Infertility: Medical Treatment

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Also see Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

Key Points

- Hypogonadotropic hypogonadism is a state of abnormal testicular function due to impaired stimulation by the gonadotropin pituitary hormones: follicle stimulating hormone and luteinizing hormone. This condition can be effectively treated by restoring testicular stimulation through human chorionic gonadotropic, human menopausal gonadotropin, or recombinant follicle stimulating hormone.
- Clomiphene citrate is a selective estrogen receptor modulator, effectively blunting the inhibitory effect that estradiol has on the hypothalamic-pituitary-gonadal axis. Clomiphene citrate treatment can result in increased levels of gonadotropins.
- Aromatase inhibitors, such as anastrazole, inhibit the conversion of testosterone into estradiol. This treatment can result in increased serum and intratesticular testosterone levels, as well as decreased estradiol levels.
- Prolactin excess can result from a variety of etiologies, including functional adenomas within the pituitary gland, and can impair the secretion of gonadotropins. Adenomas can be treated with a dopamine agonist.
- Erectile dysfunction is common among infertile men. Clinicians should screen for this and treat in accordance with clinical guidelines.
- Ejaculatory dysfunction can be due to retrograde ejaculation or failure of emission. Emission is influenced by the sympathetic nerves, and ejaculatory dysfunction can be treated with sympathomimetic agents.
- While genital flora is commonly cultured in the semen, true reproductive tract infections, accompanied by leukospermia, can impair sperm function.

Keywords

aromatase inhibitor, clomiphene citrate, estradiol, follicle stimulating hormone, human chorionic gonadotropin, hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, Kallman syndrome, Klinefelter syndrome, luteinizing hormone, prolactin, testosterone

1. Introduction

Spermatogenesis relies on the interplay between central and testicular hormonal factors. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which causes the anterior pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Inside the testicle, LH stimulates Leydig cells to produce testosterone, and FSH acts on Sertoli cells to support the production of spermatogonia.[1] Intratesticular testosterone levels are over a hundred times that measured in the serum, and this high level of intrastesticular testosterone is necessary to support spermatogenesis.[2] Endocrinopathies are the primary etiology in a minority (<3%) of the cases of male infertility and can be divided into cases of hormonal deficiency and hormonal excess.

Physiological principles must be carefully considered in managing male factory fertility. Understanding of reproductive physiology is poor among many practicing urologists. A 2012 survey indicated that 25% of urologists would treat male factor infertility with exogenous testosterone, despite the fact that direct androgen supplementation is well known to suppress spermatogenesis.[3]

2. Hormone Deficiency

Table 1. Causes of Hypogonadotropic Hypogonadism (Congenital and Acquired)

Congenital	Acquired
Kallmann syndrome	Hyperprolactinemia
DAX1 mutations	Benign/malignant tumors of the hypothalamus or pituitary
GPR54 gene mutation	Trauma
Leptin or Leptin receptor mutations	GnRH analogs
Prader-Willi syndrome	Androgen/estrogen use
β-subunit of LH mutation	Glucocorticoid treatment
β-subunit of FSH mutation	Chronic opiate use
	Chronic illness
	Critical illness
	Diabetes Mellitus
	Anorexia nervosa
	Obesity

FSH (follicle stimulating hormone); GnRH (gonadotropin releasing hormone); LH (luteinizing hormone)

2.1 Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is a state of testosterone deficiency caused by subnormal levels of gonadotropins (LH and FSH). The etiology can be congenital or acquired. (**Table 1**). Congenital causes include Kallman syndrome, characterized by anosmia, cleft palate, cryptorchidism, and failure of GnRH secretion. It is most commonly due to a mutation in the KAL1 gene. Acquired forms of hypogonadotropic hypogonadism may be due to pituitary tumors or trauma. Several options are available for the treatment of hypogonadotropic hypogonadism.

