genestin	Prevents viral entry and a disintegrin and metalloproteinase (ADAM) mediated IL6 production.[58]
Ebola, Dengue, Zika	Activation of macrophages and release of pro-inflammatory mediators		Inhibition of virus replication, Blocking of virus entry and viral transcription and translation
Erectile dysfunction (ED)	ERα and ERβ strongly stimulates NO synthase enzyme to produce NO in vascular endothelial; absence of which may lead to erectile dysfunction	Drugs specifically acts by ER2 activation	estrogen administration increases the contraction of smooth muscle in the corpus cavernosum, upregulating the RhoA/Rho-kinase signaling pathway, which is involved in ED. [59]
Sepsis	Bacteria LPS and endotoxins act via TLRs enhancing the production of cytokines such as TNF-α, IL-1β, and IL-6 by macrophages leading to ROS mediated loss of male fertility	Estradiol	Decreases inflammatory responses by increasing anti-inflammatory cytokine IL10 production and alleviating ROS induced damage to the testis, semen and MAGI
Prostatic Cancer	Loss of ER-β expression and high DHT	Diethylstilbesterol	ERβ is involved in direct inhibition of WBC, NO, H_2O_2 COX2, cyclo-oxygenase-2; augmenting TGFβ; NFκβ mediated signaling. [60]

increases expression of Major Histocompatibility factor, thus increasing autoimmunity in mice.[39,40]

Asymmetry in Th1-type to Th2- type response may aggravate or suppress inflammatory diseases is arbitrated by the level of estrogen. This focuses the paramount influence of estrogen on its immune-modulatory effect on certain inflammatory diseases. The fate of such estrogenic influence can lead to lucrative or harmful impacts depending on the type of immune cell involved. This concept is essential while considering the application of combination therapies that include estrogen.[41]

Beneficial roles of estrogen in the male reproductive tract

Loss of fertility in humans is defined to be environmental toxicants and hormonal alterations. E2 action depends on two main factors: the aromatase enzyme and the receptor specificities in reproductive and non-reproductive tissues. Mutations in estrogen receptor alpha are suspected to affect male fertility in humans. Direct evidence for the production of aromatase in male gonads is influenced by FSH and cAMP. Aromatase deficient knockout mice showed interferences in spermatogenesis between 4.5 to 1- year- old animals. Spermatogenic arrest included the appearance of multinucleated cells, reduction in the round and elongated spermatids within Sertoli cell but not on other precursor germ cells embedded in Sertoli cells E2 is housed in germ cells in balance with testosterone which otherwise would lead to aging and germ cell death.[42] Indeed, the appropriate function of estrogen helps in successful sexual maturity and maintains the integrity, growth and maturation of spermatogenic cells. Estrogen thus co-operates with testosterone to maintain the dynamics of germ cell progression towards sperm maturation without any sort of degenerative and apoptotic indulgence. The concentration of E2 as found in different testicular and accessory reproductive tissues in males is a good stimulator for sperm capacitation and acrosomal reactions sustaining male fertility. [24] Estrogen is necessary to maintain a differentiated epithelial histology and fluid reabsorption in the male reproductive tract as mentioned above. Low testosterone is reflected in lower E2 levels ending up as a loss of membrane morphology, fluid homeostasis and testicular atrophy. Patients with Werner's syndrome reported to have low E2 essential for WRN gene expression unlike testosterone delineating the fact the E2 is essential for normal Leydig cell and testicular function. The blood-testis barrier (BTB) is an important aspect to be considered in Sertoli cell functions and defence for gonocytes and germ cells against the autoimmune attack. Certain functional cytoskeletal elements of the Sertoli cells, gap junctions, connexin protein 43 composing the BTB are sustained by the E2 level present in this testicular compartment which would otherwise lead to the disputation of BTB and loss of Sertoli cell plasticity.[43] E2 in the association with testosterone and alike iodinated hormones regulates the expression of Krŭppel factors for the maintenance of Sertoli cell junctional integrity essential for gonocyte translocation towards the luminal side. Sertoli cells express a higher level of BCL2 proteins that prevent caspase-mediated apoptosis. The heirs of spermatogonial transition from mitotic to meiotic spermatocytes within the Sertoli cell microenvironment are also dependent on E2 activity. E2 promotes the transformation of cytoplasmic bridged spermatogenic cells to motile sperms by excision of perikaryon, and cytoplasmic quenching assisting in sperm motility. Microtubular cytoskeletal regulatory protein claudin 11 is essential towards the maintenance of normal spermatogenesis and is dependent on the paracrine action of E2 along with other hormones. ERs are identified in the middle piece endoplasmic reticulum, Golgi apparatus, mitochondrion of all types of spermatids, and mature spermatozoon as well. Mitochondria of mature spermatozoon express ER2 along with androgens to maintain normal OXPHOS and prevents ROS-induced damage to mitochondrial DNA and autophagic tendency.[44]

