Endotext

MALE GONADAL DISORDERS IN THE TROPICS

Shreya Sharma, MD, DM, Consultant, Department of Endocrinology, Max Hospital, Dehradun, Uttarakhand, India 248009. dr.shreya24@gmail.com
Saptarshi Bhattacharya, MD, DM, Senior Consultant, Department of Endocrinology, Indraprastha Apollo Hospitals, Delhi, India 110076. saptarshi515@gmail.com
A.B.M. Kamrul-Hasan, MBBS, MD, Assistant Professor, Department of Endocrinology, Mymensingh Medical College, Mymensingh, Bangladesh 2200. rangassmc@gmail.com

Received May 29, 2024

ABSTRACT

Male hypogonadism arising from disorders of the hypothalamic-pituitary-gonadal axis is characterized by insufficient testosterone production. It is usually associated with subfertility or infertility. While hypogonadism is a global health concern, its diagnosis and management in tropical regions present unique challenges due to a combination of factors. Infectious etiologies often dominate the cause of male hypogonadism in certain areas of the tropics, but other factors such as environmental toxins, heat exposure, and high prevalence of metabolic disorders can also contribute. Atypical but not uncommon etiologies in the context of tropical conditions include snake envenomation, calorie deficiency, trauma, and of hormones and feedback mechanisms. The hypothalamic-pituitary-gonadal (HPG) axis is the critical regulatory system that governs the function of the testes in producing sex hormones and sperm (1).

Male hypogonadism encompasses abnormalities in sperm production, including changes in quantity or quality, alongside androgen deficiency. In tropical regions, male hypogonadism can arise due to diverse factors such as heat exposure, nutritional deficiencies, infectious diseases, toxins, genetic disorders, and metabolic dysfunction. Effective management in tropical areas necessitates a comprehensive androgen and recreational drug abuse. Understanding the specific causes of male hypogonadism in tropical regions requires a comprehensive assessment considering both medical and contextual factors. Addressing these causes involves targeted interventions, including infectious disease management, environmental regulations, genetic screening, appropriate medication use, and culturally sensitive healthcare approaches.

INTRODUCTION

Male gonadal function primarily refers to the role of the testes in producing testosterone and sperm. It is regulated by a complex interplay

approach that takes into account environmental, nutritional, hormonal, and metabolic factors.

EPIDEMIOLOGY

The epidemiology of male hypogonadism remains insufficiently researched, particularly in tropical countries. Among the known causes of endogenous androgen deficiency, Klinefelter syndrome is relatively common, with a likely population prevalence ranging from 5 to 25 cases per 10,000 men (2). The percentage of infertile men varies widely, ranging from 2.5% to 12%. Infertility rates tend to be highest in Africa and Central/Eastern Europe (3).

In many tropical countries, endemic infections such as tuberculosis, leishmaniasis, leprosy, and schistosomiasis persist, leading to hypogonadism due to scrotal involvement (4). The precise prevalence, however, remains unknown.

INFECTIOUS CAUSES

Infectious causes of hypogonadism can result from various pathogens, including bacteria, viruses, and protozoa, that directly or indirectly affect the gonads or disrupt hormonal regulation. Bacterial infections ascending through the urogenital tract primarily affect the epididymis and accessory glands, whereas viral infections transmitted via the bloodstream predominantly involve the testes (5). Infections of the male genitourinary tract are responsible for 10% to 15% of cases of male infertility and may be especially relevant in the tropics (6). These conditions present as urethritis, prostatitis, orchitis, or epididymitis and are potentially curable (7).

The testis is considered an immune-privileged organ, crucial for safeguarding immunogenic germ cells during spermatogenesis from immune system activation. This protection is primarily achieved through a local immunosuppressive environment and systemic immune tolerance (8). The testis induces local innate immune responses to counter pathogens despite its immune privilege. However, certain pathogens can evade these defenses, leading to infection and persistence in the male reproductive tract (9).

Viral infections

Mumps virus and human immunodeficiency virus (HIV) infections are recognized viral causes of orchitis and male infertility. Additionally, various emerging viral infections, including tropical ones, can affect male gonads.

MUMPS

Mumps infection is known to cause hypogonadism and male infertility. The extensive use of mumps vaccines has reduced the occurrence and severity of mumps-related complications. In Asia, infection is more prevalent during summer months, and a correlation between increased temperature and humidity has been suggested (10). A possible cause of mumps outbreak in many tropical countries could be inadequate vaccine coverage.

Clinical orchitis is rare in prepubertal males but affects 15-25% of adult men about a week after parotitis. Infertility or subfertility occurs in about 30% of orchitis cases, likely due to germinal cell damage, ischemia, or immune responses to the infection (10,11). Germ cell failure is more common than androgen deficiency in mumps and related viral infections. Treatment during the acute phase is supportive, as no proven therapy prevents sperm cell damage. Universal vaccination remains the primary strategy for preventing mumps-related infertility (12).

HIV INFECTION

Epidemiology

Studies report low serum testosterone in HIV-positive men ranging from 13% to 40%, with a recent meta-analysis suggesting a 26% prevalence (13,14). Secondary hypogonadism accounts for up to 80% of the cases and is attributable to functional hypogonadotropic hypogonadism (FHH) (13). In tropical countries, socioeconomic factors such as poverty, limited education, and inadequate healthcare resources contribute to increased rates of HIV transmission and hinder access to testing and highly active antiretroviral therapy (HAART). Studies conducted in tropical Africa show a prevalence of hypogonadism ranging from 8.7% to 37% in men with HIV (15,16).

Etiology

HIV-specific factors, alongside traditional ones, contribute to testosterone deficiency in men with HIV. While some association exists between testosterone levels and HIV-related parameters, such as low CD4

count, uncontrolled HIV viremia, weight loss, and acquired immunodeficiency syndrome (AIDS) wasting, the evidence is not strong (17). The pathogenesis of hypogonadism in these men is multifactorial and complex, with classical risk factors playing a minor role compared to HIV-negative men. It's essential to note that the lack of a strong association between testosterone levels and traditional risk factors doesn't exclude their involvement; rather, numerous HIV-specific factors can mask their significance statistically (13).

Role of HIV-Related Comorbidities

HIV-related co-morbidities, chronic inflammation, illicit drug use, and body composition changes from HAART have been implicated in the development of hypogonadism. HIV infection makes the testes more susceptible to opportunistic infections like cytomegalovirus (CMV), Epstein-Barr virus, and tuberculosis (18). Up to 25% of individuals with AIDS will demonstrate testicular involvement with widespread opportunistic infection or systemic neoplasms, including CMV, toxoplasmosis, Kaposi sarcoma, and testicular lymphoma. However, primary hypogonadism may not develop in all cases (19).

Drug-Induced Hypogonadism

Several medications used for the treatment of HIV and AIDS may affect the HPG axis. Ketoconazole inhibits side-chain cleavage enzymes and other critical enzymes in testicular steroidogenesis. Megestrol acetate is used to increase appetite, but as a synthetic progesterone agent it suppresses gonadotropin secretion and results in hypogonadism. Central hypogonadism can also occur from opiate-induced inhibition of gonadotropin-releasing hormone (GnRH) release.

Hyperprolactinemia and Gynecomastia

Increased prolactin levels are reported in almost 20% of men living with HIV (20,21). In a case-control study, gynecomastia was seen in 1.8% of 2275 consecutively screened cases and was associated with hypogonadism, hepatitis C, and the degree of lipoatrophy associated with HAART (22). Efavirenz, a commonly used HAART, is often responsible for gynecomastia which is due to direct activation of the estrogen receptor (23). Hyperprolactinemia has been reported in 21% men with stable disease and was significantly associated with opioid and protease inhibitor usage.

Testicular Changes

HIV infection itself doesn't result in observable morphological changes, especially with the advent of HAART, which has majorly reduced the risk of primary testicular damage (24). An earlier autopsy-based study had categorized testicular findings in AIDS into five groups: "Sertoli cell-only" syndrome (43%), germ cell damage (27%), peritubular fibrosis (15%), maturation arrest (12%), and normal appearance (3%) (25). A subsequent study reported decreased spermatogenesis, subacute interstitial inflammation, or their combination in autopsy (26).

Diagnosis and Management

The approach to diagnosis and management is generally similar to other causes of male hypogonadism. Readers can refer to relevant sections in endotext.com for more detailed information (27–29). Of note, about 30% to 55% of men with HIV have increased sex hormone–binding globulin (SHBG). As a result, using bioavailable or free testosterone instead of total testosterone is recommended for diagnosis. Though, in cases of hypogonadotropic hypogonadism, addressing the primary pathology is the standard treatment, the chronic nature of the condition demands more frequent consideration for testosterone replacement therapy (TRT) for men with hypogonadism and HIV (30).

Treatment options include TRT, addressing underlying comorbidities, optimizing HAART regimens to minimize side effects, and promoting healthy lifestyle practices to prevent metabolic disorders. Regularly

monitoring hormone levels, bone health, and metabolic parameters is crucial for long-term management.

ZIKA VIRUS INFECTION

Zika virus is a flavivirus borne by mosquito vectors such as *Aedes aegypti* and *Aedes albopictus*. It is endemic to tropical countries of Africa, Asia, and South America. The virus can also spread through sexual contact, blood transfusion, and from mother to fetus (31).

The infection remains asymptomatic in the majority, but manifestations may include low-grade fever, rash, conjunctivitis, myalgia, and arthralgia. Zika virus RNA persists in the semen and in male and female reproductive tracts. Zika virus has been associated with testicular inflammation and damage, leading to infertility in some cases (32,33). The virus's ability to alter mature sperm can reduce fertility and has implications for assisted reproduction, particularly due to its teratogenic potential (34). Typically, the testes do not show any inflammatory response, and normal morphology and hormone production are maintained. This enables the virus to remain dormant, acting as a covert carrier for asymptomatic sexual transmission.