2.1.1 Gonadotropin Agents

Rationale: Gonadotropin agents replace the deficient levels of LH and/or FSH. The aims of therapy are to: (i) Increase serum and intratesticular testosterone levels to normal and (ii) induce spermatogenesis. Pharmacologic agents used include human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and recombinant-follicle stimulating hormone (r-FSH). For gonadotropin dosing information see **Table 2**. Similar to LH, hCG is a heterodimeric protein, with an α subunit identical to that of FSH, thyroid stimulating hormone, and LH. The β subunits of these protein hormones differ, however, hCG does cross react with the LH receptor, allowing us to use hCG clinically to mimic LH. hMG is a combination of LH and FSH extracted and purified from the urine of post-menopausal women (who have high levels of both hormones). While hMG has activity for both hormones, it is used primarily for its FSH activity. However, r-FSH is simply pure FSH harvested from cell lines. Regimens of replacement typically begin with hCG administration for 3-6 months. After sustained normal testosterone levels are achieved, either hMG or r-FSH is added to the therapy.

Outcomes: A majority of men will have sperm present in the ejaculate after 6 months of therapy, but this outcome can take up to 12 months to occur. Notably, a full sperm production cycle takes approximately 72 days; therefore, checking repeat semen testing prior to 3 months' time is generally not recommended. Most men with hypogonadotropic hypogonadism who are treated with gonadotropins will be able to achieve a pregnancy, yet 71% of those with ultimate fertility will have abnormally low sperm concentrations. [4]

Adverse Effects: Adverse side effects are uncommon, but can include nausea (12%), breast enlargement/tenderness (1-10%), headache (34%), and discomfort at the injection site (1-10%).

2.1.2 Anti-estrogen Agents

Rationale: Anti-estrogen agents have also been used to treat hypogonadotropic hypogonadism. The most commonly used drug in this class is clomiphene citrate. Clomiphene citrate binds to the hypothalamic and pituitary estrogen receptor sites, thereby blocking estrogen's central feedback inhibition of gonadotropin secretion. This causes increased gonadotropin levels with subsequently increased testosterone production. Dosing of clomiphene citrate is usually 25 mg per day. It can be increased to 50 mg/day if needed, or lowered to 25 mg every other day based on response.

Outcomes: The use of clomiphene citrate in men with hypogonadotropic hypogonadism has been shown to increase testosterone levels and improve semen parameters in several studies.[5,6,7] Clomiphene citrate use for the treatment of male infertility is done in an “off-label” fashion. While historical manuscripts have reported divergent outcomes in terms of effects on semen parameters with the use of clomiphene citrate in infertile males, these studies were conducted in eugonadal, oligiospermic males.[8,9] Katz et al reported in 2012 that the long-term use of clomiphene citrate was both effective and safe in increasing serum testosterone levels in 86 young hypogonadal men. While semen parameters were not tracked in this cohort, the study subjects demonstrated increased mean serum testosterone levels and subjective improvement in hypogonadism symptoms.[10,11]

In 2015, Helo et al reported the results of a randomized, prospective, double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone levels in hypogonadal infertile males.[12] The authors did *not* demonstrate equivalence between clomiphene citrate and anastrozole, as the former resulted in significantly higher testosterone levels while the latter resulted in higher testosterone:estradiol (T:E2) ratios. More recently, Chandrapal et al studied a series of 77 males on clomiphene citrate therapy and reported increased serum testosterone levels without an accompanying increase in serum PSA or hematocrit levels.[13] A multi-center, prospective, double-blinded, placebo-controlled study of clomiphene citrate use in hypogonadal infertile men with tracking of changes in semen parameters and reproductive outcomes is needed.

Adverse Effects: Side effects of clomiphene citrate are generally self-limited, but can include headache (1%), blurred vision (2%), flushing (10%), breast discomfort (2%), and nausea (2%).

2.2 Hypergonadotropic Hypogonadism

Hypergonadotropic hypogonadism results from testicular failure, including low testosterone levels. Gonadotropins are appropriately elevated due to a lack of negative feedback by testosterone, estradiol (E2), and inhibin B from the testis. Without appropriate intratesticular testosterone secretion, spermatogenesis is impaired. Hypergonadotropic hypogonadism can be either congenital or acquired. The most common congenital etiology is Klinefelter syndrome (KS), or 47 XXY on karyotype. In addition to elevated FSH and LH, KS patients often present with a eunachoid body habitus, gynecomastia, and small testes. Acquired hypergonadotropic hypogonadism can arise due to chemotherapy, radiation therapy, and post-pubertal mumps orchitis.

