The Application of Clomiphene citrate in the Management of Hypogonadism Secondary to Concussive and Subconcussive Brain Traumas.

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Abstract

A decline in testosterone levels, observed in both men and women, has been associated with decreased quality of life and mental health issues. Testosterone appears to play a crucial role in personality with a low level being linked to psychological disorders such as depression and anxiety. Decades of research have established that testosterone replacement therapy could alleviate mood disorders in individuals with low testosterone and depressive symptoms. However, testosterone replacement therapy typically involves methods such as injectable testosterone, topical gels, or pellets, which may not be suitable for everyone due to age, gender consideration, maintenance of biological integrity, needle phobia, inconvenience, and potential side effects.

As an alternative to injectable testosterone, clomiphene citrate, a medication conventionally used to stimulate ovulation in women, has gained attention for managing testosterone insufficiency in men. Clomiphene citrate can effectively increase testosterone levels by stimulating the body's own production through enhanced luteinizing hormone release from the anterior pituitary gland. This makes it an attractive option for addressing low testosterone levels without resorting to injections, gels, or pellets.

In addition, testosterone's role in cognitive functions, including memory and spatial abilities, suggests that optimizing testosterone levels could also benefit cognitive performance. Since cognitive decline often accompanies psychiatric conditions, maintaining an optimal testosterone level may also support cognitive health. Clomiphene citrate's non-invasive administration makes it particularly appealing in this context.

Furthermore, testosterone influences stress and anxiety responses, with higher levels linked to reduction of panic attacks, hypervigilance, startle response, and improved stress resilience. The oral and non-invasive nature of clomiphene citrate makes it a preferable choice for addressing symptoms associated with testosterone deficiency as well as insufficiency.

Testosterone's neuroprotective properties, derived from its ability to modulate the central nervous system's microglia, can help protect against chronic neuroinflammation, a factor responsible for initiation and propagation of neurodegenerative diseases. Although indirectly related to psychiatric health, protecting against neurodegeneration can positively affect the brain's neurochemistry thereby supporting overall well-being. Thus, clomiphene citrate, by enhancing one's testosterone level, can contribute to neuroprotection and underscore its broader benefits.

Abbreviations: GnRH, gonadotropic releasing hormone; LH, luteinizing hormone; FSH, follicular stimulating hormone; HPG axis, hypothalamic-anterior pituitary-gonadal axis; MHC, Millennium Health Centers; DHT, dihydrotestosterone.

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Introduction

The Millennium Health Centers (MHC) have been at the forefront of innovations for the assessment and treatment of the causation for symptoms associated with traumatic and non-traumatic events. These traumatic events might be represented by a road-side bomb (IED), blast wave trauma (over-pressure), roar of jet engines, repetitive gun fire, motor vehicle accidents, blunt head trauma, subconcussive sports injuries, chronic emotional stress, chemotherapy, medication, or a prolonged surgical procedure (1,2).

Each of the aforementioned traumas, seemingly unique, nonetheless have a common thread that ties them together, that is, inflammation or more precisely neuroinflammation (3). No matter how minimal an injury is perceived to have been, there is an incremental effect with each subsequent trauma that can ultimately equate to the impact of one major traumatic event (4).

The analogy that ten dimes make up a dollar clearly represents the fact that you can have many subconcussive traumas or one major concussive trauma that creates the same damaging effects. The football player who experiences repetitive subconcussive impacts as well as the breacher who has been exposed to numerous blast waves will both succumb, over time, to the development of symptoms affecting their neuropsychiatric well-being and cognition (5).

In many of those that become symptomatic, the presence of depression, anxiety, panic attacks, bi-polar disorder, obsessive compulsive behavior, emotional volatility, anger, aggression, fatigue, and loss of libido are commonly associated with one or more hormonal deficiencies and neuroinflammation (6**)**.

It has been the operational philosophy of the MHC, based upon clinical experience and the scientific literature, that neuroinflammation is precipitated by trauma and can be associated with cerebral contusion, shearing of axons, and microvascular disruption (7**)**. In an acute traumatic scenario, inflammation induced by trauma is short lived resolving with minimal to no after-effects. These individuals, in essence, have completely recovered and any vestige of neuropsychiatric symptoms have abated along with the re-establishment of a healthy neuropermissive environment (8).