OTHER VIRAL INFECTIONS

Several viruses prevalent in tropical countries have been linked to testicular damage and infertility. Human papillomavirus (HPV) infection in males is often linked to external genital warts, but asymptomatic infections are equally common. HPV has been detected in the epididymis, testicles, vas deferens, prostate, and seminal fluid. High-risk HPV strains such as HPV-16 can affect sperm parameters, including count and motility, possibly reducing fertility (35,36). Both herpes simplex virus (HSV)-1 and HSV-2, like HPV, can localize in the male genital tract, but it's unclear if they affect fertility (37).

Hepatitis B virus (HBV) can enter male germ cells by crossing the blood-testis barrier, integrating its genome, and inducing oxidative stress and reactive oxygen species (ROS) production, leading to sperm apoptosis. HBV infection in chronic cases results in higher apoptotic sperm cells and membrane integrity loss (38). Despite its effects on sperm, fertility outcomes in assisted reproduction remain unaffected, with vertical transmission being unlikely, especially with a vaccinated female partner (39).

Hypogonadism has been documented in men infected with the hepatitis C virus (HCV), but the etiology has not been clearly established and is likely to be multifactorial. While systemic inflammation associated with HCV may suppress the HPG axis, the effect of advanced liver disease on testosterone metabolism may also be responsible (40). HCV infection reduces sperm count, motility, and morphology, affecting fertility potential. Elevated oxidative stress can lead to sperm chromatin condensation and cell death. It can also trigger an autoimmune response. Interestingly, treatment with ribavirin and interferon can also worsen semen parameters (41).

Male reproductive organs have been found to be vulnerable in moderate to severe illness with severe acute respiratory syndrome coronavirus 2 (42,43). The negative effect on seminal parameters was found to persist even at six months (44).

Bacterial Infection

Bacterial infections in the male reproductive tract can lead to epididymitis, orchitis, prostatitis, and urethritis. These infections are typically caused by *Chlamydia trachomatis, Neisseria gonorrhoeae*, ureaplasmas, mycoplasmas, and other bacteria. They are more common in tropical developing countries. Mycobacterial affection of the male genital tract is also prevalent in these regions. Symptoms include pain and swelling of the genitalia, penile discharge, and discomfort during urination or ejaculation. Treatment usually involves antibiotics targeted at the specific bacteria causing the infection (45).

Infertility can result from these infections, with underlying mechanisms possibly including damage to the germinal epithelium, ischemia, immune dysfunction, and cell damage from increased ROS (46). Spermatozoa can be affected at various stages of their development, maturation, and transport. Infections are also associated with obstruction along the seminal tract, such as urethral strictures.

Many pathogens of the male genitourinary tract are asymptomatic, and it is often difficult to distinguish colonization from infection detrimental to fertility (47). Bacteriospermia is suspected when there are more than one million peroxidase-positive white blood cells per milliliter of ejaculate (leukocytospermia). It is confirmed through a semen culture or polymerase chain reaction (PCR) to identify the pathogen. Antibiotic treatment may improve sperm quality and prevent testicular damage and complications, but its effects on natural conception are not clear (48). Furthermore, leukocytospermia is a sign of inflammation and may not be associated with a bacterial or viral process, hence its clinical significance in the ejaculate is controversial (49).

CHLAMYDIA

C. trachomatis, an intracellular gram-negative bacterium, causes asymptomatic infection of the genital tract in 85%–90% of cases. Symptoms of epididymo-orchitis and prostatitis include mucoid or watery urethral discharge and dysuria. Some but not all studies have demonstrated an association with male infertility and altered semen quality (45,50,51).

While some research suggests that *C. trachomatis* could affect sperm-egg penetration, impacting fertilization potential, others propose that its impact on male fertility might be related to transfer to a female partner and resulting inflammatory processes, anti-sperm antibody generation, or defective implantation. Overall, the association between *C. trachomatis* and male fertility remains complex and may vary depending on individual cases (45).

NEISSERIA

N. gonorrhoeae is a leading cause of genital infection in the tropics. It primarily spreads through sexual contact and can lead to asymptomatic colonization or inflammatory diseases like urethritis, orchitis, prostatitis, and epididymitis. These infections can manifest as mucopurulent urethral discharge, or infertility from testicular damage or ductal obstruction. The bacteria attach to spermatozoa using pili or direct contact, and their infection triggers an influx of inflammatory cells. While the exact causative role of *N. gonorrhoeae* in pathogenesis of male infertility remains unclear, studies have noted higher infection rates in men with infertility compared to those without fertility issues (52).

GENITAL UREAPLASMAS AND MYCOPLASMAS

Of the genital ureaplasmas and mycoplasmas, *Ureaplasma urealyticum,* and *Mycoplasma hominis* are potentially pathogenic and can contribute to both genital infections and male infertility (53,54). The prevalence of *U. urealyticum* ranges from 10 to 40%. Both *U. urealyticum* and *M. hominis* have been linked to prostatitis and epididymitis (45). The mechanism of infertility could be due to a reduction in ejaculate's oxidoreductive potential, making sperms more susceptible to peroxidative damage (55).

LEPROSY

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, primarily affecting the skin, peripheral nerves, mucosa of the upper respiratory tract, and eyes. The condition is prevalent in tropical countries, and according to World Health Organization (WHO) estimates, over 17 million patients received multidrug therapy (MDT) for leprosy in the past four decades. The lower temperature of the scrotal contents, between 27–30˚C, makes the testes prone to infection in those with the lepromatous form and during flares of erythema nodosum leprosum (type 2 reaction).

The testes can serve as a reservoir for leprosy bacilli, potentially leading to testicular atrophy through the mediation of inflammatory cytokines and endarteritis, ultimately resulting in fibrosis. Early symptoms include testicular pain or swelling. Hypogonadism can lead to decreased or absent libido (28%), followed by gynecomastia (16.3%). Smaller, softer, and less sensitive testes is a characteristic feature of leprosy. Ultrasonography demonstrates reduced testicular volume in 72% of affected males (56). Laboratory investigations reveal oligospermia or azoospermia, elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and low serum testosterone levels (57–59).

TUBERCULOSIS

Epidemiology

Male genital tuberculosis is found worldwide but is more common in regions with high tuberculosis prevalence, such as parts of Asia, Africa, and Latin America. Genitourinary involvement accounts for 20-40% of extrapulmonary forms. Isolated genital infection is uncommon and occurs in 5–30% of the cases of genitourinary infection (60). Clinical reports likely underestimate the actual prevalence of male genital tuberculosis as symptoms are often absent (61).

Mode of Infection

*Male genital tuberculosis typically originates from bacillaemia following primary infection of the lungs. Older studies suggest that the prostrate is often seeded by infected urine, with sub*sequent *canicular or lymphatic spread to the epididymis (62). Though current literature suggests that direct hematogenous spread may be the primary mode of initial genital infection, especially in miliary cases. Granulomas formed systematically during primary infection can harbor bacilli for long periods, and reactivation can lead to genital tuberculosis. Disease progression often involves adjacent sites through direct extension, with orchitis almost always occurring secondary to epididymal disease. Concurrent or sequential involvement of multiple genital sites is common (63).*

Clinical Features

Epididymis and prostate are the most commonly affected sites. Epididymitis is the most frequently reported form of male genital tuberculosis, characterized by gradual onset of swelling and pain. Acute infections are also observed. Spread to the testis can manifest as non-tender testicular mass, with coexisting enlarged, hard epididymis, beaded vas deferens, and sometimes scrotal edema. Oligospermia or azoospermia can occur from occlusion or granulomatous destruction of vas deferens or epididymis. Prostatic tuberculosis may present with dysuria, frequency, hematuria, and hemospermia. Physical examination may reveal firm enlargement, nodularity, or soft areas of necrosis (61,63).

Diagnosis and Treatment

Diagnosing male genital tuberculosis often requires a combination of clinical evaluation, imaging studies (such as ultrasound or magnetic resonance imaging), laboratory tests (including semen analysis, urine analysis, and tuberculosis-specific tests like PCR or culture), and sometimes biopsy of affected tissues. All patients with genital tuberculosis should be screened for pulmonary and renal lesions. Treatment typically involves conventional tuberculosis chemotherapy courses. In cases of infertility or complications, additional management strategies such as surgical interventions or assisted reproductive techniques may be considered. Early recognition and treatment are crucial in managing male genital tuberculosis and preventing complications such as infertility (64).

Other Mechanisms of Gonadal Dysfunction

Central nervous system tuberculosis, including tuberculomas involving the sellar region, can lead to hypogonadotropic hypogonadism (65). Pro-inflammatory cytokines, such as tissue necrosis

factor-α (TNFα), interferon-γ, and interleukin (IL)-6, have been implicated in the impaired production of gonadal androgens in cases with pulmonary tuberculosis. These cytokines can disrupt the normal functioning of Leydig cells, leading to reduced testosterone synthesis (66).

OTHER BACTERIAL INFECTIONS

Brucellar epididymo-orchitis is a rare infection affecting the testis and epididymis, occurring in approximately 2–14% of cases of brucellosis. Brucellosis is still prevalent in individuals dealing with livestock in developing countries and is reported to be hyper-endemic in Iran. Necrotizing orchitis, testicular abscess, infarction, atrophy, suppurative necrosis, azoospermia, and infertility can occur if diagnosis is delayed or management is inappropriate (67).

Several other bacteria, such as *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Streptococcus agalactiae, Gardnerella vaginalis, Treponema pallidum, Helicobacter pylori* have been linked to male infertility through different mechanisms (45). However, more research is needed to fully comprehend their roles, particularly in tropical regions where these bacterial infections are more prevalent.