The optimal medical treatment of hypergonadotropic hypogonadism has not been conclusively established. Aromatase inhibitors, gonadotropins, and anti-estrogen agents have all been investigated, particularly in the subset of hypergonadotropic hypogonadal men with KS. The mainstay of treatment for KS patients with azoospermia is testicular sperm extraction (TESE), and improved success rates have been reported when the patient’s preoperative endocrine status is optimized.[14,15]

2.2.1 Aromatase Inhibitors

Rationale: Testosterone (T) is converted to E2 in peripheral adipose tissue by the enzyme

aromatase. Men with KS often have an imbalance in their T:E2 ratios, with ratios < 10:1 suggested to be abnormal. The rationale for aromatase inhibitor therapy is to diminish E2 conversion, thereby decreasing E2's central feedback inhibition, and increasing serum testosterone levels.[14] Pavlovich et al proposed a cut-point of 10 for the lower limit of normal for testosterone: estradiol ratio, with testosterone measured in ng/dL and estradiol measured in pg/mL.[16]

Outcomes: At this time, the two aromatase inhibitors that are commercially available in the United States are anastrozole and letrozole, and neither is FDA approved for use in fertility. Most studies of aromatase inhibitors have not been well controlled and suffer from design limitations, such as small subject numbers and possible selection bias. Nonetheless, treatment with aromatase inhibitors has revealed improvement in T:E2 ratios as well as increased sperm concentration and motility in men with hypogonadism and abnormalT:E2 ratios. [14,17,18,19] Treatment with aromatase inhibitors, used in various combinations with gonadotropin agents and/or anti-estrogen agents, has also been shown to result in higher sperm retrieval rates on microdissection TESE in men with KS when the resultant serum testosterone level was > 250 ng/dL.[15] The preoperative serum testosterone level was found to be more predictive of successful sperm retrieval than the specific combination of medications used in these patients. Anastrozole is dosed at 1 mg/day and letrozole is 2.5 mg/day.

Adverse Effects: Side effects associated with aromatase inhibitors can include nausea (11-19%), headache (9-10%), hot flashes (12-26%), and chest discomfort (2-12%).

2.2.2 Gonadotropin Agents

Rationale: Gonadotropin agents can be used to further augment the already elevated LH and/or FSH levels in patients with hypergonadotropic hypogonadism. These agents have not been well studied in isolation in the setting of hypergonadotropic hypogonadism, but they have been investigated in combination with other agents such as aromatase inhibitors and anti-estrogen agents in men with KS, as alluded to previously.[15] Gonadotropin agents used in this setting include hCG, hMG, and r-FSH.

Outcomes: To date, there are no published reports specifically evaluating the outcomes associated with gonadotropin therapy alone in the setting of hypergonadotropic hypogonadism.

However, treatment with gonadotropin agents, when used in various combinations with aromatase inhibitors and/or anti-estrogen agents, has been shown to result in higher sperm retrieval rates on microdissection TESE in men with hypergonadotropic hypogonadism and KS if the resultant serum testosterone level was > 250 ng/dL.[15]

Adverse Effects: Adverse side effects due to gonadotropins are uncommon, but can include nausea (12%), breast enlargement/tenderness (1-10%), headache (34%), and discomfort at the injection site (1-10%)

2.2.3 Anti-estrogen Agents

Rationale: Like gonadotropins, anti-estrogen agents can be used to augment the already elevated LH and/or FSH levels by blocking estrogen's central feedback inhibition of gonadotropin secretion. These

drugs are typically not used in isolation in the setting of hypergonadotropic hypogonadism, but they have been investigated in combination with other agents such as aromatase inhibitors and gonadotropins in the treatment of men with KS.[15] Clomiphene citrate is the most commonly used drug in the anti-estrogen class. As discussed above, clomiphene binds to the hypothalamic and pituitary estrogen receptor sites, thereby blocking estrogen's central feedback inhibition of gonadotropin secretion. This can result in increased gonadotropin levels and potentially increased testosterone production, although by definition men with hypergonadotropic hypogonadism already have elevated LH and FSH serum levels.