Studies reveal that the GPR30 receptor, is related to the proliferation-inducing effects of estrogens in a GC1 cell line34, in human and in rodent testicular cells.[45] GPR30 is reported to be associated with estradiol-induced expression of apoptotic markers (e.g., FAS, BAX, and FASL) in rat pachytene spermatocytes and round spermatids.[45] Genes for androgen metabolism and Leydig cell functions like steroidogenic acute regulatory protein (StAR), 11-beta HSD, alcohol dehydrogenase, carboxylesterase 3 (Ces3), Acyl-CoA cholesteryl acyl transferase type 2 (Acat 2) , Corticosteroid 11-beta-dehydrogenase isozyme 1 (Hspd11b1) and sulfotransferase family 1A, phenol-preferring, member 1 (Sult1a1) has estrogen responsive element (ERE) suggesting a putative influence of estrogen on these gene expressions as well.[46]

Male reproductive tract infection and involvement of estrogen

The testis is immune-privileged organ that is helpful for maintaining normal germ cell dynamics, apoptosis of residual bodies, sperm production and spermiation. The immune-suppressive microenvironment is maintained by its normal histoarchitecture by certain paracrine and imunerepressive factors. The BTB shields against perturbations of interstitial immune cells into the germ cell milieu. Sertoli cells secrete Activin A, transforming growth factor-beta (TGFβ) that suppresses the immune response of dendritic cells, and macrophages. Gas6, TGF-β, and testosterone secreted from Leydig cells also inhibit the immune response of dendritic cells and macrophages (Mϕ). Mϕ cells exhibit their immune suppressive actions by producing anti-inflammatory cytokines IL10 to impede effective T cell responses. Indeed, a balance between T_{reg} cells and T_{eff} cells in the testes fosters normal spermatogenesis and testicular homeostasis. Normally, T_{regs} effectively control T_{eff} cells through several immunosuppressive mechanisms that maintain sustained spermatogenesis.[47,48] Testicular germ cells produce Fas ligand that promotes apoptosis of T cells with the assistance of program death. Numerous subtypes of pattern recognition receptors (PRRs), including TLR2, TLR4, TLR5 ate also present in testis for defence against pathogens.[49]

In the epididymis, the blood epididymal barrier is partially permeable to leucocytes like dendritic cells and macrophages. Dendritic cells be located in the basal region of the epididymal tubule, and their protrusions can reach the lumen side. Mφ are dispersed in the stroma along with minor T lymphocytes. Various pattern recognition receptors (PRRs), including TLR2, TLR4,

TLR5, DNA, and RNA sensors are expressed in principal cells, and the principal cells also produce defensins to counteract microbial infections.[50]

Leucocyte infiltration and innate immune response elements including proinflammatory cytokines, IL-6 and TNFα, chemokines hasten chemoattraction of WBCs. IL6 expression is related to induction generation of ROS causing oxidative stress. TNFα is also accountable for the induction of chemokine expression which may be associated with germ cell apoptosis, thereby impairing spermatogenesis and sperm development. Neutrophil chemo-attractant IL8 may also contribute to infection related immune inflammatory outcomes.[51] Thus innate adaptive immune components are the primary responses to testicular pathogenic insults leading to a disbalance of pro and anti-inflammatory cytokines that is responsible for MAGI. IL1, IL2 and IL8 penumbrae testicular production in Leydig cells. This may totter germ cell, Sertoli cell and blood testicular barrier integrity with spermatogenic cell loss and consequently loss of male fertility.[52]