Protozoa

Protozoan parasitic diseases are endemic in many tropical countries. Protozoan infections of the male genital tract are rare, and only a few species, such as *Trichomonas vaginalis*, *Trypanosoma species, Leishmania donovani, Entamoeba histolytica*, Acanthamoeba*, Toxoplasma gondii*, and *Plasmodium falciparum*, have been linked to pathogenesis of testicular damage (68).

TRICHOMONAS

T. vaginalis is a common sexually transmitted infection that can affect various parts of the male genital tract, including the urethra, prostate, and epididymis. Although uncommon, *T. vaginalis* can impact male fertility. Studies indicate a higher prevalence of *T. vaginalis* in infertile men compared to fertile individuals, and its presence in semen is linked to decreased sperm motility, normal morphology, and viability. In vitro studies confirm that T. vaginalis and its secretions can reduce sperm motility and fertilizing capacity (68,69).

TOXOPLASMOSIS

Congenital toxoplasmosis is characterized by meningoencephalitis with significant perivascular inflammation, particularly in the basal ganglia and periventricular regions. This condition likely affects important hypothalamic regulatory centers, resulting in hypothalamo-pituitary dysfunction. The clinical features of toxoplasmosis stem from both direct tissue destruction by the parasite and immunopathological changes mediated by inflammatory cytokines. Hypothalamic-pituitary dysfunction, precocious puberty, and central diabetes insipidus with hypogonadism have all been described in association with congenital toxoplasmosis (70–73). In immunocompromised individuals, such as individuals with AIDS, the male reproductive tract can rarely be affected, leading to conditions like epididymitis or orchitis. Although direct links to infertility aren't fully established, some studies suggest potential negative impacts on sperm health.

LEISHMANIASIS

Infections with Leishmania can lead to genital lesions and testicular amyloidosis, contributing to hypogonadism. Parasitism of the testes and reduced testicular size with fewer Sertoli and Leydig cells have been reported (74). Evidence of involvement of several endocrine organs- pituitary, adrenal, thyroid, and sex glands- via histopathologic studies have been documented in Visceral Leishmaniasis (75). However, abnormal endocrine function tests in some instances without clinical manifestations have been documented. Genital leishmaniasis lesions on the penis, mimicking a painless, slow-growing scabies-like ulcers, can occur uncommonly (76).

TRYPANOSOMIASIS

African trypanosomiasis, also known as sleeping sickness, is caused by the protozoan parasite *Trypanosoma brucei*, which is transmitted by the bite of a tsetse fly. In a study involving 31 Congolese men with confirmed trypanosomiasis, 70% experienced impotence, and 50% exhibited decreased testosterone levels (77). The gonadotrophins were found to be disproportionately normal, suggesting hypothalamic-pituitary involvement (78). The endocrine dysfunction observed in patients with trypanosomiasis may be secondary to inflammatory cytokines (79,80). However, further studies are required to confirm the hypothesis.

Chagas disease, caused by *Trypanosoma cruzi*, affects 6–7 million people worldwide, mainly in Latin America. It is primarily transmitted by triatomine bugs, with congenital and blood-transfusion transmission also reported. In its chronic phase, the disease commonly leads to cardiac, digestive, or neurological disorders. Early antiparasitic treatment can cure the acute phase, while treatment during the chronic phase can slow progression (81). Animal experiments demonstrated the presence of amastigote forms in seminiferous tubules of infected mice (82). Subsequent autopsy studies only revealed focal chronic phlebitis and mononuclear interstitial infiltration of the testis and failed to show any parasites (83). Early studies of testicular biopsies in chronic Chagas disease revealed arrested germ cell maturation and regressive alterations, worsening progressively from normospermia to azoospermia (84). Immune neuro-endocrine disturbance could possibly play a role in the pathogenesis (85).

OTHER PROTOZOAL INFECTIONS

Rare cases of scrotal and penile amebiasis have been described (86,87). Rare reports in the medical literature have mentioned cases where infections caused by *Plasmodium falciparum* or *Plasmodium vivax*, the parasites responsible for malaria, have led to testicular pain or hypogonadism (88,89).

Fungus

CANDIDA

Fungal epididymitis, caused by *Candida glabrata*, is uncommon but should be considered, especially in individuals with diabetes and a history of catheterization or antibiotic use. Rare cases with enlarged and tender hemiscrotum responding to fluconazole and surgical excision have been described (90). The risk of epididymitis in individuals with diabetes with *C. glabrata* and *C. albicans* increases with urinary tract instrumentation and prior antibiotic therapy. Diagnosis relies on recognizing fungi in histology or pus cultures, often indicating retrograde spread from urine. Fungal epididymo-orchitis can occur as an isolated entity or, more often, during disseminated infection (91).

As with any gonadal infection, fungal epididymo-orchitis can cause infertility because of gonadal destruction and resultant azoospermia. In addition to invading tissue, fungi can contribute to infertility by inducing anti-sperm effects and secreting mycotoxin. *C. guilliermondii* and *C. albicans* are able to inhibit sperm viability and motility in vitro. A proportion of infertile men and women have antibodies positive for *C. guilliermondii, the implications of which are unknown.* Restoration of fertility was achieved in some patients after the eradication of *C. guilliermondii* by ketoconazole (92).

OTHER FUNGAL INFECTIONS OF GONADS

Other fungi reported to infect testis and epididymis include blastomycosis, histoplasma, aspergillus, and cryptococcus (93–95). *Cryptococcus neoformans* can also cause hypospermia and teratospermia (96). The *fusarium* toxin zearalenone and its metabolite zearalenol bind as agonists to estrogen receptor-α and -β, causing hyperestrogenism-mediated decreases in testosterone and libido, azoospermia, and feminization in mammals. Whether such hyperestrogenic effects occur in humans with fusariosis is unclear (97).

Granulomatous epididymo-orchitis can also occur as a part of disseminated histoplasmosis in an immunocompromised state (94). Genital blastomycosis is described mostly as a part of disseminated disease. Majority present with unilateral or bilateral pain and swelling of the scrotum. Onset can be acute or insidious, with symptoms lasting from days to months. Bacterial infection on the other hand is typically unilateral and acute (93). Some fungal infections may remain asymptomatic and only get detected during autopsy.

PITUITARY FUNGAL INFECTIONS

Pituitary fungal infections or abscesses are extremely unusual and mostly found in immunocompromised states. (98). The mode of spread could be hematogenous, extension from adjacent structures like meninges, sphenoid sinus, cavernous sinus, and skull base, or iatrogenic during transsphenoidal procedures. Aspergillus is the most frequently reported fungal infection of the pituitary (99). Candida, *Pneumocystis jirovecii* in HIV/AIDS, and coccidia are also reported to infect the pituitary (100–102). Gonadotrophin and other pituitary hormone secretion can be affected, but such reports are very rare (103). Pituitary stalk compression due to fungal lesion can induce hyperprolactinemia (104).

Helminths

SCHISTOSOMIASIS

Schistosomiasis, caused by *Schistosoma haematobium*, *S mansoni,* and *S. japonicum,* represent a major tropical disease transmitted through contact with infested freshwater. *S. haematobium*, common in sub-Saharan Africa, infects around 112 million people and often affects the urinary tract, with potential extension to the genitalia. The infection can persist for decades and, if untreated, becomes chronic, with potential for causing complications (105). *S. manson, i* prevalent in the Caribbean, South America, and Africa, and *S. japonicum* in Southeast Asia are primarily associated with hepato-intestinal infection with very rare occurrence of genital disease. Genital involvement is primarily observed with *S. haematobium* (106).

Early symptoms include hemospermia, that results from mucosal ulceration caused by egg penetration into the seminal vesicle. Schistosoma eggs can become entrapped in the prostate, vas deferens, epididymis, or testes, and trigger immune reactions and granuloma formation. Clinical features include genital or ejaculatory pain, infertility, and abnormally enlarged organs from granulomatous infiltration, fibrosis, and calcifications (105–107). Diagnosis depends on identifying ova in semen or urine, but detecting chronic infection is challenging as ova might often be absent. Praziquantel (at 40 mg/kg) is the standard treatment for most forms of schistosomiasis (106).

S. mansoni infection has been associated with low normal testosterone and elevated estrogen levels in males, although hepatic dysfunction may play a role in these abnormalities (108).

FILARIASIS

Filariasis is a neglected tropical disease transmitted by mosquitos caused by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. Filariasis occurs in Africa, Asia, South America, the Caribbean, and the Pacific. Globally, it is estimated that 25 million men have hydrocele due to lymphatic filariasis, and over 15 million people are affected by lymphoedema (109). Initial infections are often asymptomatic, but chronic disease can damage the lymphatics of the spermatic cord. Common genital manifestations include recurrent scrotal pain and swelling, hydrocele, and epididymo-orchitis (110). Azoospermia and oligospermia are also described (111). The WHO's Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 2000 with a strategy focused on large-scale annual treatment in endemic areas to stop infection spread and provide essential care.

Ecdysteroids are compounds related to 20-hydroxyecdysone, the insect molting hormone, in *Loa Cystoids* and *Mansonella perstans* infections, the other form of filariasis. Microfilaremic males with these infections had low testosterone in 12%, and high gonadotrophins in 24%, and abnormal levels of both in 21%. Ecdysteroids were found in the serum of 90% of individuals with microfilaremia and in all urine samples, but their levels did not correlate with hormonal changes. A possible link between microfilaremia and endocrine disruptions, including hypogonadism, has been suggested, but the direct role of parasitic ecdysteroids remains unproven (112).