Outcomes: To date, there are no published reports specifically evaluating the outcomes associated with clomiphene citrate monotherapy in the setting of hypergonadotropic hypogonadism.

Adverse Effects: Side effects of clomiphene citrate are generally self-limited, but can include headache (1%), blurred vision (2%), flushing (10%), breast discomfort (2%), and nausea (2%).

Table 2. Dosing Information For Gonadotropin Agents

Drug	Dose	Route	Frequency
hMG	75-150 IU	IM/SC	3 times per week
hCG	1000-2000 USP units	IM/SC	3 times per week
r-FSH	75-150 IU	SC	3 times per week

FSH/r-FSH (follicle stimulating hormone/recombinant-follicle stimulating hormone); hCG (human chorionic gonadotropin); hMG (human menopausal gonadotropin); IM (intramuscular); international units (IU).

View Image.

3. Hormone Excess

3.1 Androgen Excess

Androgen excess usually occurs in men taking exogenous testosterone or illicit anabolic steroids. The use of either over time can result in suppressed FSH and LH levels in the presence of normal to high testosterone levels. Use of exogenous androgens leads to decreased intratesticular testosterone production and partial or complete suppression of spermatogenesis. When these findings are present in a male with a history of use of anabolic steroids, the condition is called “anabolic steroid induced hypogonadism” (ASIH). Treatment involves stopping the exogenous testosterone or illicit anabolic steroid exposure. Sperm returns to the ejaculate in many patients within 3 months of exogenous androgen cessation; in other cases recovery may take up to 3 years.[20,21] Some men, particularly those with a longer history of exogenous androgen exposure, may suffer from permanent oligospermia or azoospermia even after androgen cessation.

If the patient remains oligospermic or azoospermic after androgen cessation, hCG with or without hMG may be used to help optimize the function of the hypothalamic-pituitary-gonadal axis, as detailed below.[22,23,24] Some studies suggest that these agents may restore testosterone levels and possibly, facilitate recovery of spermatogenesis. While no large scale studies on this approach to the treatment of infertility associated with exogenous androgen exposure have been conducted, several case reports suggest that hCG with or without hMG will facilitate the recovery of spermatogenesis in some patients.[21,22] These studies show that while most patients with exogenous androgen exposure will have spontaneous recovery of spermatogenesis simply with cessation of the androgens, some patients with persistent azoospermia will achieve return of sperm to the ejaculate with hCG and/or hMG therapy.[21,22]

3.1.1 Gonadotropin Agents

Rationale: Long-standing use of exogenous androgens can lead to persistent down-regulation of LH and FSH secretion. hCG is an LH agonist that can stimulate intratesticular testosterone production by Leydig cells. hMG and r-FSH are both options to support Sertoli cell function and stimulate spermatogenesis when FSH is persistently down-regulated due to exogenous androgen exposure. Case reports and studies of small series of patients have been published that describe successful return of sperm to the ejaculate with the use of hCG and/or hMG.[22,23] To date, no published studies assess the specific use of r-FSH in patients with persistent FSH deficits due to exogenous androgen exposure. r-FSH is commonly used to treat patients with low serum FSH levels and impaired spermatogenesis for other reasons.

Outcomes: There is no level I evidence for the use of gonadotropins in men with impaired spermatogenesis resulting from exogenous androgen exposure. However, case reports and studies of small series of patients have been published that describe the successful return of sperm to the ejaculate with the use of hCG and/or hMG.[22,23] To date, no published studies discuss the specific use of r-FSH in patients with persistent FSH deficits due to exogenous androgen exposure, but r-FSH is

commonly used to treat patients with low serum FSH levels and impaired spermatogenesis due to other causes.

Adverse Effects: Adverse side effects due to gonadotropins are uncommon, but can include nausea (12%), breast enlargement/tenderness (1-10%), headache (34%), and discomfort at the injection site (1-10%).