Unfortunately, this is not always the case in our soldiers or professional athletes who are exposed to repetitive subconcussive and concussive traumas that tend to prolong the inflammatory process and create a chronic traumatic scenario (9**)**. In these individuals, their neuropsychiatric symptoms tend to be progressive while paralleling the magnitude of their neuroinflammation.

As neuroinflammation continues, there are alterations in biochemical processes in the production of important neuropeptides and proteins as well as in the recognition of these messengers by their receptors. The important neurotransmitters GABA, Dopamine, Serotonin, Norepinephrine, and Glutamine that are responsible for regulation of neuroendocrine functions in the hypothalamus are diminished (10).

The presence of neuroinflammation interrupts the ability of these neurotransmitters to influence the hypothalamic induction and release of gonadotropic releasing hormone (GnRH) (11**)**. Thereby diminishing the chemical signal to the pituitary for the release of FSH and LH, which ultimately causes the loss of gonadal production of testosterone, estrogens, and progesterone (12**)**. Although this article is not specifically about traumatic brain injury, it is about the use of clomiphene citrate to repair the effects of trauma-induced neuroinflammation that causes the loss of not only testosterone and estradiol, but the regulation of steroidogenesis through adequate production of luteinizing hormone (13).

Hypogonadism – Identifying the Causation.

The present standard approach for treating an individual with a finding of a low or low-normal testosterone level is with the application of testosterone as a topical gel, injection, or as pellets (14). All of these modalities have been shown to be efficacious in returning testosterone to an optimal physiologic level. But the overlooked issue is in answering where in the HAP-G axis is the deficiency arising.

The relationship between the hypothalamic release of GnRH, its stimulation of the pituitary's release of luteinizing hormone (LH), and the ultimate effect on testicular leydig cells or ovarian thecal cells, is what needs to be elucidated in order to optimize the patient's well-being while doing the least amount of harm (15). In essence, we need to define if the deficiency or insufficiency is from the hypothalamus, pituitary, or gonads (16)?

A shotgun approach with the random application of testosterone for all causes of deficiency can obscure the opportunity to identify the mechanism causing the deficiency which could possibly be reversed. Ideally, recovering the patient's endogenous production of testosterone has a multitude of benefits as opposed to making them reliant on continuous supplementation with testosterone (17) due to permanent damage to their HAPG axis.

In the sections that follow, we will address the key question of how to determine where in the biological circuitry is the disruption occurring. Once this is identified, a more accurate correction can be designed and provided to the patient.

Primary Hypogonadism

Primary hypogonadism is a condition characterized by impaired testosterone production due to intrinsic dysfunction of the testes, specifically involving the Leydig cells. This intrinsic testicular failure leads to reduced testosterone levels despite normal or elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, indicating a problem at the gonadal level.

Hypogonadism in a male patient can be caused by testicular failure due to genetic disorders (18), exposure to high levels of luteinizing hormone, orchitis, trauma, radiation, chemotherapy, NSAIDs, or undescended testes, and is known as hypergonadotropic hypogonadism or Primary Hypogonadism (19). In primary hypogonadism it is assumed that the causative factor accounting for testicular Leydig cells failure to produce testosterone, is because they have become insensitive to LH (20).

In response to prolonged stimulation, the Leydig cells may downregulate the number of LH receptors, thereby limiting the number of potential ligand-receptor interactions. As individuals get older, Leydig cells may become less responsive to LH's ability to initiate the transcriptional sequence leading to the production of testosterone (21). Metabolic disorders and obesity are associated with chronic low-grade inflammation that can epigenetically alter hormonal signaling. These conditions can directly disrupt Leydig cell functioning and make them less responsive to LH signaling (22).

The use of exogenous testosterone or anabolic steroids can lead to Leydig cell desensitization, as the body may perceive sufficient testosterone levels and reduce its own production. This is often seen in individuals who misuse anabolic steroids (23). The active metabolite of testosterone, dihydrotestosterone (DHT), has

been found to be 3 times more suppressive of GnRH than testosterone (24) and accounts for suppressed production of LH under anabolic steroid use.

Exposure to endocrine-disrupting chemicals, such as certain pesticides or industrial chemicals, interferes with Leydig cell function and LH receptor sensitivity (25). Identifying and addressing the underlying cause is essential for effective treatment, which may include hormone replacement therapy or lifestyle modifications, depending on the specific case (26).