ENVIRONMENTAL CAUSES

Endocrine Disrupting Chemicals (EDCs)

DEFINITION AND CONTEXT

EDCs pose a significant and ubiquitous threat to global and tropical health. EDCs include both natural and synthetic chemicals widely dispersed in the environment. These chemicals can be ingested, inhaled, or absorbed through various media, including food, water, air, and consumer products, and can interfere with any aspect of hormone action. EDCs can bind to hormone receptors, such as estrogen and steroid receptors, disrupting development and reproductive function, among many other health impacts.

Common EDCs include bisphenol A (BPA), found in plastics and food containers, and phthalates, used to make plastics more flexible and present in products like cosmetics and toys. Polychlorinated biphenyls (PCBs), industrial chemicals in electrical equipment and paints, and dioxins, by-products of industrial processes and combustion, are also significant EDCs. Pesticides such as dichlorodiphenyltrichloroethane (DDT) and glyphosate, widely used in agriculture represent another major group of EDCs. For more details, please refer to the sections on EDC in Endotext (113).

EDCS IN TROPICS

Despite growing recognition of their impact, the full extent of their damage remains inadequately addressed due to insufficient evidence and lack of comprehensive testing (114). In tropical regions, extensive use of pesticides and industrial chemicals increases exposure to EDCs. For example, glyphosate, a commonly used herbicide, has been linked to endocrine disruption and adverse reproductive health outcomes (115). Similarly, heavy metals like lead and arsenic, prevalent in some tropical areas, cause significant endocrine-related health issues (116,117).

A review of data on prioritized EDCs (e.g., DDT, lindane, PCBs, etc.) reported elevated concentrations in the Indian environment and human population compared to the international context (118). A recent nationwide pilot study has reported the widespread occurrence of per- and polyfluoroalkyl substances (PFASs) and phthalates in humans from different locations across India, including those residing along the Indian Himalayas (119,120). Both DDT and pyrethroids used for malaria control in African countries have endocrine-disrupting potential (121).

EDCS AND MALE GONADAL DYSFUNCTION

Hypogonadism

EDCs act as anti-androgens, mimic estrogens, and inhibit steroidogenic enzymes, interfering with androgen production and function. Phthalate esters like di-(2-ethylhexyl) phthalate (DEHP) and BPA can reduce testosterone synthesis and disrupt gene expression related to hormone balance. DDT, PCBs, and their metabolites can also block hormone receptors, affecting estrogen and androgen signaling crucial for spermatogenesis and testicular development (122).

Infertility

EDCs are known to disrupt hormonal balance and have been linked to impaired sperm production, quality, and function. Factors such as type of EDCs, duration of exposure, and individual susceptibility play roles in their effects on reproductive health. EDCs impact sperm function by targeting testicular development and influencing the HPG axis, affecting estrogen and androgen receptors, influencing ROS production, inducing epigenetic modifications, and directly affecting spermatozoa and testicular tissue cells (123). Pesticides have been extensively studied for their effects on sperm parameters and DNA integrity. While some studies report reductions in sperm concentration and alteration in sperm morphology due to pesticide exposure, others show no significant impact (124). DDT, BPA, and phthalates are associated with decreased semen volume and sperm concentration, motility, and abnormal morphology (125). Increased urinary BPA level is associated with reduced number, motility, and sperm vitality, leading to male infertility (126). Continued research is needed to better understand the effect of EDCs on reproductive health.

Developmental Disorders

Testicular dysgenesis syndrome (TDS) is a condition linking poor semen quality, testicular cancer, undescended testes, and hypospadias. Experimental and epidemiological studies indicate that TDS stems from disturbances in embryonic programming and gonadal development during fetal stages. These disorders share a common pathway by which environmental chemicals and genetics result in abnormal development of the fetal testis (127,128). Though harmful effects on testicular development in animals have been demonstrated, the current evidence does not conclusively clarify the impact of EDCs on human male reproductive development (129).

Gynecomastia

Gynecomastia prevalence has increased over recent decades, partly attributable to exposure to EDCs. Higher plasma concentrations of DEHP and its major metabolite mono(2-ethylhexyl) phthalate (MEHP) in boys with gynecomastia have been demonstrated (130). Another study reported an outbreak of gynecomastia linked to the anti-androgenic delousing agent phenothrin (131). Additionally, essential oils like lavender and tea tree oil have been associated with gynecomastia. Components of these oils have estrogen receptor (ER) agonist activities (132). Occupational exposure to gasoline vapors and combustion products may play a role in the causation of male breast cancer (133).

Current literature indicates a possible link between EDC exposure and development of gynecomastia. Increasing rates of the condition indicate that environmental factors are important to disease etiology. The data from tropical countries is sparse, and epidemiological studies to evaluate the influence of EDCs on diseases of the male reproductive tract, including gynecomastia, are necessary (134).

Testicular Cancers

Few studies have explored the correlation between EDC exposure and testicular cancer, and even less so in tropical countries. The results are inconsistent, with some but not all studies showing an association between pesticide exposure and testicular cancer. Dichlorodiphenyldichloroethylene (DDE), chlordane, and PCB exposure have been linked to testicular cancer (135–137)*. These mixed findings highlight the need for more focused research on EDCs and testicular cancer, especially in tropical countries with high exposure to pesticides (129).*

PREVENTION

Reducing exposure to EDCs through lifestyle changes, environmental regulations, and occupational safety measures can help mitigate their potential impact on male gonadal disorders. Additionally, further research is needed to understand better the

mechanisms by which EDCs affect male reproductive health and to develop strategies for prevention and treatment.

Temperature

Heat exposure is a significant factor in male infertility, affecting sperm production and quality. Global warming and episodes of heat stress, occupational exposure, and lifestyle factors can be responsible for increasing scrotal temperature (138).

The testes are located outside the body in the scrotum to maintain a temperature of 2-4°C below core body temperature, optimal for spermatogenesis. A recent meta-analysis concluded that high ambient temperatures in tropical climates can negatively affect sperm quality, including decreased semen volume, sperm count, sperm concentration, motility, and normal morphology (139). This may be especially relevant for men working in high-temperature environments (e.g., welders, bakers, and drivers) or exposed to prolonged heat (e.g., saunas and hot tubs) (140,141). Studies have shown that even temporary exposure to high temperatures can significantly impact sperm parameters (142).

Similarly, febrile illness, prolonged sitting during work or truck driving, tight-fitting underwear, and laptop use with increased heat to the testes have been proposed to affect male fertility adversely (146,147). Studies in men have shown that small increases in testicular temperature accelerate germ cell loss through apoptosis. The data to support these associations are, however, inconsistent (143).

Trauma

Traumatic injuries to the genitalia, common in tropical regions due to occupational hazards, accidents, and interpersonal violence, can cause direct damage to the testes. Severe trauma can result in testicular rupture or vascular compromise, leading to hypogonadism due to impaired blood supply or loss of testicular tissue. Radical prostatectomy or other overt genital tract trauma is a physical cause of a sudden loss of male sexual function (144).

Males who experience a traumatic pelvic fracture or genital trauma may also have psychogenic erectile dysfunction (145). Post-traumatic hypopituitarism is responsible for about 7.2% of all causes of hypopituitarism and can develop after road traffic accidents, sports injuries, blast injuries, and other trauma. Peripherally placed somatotrophs and gonadotrophs are first affected by ischemic damage, while centrally located corticotrophs and thyrotrophs are subsequently involved (146).

Snake Envenomation

Snakebite envenoming is a medical emergency prevalent in tropical regions of Asia, Africa, and Latin America. Venom toxins can cause severe local damage and multi-organ dysfunction, impacting the neurological, hematological, and vascular systems. Endocrine disorders, though less frequently reported, can occur, with anterior pituitary insufficiency being the most common. This is typically found following bite from Russell's viper (*Daboia russelii* and *D. siamensis*). The presentation of hypopituitarism can be acute or delayed (147).

Pathophysiology is similar to Sheehan's syndrome and results from hemorrhagic infarction in an engorged gland, made susceptible by venom toxin. Kidney injury and disseminated intravascular coagulation (DIC) are predictors of the development of hypopituitarism. Pituitary imaging may show a spectrum of findings from completely normal to an empty sella (148). Hypogonadotropic hypogonadism may present as erectile dysfunction. Delayed puberty has been reported in males (149). The interested reader may refer to the Endotext chapter "Snakebite Envenomation and Endocrine Dysfunction" for further details (150).

CHRONIC SYSTEMIC DISEASES

The prevalence of diabetes and metabolic syndrome in tropical countries has been rising significantly in recent years (151). Type 2 diabetes in tropical countries shows distinctive features such as onset at younger ages and lower levels of obesity compared to Caucasians (152). Functional hypogonadotropic hypogonadism (FHH) has emerged as an important complication of diabetes, obesity, and metabolic syndrome across the globe. FHH results from impaired HPG axis function in the absence of an organic cause, leading to decreased testosterone levels, low or normal gonadotropin levels, and subfertility or infertility (153).

In a study from China, 26% of men with diabetes had hypogonadotropic hypogonadism and its presence correlated with BMI (154). Lifestyle changes and weight loss can improve insulin sensitivity and restore normal HPG axis function. Testosterone replacement therapy (TRT) may be indicated in some men, although it should be used cautiously and monitored for potential side effects. Optimizing diabetes management and treating obesity are crucial and may improve hypogonadal status (155).

FHH can coexist in individuals with malnutrition and chronic energy deficit, malignancy, chronic opioid exposure, chronic kidney disease, chronic liver disease, rheumatoid arthritis, chronic obstructive pulmonary disease, depression, and other psychiatric disorders. Systemic diseases can downregulate GnRH secretion by the hypothalamus and lead to secondary hypogonadism. This is thought to be at least partly due to the direct effects of elevated inflammatory cytokines, such as IL-1, IL-6, and TNFα (156). Sickle cell disease can cause vaso-occlusive crises and can induce both primary and/or secondary hypogonadism (157,158).

