Pharmrev Fast Forward. Published on 21 October 2024 as DOI 10.1124/pharmrev.124.001085 This article has not been copyedited and formatted. The final version may differ from this version.

Pharmacological Therapies for Male Infertility

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Running Title: Pharmacological Therapies for Male Infertility

Total manuscript pages: 38
Total figures: 2

Total tables: 5
Total word count: 8368
Total word count abstract and significance statement: 180 words

Authorship contributions
Participated in research design: Rambhatla A, Shah R, Saleh R, Agarwal A
Contributed to writing of the manuscript: Rambhatla A, Shah R, Pinggera G, Taymour M, Atmoko W, Saleh R, Chung E, Hamoda T, Cayan S, Park H, Kadioglu A, Hubbard L, Agarwal A

Funding: This work received no external funding.

Table of Contents

Conflict of Interest: No author has an actual or perceived conflict of interest with the contents of this article.

Abbreviations

AIs: Aromatase inhibitors; ARTs: assisted reproductive techniques; ASA: anti-sperm antibodies; AZF: azoospermia factor; DM: diabetes mellitus; FSH: follicle stimulating hormone; ITT: intra-testicular testosterone; GnRH: gonadotropin releasing hormone; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; LH: luteinizing hormone; KS: Klinefelter syndrome; MAGI: male accessory gland infection; NOA: non obstructive azoospermia; OS: oxidative stress; pFSH: purified follicle stimulating hormone; RCTs: randomized-controlled trials; rFSH: recombinant follicle stimulating hormone; RE: retrograde ejaculation; SERMs: selective estrogen receptor modulators; SCOS: Sertoli cell only syndrome; SSR:

surgical sperm retrieval; T: testosterone; TRT: testosterone replacement therapy; UDT: undescended testis

Abstract:

Male factor infertility is a multifaceted problem that affects approximately 50% of couples suffering from infertility. Causes of male infertility include endocrine disturbances, gonadotoxins, genetic abnormalities, varicocele, malignancies, infections, congenital or acquired urogenital abnormalities, iatrogenic factors, immunological factors, genetic causes, and idiopathic reasons. There are a variety of treatment options for male infertility, depending on the underlying cause(s). These can include surgical treatments, medical/hormonal therapies, and assisted reproductive techniques (ART), which can be combined with surgical sperm retrieval (SSR) if necessary. In this review article, the pharmacological therapies for male infertility are grouped by their underlying causes. Some of these therapies are targeted and specific, while others are used empirically to treat idiopathic male infertility. This will include treatments to optimize infertility in patients who have hypogonadism, ejaculatory dysfunction, infections, or idiopathic male infertility. Finally, we will provide an overview of the future directions of pharmacological therapies for male infertility.

Significance Statement:
Male infertility is a significant worldwide problem. Detailed knowledge of the pharmacological therapies available will ensure the prescription of appropriate therapy and avoid the use of unnecessary or harmful treatments.

Keywords: antioxidants, empiric medical therapy, hypogonadism, male infertility, pharmacology, testosterone,

Introduction

The most recent World Health Organization (WHO) update on infertility prevalence estimates 17.5% of the adult population, around 1 in 6, with men being responsible for 50% of couples' infertility (WHO, 2023; Vander Borght et al.; 2018). The causes of male infertility include endocrine disturbances, gonadotoxins, genetic abnormalities, varicocele, malignancies, infections, congenital or acquired urogenital abnormalities, iatrogenic factors, immunological factors, genetic causes, and idiopathic reasons (Salonia et al., 2023). The treatment options for male infertility encompass a broad spectrum, including medical/hormonal therapies, surgical intervention, different SSR techniques, and ART. However, despite all these medical advancements, many couples are unable to conceive, especially in instances of non-obstructive azoospermia (NOA) and in idiopathic or unexplained infertility.

Therapies may be directed to improve spermatogenesis, to enhance sperm function, or to facilitate sperm delivery. Some of these therapies specifically target a precise category of male factor infertility, while others are used empirically to treat idiopathic male infertility. Specific therapies can be arbitrarily divided into hormonal and non-hormonal agents. Hormonal agents include the various formulations of gonadotropins, dopaminergic agonists, aromatase inhibitors (AIs), and selective estrogen receptor modulators (SERMs) (Salonia et al., 2023; Dabaja & Schegel, 2014). Non-hormonal agents include antibiotics, anti-inflammatory medications, antioxidants (AOXs), or medications to improve semen parameters (Calogero et al., 2017). Otherwise, empirical therapies are often utilized for idiopathic or unexplained infertility when the cause is not clear.

It is imperative for practicing physicians who treat male infertility to have a robust understanding of the available pharmacologic options for managing male infertility. This review was created through careful analysis and consideration of systematic reviews, professional society guidelines, major randomized control trials and other manuscripts relevant to pharmacological therapies for male infertility. Specific aims of the manuscript include providing an overview of the hypothalamic pituitary testicular (HPT) axis which will allow for discussion of the hormonal management of hypogonadotropic hypogonadism (HH), hypergonadotropic hypogonadism (HrH), and eugonadotropic hypogonadism (EH). Medications used in the treatment of ejaculatory disorders affecting infertility will be highlighted, including retrograde and anejaculation. This review will also discuss the medical management of male genital tract infections, inflammation, and idiopathic infertility while additionally providing updates on research and future directions in the field of pharmacologic management of male infertility.

A: Therapies to Enhance Spermatogenesis

Hypothalamic Pituitary Testicular (HPT) Axis and the Role of Intratesticular Testosterone in Spermatogenesis

The complex interplay of peptides and hormones regulating male reproductive function provides the basis for the general function of the HPT axis, a multi-level endocrine pathway composed of various finely tuned organ systems. Gonadotropin-releasing hormone (GnRH) is controlled by neuropeptides that start at the central level and govern the pulsatile release of GnRH from the

hypothalamus (Acevedo-Rodriguez et al., 2018). Kisspeptin, tachykinin-3, and neurokinin-B are GnRH activators. The neuropeptide kisspeptin, which is produced by the Kiss1 gene, is a strong inducer of GnRH (Oakley et al., 2009). On the other hand, RFamide-related peptides (RFRPs) are potent GnRH secretion inhibitors that transmit social, seasonal, and circadian signals linked with reproduction (Constantin et al., 2021). The anterior pituitary gland releases both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to the pulsatile release of GnRH. At the testicular level, LH promotes the production of testosterone (T) by acting on Leydig cells. Additionally, FSH, together with T, acts on Sertoli cells to support and stimulate the production of spermatozoa by germ cells in the seminiferous tubules (Miller et al., 2011).

In addition to inhibins A and B, T, the primary product of the HPT axis, functions via both endocrine and paracrine mechanisms to provide the pituitary and hypothalamic levels with negative feedback, thereby providing a vital hormonal communication channel (Bilezikjian et al., 2004). It has been shown that high intra-testicular testosterone (ITT) levels are critical to spermatogenic potential and high-quality sperm generation, as eugonadal T levels are at systemic levels. It is believed that ITT significantly affects male fertility through several processes that affect sperm motility, quality, and development, as well as the regulation of oxidative stress (OS) (Grande et al., 2022). This offers a framework for realizing how pharmacologically enhancing ITT and modifying the HPT axis can augment spermatogenesis.

A major challenge in the treatment of hypogonadism in a man who wants to maintain fertility is that administering exogenous testosterone will have an inhibitory effect on the HPT axis, leading to the suppression of GnRH, LH, and FSH with a subsequent decrease in ITT that can result in azoospermia/oligozoospermia (Salonia et al., 2023). Therefore, men who wish to retain their reproductive function must not be given exogenous synthetic T therapy. Various hormonal agents are used to increase or maintain spermatogenesis and eugonadal testosterone values to circumvent the inhibition of LH and FSH from the pituitary. The common medications used in this setting are depicted in Figure 1. The different hormonal agents used in male infertility treatment are grouped by class of medication and typical dosage used, as presented in Table 1.

Pharmacologic Therapy of Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism (HH), or secondary hypogonadism, occurs when inadequate testicular stimulation results from hypothalamic or pituitary dysfunction, ultimately leading to decreased LH and FSH (Young et al., 2019). Several congenital, developmental, and acquired factors contribute to HH, including drug use (e.g., opiates, glucocorticoids, exogenous T, or other androgenic anabolic steroids), brain injury, pituitary or hypothalamic tumors with or without hyperprolactinemia, inflammatory and infectious diseases (e.g., pituitary infections, Wegener's granulomatosis, sarcoidosis, lymphocytic hypophysitis, human immunodeficiency virus, hemochromatosis), and iatrogenic conditions (e.g., cranial, or pituitary irradiation) (Young et al., 2019; Fraietta et al., 2013).