3.2 Estrogen Excess

A testosterone (measured in ng/dl) to estrogen (measured in pg/mL) ratio of > 10:1 is thought to be appropriate for healthy adult males.[16] This recommendation is based on endocrine characterization of men with severe male infertility (T:E ratio=6.9) in comparison to men with normal spermatogenesis (T:E ratio=14.5). Estrogen excess results in inhibition of gonadotropin secretion and decreased intratesticular testosterone production. This series of changes commonly leads to a decline in spermatogenesis.

3.2.1 Aromatase Inhibitors

Rationale: T is converted to E2 primarily in peripheral adipose tissue by the enzyme aromatase. The rationale for aromatase inhibitors is to diminish E2 production and increase serum T levels.[14] Aromatase inhibitors can be administered in steroidal (testolactone) or non-steroidal (anastrozole, letrozole) forms. At this time, the steroidal form, testolactone, is not commercially available in the United States.

Outcomes: Treatment with aromatase inhibitors in this setting has led to improvement in T:E2 ratios as well as increased sperm concentration and motility.[14,17,18,19] However, in the subset of men with KS, testolactone appears to be more effective than anastrozole.[14] As noted above, a recent study has shown that aromatase inhibitors, gonadotropin agents, and/or anti-estrogen agents (used in various combinations) result in higher sperm retrieval rates on microdissection TESE when the resultant preoperative serum testosterone level was > 250 ng/dL. Furthermore, the preoperative serum testosterone level was found to be more predictive of successful sperm retrieval than the specific combination of medications used in these patients.[15]

Adverse Effects: Side effects associated with aromatase inhibitors can include nausea (11-19%), headache (9-10%), hot flashes (12-26%), and chest discomfort (2-12%)

4. Prolactin Excess

Prolactin excess can be caused by hypothyroidism, liver disease, stress, use of certain medications (phenothiazines and tricyclic antidepressants) and prolactin secreting pituitary tumors (prolactinomas). High levels of prolactin inhibit hypothalamic secretion of gonadotropin-releasing hormone (GnRH) resulting in decreased LH and FSH secretion, diminished testosterone levels, and impaired spermatogenesis.[25] Once hyperprolactinemia is diagnosed, a pituitary MRI should be obtained to assess for a prolactinoma.[26] These tumors can be classified as either microadenomas (< 10 mm) or macroadenomas (> 10 mm). Medical therapy consists of dopamine agonists. Radiation

therapy and transphenoidal surgical resection are also treatment options. Ablative therapy is typically reserved for those who fail medical management. Following the treatment of a prolactinoma, the patient's gonadotropin levels should be assessed because gonadotropin therapy may still be necessary despite normalization of prolactin levels.

4.1 Dopamine Agonists

Rationale: Medical treatment of a prolactinoma consists of blocking prolactin secretion through the use of dopamine agonists (e.g. bromocriptine, cabergoline, pergolide, and quinagolide). The most commonly used of these agents are bromocriptine and cabergoline. Both inhibit prolactin secretion and typically lead to regression of prolactin producing tumors.

Outcomes: Both bromocritpine and cabergoline have been shown to improve sperm concentration, motility, and morphology.[27] Cabergoline is more efficacious than bromocriptine at normalization of prolactin levels and reducing tumor burden. Carbergoline is typically better tolerated than bromocriptine.[28] As a result, cabergoline is generally considered first line medical therapy. The dose for cabergoline is 0.25 mg twice per week. This can be increased to 1 mg per twice per week based on prolactin levels.

Adverse Effects: Dopamine agonist side effects can include headache (26%), dizziness (15-17%), nausea (27-29%), and constipation (7-10%).

5. Erectile and Ejaculatory Dysfunction

Figure 1. Diagnosis and Medical Treatment of Men with Ejaculatory Dysfunction. POU: Post-orgasmic urinalysis; mL: milliliter.