HORMONE ABUSE AND RECREATIONAL DRUG-RELATED HYPOGONADISM

The misuse of anabolic steroids and other hormones for performance enhancement is described among athletes and bodybuilders. Chronic abuse of these hormones can disrupt normal endocrine function, leading to hypogonadism, testicular atrophy, gynecomastia, and infertility (159).

Impairment of sperm characteristics, including alteration in total number, concentration, motility, normal morphology, prostate gland hyperplasia, and hypertrophy are recognized (160). Androgen abuse can lead to hypogonadotropic hypogonadism also, as it negatively impacts the HPG axis (161). The adverse effects may reverse over 6-18 months after discontinuation, although testicular volume and SHBG levels may not fully recover. There can be persistent quantitative and qualitative sperm changes 8–30 weeks following withdrawal of anabolic steroids (162).

The use of recreational drugs, including cannabis and opioids, has been linked to negative effects on male reproductive health. Studies have shown that these substances can decrease sperm quality, increase sperm DNA fragmentation, and lower fertility in men (163,164). Heavy use of cannabis (marijuana) has been associated with reduced semen quality, potentially due to disruption of the endocannabinoid system (ECS) in the male reproductive tract by exogenous cannabinoids. The ECS is crucial in regulating various physiological processes, including reproduction. Exogenous cannabinoids from marijuana may interfere with the normal functioning of the ECS, leading to negative effects on semen quality (165). Additionally, opioids have been found to induce secondary hypogonadism by suppressing the activity of kisspeptin-neurokinin B-dynorphin neurons. They may directly affect the testes, through endogenous opioid receptors present there (166).

CHALLENGES TO MANAGEMENT IN TROPICS

Male gonadal disorders in the tropics face unique challenges due to a combination of healthcare, socioeconomic, and environmental factors. These include inadequate healthcare infrastructure, especially in rural areas, economic constraints with high costs of diagnosis and treatment, and limited awareness among the population and healthcare

providers, leading to underdiagnosis. Further, the cultural stigmas and beliefs around sexual health deterring men from seeking help, deficiencies in training of primary care providers to diagnose and manage gonadal disorders, complications from the tropical climate, and the high burden of infectious diseases add to the problem. There is also a scarcity of treatment guidelines tailored to regional needs and inadequate research and evidence to guide therapy.

These challenges necessitate comprehensive strategies that address healthcare infrastructure improvements, affordability, awareness campaigns, cultural sensitivity training, enhanced medical education, research into tropical-specific treatments, and telemedicine utilization for remote areas. All require collaboration among various stakeholders to improve hypogonadism management in tropical regions.

CONCLUSION

Male hypogonadism in the tropics is caused by a combination of factors, including high prevalence of infectious diseases, exposure to environmental toxins, chronic heat stress, systemic disorders including diabetes and obesity, nutritional deficiencies, and substance abuse. Significant challenges exist due to limited healthcare access, high costs, low awareness, cultural stigma, inadequate training for primary care providers, environmental factors, and a lack of region-specific treatment guidelines. These issues lead to underdiagnosis and poor management of male hypogonadism in the tropics. Improving healthcare infrastructure, raising awareness, enhancing provider training, and developing tailored treatment guidelines are essential to address these challenges effectively.

REFERENCES

1. O'Donnell L, Stanton P, de Kretser DM. Endocrinology of the Male Reproductive System and Spermatogenesis. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279031/
2. Thirumalai A, Anawalt BD. Epidemiology of Male Hypogonadism. Endocrinol Metab Clin North Am. 2022 Mar;51(1):1–27.
3. Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol. 2015 Apr 26;13:37.
4. Richens J. Genital manifestations of tropical diseases. Sex Transm Infect. 2004 Feb;80(1):12–7.
5. Liu W, Han R, Wu H, Han D. Viral threat to male fertility. Andrologia. 2018 Dec;50(11):e13140.
6. Pellati D, Mylonakis I, Bertoloni G, Fiore C, Andrisani A, Ambrosini G, et al. Genital tract infections and infertility. Eur J Obstet Gynecol Reprod Biol. 2008 Sep;140(1):3–11.
7. WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Male [Internet]. [cited 2024 May 29]. Available from: https://www.who.int/publications-detail-redirect/9780521774741
8. Zhao S, Zhu W, Xue S, Han D. Testicular defense systems: immune privilege and innate immunity. Cell Mol Immunol. 2014 Sep;11(5):428–37.
9. Filippini A, Riccioli A, Padula F, Lauretti P, D'Alessio A, De Cesaris P, et al. Immunology and immunopathology of the male genital tract: Control and impairment of immune privilege in the testis and in semen. Human Reproduction Update. 2001 Sep 1;7(5):444–9.
10. Beard CM, Benson RC, Kelalis PP, Elveback LR, Kurland LT. The incidence and outcome of mumps orchitis in Rochester, Minnesota, 1935 to 1974. Mayo Clin Proc. 1977 Jan;52(1):3–7.
11. Adamopoulos DA, Lawrence DM, Vassilopoulos P, Contoyiannis PA, Swyer GI. Pituitary-testicular interrelationships in mumps orchitis and other viral infections. Br Med J. 1978 May 6;1(6121):1177–80.
12. Wu H, Wang F, Tang D, Han D. Mumps Orchitis: Clinical Aspects and Mechanisms. Front Immunol. 2021 Mar 18;12:582946.
13. De Vincentis S, Rochira V. Update on acquired hypogonadism in men living with HIV: pathogenesis, clinic, and treatment. Front Endocrinol (Lausanne). 2023 Jun 26;14:1201696.
14. Santi D, Spaggiari G, Vena W, Pizzocaro A, Maggi M, Rochira V, et al. The Prevalence of Hypogonadism and the Effectiveness of Androgen Administration on Body

Composition in HIV-Infected Men: A Meta-Analysis. Cells. 2021 Aug 12;10(8):2067.
15. Lachâtre M, Pasquet A, Ajana F, Soudan B, Quertainmont Y, Lion G, et al. Hypogonadism: a neglected comorbidity in young and middle-aged HIV-positive men on effective combination antiretroviral therapy. AIDS. 2022 Jul 1;36(8):1061.
16. Iddi S, Dika H, Kidenya BR, Kalluvya S. Serum gonadal hormones levels and hypogonadism in ART naïve newly diagnosed HIV infected adult males in Mwanza, Tanzania. BMC Endocr Disord. 2024 Apr 23;24:50.
17. Wong WY, Zielhuis GA, Thomas CMG, Merkus HMWM, Steegers-Theunissen RPM. New evidence of the influence of exogenous and endogenous factors on sperm count in man. Eur J Obstet Gynecol Reprod Biol. 2003 Sep 10;110(1):49–54.
18. Yuan J. Genitourinary Presentation of Tuberculosis. Rev Urol. 2015;17(2):102–5.
19. Rochira V, Guaraldi G. Hypogonadism in the HIV-infected man. Endocrinol Metab Clin North Am. 2014 Sep;43(3):709–30.
20. Collazos J, Ibarra S, Martínez E, Mayo J. Serum prolactin concentrations in patients infected with human immunodeficiency virus. HIV Clin Trials. 2002;3(2):133–8.
21. Aggarwal J, Taneja RS, Gupta PK, Wali M, Chitkara A, Jamal A. Sex hormone Profile in Human Immunodeficiency Virus-Infected Men and It's Correlation with CD4 Cell Counts. Indian J Endocrinol Metab. 2018;22(3):328–34.
22. Biglia A, Blanco JL, Martínez E, Domingo P, Casamitjana R, Sambeat M, et al. Gynecomastia among HIV-infected patients is associated with hypogonadism: a case-control study. Clin Infect Dis. 2004 Nov 15;39(10):1514–9.
23. Nuttall FQ, Warrier RS, Gannon MC. Gynecomastia and drugs: a critical evaluation of the literature. Eur J Clin Pharmacol. 2015 May;71(5):569–78.
24. Le Tortorec A, Satie AP, Denis H, Rioux-Leclercq N, Havard L, Ruffault A, et al. Human prostate supports more efficient replication of HIV-1 R5 than X4 strains ex vivo. Retrovirology. 2008 Dec 31;5:119.
25. De Paepe ME, Waxman M. Testicular atrophy in AIDS: a study of 57 autopsy cases. Hum Pathol. 1989 Mar;20(3):210–4.
26. Salehian B, Jacobson D, Swerdloff RS, Grafe MR, Sinha-Hikim I, McCutchan JA. Testicular pathologic changes and the pituitary-testicular axis during human immunodeficiency virus infection. Endocr Pract. 1999;5(1):1–9.
27. Winters SJ. Laboratory Assessment of Testicular Function. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279145/
28. Hayes F, Dwyer A, Pitteloud N. Hypogonadotropic Hypogonadism (HH) and Gonadotropin Therapy. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279078/
29. Shindel AW, Lue TF. Medical and Surgical Therapy of Erectile Dysfunction. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK278925/
30. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103(5):1715–44.
31. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016 Jul;29(3):487–524.
32. Joguet G, Mansuy JM, Matusali G, Hamdi S, Walschaerts M, Pavili L, et al. Effect of acute Zika virus infection on sperm and virus clearance in body fluids: a prospective observational study. Lancet Infect Dis. 2017 Nov;17(11):1200–8.
33. Matusali G, Houzet L, Satie AP, Mahé D, Aubry F, Couderc T, et al. Zika virus infects human testicular tissue and germ cells. J Clin Invest. 2018 Oct 1;128(10):4697–710.
34. Almeida R das N, Braz-de-Melo HA, Santos I de O, Corrêa R, Kobinger GP, Magalhaes KG. The Cellular Impact of the ZIKA Virus on Male Reproductive Tract Immunology and Physiology. Cells. 2020 Apr 18;9(4):1006.
35. Depuydt CE, Donders GGG, Verstraete L, Vanden Broeck D, Beert JFA, Salembier G, et al. Infectious human papillomavirus virions in semen reduce clinical pregnancy rates in women undergoing intrauterine insemination. Fertil Steril. 2019 Jun;111(6):1135–44.
36. Lyu Z, Feng X, Li N, Zhao W, Wei L, Chen Y, et al. Human papillomavirus in semen and the risk for male infertility: a systematic review and meta-analysis. BMC Infect Dis. 2017 Nov 9;17(1):714.
37. Yas A, Mansouri Ghezelhesari E, Iranifard E, Taghipour A, Mahmoudinia M, Latifnejad Roudsari R. The Impact of Herpes Simplex Virus on Semen Parameters in Men with Idiopathic Infertility: A Systematic Review. Int J Fertil Steril. 2023;17(3):152–9.
38. Huang J, Zhong Y, Fang X, Xie Q, Kang X, Wu R, et al. Hepatitis B virus s protein enhances sperm apoptosis and reduces sperm fertilizing capacity in vitro. PLoS One. 2013;8(7):e68688.
39. Wang Z, Liu W, Zhang M, Wang M, Wu H, Lu M. Effect of Hepatitis B Virus Infection on Sperm Quality and Outcomes of Assisted Reproductive Techniques in Infertile Males. Front Med (Lausanne). 2021;8:744350.
40. Brown TT. Hypogonadism in Men With Hepatitis C: What Is a Clinician to Do? Clin Infect Dis. 2019 Aug 1;69(4):577–9.