Conversely, in cases of congenital hypogonadotropic hypogonadism (CHH), the underlying issue lies in impaired episodic secretion of GnRH, which affects the HPG axis by either altering secretion intervals or by net secretion amplitude. Almost 50% of these cases are linked with mutations or loss-of-function variants in more than 40 genes. These genes play different roles in

GnRH neuron development, migration, central neuroendocrine regulation, and function. The most frequently affected genes include ANOS1 (formerly KAL1), FGFR1 (formerly KAL2), GNRHR, PROKR2, PROK2, CHD7, SOX10, SEMA7A, KLB, SPRY4, SOX2, KISS1R, IL17RDFSHB, LHB and GnRH1 itself (Louden et al., 2021). Kallmann syndrome is a form of CHH characterized by anosmia or hyposmia, neurological impairments such as synkinesis and spastic paraplegia, cognitive delays, colour-vision abnormalities, hearing impairment, as well as absent, delayed, or incomplete puberty, and infertility (Young et al., 2019).

Low total serum T levels associated with low gonadotropin levels suggest the diagnosis of HH. Treatment aims to eliminate the underlying etiological cause, restore physiological sex steroid levels, promote sexual and spermatogenic maturation, and manage associated symptoms. For instance, pharmacological or surgical intervention for a prolactinoma can restore the HPG axis, thereby normalizing total T levels. In other cases, T replacement therapy seems adequate, provided that the patient has no intentions of fathering children. Indeed, all pharmacological treatment options must reflect the patient's fertility, expectations, age and plans for a family (Fraietta et al., 2013). Interestingly, a spontaneous reversal can be observed in about 5-20% of CHH patients (Mao et al., 2015; Anawalt et al., 2024; Sidhoum et al., 2014).

To mimic non-continuous hypophyseal gonadotropin secretion, the concept of pulsatile GnRH release was developed and has been shown to effectively restore male fertility. Pulsatile GnRH release stimulates the anterior pituitary gland and subsequently the Leydig cells in the testicles. It is administered via a portable, subcutaneous pump, releasing a GnRH bolus every 90 to 120 min, usually for a treatment period of 12 to 24 months (Young et al., 2019; Clavijo et al., 2018; Foran et al., 2023). The dose varies from 25 to 600 ng/kg/ bolus with subsequent titration according to hormonal response. The effectiveness of spermatogenesis induction relies on the patient's age, with more favorable treatment outcomes observed in patients in whom hypogonadism begins after puberty. In this population, normalization of semen parameters can typically be observed after 6-7 months of therapy. However, GnRH treatment failure may result in the presence of GnRH receptor mutations or anti-GnRH antibodies (Zitzmann et al., 2000). Treatment limitations include patient inconvenience, pump maintenance, and high costs restricting treatment to specialized hospitals (Fraietta et al., 2013; Foran et al., 2023).

For patients with GnRH receptor mutations or pituitary lesions, gonadotropin treatment is recommended to address HH. Treatment involves subcutaneous injections of hCG, which exerts an LH-like effect, human menopausal gonadotropin (hMG), pFSH or rFSH. The efficacy of pFSH and rFSH was investigated, and no differences were detected (Cannarella et al., 2020). Intramuscular injections administered in the past carry the risk of antibody induction, which is not observed with subcutaneous administration (Young et al., 2019; Fraietta et al., 2013).

In most cases, hCG and hMG are often used together, as the LH activity of hMG is too low to maintain Leydig cell function to achieve fertility (Zitzmann et al., 2000). Treatment begins with an induction phase of 1500–2000 IU of hCG two to three times weekly for 8–12 weeks. In some patients with residual endogenous FSH, hCG alone can be sufficient for inducing spermatogenesis. Otherwise, an additional 75-150 IU of hMG or 150 IU of rFSH are administered two to three times a week (Cannarella et al., 2020; Zitzmann et al., 2000). However, some patients still require a higher FSH dose. A meta-analysis of randomized

controlled studies on the effects of FSH dosage on sperm parameters in men with idiopathic infertility found that a weekly FSH dose between 700 and 1050 IU increased progressive motility, total sperm count and sperm concentration, which may have a positive effect on pregnancy rates (Cannarella et al., 2020). No side effects were reported at high doses. Compared to GnRH therapy, studies have shown that pulsatile GnRH release may induce earlier sperm production, greater testicular volume, and increased sperm concentrations (Mao et al., 2017). However, gynecomastia is the most observed side effect during gonadotropin treatment but typically resolves upon reducing the hCG dosage to achieve normal 17-ß-estradiol levels (Schopohl et al., 1991). Other side effects include local irritation at the injection site and gastrointestinal symptoms.

In general, ART may be considered if a spontaneous pregnancy does not occur after therapy for several months. According to semen quality and quantity, intrauterine insemination (IUI) or intracytoplasmic sperm injection (ICSI) with or without testicular sperm extraction (TESE) can be offered in stimulation failure cases. However, an evaluation of the reproductive capacity of the female partner must also be carried out (Fraietta et al., 2013).

Prolactinomas, the most common type of pituitary tumor, can result in hyperprolactinemia suppressing kisspeptin, thereby inhibiting GnRH and subsequent gonadotropin secretion, leading to infertility and HH (Donato et al., 2016). Other causes of hyperprolactinemia include medications, hypothyroidism, stress, chronic kidney disease, and idiopathic causes. Clinically, prolactinomas can present with infertility, impotence, osteoporosis, headaches, visual impairment, and hypopituitarism. Diagnostic workup includes serum prolactin measurement and pituitary MRI if indicated. Dopamine agonists, such as cabergoline and bromocriptine, are first-line treatments, with cabergoline showing superior efficacy and a better side effect profile (Sabuncu et al., 2001). Standard cabergoline dosages range from 0.25–1 mg twice weekly, though side effects like nausea, dizziness, headaches, and constipation may occur. Surgery is reserved for refractory cases.

HH can be acquired after testosterone replacement therapy (TRT), especially with long-acting preparations, high dosages, and longer use. Exogenous T administration suppresses the HPT axis, reducing LH and FSH and impairing spermatogenesis (Fink et al., 2024; Crosnoe et al., 2013). The most important treatment for the recovery of spermatogenesis in these patients is stopping TRT. Many patients can spontaneously recover spermatogenesis within one year after TRT cessation (Crosnoe et al., 2013). To speed up the recovery of spermatogenesis after TRT, treatment can be initiated with 1500-2000 IU hCG two to three times a week for three months with a titration of up to 10,000 IU to achieve a normal T level, but the ideal dose remains undefined. If the sperm concentration is still low after three months, an additional 75-150 IU of FSH two to three times a week may be necessary (Han and Bouloux, 2010; McBride and Coward 2016).

Additionally, anti-estrogens, such as SERMs (i.e., clomiphene citrate) or AIs (i.e., anastrozole or letrozole) have been shown to enhance the serum levels of LH and FSH. These compounds restore spermatogenesis by suppressing estrogen-mediated negative feedback on the HPT axis and upregulating gonadotropins and ITT levels, though their use is off-label in some countries. An intact HPT axis is mandatory (McBride and Coward, 2016; Grossmann, 2018). Clomiphene

citrate (25-50 mg/day), anastrozole (1 mg/twice weekly to daily), and letrozole (2.5 mg/day) can increase plasma levels of LH and FSH (Varimo et al., 2019). However, a recent meta-analysis investigating the effect of SERMs on semen parameters in men with HH showed improved sperm concentration and total motile sperm count but with low certainty of evidence (de Silva et al., 2024). In contrast, a meta-analysis by Hujben et al., which included 1642 patients with hypogonadism, demonstrated that clomiphene citrate therapy improved biochemical and clinical symptoms with few adverse effects (Huijben et al., 2022).

Although exogenous T administration is considered contraindicated for restoring hypogonadism in men with incomplete family planning, novel short-acting exogenous T preparations, such as intranasal T (Natesto®) gel, may exert less suppression on the HPT axis compared to long-acting options. Studies have shown that three times daily use maintains sperm parameters, with a total number of motile sperm of more than 5 million in 93.9% of patients after six months and normal T levels in 90.9%. However, further investigations are needed before it can be widely used for males with hypogonadism who want to preserve fertility (Ramasamy et al., 2020).

Pharmacologic Therapy of Eugonadotropic Hypogonadism

In contrast to hypergonadotropic hypogonadism (HrH), which is caused by primary testicular failure (i.e., high gonadotropins with low T), and HH, which is a hypothalamic or pituitary disorder (i.e., low gonadotropins and low T), eugonadotropic hypogonadism, also known as normogonadotropic hypogonadism, is characterized by low serum T in the setting of normal gonadotropins (Ho and Tan, 2013).