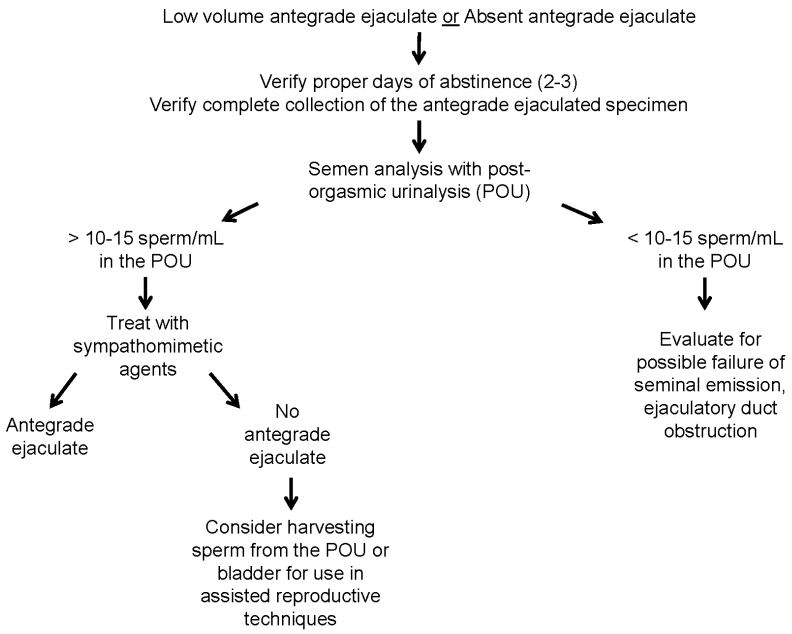

Figure 1: Diagnosis and Medical Treatment of Men with Ejaculatory Dysfunction. POU: Post-orgasmic urinalysis; mL: milliliter.

5.1 Erectile Dysfunction

Erectile dysfunction (ED) can impact fertility by impairing a couple's ability to successfully engage in sexual intercourse. Numerous studies have described a connection between infertility and impaired sexual function. [29,30,31,32] Monga et al found that infertile men had lower IIEF scores and less intercourse satisfaction than controls.[32] Shindel et al subsequently evaluated the prevalence of erectile dysfunction in male partners of infertile couples and found that 18% of the men had mild ED and 4 % had moderate ED. [33] This ED prevalence was much higher than the reference values of 7-9% ED prevalence for a young, contemporary American population as published by Laumann et al.[33] Shindel et al also found that men in infertile couples had a high rate of depressive symptoms and decreased mental health scores. [34] While the authors note that causality could not be assigned, they speculate that infertility and sexual dysfunction are conditions that synergistically exacerbate one another.

Interestingly, the relationship between these stresses and a couple's coping mechanisms help determine the overall psychosocial impact on the couple.[35] To date, no studies have prospectively tracked the specific impact of ED medical therapies on IIEF score, measures of sexual satisfaction, or depressive symptoms in men in infertile couples. (see **Figure 1**)

In infertile men diagnosed with ED, management should proceed according to the **AUA Guidelines on Erectile Dysfunction**.[36] Clinicians should be mindful of the fact that ED may be the only clinically apparent sign or symptom of underlying medical issues that might also negatively impact reproductive function and overall patient health, such as diabetes mellitus and endocrinopathies (hypogonadism, hyperprolactinemia), etc.

5.2 Ejaculatory Dysfunction

During normal ejaculation, stimulation of the sympathetic nerves, T10-L2, causes emission of semen into the posterior urethra. Antegrade ejaculation is then accomplished by sympathetically induced closure of the bladder neck and rhythmic contractions of the pelvic floor muscles under somatic control. (See **Disorders of Ejaculation: An AUA/SMSNA Guideline**) **Figure 1 details the diagnosis and medical treatment of men with ejaculatory dysfunction**, **which can be further subcategorized into retrograde ejaculation and failure of seminal emission**.

5.2.1 Retrograde ejaculation

Retrograde ejaculation is the passage of semen backwards into the bladder during an ejaculatory reflex. Retrograde ejaculation should be suspected in any patient with low semen volume (**hypospermia**) or absence of an antegrade ejaculate (**aspermia** or **anejaculation**). Patients with retrograde ejaculation may also have oligospermia or azoospermia. For individuals suspected of having retrograde ejaculation, **a post-orgasmic urinalysis** (**POU**) should be examined. Once the diagnosis is made, medical treatment with **alpha adrenergic agents** (ephedrine, pseudoephedrine, phenylpropanolamine) or the tricyclic antidepressant imipramine may result in bladder neck closure

during climax and achievement of antegrade ejaculation.[37,38,39] Kamischke and Nieschlag demonstrated that these medications are effective in up to 65% of patients.[38] If medications are not successful in converting retrograde to antegrade ejaculation, **POU sperm harvesting** (sperm retrieval from POU samples) can be performed, and the sperm can be used for intrauterine insemination (IUI) or in vitro fertilization (IVF).