Clinical laboratory testing will frequently disclose a low to low-normal free testosterone level and an elevated LH level. This laboratory pattern is due to an attempt by the hypothalamus to raise the concentration of serum testosterone. In this Positive Feedback Loop (PFL), when hypothalamic sensing detects a deficiency or insufficiency of testosterone, GnRH is secreted from the median eminence into the fenestrated capillaries of the portal circulation where it is carried to the anterior pituitary. When GnRH enters the pituitary circulation, it induces the release of LH and FSH which then circulates to attach to LH-receptors situated on the Leydig cells. Once this ligand is created the gonads are induced to convert Cholesterol down a cascade to become testosterone (27).

Upon initial consideration of these dynamics, clomiphene citrate would not be a good treatment option because you need healthy functioning Leydig cells that can recognize LH to induce testosterone production. Therefore, in all cases of Primary Hypogonadism, with elevated LH and low circulating Free Testosterone, injectable testosterone is perceived to be the best solution, **if all other parameters are normal**.

The exception to this condition is relative to a transient form of Primary Hypogonadism that is induced by the non-steroidal anti-inflammatory drug (NSAID), Ibuprofen. Details of this are found in the section "Clomiphene and Compensatory Hypogonadism."

Secondary Hypogonadism

Secondary hypogonadism is a condition characterized by insufficient production of testosterone due to impaired function of the pituitary gonadotrophs, which leads to inadequate secretion of luteinizing hormone and follicle-stimulating hormone. This impairment disrupts the normal stimulation of the testes, resulting in reduced testosterone synthesis.

Luteinizing hormone, secreted by the anterior pituitary gland, targets the Leydig cells within the testes, where it catalyzes the conversion of cholesterol into testosterone (28). However, disruption of the gonadotroph cells in the anterior pituitary can lead to decreased levels of circulating free testosterone (29). Ordinarily, a deficiency of testosterone would trigger hypothalamic release of GnRH, which in turn stimulates the pituitary to release LH. But in cases of pituitary damage, the feedback loop fails; GnRH does not provoke LH production from the gonadotroph cells. The presence of both low LH and low free testosterone levels indicates Pituitary Hypogonadism (30), suggestive of pituitary damage or failure.

To further complicate this discussion, what do you think the pattern would be if the hypothalamus was damaged? Since we cannot measure the production of GnRH with ease, there is an alternative means of determining where the problem lies with the use of a GnRH Stimulation test or the clomiphene challenge test.

The GnRH stimulation test consists of taking an initial blood sample for levels of both FSH and LH followed by an injection of GnRH. Thereafter, several blood samples are taken 15 to 30 minutes apart over a two-hour time frame with a final blood sample at 24 hours. If the pituitary gland is functional there will be a rise in the production of FSH and LH (31).

The Clomiphene challenge test requires the use of 50mg clomiphene for 2 – 4 weeks. An initial blood level for FSH and LH is drawn and compared to follow-up levels after the challenge period. Elevation in the gonadotropins (LH & FSH) is a sign that the Hypothalamic-Pituitary axis is intact (32). Failure of clomiphene to induce production of gonadotropins can be a sign of a more complex causation stemming from hypothalamic damage, neuroinflammation, or pituitary dysfunction all of which are explained in subsequent sections of this paper.

If the pituitary gland is incapable of responding to GnRH from the hypothalamus, this scenario would be best addressed with supplementation with testosterone.

Hypothalamic Hypogonadism: The role of Glia in GnRH induction.

Hypothalamic hypogonadism, a condition characterized by insufficient GnRH secretion from the hypothalamus, has garnered increasing attention among healthcare professionals in the field of neuroendocrinology (33).

Male congenital hypogonadotropic hypogonadism or Kallmann's syndrome affecting 1 in 30,000 males and 1 in 125,000 females and is associated with decreased sense of smell. This syndrome results from disturbed intrauterine migration of GnRH neurons from the olfactory placode to the hypothalamus (34,35).

While traditionally, the emphasis has centered on neurons as the primary regulators of GnRH secretion, recent research has identified a pivotal role of glial cells, particularly astrocytes, in this intricate process (36). Under ideal conditions, astrocytes, through their production of prostaglandin E2 (PGE-2), regulate neuronal GnRH activity and function by modulating neurotransmitter availability, synaptic plasticity, and the response to metabolic signals (37).