When treating men with fertility issues and concomitant male hypogonadism, it is essential to understand that many conditions, such as uncontrolled metabolic disorders (e.g., diabetes mellitus), severe systemic illness, infections or inflammatory diseases, can adversely impact the HPT axis, resulting in low T with corresponding relatively normal gonadotropins levels but poor sperm parameters (Khourdaji et al., 2018).

For patients with normogonadotropic hypogonadism, strategies to stimulate endogenous T production and spermatogenesis include pulsatile GnRH, hCG, hMG, pFSH, rFSH, SERMs, and AIs (Khourdaji et al., 2018; Shahid et al., 2021; Ide et al., 2021; Salonia et al., 2019; Attia et al., 2013; Cannarella et al., 2019; Huijben et al., 2023; Guo et al., 2022). In a Cochrane review, gonadotropins such as hCG, hMG, pFSH or rFSH were reported to provide a significant higher spontaneous pregnancy rate compared to controls (16% vs 7%) (Attia et al., 2013). Gonadotropins are a good alternative to TRT when fertility is desired and T is low but requires frequent injections and surveillance by specialists to ensure that there are no significant downstream side effects. Additionally, their use is often limited by cost, inconvenience, and lack of widely accepted standardized treatment protocols (Shahid et al., 2021; Ide et al., 2021).

SERMs such as clomiphene citrate, tamoxifen, and AIs such as letrozole or anastrozole can be prescribed off-label for the treatment of hypogonadism to boost spermatogenesis and T levels. SERMs enhance central stimulation of gonadotropins (FSH and LH), leading to improvements in T and spermatogenesis. In a systematic review and meta-analysis, clomiphene citrate or tamoxifen significantly increased sperm density, serum FSH, LH and T levels and pregnancy

rates; however, it had no impact on progressive or total sperm motility compared to the controls (Cannarella et al., 2019). In a recent systematic review and meta-analysis, consisting of 15 studies, treatment with clomiphene citrate for approximately five months provided a significant improvement in sperm density with a mean difference of 8.38 million, sperm motility with a mean difference of 8.14%, and significant increases in serum FSH, LH and total T levels (mean difference of 2.05 ng/ml) (Huijben et al., 2023). Treatment with clomiphene citrate provided a mean pregnancy rate of 17%, ranging from 0 to 40% in different studies. Mild side effects of clomiphene citrate treatment include headache, gynecomastia, dizziness, visual and mood changes, and fatigue.

AIs are medications used to target the prevention of aromatization of testosterone into estradiol. They are specifically indicated in males with a serum total T to estradiol ratio of <10:1. In a meta-analysis consisting of 10 studies, letrozole or anastrozole significantly enhanced sperm density, total sperm count, serum FSH, LH, and total T with a side effect rate of 15.2%, including decreased libido, subclinical liver dysfunction, skin rash, headache, and other discomforts (Guo et al., 2022). However, it is often necessary to take these medications for longer than 6 months, and the real clinical impact may not translate to significant improvement in semen parameters, particularly in men with azoospermia (Khourdaji et al., 2018; Shahid et al., 2021).

Pharmacologic Therapy of Hypergonadotropic Hypogonadism

HrH (primary hypogonadism) is a condition of androgen deficiency due to primary testicular dysfunction or failure (Rajbhandari et al., 2023). Impairment of Leydig cell function with consequent reduced T production/synthesis, as well as diminished inhibin B production by the Sertoli cells, will disrupt the negative feedback arc of the HPT axis, increasing gonadotropins (Sengupta et al., 2021; Niederberger, 2011). Thus, HrH is generally characterized by a varying degree of T deficiency, elevated or normal LH and FSH, and impaired spermatogenesis (Surampudi & Swerdloff, 2017; Kaprara and Huhtaniemi, 2017). In distinction to HH (secondary hypogonadism), HrH has a higher likelihood of being associated with more spermatogenesis impairment than T production (Surampudi and Swerdloff, 2017).

Any congenital or acquired pathologic conditions leading to testicular atrophy and primary testicular failure can disproportionally impact spermatogenesis to a greater extent than Leydig cell function (Setchell and Brooks, 1988; Bujan et al., 1989; Takihara, 1987; Surampudi and Swerdloff, 2017). Klinefelter syndrome (KS) is the most common chromosomal disorder associated with HrH (Bonomi et al., 2017). Other conditions implicated in HrH include inactivation mutations of FSH and LH receptor genes, steroidogenesis disorders, cryptorchidism, anorchia, orchitis, medications, gonadotoxins and varicoceles. Table 2 summarizes the common causes of HrH (Bonomi et al., 2017; Grinspon and Bergadá, 2020; Surampudi and Swerdloff, 2017; Santi et al., 2017; Latronico and Arnhold, 2013; Delli et al., 2023; Sengupta et al., 2021; Elhadd et al., 2023).

TRT for hypogonadism is contraindicated in infertile men with HrH who are aiming to conceive, as it has detrimental effects on sperm production (Salonia et al., 2023; Schlegel et al., 2021). Other strategies to stimulate endogenous T production and spermatogenesis in men with HrH

include the use of hCG, hMG, pFSH, rFSH, and AIs (Shahid et al., 2021; Guo et al., 2022; Del Giudice et al., 2020; Holtermann Entwistle et al., 2022; Efesoy et al., 2009; Saylam et al., 2011). These pharmaceutical agents with different dosages are listed in Table 1. SERMs are not indicated in this group of patients because they are hypergonadotropic, and such treatment would excessively increase gonadotropin levels without an improvement in either serum or ITT (Schlegel et al., 2021).

Hormonal stimulation has been introduced to improve SSR in men with NOA. The rationale for adjuvant hormonal treatment is to stimulate Sertoli cells to induce spermatogenesis via FSH and optimize ITT via LH. This approach is particularly relevant because most men with NOA exhibit hypergonadotropic characteristics, including low serum total T level and an abnormal T-to-E2 ratio. (Tharakan et al., 2022; Shiraishi et al., 2015; Foran et al., 2023). Since 40% to 70% of men with NOA still exhibit focal spermatogenesis, the optimization of the hormonal profile in certain patients can be beneficial. However, this optimization may not necessarily result in an improvement in spontaneous ejaculated semen parameters or SSR in men with azoospermia (Çayan and Yaman; 2021).

Based on the observed pharmacologic effects of AIs in metastatic breast cancer, they have been used to restore the T-to-E2 ratio in hypogonadal and infertile men, particularly in men with KS. Candidates for aromatase inhibition have usually been identified as males with peripheral serum total T-to-E2 ratio <10 (Saylam et al., 2011; Guo et al., 2022). While initial studies investigated the benefits of steroidal AIs such as testolactone, lately, the most used AIs in andrology have been nonsteroidal compounds such as anastrozole or letrozole (Ko et al., 2012), but no superiority in semen parameters after therapy has been shown (Raman et al., 2002). In a recent meta-analysis conducted by Del Giudice et al., the effects of AIs showed good tolerability in 436 investigated patients, with a low discontinuation rate of 3.2% attributed to side effects such as hepatic dysfunction or decreased libido. However, a statistically significant increase in total T from a baseline value of 320.1 ± 98.2 ng/dl to 475.6 ± 60.3 ng/dl was observed, corresponding to an overall mean increase of 48.5%. AI therapy normalized the T/E2 ratio from 7.4 ± 1.6 before therapy to 24.1 ± 10.1 after treatment. These findings hold significance as elevated E2 levels, combined with decreased total T levels, negatively influence the HPT axis by inhibiting FSH and LH production, thus impairing spermatogenesis. Additionally, the authors demonstrated the benefit of increasing sperm concentration and motility (Chua et al., 2013). In another meta-analysis consisting of 10 studies, letrozole or anastrozole provided significant improvement in sperm density, total sperm count, serum FSH, LH, and total T. (Guo et al., 2022).

To date, no randomized controlled study has demonstrated the effect of adjuvant medical therapy on testicular sperm production before SSR procedures. A few cohort studies have suggested that medical therapy may improve testicular SSR rates in azoospermic men and ICSI outcomes by increasing fertilization and pregnancy rates in azoospermic or oligozoospermic men (Foran et al., 2023; Çayan and Yaman, 2021; Shiraishi et al., 2012; Peng et al., 2022).