Prior to POU sperm harvesting, steps can be taken to ameliorate the bladder environment that is otherwise toxic to sperm due to urine acidity and possibly urine osmolality. Ohl et al recommend administration of 500 mg sodium bicarbonate twelve hours and two hours prior to ejaculation to help diminish urine acidity [,,31]Additionally, these same authors suggested that fluid loading prior to the procedure might help abate the potential negative effect of increased urine osmolality on sperm viability.[37]

5.2.1a Alpha Adrenergic Agonists (Ephedrine, pseudoephedrine, phenylpropanolamine)

Rationale: The rationale for therapy is to stimulate sympathetic nerves at the bladder neck that are not being sufficiently stimulated by intrinsic mechanisms. This bladder neck stimulation promotes bladder neck closure and diminishes the likelihood of retrograde ejaculation.

Outcomes: Return of sperm to the ejaculate in patients with retrograde ejaculation who are treated with sympathomimetic agents ranges from 0-50% in the published literature.[38]

Adverse Effects: Adverse side effects can include restlessness, nausea, vomiting, weakness, headache, nervousness, dizziness, and a pounding or irregular heartbeat

5.2.1b Tricyclic Antidepressant Agent (Imipramine)

Rationale: Imipramine increases the muscular tone of the bladder neck via an adrenergic agonist effect, thus reducing likelihood of retrograde ejaculation.

Outcomes: Return of sperm to the ejaculate in patients with retrograde ejaculation who are treated with tricyclic antidepressant agents ranges from 38-65% in the published literature.[38]

Adverse Effects: Nausea, vomiting, drowsiness, weakness, fatigue, excitement, anxiety, nightmares, dry mouth, muscle spasms, slow speech, rash, and irregular heartbeat.

5.3 Failure of Emission

For a patient who cannot ejaculate and whose POU does not reveal sperm, failure of emission (FOE) should be suspected. FOE is a potential complication after retroperitoneal surgery such as retroperitoneal lymph node dissection (RPLND) for testicular cancer. The sympathetic nerves responsible for seminal emission and bladder neck closure originate in the twelfth thoracic to third lumber spinal nerves. These nerves converge to the paravertebral sympathetic chain that run along the vena cava and the aorta. Any surgery that can compromises this neuroanatomy, such as spinal procedures or dissection of the retroperitoneal lymph nodes without sparing the nerves can negatively result in FOE. An attempt can be made to treat such patients with sympathomimetics, but there have been only sparse reports in the literature of success with medical therapy. [37,40] FOE

patients not responsive to the above medical therapies are usually next treated with penile vibratory stimulation or electroejaculation. If these approaches are not successful, surgical sperm extraction procedures can be considered.

5.3.1 Sympathomimetic Agents (Ephedrine, pseudoephedrine, phenylpropanolamine)

Rationale: The rationale for therapy is to stimulate sympathetic nerves that promote seminal emission and that are not being sufficiently stimulated by intrinsic mechanisms.

Outcomes: Successful antegrade ejaculation of sperm in anejaculatory patients treated with sympathomimetic agents ranges from 0-30% in the published literature.[38]

Adverse Effects: Adverse side effects can include restlessness, nausea, vomiting, weakness, headache, nervousness, dizziness, and a pounding or irregular heartbeat

5.3.2 Tricyclic Antidepressant Agent (Imipramine)

Rationale: Imipramine induces seminal emission via an adrenergic agonist effect.

Outcomes: Antegrade ejaculation of sperm in patients with failure of emission who are treated with tricyclic antidepressant agents ranges from 0-16% in the published literature.[38]

Adverse Effects: Nausea, vomiting, drowsiness, weakness, fatigue, excitement, anxiety, nightmares, dry mouth, muscle spasms, slow speech, rash, and irregular heartbeat.