Nevertheless, the astrocyte's role is intricately influenced by a state of neuroinflammation induced by trauma, viral infections, and environmental toxins. In the context of neuroinflammation, astrocytes can undergo phenotypic change that impact their production of PGE-2. Within a neuroinflammatory milieu, astrocytes can either enhance or diminish their PGE-2 production, subsequently modulating GnRH neuronal activity and function (38).

In the scenario of Kallmann's syndrome, testosterone replacement would be the obvious choice since clomiphene would not work due to the lack of GnRH neurons that would normally respond to this challenge. Therefore, testosterone by injectable or possibly pellets would be the optimal means to raise their testosterone level (39).

But in cases of subconcussive or concussive brain injury where the trauma has created a neuro-inflammatory environment, the inflammation must be mitigated along with the use of clomiphene or e-clomiphene to stimulate the release of GnRH until the inflammation is quelled (40). In our patients assessed with a hormonal biomarker panel, and then placed on Clomiphene citrate as indicated below, over 70% regained their testosterone production.

Quartile	LH level	Dosing – 50mg
Less than 1st	If LH is below the 1st Quartile of the range.	Clomiphene citrate every 48 hours at bedtime.
1st to 2nd	If LH is within the 2nd Quartile of the range.	Clomiphene citrate every 72 hours at bedtime.

Based upon the LH level we will either start with clomiphene citrate 50mg every 48 hours or 72 hours based upon the quartile results from the laboratory. Follow-up labs are initially every 90 days for two cycles.

Rationalization for Treatment with Clomiphene or Enclomiphene

How Clomiphene Citrate Works

Clomiphene citrate (CC), classified as a selective estrogen receptor modulator (SERM), functions as an antagonist at estrogen receptors (ER) situated within the hypothalamus. This antagonistic interaction disrupts the formation of receptor-hormone complexes, leading to the liberation of GnRH. Gonadotropin releasing hormone, subsequently, stimulates the anterior pituitary gland to increase secretion of both LH and FSH (41,42,43).

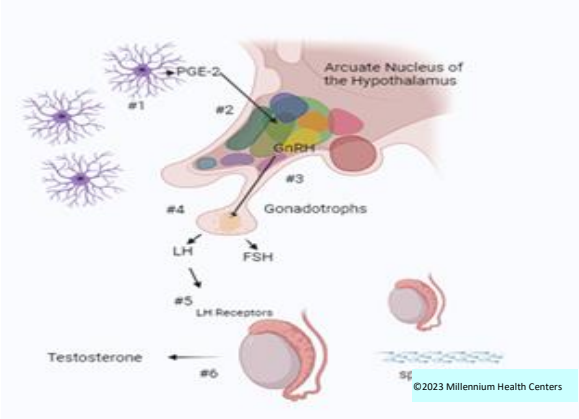

Diagram 1: By obstructing the receptor-hormone complex, CC triggers the release of GnRH, which, in turn, prompts heightened secretion of LH and FSH from the anterior pituitary gland. LH, in particular, stimulates testosterone production in Leydig cells within the testes and thecal cells in ovaries. Although primarily indicated by the FDA for ovulation induction in female infertility, numerous studies have underscored the safety and efficacy of CC in addressing male hypogonadism (44,45).

What about Enclomiphene citrate?

What we refer to as Clomiphene citrate is really a mixture of two different isomers of the drug, Zuclomiphene and Enclomiphene. It is believed that the mixture of these two isomers can account for some of the side effect attributable to the clomiphene form such as hot flashes, mood swings, and headaches (46,47). Also, Clomiphene might not be effective in all cases of hypogonadism in men and can have adverse effects on the endometrium in women (48).

It is believed that the pure Enclomiphene citrate isomer may have fewer side effects than clomiphene citrate and it may be more effective than clomiphene citrate at increasing testosterone production in men with hypogonadism. Additionally, levels of estradiol are lower than that in the clomiphene group (49). But there are those individuals using Enclomiphene that do not respond as well as in others, which is the same case with Clomiphene citrate (50).

What is extremely important in evaluating the reported side effects of clomiphene citrate is the frequency of dosing when used in male patients. As you will read in, "**The Pulsatile use of Clomiphene citrate**" and "**The Risks of Clomiphene citrate**", ocular, mood, and estradiol elevation are rare occurrences.