A systematic review and meta-analysis consisting of 22 studies with 1706 patients with NOA, including KS, demonstrated that hormonal therapy resulted in 1.96 times higher testicular SSR (Tharakan et al., 2022). However, when limiting this to men with HrH, 4 studies showed that hormonal therapy provided 1.73 times higher testicular SSR, which was not statistically

significant. Several studies have reported outcomes of combination therapy with hCG, rFSH, and AIs, and all studies reported an improvement in sperm retrieval, pregnancy, and live birth rates compared to control groups (Foran et al., 2023). In the largest cohort of men with HrH (n=542) in the literature, treatment with hCG and pFSH significantly increased the SSR compared to that in controls; however, the pregnancy and live birth rates did not differ from those in controls (Peng et al., 2022). Due to the lack of evidence, no recommendations have been provided from the American Urological Association /American Society of Reproductive Medicine (AUA/ASRM) or European Association of Urology (EAU) guidelines (Salonia et al., 2023; Schlegel et al., 2021). The presence of late maturation arrest has been demonstrated to be a predictor for positive testicular SSR (Bernie et al., 2015). Medical therapy before microscopic testicular sperm extraction (mTESE) has been found to be a positive factor for both successful SSR and higher pregnancy rates, with the total T value positively correlating with SSR. (Kızılay et al., 2022).

B: Therapies to Enhance Sperm Function and Delivery

Pharmacologic Therapy for Genital Tract Infections and Inflammation Affecting Male Fertility

Infection in male genital organs has been linked to male infertility in about 15% of male factor infertility cases (Rivero et al., 2023). Viruses, bacteria, and parasites can result in organ damage and consequent functional impairment (Henkel, 2021; Guiton and Dreyet, 2023). The consequences include scarring of the epithelium, leading to obstruction in the male genital tract, as well as directly harming germ cells, leading to a decrease in the quality of semen parameters, especially when a febrile infection occurs. This can be a transient effect, but if a pathogen can enter the testes and male reproductive tract, an infection can permanently affect spermatogenesis. Mumps orchitis is the most profound example of this and can lead to azoospermia, but since the advent of the mumps vaccine, the incidence of this complication has decreased markedly. Aside from male infertility, infection can result in a broader impact if it is transmitted to the partner during sexual intercourse (Schuppe et al., 2017). Ureaplasma and Mycoplasma have convincing evidence of being linked with male infertility (Khalafalla et al., 2023; Ahmadi et al., 2018). However, diagnosing and treating these cases can be challenging due to the absence of overt clinical signs, the presence of non-specific or idiopathic causes, and the persistence of the disease despite adequate therapies.

Male accessory gland infection (MAGI) is one of the primary causes of male infertility. MAGI can impair the secretory function of the prostate, seminal vesicles, and epididymis (Vignera et al., 2011). Vignera and colleagues (2012) pointed out that patients with MAGI had lower sperm progressive motility and sperm morphology and higher seminal leukocytes and sperm DNA fragmentation highlighting that it can alter basic and functional sperm parameters. The primary therapy for MAGI is antibiotics which can initially be given as broad spectrum or targeted toward the semen culture sensitivity examination which can improve the quality of spermatozoa (Haidl et al., 2019). Antibiotics of choice are summarized in Table 3.

Several studies reported that the efficacy of antibiotics for treating MAGI is the highest for prostatitis at up to 92.5%, followed by prostatovesiculitis, and prostatovesiculoepididymitis at

about 50%. Not only being challenging to treat, prostatovesiculoepidiymitis is also prone to re-infection following antimicrobial treatment (Vicari, 2000). Consequently, it results in increased OS. Other studies have addressed that around 10% of men with acute epididymitis can develop persistent azoospermia, as post-inflammatory obstruction is thought to be the cause.

Additional regimens including probiotics, steroids, or anti-inflammatory medications have been reported for the treatment of MAGI. In a study of 84 patients, additional probiotics with *Enterococcus faecium* and *Saccharomyces boulardii* during antibiotic treatment and Lactobacilli after treatment resulted in complete microbial eradication in semen (Grande et al., 2022). Besides, daily oral prednisone at 5-12.5 mg has also been reported to be able to improve sperm parameters and fertility outcomes in patients with idiopathic oligozoospermia and accessory gland inflammation (Milardi et al., 2017). Antioxidants also show a benefit in improving leukocytospermia in *in vitro* studies (Jung et al., 2016). Nevertheless, these additional therapies lack robust evidence to be used regularly.

Chronic infections usually require a longer duration of combination therapy. Chronic prostatitis/chronic pelvic pain syndrome is most frequent in men younger than 50 years of age and has been correlated with male infertility (Graziani et al., 2023). In a study of 110 men with chronic bacterial prostatitis, 500 mg levofloxacin daily for 14 consecutive days per month for 3 months resulted in microbial eradication of about 71% of bacteria, with increased sperm progressive motility and seminal viscosity, However, in the remaining 29% with poor antibiotic responsiveness, a deterioration in all semen variables was observed (Vicari et al., 2016).

Tuberculosis (TB), which is prevalent in tropical and developing areas is an important infection in the genitourinary tract which can result in OA due to granulomatous tissue and scarring in reproductive tract (Kumar, 2008). Antibiotic regimens for tuberculosis, which include rifampicin, isoniazid, pyrazinamide, and ethambutol for 6-9 months are required for complete resolution of the disease. Streptomicin is given in cases of relapse. (Yadav et al., 2017). The duration of the regimen depends on the sensitivity and type of the cases (Muneer, 2019). Reconstructive surgery is not feasible due to multiple areas of obstruction and scarring and sperm retrieval with ART is needed to achieve pregnancy. A recent study in male mice found that TB regimens, but not in their fixed-dose combination (FDC), can induce a histological lesion and abnormal sperm morphology (Bakare, 2022). However, further studies are needed to confirm the superiority of FDC protocols in terms of reproductive function within the clinical setting.

In an endemic area of filariasis, patients with non-specific epididymo-orchitis should be evaluated for the possibility of filarial epididymo-orchitis, especially when there is no response to the conventional antimicrobials. Filarial orchitis can result in testicular atrophy, granulomatous histology, and impaired spermatogenesis, while epididymitis can result in obstruction. Diethylcarbamazine is the drug of choice in this situation (Ekwere et al., 1989) with the dose of 6–10 mg/kg for up to 2 (3) weeks (Janssen et al., 2017; Dietrich et al., 2019)

Retrograde Ejaculation/Seminal Anemission

The transport of seminal fluid from the testicles and male excurrent ductal system depends upon the anatomical and functional integrity of the bladder neck and the sympathetic (α-adrenergic)

innervated internal urethral sphincter complex for both the emission and expulsion processes. In both circumstances, timely, well-defined closure of the urinary bladder neck must take place first to allow an antegrade expulsion of seminal fluid by supporting rhythmic muscular contractions of the ischiocavernosus and bulbocavernosus muscles (Revenig et al., 2014). This closure mechanism is of paramount importance for adequate physiologic functioning. In cases of absent or incomplete closure of the urinary bladder neck, retrograde ejaculation (RE) or anejaculation must be suspected, particularly in cases of low-volume ejaculate, azoospermia or presence of spermatozoa and fructose in the centrifuged postejaculatory voided urine. The incidence of RE was reported to be 0.3-2% in men seeking help for fertility and up to 18% in a small case series of azoospermia (Yavetz et al., 1994). In clinical settings, the diagnostic classification of RE is based on differentiating between congenital, acquired neurogenic, pharmacologic, or anatomical disease (Parnham and Serefoglu, 2016). Table 4 outlines the various causes of RE. In this context, the therapeutic approaches for RE depend on the underlying diagnostic cause.

Damage to the sympathetic nerve pathways during surgical procedures, such as pelvic surgery or retroperitoneal lymph node dissection (RPLND), mainly for testicular cancer, can lead to RE and an inability to ejaculate due to disrupted nerve signals to the bladder neck and prostate tissues. The adoption of modified RPLND techniques by Jewett et al. (Jewett et al.,1988) and Donohue et al. (Donohue et al.,1990) and the introduction of robotic surgeries with higher magnification views are considered appropriate for preservation of ejaculatory function in most patients undergoing unilateral or bilateral nerve-sparing RPLND with all its template modifications (Görgen et al., 2022).

There were 94.0 million men globally suffering from benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms (LUTS) in 2020, with increasing trends in many parts of the world. (Collaborators, 2022) It has been estimated that the prevalence of BPH increases with age: approximately 8% in men in their 40s, 50% in men in their 50s, and 80% in men in their 80s due to an annual increase in prostate volume of about 2.2%/year in older men (Berry et al., 1984; Bosch et al., 2007; Loeb et al., 2009). The most prescribed medications for this disorder are 5-α-reductase inhibitors (finasteride or dutasteride) and α_1-adrenergic receptor blockers (tamsulosin, silodosin, alfuzosin, terazosin, doxazosin) or tadalafil at a daily dose of 5 mg. In instances where 8 mg of silodosin and the combination of silodosin and tadalafil were administered, there was an increase in RE compared to the administration of 5 mg of tadalafil monotherapy for LUTS, with rates of 5.9%, 9.5%, and 0%, respectively (AbdelRazek et al., 2022). According to the Food and Drug Administration Adverse Event Reporting System (FDA-FAERS) for the USA and the Eudra-Vigilance database for European Union countries, these prostate-related medications are among the ten most frequently recognized drugs for significant reporting of ejaculatory disorders, among others (fluoxetine, paroxetine, sertraline, risperidone, venlafaxine, and atomoxetine). RE and general ejaculatory disorders, were recorded for tamsulosin, finasteride, sildenafil and tadalafil at 68%, 6%, and 1%, 3% and 15%, 28%, 20%, and 3%, respectively. (Nacchia et al., 2024) The efficacy of combination therapy of any PDE5is and any of the "off-label" drugs used to treat RE has still not been investigated in detail. It should be reserved only for those men suffering from moderate to severe ED, a condition that is detected in up to 70% of cases with preexisting DM.