41. Dabizzi S, Maggi M, Torcia MG. Update on known and emergent viruses affecting human male genital tract and fertility. Basic Clin Androl. 2024 Mar 14;34:6.
42. Kalra S, Bhattacharya S, Kalhan A. Testosterone in COVID-19 – Foe, Friend or Fatal Victim? Eur Endocrinol. 2020 Oct;16(2):88–91.
43. Nassau DE, Best JC, Kresch E, Gonzalez DC, Khodamoradi K, Ramasamy R. Impact of the SARS-CoV-2 virus on male reproductive health. BJU Int. 2022 Feb;129(2):143–50.
44. Can Balcı MB, Can Çilesiz N. Investigation of the relationship between COVID-19 disease and semen parameters in idiopathic male infertility patients. Eur Rev Med Pharmacol Sci. 2023 Jan;27(1):378–83.
45. Farsimadan M, Motamedifar M. Bacterial infection of the male reproductive system causing infertility. J Reprod Immunol. 2020 Nov;142:103183.
46. Das S, Roychoudhury S, Dey A, Jha NK, Kumar D, Roychoudhury S, et al. Bacteriospermia and Male Infertility: Role of Oxidative Stress. Adv Exp Med Biol. 2022;1358:141–63.
47. Gimenes F, Souza RP, Bento JC, Teixeira JJV, Maria-Engler SS, Bonini MG, et al. Male infertility: a public health issue caused by sexually transmitted pathogens. Nat Rev Urol. 2014 Dec;11(12):672–87.
48. Weidner W, Ludwig M, Miller J. Therapy in male accessory gland infection--what is fact, what is fiction? Andrologia. 1998;30 Suppl 1:87–90.
49. Trum JW, Mol BW, Pannekoek Y, Spanjaard L, Wertheim P, Bleker OP, et al. Value of detecting leukocytospermia in the diagnosis of genital tract infection in subfertile men. Fertil Steril. 1998 Aug;70(2):315–9.
50. Boeri L, Pederzoli F, Capogrosso P, Abbate C, Alfano M, Mancini N, et al. Semen infections in men with primary infertility in the real-life setting. Fertil Steril. 2020 Jun;113(6):1174–82.
51. Puerta Suarez J, Sanchez LR, Salazar FC, Saka HA, Molina R, Tissera A, et al. Chlamydia trachomatis neither exerts deleterious effects on spermatozoa nor impairs male fertility. Sci Rep. 2017 Apr 25;7:1126.
52. Chemaitelly H, Majed A, Abu-Hijleh F, Blondeel K, Matsaseng TC, Kiarie J, et al. Global epidemiology of Neisseria gonorrhoeae in infertile populations: systematic review, meta-analysis and metaregression. Sex Transm Infect. 2021 Mar;97(2):157–69.
53. Huang C, Zhu HL, Xu KR, Wang SY, Fan LQ, Zhu WB. Mycoplasma and ureaplasma infection and male infertility: a systematic review and meta-analysis. Andrology. 2015 Sep;3(5):809–16.
54. Cheng C, Chen X, Song Y, Wang S, Pan Y, Niu S, et al. Genital mycoplasma infection: a systematic review and meta-analysis. Reprod Health. 2023 Sep 12;20(1):136.
55. Fraczek M, Szumala-Kakol A, Jedrzejczak P, Kamieniczna M, Kurpisz M. Bacteria trigger oxygen radical release and sperm lipid peroxidation in in vitro model of semen inflammation. Fertil Steril. 2007 Oct;88(4 Suppl):1076–85.
56. Mohta A, Agrawal A, Sharma P, Singh A, Garg S, Kushwaha RK, et al. Endocrinological Testicular Dysfunction in Patients with Lepromatous Leprosy and the Impact of Disease on Patient's Quality of Life. Indian Dermatol Online J. 2020;11(6):959–64.
57. Gunawan H, Achdiat PA, Rahardjo RM, Hindritiani R, Suwarsa O. Frequent testicular involvement in multibacillary leprosy. Int J Infect Dis. 2020 Jan;90:60–4.
58. Aggrawal K, Madhu SV, Aggrawal K, Kannan AT. Hypogonadism in male Leprosy patients--a study from rural Uttar pradesh. J Commun Dis. 2005 Sep;37(3):219–25.
59. Morley JE, Distiller LA, Sagel J, Kok SH, Kay G, Carr P, et al. Hormonal changes associated with testicular atrophy and gynaecomastia in patients with leprosy. Clin Endocrinol (Oxf). 1977 Apr;6(4):299–303.
60. Figueiredo AA, Lucon AM. Urogenital tuberculosis: update and review of 8961 cases from the world literature. Rev Urol. 2008;10(3):207–17.
61. Jacob JT, Nguyen TML, Ray SM. Male genital tuberculosis. Lancet Infect Dis. 2008 May;8(5):335–42.
62. Gorse GJ, Belshe RB. Male genital tuberculosis: a review of the literature with instructive case reports. Rev Infect Dis. 1985;7(4):511–24.
63. Muneer A, Macrae B, Krishnamoorthy S, Zumla A. Urogenital tuberculosis — epidemiology, pathogenesis and clinical features. Nat Rev Urol. 2019 Oct;16(10):573–98.
64. Kulchavenya E. Best practice in the diagnosis and management of urogenital tuberculosis. Ther Adv Urol. 2013 Jun;5(3):143–51.
65. Genkil JS, Ahsun S, Mohan N, Anastasopoulou C. FRI330 A Rare Case Of Hypogonadotropic Hypogonadism In A Patient With Disseminated Tberculosis And Tuberculoma Involving Tuberculum Sellae. J Endocr Soc. 2023 Oct 5;7(Suppl 1):bvad114.1265.
66. Bini EI, D'Attilio L, Marquina-Castillo B, Mata-Espinosa D, Díaz A, Marquez-Velasco R, et al. The implication of pro-inflammatory cytokines in the impaired production of gonadal androgens by patients with pulmonary tuberculosis. Tuberculosis (Edinb). 2015 Dec;95(6):701–6.
67. Khodadadi J, Dodangeh M, Nasiri M. Brucellar epididymo-orchitis: Symptoms, diagnosis, treatment and follow-up of 50 patients in Iran. IDCases [Internet]. 2023 [cited 2024 May 14];32. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10020095/
68. Martínez-García F, Regadera J, Mayer R, Sanchez S, Nistal M. Protozoan infections in the male genital tract. J Urol. 1996 Aug;156(2 Pt 1):340–9.
69. Lloyd GL, Case JR, De Frias D, Brannigan RE. Trichomonas vaginalis orchitis with associated severe oligoasthenoteratospermia and hypogonadism. J Urol. 2003 Sep;170(3):924.
70. Setian N, Andrade RSF, Kuperman H, Manna TD, Dichtchekenian V, Damiani D. Precocious puberty: an