In the semen and prostate, the leucocyte population including granulocyte, macrophages and T lymphocytes are critically involved in maintaining an immune-privileged milieu. These cells are involved in the production of cytokines, and other leukocyte-derived pro-inflammatory mediators like nitric oxide, prostaglandins and chemokines.[53] However during UTI pathogenic insults including bacterial lipopolysaccharide, viral shedding, etc. the seminal pro-inflammatory mediators may increase the production of ROS and RNS that may nullify such pathogenic insults but at the same time excess ROS may impair normal sperm function.[54]

Estrogens hasten cell-mediated and humoral immune responses to microbial infection. ERs expressed in various lymphoid tissue cells as well as in peripheral lymphocytes and macrophages contribute to resistance against infections by enhancing NK cell cytotoxicity and stimulating the synthesis of

Table 3. Adverse Effects of Xeno-, phyto- and mycoestrogens, dietary phthalates etc. on male fertility

Possible disease trends	Causes	Hormonal changes	Immunological effects
Cryptorchidism	Maternal exposure to 17alpha- and beta-estradiol, as well as DES, downregulates insulin-like peptide 3(Insl3) expression in embryonic Leydig cells, contributing to the development of cryptorchidism. Other factors include gene polymorphism.[62]	High estrogen reduces the gonadotropin induced testosterone production, AMH related immature Sertoli cell function	Xenoestrogens like Bisphenol A affects the expression of CD11c, CD14, CD15, CD16, CD62L and CD284 compounds on the surface of neutrophils in males persuade changes in the immunophenotype of human neutrophils, resulting in immunity disorganization linked with the dysfunction of these cells.[63]
Hypospadias	Bisphenol A exposure to mothers may reduce testosterone synthesis by altering expression of 3β HSD and also altered ER expression may lead to the progression of this defect.[64]	Exposure to phthalates and other xenoestrogens alter maternal cortisol, and hormonal levels may lead to androgen insufficiency in the fetus and downregulation of androgen receptors function in male fetus	Altered mesenchymal fibroblastic cell signaling, penile foreskin Langerhans cells functioning in association with CD8+ cells may be responsible for immunosuppression and pathogenic invasion in the foreskin.[65]
Male Breast Cancer	Xenoestrogens, phenol estrogens may assist in progression of this disease. Metabolic syndrome, obesity, rapid weight gain, elevated blood cholesterol, non-insulin-dependent diabetes may increase physiological aromatization of peripheral adipose tissue and higher levels of circulating estrogens in males.[66] The roles of adipokines are also to be considered.[67]	High estrogens may suppress hypothalamo- pituitary testicular axis and thereby lowering normal testosterone levels in males	High adiposity may recruit macrophages and immune cells in breast tissue along with high estrogen, low adiponectin, elevated adipokines, leptin may increase inflammatory mediators may induce nuclear factors,[68] cell cycle inducers.[70,71] sustaining increased cell mass, proliferation, promoting cell growth and survival hindering the suppressive action of p^{53} gene product.[72]
Testicular cancer	Xenoestrogens, occupational exposure to organochlorines and endogenous estrogens may be a concern.	Higher maternal estrogen and progesterone, or insulin like growth factor, epidermal growth factor and androgens are some hormonal factors involved	Non-transcriptional effects by membrane-mediated signaling pathways leading to calcium influx, cAMP or nitric oxide production, or MAPK ERK1/2 activation Inhibition of adaptive immune responses, retarded apoptotic activity.[72]

pro-inflammatory cytokines such as IL-1, IL6, and TNFα.[55] Estradiol exhibits its suppressive effects that rely upon the production of IL-4, IL-10, transforming growth factor beta (TGF-β) and interferon gamma (IFN-γ). Furthermore, estrogens may also prevent apoptosis of the immune cell population.[3]

Estrogen may be beneficial in preventing inflammatory responses in male pathogenic insults by activating peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ is a regulator of adaptive immunity by negative regulation of T cell activation proliferation and differentiation. PPARγ mediated inhibition of Th1, Th2, and Th17 differentiation of naïve CD4 T cells in males to curb inflammatory responses in testis and in MAGI. [56, 57]

Effect of exogenous estrogens, phytoestrogen, estrogen agonists or xenoestrogens – An adverse effect on male reproduction.