Since peripheral neuropathy is a common sequela in individuals with endocrine-metabolic disorders such as diabetes mellitus, 35-50% of these men overall suffer from some kind of ejaculation disorder, and the incidence of RE (6-34.6%) is estimated to be higher than that in the general population. (Desai et al., 2023, Di Sante et al 2016) Therapeutic options for RE are determined mainly by the desire for fertility. Pharmacological approaches to treat RE in DM patients who aim to increase the sympathetic tone in the bladder neck area or to reduce parasympathetic activity are limited by their adverse effects. The pharmacological treatment strategies are based on empirical values from studies with low case numbers, and in many cases, this is an off-label form of treatment (Table 5). Therefore, ART is often used either via TESE or after the collection of post-ejaculatory urine, which is collected after spontaneous voiding or after the insertion of a catheter, the sample is then centrifuged and resuspended in a medium such as bovine serum albumin, human serum albumin, or Earle's/Hank's phosphate-buffered medium. This results in a 15% pregnancy rate/cycle (Jefferys et al., 2012) The Hotchkiss method requires pre-orgasmic emptying of the bladder and installation of a specific, 1.6- 4 g $NaHCO_3$-rich medium, resulting in higher pregnancy rates of 24%/cycle (Jefferys et al., 2012) and up to 28% when using frozen-thawed sperm after collecting. (Philippon et al., 2015) Alternatively, the patient can ingest 1 gram of oral $NaHCO_3$ the night before and on the morning of the sperm retrieval to help alkalinize the urine (Nikolettos et al., 1999). Sperm can then be recovered with a post-ejaculate urine sample and be used for IUI or ICSI.

The most commonly used medications for the treatment of RE in diabetic patients are imipramine, ephedrine, and pseudoephedrine at doses of 25-75 mg, 15-75 mg, and 60-120 mg on demand, respectively. Imipramine is a tricyclic antidepressant characterized by its three-ring central structure and blocks the reuptake of norepinephrine (noradrenaline) and serotonin at the synaptic cleft. Therefore, by increasing the concentration of these neurotransmitters in the synaptic cleft, imipramine enhances neurotransmission. Furthermore, it has a high affinity for α_1-adrenergic and muscarinic receptors with resultant anticholinergic effects which explains its therapeutic effects when treating diabetic RE. Both ephedrine and pseudoephedrine are phenethylamines with different hydroxyl groups, and ephedrine itself is a chiral compound with two enantiomers, and the (−)-ephedrine form is more active. Both ephedrine and pseudoephedrine exert their effects principally through the indirect release of norepinephrine from presynaptic nerve terminals, and they have both alpha- and beta-adrenergic agonist activity, which stimulates the sympathetic nervous system. They are used for "off-label" RE treatment due to their ability to activate α_1-adrenergic receptors on the smooth muscle of the bladder neck, causing contraction of the bladder neck during ejaculation and preventing the retrograde flow of semen. Ephedrine, due to its mixed α-- and β-adrenergic effects, may be more potent but more likely to cause side effects than pseudoephedrine. With prolonged and repeated use of ephedrine and pseudoephedrine, some men may develop a tachyphylaxis which limits their use.

In summary, according to a meta-analysis of 253 individuals receiving treatment with α-adrenergic agonists, anticholinergics, or antihistamines, 133 participants (~ 53%) succeeded in attaining antegrade ejaculation, whether through single-agent therapy or a combination approach. Additionally, 33% of the partners of patients experiencing RE who engaged in sexual activity during treatment with these medications became spontaneously pregnant. (Kamischke and Nieschlag, 2002) Despite its off-label use, imipramine is the principal drug utilized in the therapeutic approach to RE treatment, with midodrine and ephedrine/pseudoephedrine also

frequently prescribed. Efficacy assessments revealed that imipramine achieved a success rate of 65% (78 out of 121 patients) in restoring antegrade ejaculation and supported a spontaneous pregnancy rate of 40% (30 out of 76 patients). (Kamischke and Nieschlag, 2002). A detailed summary can be found in table 5.

Idiopathic Male Infertility

Idiopathic male infertility (IMI) occurs when semen analysis parameters are impaired without an identifiable cause. This can affect up to 30-40% of couples with male factor infertility (Salonia et al., 2023). Unexplained infertility affects about 20-30% of couples and occurs when there are both normal semen analysis parameters and a normal female partner evaluation. In both situations, physical examination is normal, and history does not point to a particular cause for infertility. OS, endocrine disrupting chemicals, and genetic/epigenetic mechanisms have been raised as major causes of male infertility in men diagnosed with IMI or unexplained infertility (Agarwal and Sengupta, 2020). Mechanisms that have been suggested for OS-mediated male infertility include high sperm DNA fragmentation and low sperm fertilizing potential (Agarwal and Sengupta, 2020). The concept of Male Oxidative Stress Infertility (MOSI) was recently introduced to define a category of infertile men with abnormal sperm parameters and high seminal OS that was previously classified as IMI (Agarwal et al., 2019). When a couple is diagnosed with IMI or unexplained infertility, assisted reproductive technologies can be considered without delay based on the age and reproductive status of the female partner.

Medical treatment for male infertility can be divided into two main categories:

1. Specific targeted treatments are used for certain etiologies such as HH, genital tract infection, RE, and immunological infertility.
2. Non-specific empirical treatments used in men with IMI.

In this section we will focus on the treatment of IMI. Figure 2 provides an overview of the treatment strategies used in IMI.

Hormonal Treatment

Gonadotropins

Circulating gonadotropins FSH and LH play critical roles in spermatogenesis and steroidogenesis. Purified urinary extractions of hCG, FSH, and hMG, along with the recombinant forms of FSH and LH, are used in treating IMI (Kumar et al., 2006; Jung and Seo, 2014). Several studies have shown that gonadotropin treatment significantly increases sperm parameters (Arnaldi et al., 2000; Cannarella et al., 2020).

Follicle-stimulating hormone (FSH)

Therapy with pFSH has been used in patients with IMI and normal levels of gonadotropins and T to improve sperm concentration, but the results are controversial (Barbonetti et al., 2018). Santi et al. (2017) included all available controlled clinical trials with FSH treatment and reported a significant increase in sperm concentration. Other studies have confirmed the effectiveness of FSH in improving sperm parameters in normogonadotropic oligozoospermic infertile men (Garolla et al., 2017; Casamonti et al., 2017). Other authors have also reported a decreased sperm

DNA fragmentation rate in patients who have FSH receptor polymorphisms when treated with FSH (Simoni et al., 2016).

Human chorionic gonadotropin (hCG)

Adequate ITT concentrations are essential for spermatogenesis by inducing Sertoli cell maturation, resulting in downregulation of anti-mullerian hormone expression and in triggering germ cell meiosis (Rey et al., 2009). hCG exerts LH-like effects, leading to increased ITT concentration compared to serum (Lee and Ramasamy, 2018). Vicari et al. (1992) reported that the administration of hCG alone proved effective in restoring ITT concentrations and inducing spermatogenesis. However, most studies were performed in association with hMG, showing improved sperm parameters and pregnancy rate (Knuth et al., 1987; Santi et al., 2020; Santi et al., 2023).

Selective estrogen receptor modulators and aromatase inhibitors (SERMs and AIs)

Estrogen, peripherally aromatized from T by the cytochrome P450 enzyme, provides negative feedback to the hypothalamus and pituitary gland. SERMs act by blocking the negative feedback exerted at the hypothalamus-pituitary level by estrogens causing increased secretion of both GnRH and gonadotropins. A rise in LH stimulates Leydig cells, leading to an increase in the T concentration; while increased FSH improves spermatogenesis (Shahid et al., 2021). According to an American survey, clomiphene citrate is the most commonly used drug in the empirical medical management of IMI (Ko et al., 2012).