endocrine manifestation in congenital toxoplasmosis. J Pediatr Endocrinol Metab. 2002;15(9):1487–90.
71. Massa G, Vanderschueren-Lodeweyckx M, Van Vliet G, Craen M, de Zegher F, Eggermont E. Hypothalamo-pituitary dysfunction in congenital toxoplasmosis. Eur J Pediatr. 1989 Aug;148(8):742–4.
72. Bruhl HH, Bahn RC, Hayles AB. Sexual precocity associated with congenital toxoplasmosis. Proc Staff Meet Mayo Clin. 1958 Dec 24;33(26):682–6.
73. Oygür N, Yilmaz G, Ozkaynak C, Güven AG. Central diabetes insipitus in a patient with congenital toxoplasmosis. Am J Perinatol. 1998 Mar;15(3):191–2.
74. Shiadeh MN, Niyyati M, Fallahi S, Rostami A. Human parasitic protozoan infection to infertility: a systematic review. Parasitol Res. 2016 Feb;115(2):469–77.
75. Pace D. Leishmaniasis. J Infect. 2014 Nov;69 Suppl 1:S10-18.
76. Castro Coto A, Hidalgo Hidalgo H, Solano Aguilar E, Coto Chacón F. [Leishmaniasis of the genital organs]. Med Cutan Ibero Lat Am. 1987;15(2):145–50.
77. Boersma A, Noireau F, Hublart M, Boutignon F, Lemesre JL, Racadot A, et al. Gonadotropic axis and Trypanosoma brucei gambiense infection. Ann Soc Belg Med Trop. 1989 Jun;69(2):127–35.
78. Hublart M, Lagouche L, Racadot A, Boersma A, Degand P, Noireau F, et al. [Endocrine function and African trypanosomiasis. Evaluation of 79 cases]. Bull Soc Pathol Exot Filiales. 1988;81(3 Pt 2):468–76.
79. Reincke M, Allolio B, Petzke F, Heppner C, Mbulamberi D, Vollmer D, et al. Thyroid dysfunction in African trypanosomiasis: a possible role for inflammatory cytokines. Clin Endocrinol (Oxf). 1993 Oct;39(4):455–61.
80. Petzke F, Heppner C, Mbulamberi D, Winkelmann W, Chrousos GP, Allolio B, et al. Hypogonadism in Rhodesian sleeping sickness: evidence for acute and chronic dysfunction of the hypothalamic-pituitary-gonadal axis. Fertil Steril. 1996 Jan;65(1):68–75.
81. Lidani KCF, Andrade FA, Bavia L, Damasceno FS, Beltrame MH, Messias-Reason IJ, et al. Chagas Disease: From Discovery to a Worldwide Health Problem. Front Public Health. 2019 Jul 2;7:166.
82. Carvalho TL, Ribeiro RD, Lopes RA. The male reproductive organs in experimental Chagas' disease. I. Morphometric study of the vas deferens in the acute phase of the disease. Exp Pathol. 1991;41(4):203–14.
83. Rocha A, Miguel OF, Barbosa HM, Candelori I, da Silva AM, Lopes ER. [The pampiniform plexus in the chronic phase of human Chagas disease: histologic assessment]. Rev Soc Bras Med Trop. 2000;33(5):413–6.
84. Lamano Carvalho TL, Ferreira AL, Sahão MA. [Changes in the human testis in Chagas' disease. I. Evaluation of the kinetics of the spermatogenesis]. Rev Inst Med Trop Sao Paulo. 1982;24(4):205–13.
85. González FB, Villar SR, Pacini MF, Bottasso OA, Pérez AR. Immune-neuroendocrine and metabolic disorders in human and experimental *T. cruzi* infection: New clues for understanding Chagas disease pathology. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2020 Mar 1;1866(3):165642.
86. Prasetyo RH. Scrotal abscess, a rare case of extra intestinal amoebiasis. Trop Biomed. 2015 Sep;32(3):494–6.
87. Abdolrasouli A, de Vries HJC, Hemmati Y, Roushan A, Hart J, Waugh MA. Sexually transmitted penile amoebiasis in Iran: a case series. Sex Transm Infect. 2012 Dec;88(8):585–8.
88. Virmani SK. Falciparum malaria presenting as testicular pain and swelling--a rejoinder. J Assoc Physicians India. 1988 Apr;36(4):295.
89. Muehlenbein MP, Alger J, Cogswell F, James M, Krogstad D. The reproductive endocrine response to Plasmodium vivax infection in Hondurans. Am J Trop Med Hyg. 2005 Jul;73(1):178–87.
90. Giannopoulos A, Giamarellos-Bourboulis EJ, Adamakis I, Georgopoulou I, Petrikkos G, Katsilambros N. Epididymitis Caused by Candida glabrata: A novel infection in diabetic patients? Diabetes Care. 2001 Nov 1;24(11):2003–4.
91. Jenkin GA, Choo M, Hosking P, Johnson PDR. Candidal Epididymo-Orchitis: Case Report and Review. Clinical Infectious Diseases. 1998 Apr 1;26(4):942–5.
92. Nagy B, Sutka P. Demonstration of antibodies against Candida guilliermondii var. guilliermondii in asymptomatic infertile men. Mycoses. 1992;35(9–10):247–50.
93. Eickenberg H-U null, Amin M, Lich R. Blastomycosis of the genitourinary tract. J Urol. 1975 May;113(5):650–2.
94. Tichindelean C, East JW, Sarria JC. Disseminated histoplasmosis presenting as granulomatous epididymo-orchitis. Am J Med Sci. 2009 Sep;338(3):238–40.
95. Staib F, Seibold M, L'age M, Heise W, Skörde J, Grosse G, et al. Cryptococcus neoformans in the seminal fluid of an AIDS patient. A contribution to the clinical course of cryptococcosis. Mycoses. 1989 Apr;32(4):171–80.
96. Staib F Seibold M L'age M et al. Cryptococcus neoformans in the seminal fluid of an AIDS patient: a contribution to the clinical course of cryptococcosis. Mycoses. 1989; 32: 171-180.
97. Zinedine A, Soriano JM, Moltó JC, Mañes J. Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: an oestrogenic mycotoxin. Food Chem Toxicol. 2007 Jan;45(1):1–18.
98. Pekic S, Miljic D, Popovic V. Infections of the Hypothalamic-Pituitary Region. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2021 Mar 12]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532083/
99. Moore LA, Erstine EM, Prayson RA. Pituitary aspergillus infection. J Clin Neurosci. 2016 Jul;29:178–80.
100. Strickland BA, Pham M, Bakhsheshian J, Carmichael J, Weiss M, Zada G. Endoscopic Endonasal Transsphenoidal

Drainage of a Spontaneous Candida glabrata Pituitary Abscess. World Neurosurg. 2018 Jan;109:467–70.
101. Sano T, Kovacs K, Scheithauer BW, Rosenblum MK, Petito CK, Greco CM. Pituitary pathology in acquired immunodeficiency syndrome. Arch Pathol Lab Med. 1989 Sep;113(9):1066–70.
102. Scanarini M, Rotilio A, Rigobello L, Pomes A, Parenti A, Alessio L. Primary intrasellar coccidioidomycosis simulating a pituitary adenoma. Neurosurgery. 1991 May;28(5):748–51.
103. Stalldecker G, Molina HA, Antelo N, Arakaki T, Sica RE, Basso A. [Hypopituitarism caused by colonic carcinoma metastasis associated with hypophysial aspergillosis]. Medicina (B Aires). 1994;54(3):248–52.
104. Ouyang T, Zhang N, Wang L, Jiao J, Zhao Y, Li Z, et al. Primary Aspergillus sellar abscess simulating pituitary tumor in immunocompetent patient. J Craniofac Surg. 2015 Mar;26(2):e86-88.
105. Roure S, Vallès X, Pérez-Quílez O, López-Muñoz I, Chamorro A, Abad E, et al. Male genitourinary schistosomiasis-related symptoms among long-term Western African migrants in Spain: a prospective population-based screening study. Infectious Diseases of Poverty. 2024 Mar 7;13(1):23.
106. Kayuni S, Lampiao F, Makaula P, Juziwelo L, Lacourse EJ, Reinhard-Rupp J, et al. A systematic review with epidemiological update of male genital schistosomiasis (MGS): A call for integrated case management across the health system in sub-Saharan Africa. Parasite Epidemiol Control. 2018 Nov 23;4:e00077.
107. Kini S, Dayoub N, Raja A, Pickering S, Thong J. Schistosomiasis-induced male infertility. Case Rep. 2009;2009:bcr0120091481.
108. Saad AH, Abdelbaky A, Osman AM, Abdallah KF, Salem D. Possible role of Schistosoma mansoni infection in male hypogonadism. J. Egypt. Soc. Parasitol. 1999;29(2):307–323.
109. Panda DK, Mohapatra DP. Bancroftian filariasis associated with male sterility. BMJ Case Rep. 2018;2018:bcr-2017-223236.
110. Guiton R, Drevet JR. Viruses, bacteria and parasites: infection of the male genital tract and fertility. Basic Clin Androl. 2023 Jul 20;33:19.
111. Ekwere PD. Filarial orchitis: a cause of male infertility in the tropics--case report from Nigeria. Cent Afr J Med. 1989 Aug;35(8):456–60.
112. Lansoud-Soukate J, Dupont A, De Reggi ML, Roelants GE, Capron A. Hypogonadism and ecdysteroid production in Loa loa and Mansonella perstans filariasis. Acta Trop. 1989 Jul;46(4):249–56.
113. Anne B, Raphael R. Endocrine Disruptor Chemicals. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 23]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK569327/
114. Vandenberg LN. Toxicity testing and endocrine disrupting chemicals. Adv Pharmacol. 2021;92:35–71.
115. de Araújo-Ramos AT, Passoni MT, Romano MA, Romano RM, Martino-Andrade AJ. Controversies on Endocrine and Reproductive Effects of Glyphosate and Glyphosate-Based Herbicides: A Mini-Review. Front Endocrinol [Internet]. 2021 Mar 15 [cited 2024 May 25];12. Available from: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2021.627210/full
116. Doumouchtsis KK, Doumouchtsis SK, Doumouchtsis EK, Perrea DN. The effect of lead intoxication on endocrine functions. J Endocrinol Invest. 2009 Feb 1;32(2):175–83.
117. Sun H, Xiang P, Luo J, Hong H, Lin H, Li HB, et al. Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: A review. Environment International. 2016 Oct 1;95:61–8.
118. Sharma BM, Bharat GK, Tayal S, et al. The legal framework to manage chemical pollution in India and the lesson from the persistent organic pollutants (POPs) Sci Total Environ. 2014;490:733–747.
119. Babu-Rajendran R, Preethi G, Poopal RK, et al. GC–MS determination of phthalate esters in human urine: a potential biomarker for phthalate bio-monitoring. J Chromatogr B. 2018;1079:15–24.
120. Mukherjee Das A, Gogia A, Garg M, et al. Urinary concentration of endocrine-disrupting phthalates and breast cancer risk in Indian women: a case-control study with a focus on mutations in phthalate-responsive genes. Cancer Epidemiol. 2022;79:102188. doi: 10.1016/j.canep.2022.102188.
121. Eskenazi B, An S, Rauch SA, Coker ES, Maphula A, Obida M, et al. Prenatal Exposure to DDT and Pyrethroids for Malaria Control and Child Neurodevelopment: The VHEMBE Cohort, South Africa. Environmental Health Perspectives [Internet]. 2018 Apr [cited 2024 May 25];126(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6071803/
122. Jeng HA. Exposure to Endocrine Disrupting Chemicals and Male Reproductive Health. Front Public Health. 2014 Jun 5;2:55.
123. Sharma A, Mollier J, Brocklesby RWK, Caves C, Jayasena CN, Minhas S. Endocrine-disrupting chemicals and male reproductive health. Reprod Med Biol. 2020 Jul;19(3):243–53.
124. Lahimer M, Abou Diwan M, Montjean D, Cabry R, Bach V, Ajina M, et al. Endocrine disrupting chemicals and male fertility: from physiological to molecular effects. Front Public Health. 2023 Oct 10;11:1232646.
125. Jaeger C, Allend€orfer J, Hatziagelaki E, Dyrberg T, Bergis K, Federlin K, et al. Persistent GAD 65 Antibodies in Longstanding IDDM are not Associated with Residual Beta-Cell Function, Neuropathy or HLA-DR Status. Horm Metab Res 1997; 29: 510–515.