6. Infection and Inflammation

Infection and inflammation of the male reproductive tract can occur in concert with one another or independently. Numerous in vitro studies have demonstrated that certain bacteria have a direct detrimental effect on sperm function and viability. Additionally, leukocytes in the genital tract have been linked to resultant fertility impairment. Inspection of semen for leukocytes should be done with the understanding that “round cells” on semen analysis may either represent leukocytes or immature germ cells. The WHO defines leukocytospermia as seminal WBC concentrations > 1 million per ml.

A role for semen culture in assessment of infertility has not been established. Pathogens such as U. urealyticum, E. coli, Enterococcus, P. mirabilis, and M. hominis have been found at the same frequency in men who have leukocytospermia as men who do not have leukocytospermia.[41] Furthermore, 83% of healthy men presenting for vasectomy were found to have bacterial growth on semen culture, with 44% of the strains found in the semen also being found in the urethra.[42] The implication of this finding is that semen cultures tend to be positive even in asymptomatic men with demonstrated fertility, which calls into question the utility of semen culture in practice.

Organisms such as Chlamydia trachomatis, N. gonorrhea, T. pallidum, M. tuberculosis, H. ducreyi, herpes simplex virus, HPV and T. vaginalis have been associated with impaired sperm function in vitro[43,44,45] or found to bind to human sperm.[46,47] Treating known pathogenic organisms is appropriate regardless of fertility concerns.

In addition to the adverse effect of certain pathogens on sperm function, leukocytospermia itself can

be detrimental in the absence of bacteria. Several studies have found poor semen parameters in men with leukocytospermia.[48,49] However, this is controversial, as not all studies support the association between leukocytospermia and infertility.[50] One proposed mechanism by which leukocytospermia can negatively influence semen parameters is through reactive oxygen species (ROS). Leukocytes produce ROS, and ROS are known to cause oxidative stress induced cellular damage.[51] Several treatment options exist to protect spermatozoa from the deleterious effects of leukocytes, and therefore optimize semen quality. The four major pharmacologic approaches are antimicrobial therapy to treat clinical or subclinical infection, anti-inflammatory medications (cyclooxygenase-2 inhibitors), antioxidant therapy to minimize associated oxidative stress, and anti-histamines to stabilize mast cells. While findings in the literature are not uniform, some authors report that antimicrobial therapy targeted to semen culture bacterial sensitivities leads to improvement in sperm concentration, sperm motility, and semen antioxidant capacity. [52] Anti-inflammatory agents (cyclooxygenase-2 inhibitors) have been studied in a small cohort of men with abacterial leukocytospermia, and sperm concentration increased with no change in sperm motility or morphology.[53] The literature regarding the use of antioxidants is also very limited, but one study found that treatment with the antioxidant carnitine, after a course of an anti-inflammatory agent, led to a reduction in seminal leukocytes, an increase in viable sperm, and an increase in sperm forward motility in men with chronic abacterial prostatovesiculoepididymitis and pyospermia.[54] while antihistamine agents have not been extensively studied, an open, noncontrolled study of ketotifen demonstrated reduced semen white blood cell concentration, improved sperm motility, and improved sperm morphology.[55] Interestingly, ketotifen was also shown to increase sperm motility in the setting of asthenozoospermia *without* concomitant leukocytospermia, although the mechanism of action in this instance needs further clarification.[56]

7. Abbreviations

- **COX-2 inhibitor** – Cyclooxygenase-2 inhibitor
- **ED** – Erectile dysfunction
- **E2** - Estradiol
- **FSH** – Follicle stimulating hormone
- **GnRH** – Gonadotropin releasing hormone
- **hCG**- Human chorionic gonadotropin
- **hMG**- Human menopausal gonadotropin
- **IVF** – In vitro fertilization
- **KS** – Klinefelter syndrome
- **LH** – Luteinizing hormone
- **PEU** – Post-ejaculate urinalysis
- **r-FSH**- Recombinant Follicle stimulating hormone
- **ROS** – Reactive oxygen species
- **SA** – Semen analysis/es

- **T** - Testosterone
- **TESE** – Testicular sperm extraction

Presentations

MEDICAL TREATMENT Presentation 1

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