Along with their meta-analysis of 11 randomized controlled trials, Chua et al. (2013) found that anti-estrogen therapy was associated with a significant increase in the pregnancy rate, sperm concentration, and sperm motility. These authors concluded that clomiphene (25-50 mg daily) or tamoxifen (20-30 mg daily) administered for 3-6 months had a 2.4-fold greater chance of pregnancy among patients in the IMI group compared to the control group. Some studies have shown that clomiphene citrate combined with vitamin E can significantly increase the pregnancy rate and improve sperm concentration and progressive motility in patients with idiopathic oligoasthenozoospermia. (Ghanem et al., 2010). Guo et al. (2015) showed tamoxifen has antioxidant properties as it significantly increased sperm mitochondrial function and motility by reducing OS.

AIs interfere with the normal synthesis of estrogen by blocking T aromatization, resulting in increased gonadotropin secretion, which in turn stimulates spermatogenesis and steroidogenesis (Huijben et al., 2023). Small studies using letrozole or anastrozole showed a significant improvement in sperm parameters and correction of hormonal abnormalities. Generally, estrogen antagonists are relatively safe, although, they have the disadvantage of increasing estrogen levels through aromatization of T. The long-term use of AIs can lead to chronic suppression of estrogen levels which can have adverse effects as well since all men need some estrogen for normal function (Schlegel, 2021)

Antioxidants

Antioxidants (AOXs) can be used to improve fertility potential by counteracting OS in infertile men with IMI. AOXs are substances that neutralize or protect cells against the effects of oxidation and free radicals (Valko et al., 2006). The protective mechanism of AOXs includes

scavenging free radicals, preserving sperm DNA integrity, and facilitating mitochondrial transport (Ali et al., 2020). The supplementary AOXs that are predominantly used as therapeutic interventions for male infertility in clinical trials include vitamin E, vitamin C, carotenoids, carnitine, cysteine, coenzyme Q10, selenium, zinc, and folate (Majzoub and Agarwal, 2018; Barati et al., 2019). A recent systematic review indicated a positive impact of AOX supplementation in cases of idiopathic and unexplained male infertility (grade B recommendation). (Agarwal et al., 2021). A recent meta-analysis indicated that the use of AOXs in infertile men significantly improved sperm concentration, total and progressive sperm motility, and normal sperm morphology (Agarwal et al., 2023). Additionally, a Cochrane review found a significant positive impact of AOX supplementation in infertile men on the pregnancy rate (OR =2.97, 95% CI 1.91-4.63) although the level of evidence was found to be low (Smits et al., 2019). Similarly, a recent meta-analysis found a significant increase in the odds of spontaneous clinical pregnancy following AOX therapy in infertile men [OR= 1.97 (95% CI: 1.28, 3.04; $p<0.01$) (Agarwal et al., 2023). Along with their meta-analysis for randomized controlled trials, Wang et al. (2022) addressed that vitamin E could increase the total sperm count and, with long-term treatment, could improve the progressive motility rate of spermatozoa. However, the current guidelines of the EAU (Salonia et al., 2023) and AUA/ASRM (Schlegel et al., 2021) do not provide a firm conclusion on the beneficial effects of AOX therapy in male infertility. The reported duration of AOX therapy for the treatment of infertile men is variable, ranging from 1 month (Stanislavov et al., 2009) to 12 months (Enert al., 2016). Additionally, the dose of AOXs prescribed is variable and determined mainly by the manufacturer and experience of the individual physician (Agarwal et al., 2021).

AOXs are generally well tolerated and have a good safety profile. However, too high or inappropriate mixture of AOXs can lead to reductive stress (Dutta et al., 2022). Adverse effects of AOXs include gastrointestinal symptoms commonly encountered with administration of carnitines, folate, selenium, zinc, coenzyme Q10, vitamin C, and vitamin D. Also, selenium may cause halitosis with a garlic odor as well as a metallic taste in the mouth.

Probiotics and prebiotics

Lately, it has been discovered that the gut microbiota has pleiotropic physiological effects that regulate not only intestinal function but also the immune system, organ morphogenesis, tissue homeostasis, and metabolic profiles. The gut microbiota regulates estrogen concentration by secreting the β-glucuronidase enzyme which deconjugates estrogens into their active form causing alterations of circulating estrogen (Baker et al., 2017). In men, it can be assumed that, by regulating estrogen levels, the microbiota can exert some influence on the HPT feedback mechanisms. Maretti et al. (2017) carried out a pilot placebo-controlled study to evaluate the effect of probiotics on sperm parameters (Maretti and Cavallini, 2017). Patients in the treatment group showed a significant increase in semen volume, sperm concentration, progressive motility, and percentage of typical forms compared to the placebo group. Furthermore, there was an increase in the serum FSH, LH and T levels, resulting in five pregnancies in the treated patients, while no pregnancies occurred in the placebo group. These authors hypothesized that probiotics influence hypothalamic kisspeptin production with consequent improvements in the pulsatile secretion of gonadotropins and T, optimization of seminal free radical concentration, regulation of intestinal bacterial flora, and improvement of the prostatic microenvironment.

Insights to the Future Research on Pharmacological Therapies of Male Infertility

Despite advancements in assisted reproductive technologies, the need for effective, targeted pharmacological therapies for male infertility remains a significant and under-addressed challenge in reproductive medicine. Given that the etiology of male factor infertility can often be multifactorial or perhaps unknown in some instances, the clinical effectiveness of various pharmacological agents such as hormonal therapy, antioxidant supplements, and vitamins alone or in combination may not be guaranteed (Wang et al., 2022), regardless offering some significant and not fully elucidated potential for improving male fertility outcomes (Kallinikas et al., 2024). In fact, systematic reviews and meta-analyses have highlighted the uncertain outcomes of pharmacological interventions for male infertility (Shahid et al., 2021; Semet et al., 2017; Salas-Huetos et al., 2018). Nonetheless, these pharmacological interventions are likely to have additional clinical benefits beyond sperm concentration, sperm motility, and sperm morphology, extending to improvements in general and sexual health.

The current strategy to optimize the clinical effectiveness of these pharmacological therapies centers on identifying the underlying causative factors for male infertility, optimizing medical comorbidities, and ensuring therapeutic compliance. Strict adherence to pharmacological therapy, along with a healthy diet and lifestyle modifications coupled with a normal hormonal profile, is critical for increasing the chances of conception among couples. Future research in the field of pharmacological therapies for male infertility should aim to identify useful biomarkers for specific aspects of male infertility interventions and better diagnostic algorithms to identify the right patient populations to receive these treatments, coupled with better synergy among the pharmacological strategies to improve sperm parameters and aid in the success of SSR if necessary. Even if spermatogenesis or sperm function are improved or better techniques for SSR are developed, future research needs to help address the underlying cause(s) for the couple’s infertility so that treatments can be curative as opposed to therapeutic.

The current published literature on pharmacological interventions is fraught with inconsistent methodical contents and the varied nature of interventions, making it difficult to determine which type, time and duration of pharmacological agents will be the most effective. On the other hand, certainly, the indiscriminate use of pharmacological substances or antioxidants for treating male infertility can trigger "reductive stress," potentially clarifying why outcomes have not met expectations in some meta-analyses. Therefore, future studies require proper standardization of patient demographics, better descriptions of methods and replicable pharmacological protocols to capture desired clinical outcomes while simultaneously providing cost-effective interventions. With further research focused on personalized medicine, mechanistic understanding, novel targets and the use of nanotechnology as a tool for bypassing the blood–testis barrier for specific molecules, hopefully these advancements will unlock the full potential of these therapies, empowering men on their journey to fatherhood.

Concluding Remarks

In conclusion, male infertility represents a multifaceted problem with significant implications for affected couples. Even in today's times of remarkably good live birth rates, thanks to various

advanced ART techniques, it is still true that a viable sperm is essential in the pursuit of a pregnancy. Thus, effective pharmacological therapies remain essential in the management of male infertility, whereby these principles have demonstrated varying levels of efficacy and degrees of success in enhancing spermatogenesis. Hormonal treatments, such as gonadotropins, SERMs and AIs, have shown promise in restoring hormonal disbalance. Indeed, only in a well-balanced cellular environment spermatogenesis can be stimulated in men with hypogonadotropic hypogonadism and other endocrine disorders. Non-hormonal strategies, such as the use of antibiotics and anti-inflammatory medications, aim to address infections and inflammation, known to compromise male fertility and adversely affect reproductive health. In addition, empirical therapies containing antioxidants aim to counteract seminal oxidative stress. The intestinal microbiota has emerged as an influencing factor in male reproductive health, with studies showing its role in regulating systemic hormone levels, including estrogen, thus influencing the HPT axis and spermatogenesis. Preliminary research suggests that probiotics may improve sperm quality and hormonal profiles, although more research is needed to confirm these findings and elucidate the underlying mechanisms. Although pharmacological interventions offer hope, their effectiveness can be inconsistent due to the heterogeneous nature of male infertility and the variability of individual responses to treatment. Future research should focus on identifying reliable biomarkers to diagnose specific causes of infertility, optimize patient selection for targeted therapies, and develop personalized treatment protocols. The integration of advanced technologies, such as nanotechnology, can also improve the delivery and effectiveness of drugs, including crossing the blood testicle barrier. In summary, pharmacological therapies play a crucial role in the overall management of male infertility. A combination of targeted treatments, lifestyle modifications, and adherence to prescribed diets is essential to optimize fertility outcomes. Continuous research and innovations are essential to perfect these therapies, ensuring that they are effective and accessible, empowering men in their journey to fatherhood.