126. Li DK, Zhou Z, Miao M, et al. Urine bisphenol A (BPA) level in relation to semen quality. Fertil Steril 2011;95:625–30.
127. Skakkebaek NE. Testicular dysgenesis syndrome. Horm Res. 2003;60 Suppl 3:49.
128. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001 May;16(5):972–8.
129. Cargnelutti F, Di Nisio A, Pallotti F, Sabovic I, Spaziani M, Tarsitano MG, et al. Effects of endocrine disruptors on fetal testis development, male puberty, and transition age. Endocrine. 2021;72(2):358–74.
130. Durmaz E, Ozmert EN, Erkekoglu P, Giray B, Derman O, Hincal F, et al. Plasma phthalate levels in pubertal gynecomastia. Pediatrics. 2010 Jan;125(1):e122-129.
131. Brody SA, Loriaux DL. Epidemic of gynecomastia among haitian refugees: exposure to an environmental antiandrogen. Endocr Pract. 2003;9(5):370–5.
132. Ramsey JT, Li Y, Arao Y, Naidu A, Coons LA, Diaz A, et al. Lavender Products Associated With Premature Thelarche and Prepubertal Gynecomastia: Case Reports and Endocrine-Disrupting Chemical Activities. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5393–405.
133. Hansen J. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am J Ind Med. 2000 Apr;37(4):349–52.
134. Szabo GK, Vandenberg LN. REPRODUCTIVE TOXICOLOGY: The male mammary gland: a novel target of endocrine-disrupting chemicals. Reproduction. 2021 Nov 1;162(5):F79–89.
135. Koifman S, Koifman RJ, Meyer A. Human reproductive system disturbances and pesticide exposure in Brazil. Cad Saude Publica. 2002;18(2):435–45.
136. McGlynn KA, Quraishi SM, Graubard BI, Weber JP, Rubertone MV, Erickson RL. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst. 2008 May 7;100(9):663–71.
137. Biggs ML, Davis MD, Eaton DL, Weiss NS, Barr DB, Doody DR, et al. Serum organochlorine pesticide residues and risk of testicular germ cell carcinoma: a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2008 Aug;17(8):2012–8.
138. Bhattacharya S, Sahay R, Afsana F, Sheikh A, Widanage NM, Maskey R, et al. Global Warming and Endocrinology: The Hyderabad Declaration of the South Asian Federation of Endocrine Societies. Indian Journal of Endocrinology and Metabolism. 2024 Apr;28(2):129.
139. Hoang-Thi AP, Dang-Thi AT, Phan-Van S, Nguyen-Ba T, Truong-Thi PL, Le-Minh T, et al. The Impact of High Ambient Temperature on Human Sperm Parameters: A Meta-Analysis. Iran J Public Health. 2022 Apr;51(4):710–23.
140. Barratt CLR, Björndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysisof the evidence to support the development of global WHO guidance-challenges andfuture research opportunities. Hum Reprod Update 2017; 23:660.
141. Bonde JP, Giwercman A, Ernst E. Identifying environmental risk to male reproductive function by occupational sperm studies: logistics and design options. Occup Environ Med. 1996 Aug;53(8):511–9.
142. Wang C, Cui YG, Wang XH, et al. transient scrotal hyperthermia and levonorgestrelenhance testosterone-induced spermatogenesis suppression in men through increasedgerm cell apoptosis. J Clin Endocrinol Metab 2007.
143. Thonneau P, Ducot B, Bujan L, et al. Effect of male occupational heat exposure on timeto pregnancy. Int J Androl 1997; 20:274.
144. Bolt JW, Evans C, Marshall VR. Sexual dysfunction after prostatectomy. Br J Urol 1987;59:319.
145. Copuroglu C, Yilmaz B, Yilmaz S, et al. Sexual dysfunction of male, after pelvic fracture.Eur J Trauma Emerg Surg 2017; 43:59.
146. Hari Kumar KV, Swamy MN, Khan MA. Prevalence of hypothalamo pituitary dysfunction in patients of traumatic brain injury. Indian J Endocrinol Metab. 2016 Nov-Dec;20(6):772-778.
147. Bhattacharya S, Krishnamurthy A, Gopalakrishnan M, Kalra S, Kantroo V, Aggarwal S, et al. Endocrine and Metabolic Manifestations of Snakebite Envenoming. Am J Trop Med Hyg. 2020 Oct;103(4):1388–96.
148. Yerawar C, Punde D, Pandit A, Deokar P. Russell's viper bite and the empty sella syndrome. QJM Mon J Assoc Physicians. 2021 Jul 28;114(4):255–7.
149. Shivaprasad C, Aiswarya Y, Sridevi A, Anupam B, Amit G, Rakesh B, et al. Delayed hypopituitarism following Russell's viper envenomation: a case series and literature review. Pituitary. 2019 Feb;22(1):4–12.
150. Bhattacharya S, Nagendra L, Tyagi P. Snakebite Envenomation and Endocrine Dysfunction. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK575924/
151. Unnikrishnan R, Mohan V. Diabetes in the tropics: prevalent, increasing and a major public health problem. Trans R Soc Trop Med Hyg. 2016 May;110(5):263–4.
152. Kapoor N. Thin Fat Obesity: The Tropical Phenotype of Obesity. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK568563/
153. Spaziani M, Carlomagno F, Tarantino C, Angelini F, Vincenzi L, Gianfrilli D. New perspectives in functional hypogonadotropic hypogonadism: beyond late onset

hypogonadism. Front Endocrinol (Lausanne). 2023;14:1184530.
154. Zhou Y, Tian R, Wang X, Sun J, Zhu L, An X. The occurrence of hypogonadotropic hypogonadism in Chinese men with type 2 diabetes. Clinical Endocrinology. 2022;96(6):837–46.
155. Corona G, Rastrelli G, Morelli A, Sarchielli E, Cipriani S, Vignozzi L, et al. Treatment of Functional Hypogonadism Besides Pharmacological Substitution. World J Mens Health. 2020 Jul;38(3):256–70.
156. Esquivel-Zuniga R, Rogol AD. Functional hypogonadism in adolescence: an overlooked cause of secondary hypogonadism. Endocrine Connections [Internet]. 2023 Nov 1 [cited 2024 May 28];12(11). Available from: https://ec.bioscientifica.com/view/journals/ec/12/11/EC-23-0190.xml
157. Musicki B, Burnett AL. Testosterone Deficiency in Sickle Cell Disease: Recognition and Remediation. Front Endocrinol (Lausanne). 2022 May 3;13:892184.
158. Ribeiro APMR, Silva CS, Zambrano JCC, Miranda J de OF, Molina CAF, Gomes CM, et al. Compensated hypogonadism in men with sickle cell disease. Clinical Endocrinology. 2021;94(6):968–72.
159. Solanki P, Eu B, Smith J, Allan C, Lee K. Physical, psychological and biochemical recovery from anabolic steroid-induced hypogonadism: a scoping review. Endocrine Connections [Internet]. 2023 Dec 1 [cited 2024 May 28];12(12). Available from: https://ec.bioscientifica.com/view/journals/ec/12/12/EC-23-0358.xml
160. El Osta R, Almont T, Diligent C, Hubert N, Eschwège P, Hubert J. Anabolic steroids abuse and male infertility. Basic Clin Androl. 2016 Feb 6;26:2.
161. Dohle GR, Smit M, Weber RF. Androgens and male fertility. World J Urol. 2003;21(5):341–345.
162. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J Androl. 2016;18(3):373–80.
163. Bracken MB, Eskenazi B, Sachse K, McSharry JE, Hellenbrand K, Leo-Summers L. Association of cocaine use with sperm concentration, motility, and morphology. Fertil Steril. 1990;53(2):315–322.
164. Safarinejad MR, Asgari SA, Farshi A, et al. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reprod Toxicol. 2013;36:18–23.
165. Nielsen JE, Rolland AD, Rajpert-De Meyts E, Janfelt C, Jørgensen A, Winge SB, et al. Characterisation and localisation of the endocannabinoid system components in the adult human testis. Sci Rep. 2019 Sep 19;9(1):12866.
166. Subirán N, Casis L, Irazusta J. Regulation of male fertility by the opioid system. Mol Med. 2011;17(7–8): 846–853.