Intratesticular estrogen elevations by external estrogen supplementation led to suppression of FSH and intratesticular estrogen levels in mice with a concomitant regression in stages VII-VIII of spermatogenic cycles resulting in failure of spermiation. Such alterations are attributable to defects of testis-specific cell junctions and disorganization of Sertoli cell cytoskeletal elements. Further germ cell apoptosis may be an outcome. High estradiol is reported to supress a number of enzymes involved in testicular metabolism, iron binding and transport, cytochrome P450, endocytosis and cell apoptosis. Even, a negative effect of estrogenic xenobiotic genistein on capacitation in human and mouse spermatozoa is known.[61] Adverse effects of exposure to phenolic compounds, bisphenols, phthalates dietary flavonoids may mimic conditions of estrogen excess promoting estrogen toxicity in adults and in foetus as enlisted in the table 3.

Conclusion

More than 30% of men across the globe are suffering from the problem of male infertility which may be multifactorial. Intrauterine development of male fetal gonad, juvenile gonadal function, the pattern of germ cells proliferation and differentiation in post-pubertal adult male, nursing of spermatogenic lineage germ cells within male reproductive tissues, formation of the mature spermatozoon, sperm capacitation and motility are supposed to be related with conventional dosage of various hormones and their paracrine interactions fosters male reproductive fertility.[73] Further, infection-mediated inflammatory complications and immune homeostatic disbalances are reported to be another leading cause of male sterility.[74-76] Although androgen, the chief male hormone traditionally responsible for such consequences, estrogens too contribute to immune-modulatory effects may be considered the other important factor for male hypogonadism and infertility. Estrogen has a contributory role from fetal to pubertal, adult and senile stages in men in promoting good sexual and reproductive health. The other factor related to the role of estrogen in males encompasses the consequences of estrogen on governing the types of the immune cells responsible for inflammation or autoimmune responses. As reported, mononuclear cells, TLR, Pathogen associated molecular patterns (PAMPs), T cell homing, Th1: Th2 ratio, thymic epithelial cells, INF-γ, pro- or anti-inflammatory cytokines, interleukins, NK cells, TH17 responses, B cell homeostasis feedbacks on levels of estrogen. ER signaling in various components of male reproductive systems may also assist in T_{reg} cells functions, suppression of self-reactive antigen production, leading to immune protection to germ cells, pathogenic /nonpathogenic testicular microenvironmental insults, maintenance of efficient BTB and Sertoli cell cytoskeletal dynamics, maintenance of normal fluid balance in testis, vas deferens, epididymis, prostate, healthy spermatozoon.[72] Moreover, ROS-dependent loss of male reproductive organ function and semen quality is improved by estrogen administration.

On the contrary elevated estrogen levels as in case of exposure to excess estrogenic toxicity, may induce autoimmune disorders as testicular tumors outcomes or estrogen- dependent suppression of HPG axis, aromatase gene expression in the hypothalamus or LHRH insufficiency and pituitary gonadotropin suppression, androgen insufficiency and also the progression of male prostatic hyperplasia, (though controversial), autoreactive sperm antibody formation and failure of successful embryo formation. Hypogonadotropic hyperestrogenic hypogonadism is also reported in obese men due to aromatization of estrogen in peripheral tissues.[77]

Thus, a conflict between beneficial and adverse effects of estrogen is a critical issue. Extensive empirical research for justifying the beneficial effects of estrogen in curbing the immune inflammatory effects upon male infertility obscuring its adverse effects is necessary.

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Conflict of Interest

Authors declare no conflict of interest

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