Take Home Message

- Male infertility may result from a variety of congenital or acquired causes, and in many cases no etiological factor can be identified. Some of these causes are amenable to medical therapy.
- In hypogonadotropic hypogonadism, there is strong evidence favoring the use of gonadotropins to achieve sperm production.
- In eugonadotropic hypogonadism there is a more limited role for hormonal therapy, using either injectable gonadotropins or oral medications such as SERMs or AIs.
- In hypergonadotropic hypogonadism, the utility of any form of hormonal therapy is still uncertain. However, hormone therapy is widely prescribed prior to surgical sperm retrieval in the hope of marginally improving the chances of sperm retrieval.
- Long-term antibiotics can improve semen parameters when the diagnosis of accessory gland infection has been made accurately.
- Retrograde ejaculation, or failure of emission, when due to a neurological cause may be treated with a combination of sympathomimetic and anticholinergic agents.
- Idiopathic infertility can be treated empirically with hormonal modulators, antioxidant combinations, and/or probiotics with a modest expectation of benefit.

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Table 1. Various pharmaceutical agents with suggested dosages to induce spermatogenesis and serum testosterone levels in men with infertility.

Treatment agents	**Suggested dosages**
Gonadotropins	
Gonadotropin-releasing hormone	25-600 ng/kg/bolus via subcutaneous pump every 90-120 mins
Human chorionic gonadotropin (hCG)	1500–5000 IU, 2–3 times/week, intramuscular or subcutaneous
Recombinant hCG	250 IU, 2 times/week, intramuscular or subcutaneous
Purified/highly purified FSH	75–150 IU, 2–3 times/week, intramuscular or subcutaneous
Recombinant FSH	75–150 IU, 2–3 times/week, intramuscular or subcutaneous
Human menopausal gonadotropin	75–150 IU, 2–3 times/week, intramuscular or

Treatment agents	**Suggested dosages**
(hMG)	subcutaneous
Selective estrogen receptor modulators	
Clomiphene citrate (Clomid)	25-50 mg daily, per oral
Tamoxifen	10-20 mg daily, per oral
Aromatase inhibitors	
Anastrozole	1 mg, twice weekly to daily, per oral
Letrozole	2.5 mg, twice weekly to daily, per oral

Table 2: Common congenital and acquired causes of hypergonadotropic hypogonadism*

Condition		**Characteristics / Comments**
Congenital or Developmental	Klinefelter syndrome	47, XXY aneuploidy. Most common male chromosomal abnormality associated with primary hypogonadism and infertility. Gynecomastia, small firm testes, and azoospermia or severe oligospermia.
	XX male syndrome 47 XYY syndrome 48 XXYY syndrome	Other less common chromosomal disorders
	Y-chromosome microdeletion	Associated with azoospermia or severe oligospermia
	Gonadotropin resistance	Inactivating mutations of LH and FSH receptors
	Androgen insensitivity syndrome	Peripheral androgen resistance due to androgen receptor gene mutations in subjects with 46 XY karyotype
	Testosterone biosynthesis enzymatic defects (genetic mutations)	17β-hydroxylase dehydrogenase deficiency 17-hydroxylase deficiency 5α-reductase deficiency
	Prenatal diethylstilbestrol syndrome	Maternal exposure

	Myotonic dystrophy	Type I or type II
	Autoimmune syndromes	Autoimmune Testicular Failure. Isolated, or multiglandular disorder.
	Cryptorchidism, Anorchism	
	Disorders of sex development (DSD)	Gonadal dysgenesis
	Sertoli-cell-only syndrome	
Acquired	Infections and inflammation	Mumps orchitis, HIV and other viruses, Testicular granulomatous disease.
	Testicular torsion	
	Testicular trauma	
	Testicular tumor	
	Orchiectomy	
	Varicocele	
	Chemotherapy	
	Radiotherapy	
	Medications	Ketoconazole, spironolactone, cimetidine, flutamide
	Toxins, Gonadotoxins	Alcohol, insecticides fungicides, heavy metals, environmental toxins
	Systemic Diseases	Hepatic failure, chronic renal failure, diabetes mellitus, sickle cell disease, amyloidosis
	Aging	Age-related hypergonadotropic hypogonadism. More subtle and less abrupt. Diagnosed as late-onset hypogonadism.

* Bonomi et al 2017; Grinspon and Bergadá 2020; Surampudi and Swerdloff 2017; Santi and Corona 2017; Latronico and Arnhold 2013; Delli et al 2023; Sengupta et al 2021; Elhadd et al 2023.

Pharmrev Fast Forward. Published on 21 October 2024 as DOI 10.1124/pharmrev.124.001085 This article has not been copyedited and formatted. The final version may differ from this version.

Table 3. Antibiotic options for male accessory gland infections

Male accessory gland infection	Antibiotics	Dose and Duration	Common Side Effect
Chronic bacterial prostatitis	Fluoroquinolones	Daily dose (4-6 weeks	Nausea, vomiting, diarrhea, abdominal pain dizziness, headache, and/or insomnia
	Doxycycline	100 mg twice a day (10 days)	Nausea, vomiting, skin rash, photosensitivity
	Azithromycin	500 mg once a day (3 weeks)	Diarrhea, abdominal pain, and other gastrointestinal symptoms
	Metronidazole	500 mg three times a day (2 weeks)	Nausea, abdominal pain, diarrhea, Neuropathy
Epididymitis with low risk of gonorrhea	Fluoroquinolones	Daily dose (10-14 days)	Nausea, vomiting, diarrhea, abdominal pain dizziness, headache, and/or insomnia
	Doxycycline	200 mg initial dose followed with 100 mg twice a day (14 days)	Nausea, vomiting, skin rash, photosensitivity
Acute epididymitis due to gonorrhea*	Ceftriaxone	1000 mg IM	Nausea, vomiting, diarrhea, skin rash
	Doxycycline	200 mg initial dose followed with 100 mg twice a day (14 days)	Nausea, vomiting, skin rash, photosensitivity

*Both antibiotics should be used

References: Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, Kranz J, Schubert S, Pilatz A, Veeratterapillay R, et al. (2014) EAU Guidelines on Urological Infection. Available from: https://uroweb.org/guidelines/urological-infections

Table 4. Causes of retrograde ejaculation

Anatomical	Congenital: - Abnormal localization of ejaculatory duct orifice - Bladder neck incompetence - Epispadias/Exstrophy - Utricular cyst - Posterior urethral valve/prolapse Acquired: - Prostatectomy - Trauma - Bladder neck surgery - Urethral stricture/meatal stenosis - Ureterocele
Pharmacologic	- Alpha-adrenergic receptor blockers - Antihypertensives - Antipsychotics - Antidepressants
Neurogenic	- Diabetes mellitus - Multiple sclerosis
Substance abuse	- Alcohol - Dopamine - Cocaine

Table 5. Drugs used in the treatment of RE. Note that the use is considered “off-label”. Adapted from (Kamischke and Nieschlag, 2002)

Drug	Dosage	Time	Side-effects
Ephedrine	15–100 mg/d po (120mg /BID)	60-120 min before effect after 2-4 weeks	hypervigilance, anxiety hypertension, palpitations, tachycardia, headache, dizziness, and insomnia
Synephrine	60 mg iv	60 min	
Pseudoephedrine	60–120 (240) mg po	120–150 min before	hypervigilance, anxiety, see above
Imipramine	25–75 mg/d po Mostly used 50 mg/d	After 1 week	dry mouth, constipation, red vision, constipation, urinary retention, and sometimes confusion or memory problems, orthostatic hypotension, dizziness, sedation, Reduced libido, erectile dysfunction, and difficulties achieving orgasm
Imipramine & Pseudoephedrine	50+120mg/d po	60 min before effect after 2 weeks	See above, ? more pronounced
Midodrine	4-40 mg iv 15 mg/d po	30 min -120 min	
Phenylpropylamine	150mg/d po	120 min	
Brompheniramine	14-24 mg/d po 16mg/d po	12h before, after 2 w induction	dizziness, dry mouth, constipation, urinary retention, blurred vision, fast heartbeat
Brompheniramine & phenylephrine	112 mg/d po	N/A	
Chlorphenyramine & phenylpropylamine	50 mg/d po	N/A	
Dextroamphetamine	20 mg/d po		
Amoxapine	50mg/d	Effect after 1 month	Unclear, probably similar to TCAs

Figure Legends

Figure 1: Hypothalamic-pituitary-testicular axis and mechanism of action of different modalities for treating hypogonadism. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; SERM, selective estrogen receptor modulator; HCG, human chorionic gonadotropin; HMG, human menopausal gonadotropin; rFSH, recombinant follicle-stimulating hormone.