Nonetheless, the Millennium recommends that enclomiphene be dosed at either 12.5mg or 25mg every 72hrs at bedtime for optimal benefits with minimal side effects.

Clomiphene and Primary Hypogonadism

Laboratory results suggestive of primary hypogonadism would include an elevation in LH and a low to low-normal level of free testosterone (fT). In individuals with a history of subconcussive or concussive head trauma, the regulation of LH by GnRH might be affected by the presence of inflammation (51). Consequently, the laboratory results might present with both LH and fT being low to low-normal. Therefore, the patient's history of neurotrauma (52) and possibly Ibuprofen (53) use will give important information to help define causation and to direct treatment.

When primary hypogonadism is not associated with a medical history of genetic abnormalities, testicular trauma, autoimmune disorders affecting the testes, infections like mumps orchitis, or exposure to toxins or radiation, the use of either clomiphene or enclomiphene would not resolve this particular form of hypogonadism. Therefore, the use of testosterone in the form of injectable cypionate, or a blended injectable cypionate/propionate combination, subcutaneous pellets, and lastly topical creams are all options.

1i - Clomiphene and Compensatory Hypogonadism

Recent research suggests that ibuprofen, a widely used nonsteroidal anti-inflammatory drug (NSAID), may influence Leydig cell function and the transcription of the LH receptor, a crucial regulator of testosterone production (54). Ibuprofen inhibits the enzyme cyclooxygenase (COX), particularly the COX-2 isoform, affecting Leydig cell transcription of the LH receptor. Located in the testes, Leydig cells produce testosterone in response to LH stimulation, which binds to its receptor on the Leydig cell membrane, activating signaling pathways that culminate in testosterone transcription and synthesis. Ibuprofen disrupts the prostaglandin signaling pathway, regulated by COX enzymes, which is implicated in LH receptor expression regulation (55).

Prostaglandins, lipid signaling molecules derived from arachidonic acid metabolism by COX enzymes, exert various physiological effects, including inflammation modulation and hormone synthesis and secretion regulation. Within Leydig cell function, prostaglandins have been associated with LH receptor expression and testosterone production regulation. Ibuprofen's COX-2 inhibition reduces prostaglandin synthesis, potentially affecting LH receptor gene transcription regulation.

Studies indicate that ibuprofen exposure may decrease LH receptor expression in Leydig cells, potentially impairing responsiveness to LH stimulation and reducing testosterone synthesis. Such effects could impact male reproductive health, given testosterone's crucial role in spermatogenesis, sexual function, and overall well-being.

Fortunately, emerging research suggests that selenium supplementation may hold promise in mitigating the adverse effects of ibuprofen on Leydig cell function and testosterone production. Selenium, an essential

micronutrient with antioxidant properties, has been shown to counteract oxidative stress and inflammation, which are implicated in ibuprofen-induced disruptions to Leydig cell activity. By scavenging reactive oxygen species (ROS) and modulating inflammatory pathways, selenium may help protect Leydig cells from the detrimental effects of ibuprofen, thereby preserving their ability to produce testosterone (56).

When the primary hypogonadism is associated with a history of ibuprofen use (or any other gonadal toxin) and laboratory results show an elevated LH with a low to low-normal fT, with or without a head trauma history, I would start them on a program of Selenium 200mcg BID for 8 weeks, and Clomiphene citrate 50mg every other night for an initial 90 days and then retest. Clomiphene might need to be extended for another 90 days as well as the dosing frequency might need to be moved to every 72 hrs. based upon the level of LH.

1j - Clomiphene and Secondary Pituitary Hypogonadism

Clomiphene citrate and its isomer, enclomiphene citrate, are effective treatments for secondary hypogonadism. Clinical studies have demonstrated that clomiphene citrate can significantly improve testosterone levels in men with secondary hypogonadism, with some studies reporting increases in testosterone levels by as much as 100% to 200% after treatment (57). Enclomiphene citrate, specifically targeting the estrogen receptors without the antiestrogenic effects on bone and lipid profiles seen with clomiphene, has also shown promise (58,59). Data indicates that enclomiphene citrate can achieve similar or superior improvements in testosterone levels, often normalizing in up to 80% of patients (60). Additionally, these treatments have been shown to improve symptoms of hypogonadism and fertility parameters, with clomiphene citrate increasing sperm concentration by 106% and motility by 57% in some studies, making them valuable options in the therapeutic arsenal against secondary hypogonadism (61,62).