Figure 2: Different modalities for idiopathic male infertility treatment. AI, aromatase inhibitor; FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; SERM, selective estrogen receptor modulator.

Acknowledgment: Daniela Delgadillo, BS provided help with manuscript submission.

Data Availability Statement: This review article contains no datasets generated or analyzed during the current study.

Figure 1

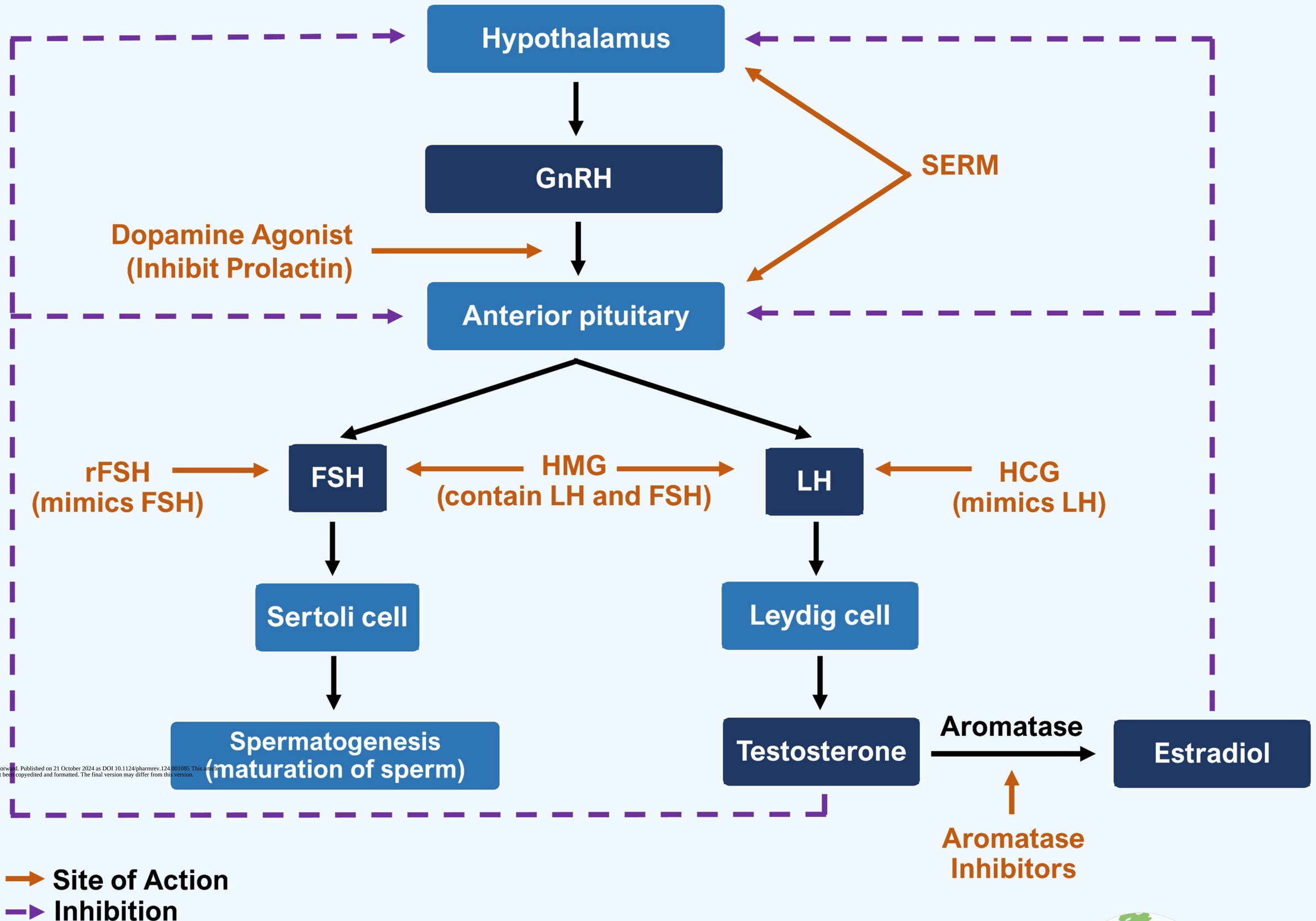

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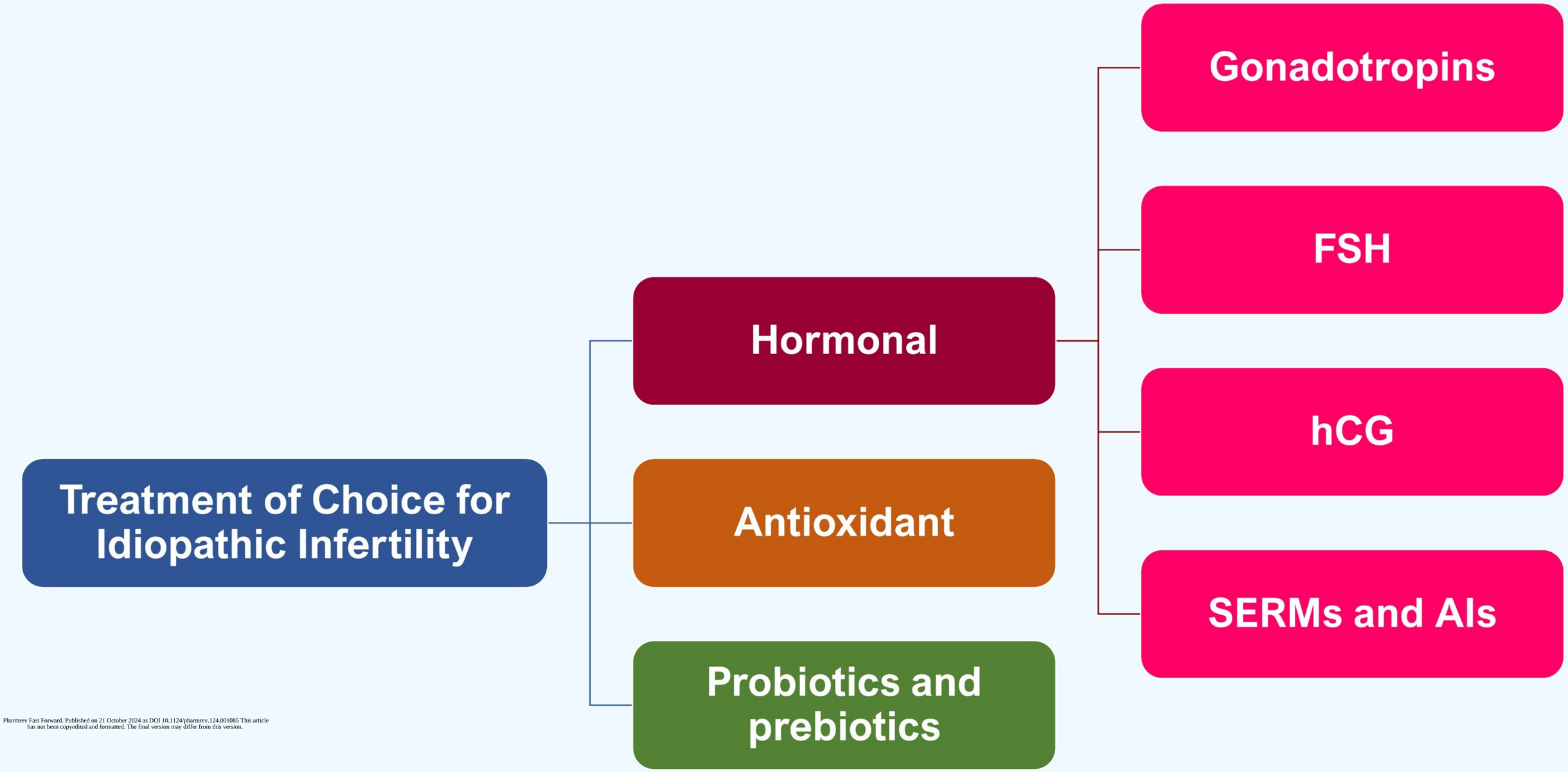
Figure 2



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