1k - Hypothalamic Hypogonadism and Clomiphene

The use of pulsatile clomiphene or enclomiphene citrate for the treatment of tertiary hypogonadism, which involves hypothalamic dysfunction resulting in inadequate GnRH secretion, is less frequently discussed compared to secondary hypogonadism. However, these SERMs can indirectly stimulate the hypothalamic-pituitary-gonadal axis. By blocking estrogen receptors, they reduce negative feedback on the hypothalamus, enhancing GnRH secretion, thereby increasing LH and FSH levels and improving testosterone production (63).

Clomiphene citrate has shown efficacy in increasing testosterone levels by 100% to 200% and has led to significant symptom improvement in up to 70% to 80% of men with hypogonadism. Enclomiphene citrate has demonstrated similar effectiveness, making these treatments valuable for addressing hormonal deficiencies in tertiary hypogonadism (64).

1l - The Pulsatile production of GnRH with Clomiphene citrate.

The articles "Hypophysial responses to continuous and intermittent delivery of hypothalamic gonadotropin-releasing hormone" (65) and "GnRH Pulsatility, the Pituitary Response and Reproductive Dysfunction"

(66) both emphasize the critical role of GnRH pulsatility in reproductive health. The first study demonstrated that continuous GnRH administration fails to sustain gonadotropin secretion, while intermittent delivery restores normal function, highlighting the necessity of pulsatile GnRH for proper pituitary response. The review further explores how disrupted GnRH pulsatility leads to reproductive dysfunctions such as hypogonadotropic hypogonadism and PCOS, stressing the importance of mimicking natural GnRH rhythms in therapeutic approaches (67).

It was from a consensus of a number of journal articles that discussed the use of SERMs in a pulsatile manner that led the Millennium to perform the 2014-2016 Veterans' Three-year study on the use of Clomiphene Citrate for Hypogonadism. We studied a 72-hour, 48-hour and 24-hour dosing regimen and found that 50mg every 72 hours was the most effective at raising testosterone levels.

2a - Risks and Benefits of Clomiphene citrate

Since 2010, the Millennium has been using clomiphene citrate to treat low to low-normal levels of Free Testosterone as a means of preserving both endogenous testosterone production and fertility. In the **Three-Year Veterans' Study** (2014-2016), we looked for the dosage and frequency of dosing that provided the highest luteinizing hormone response with a corresponding elevation in the free testosterone level. We found that the preponderance of benefits was attained with a 50mg dose of clomiphene citrate, every 72 hours, which effectively raised the level of free testosterone to within the median of the physiological range. According to a 2015 metanalysis consisting of 26 different studies between 1989 to 2014 on the use of Clomiphene (SERMS), they concluded that the "Off-label use of SERMs, such as clomiphene citrate, are effective for maintaining testosterone production long-term and offer the convenience of representing a safe, oral therapy" (68.69).

The medical literature still contains clinical cases of perceived side-effects from the use of clomiphene citrate as well as with enclomiphene citrate. However, within the Millennium's population of patients on clomiphene, we rarely encounter those who develop symptoms relative to mood, libido, or ophthalmologic complaints. Nonetheless, and for completeness, here are some of the side-effects and additional benefits reported in the medical literature.

2b - Ophthalmologic Effects of Clomiphene Citrate

While clomiphene citrate is generally considered safe and effective (70,71), like any medication, it carries uncommon but potential side effects including ophthalmologic complications associated with visual disturbances. Patients may experience symptoms such as blurred vision, floaters, or changes in color perception (72). These symptoms typically occur during treatment and usually resolve upon discontinuation of the medication (73). However, in some cases, visual disturbances can persist even after cessation of clomiphene therapy. The exact mechanism underlying these visual disturbances is not fully understood, but it is believed to be related to the anti-estrogenic effects of clomiphene on the retina and optic nerve (74).

The visual disturbances presumed to be associated with the use of clomiphene citrate have been weakly documented in single case studies or in small groups of almost exclusively female patients (75). In a series of articles looking at side-effects of clomiphene citrate in women who used high doses over a short duration, found some occurrences of visual hallucinations (76), flickering, shimmering of visual fields, and the

perception of floaters (77). A report out of the University of Ottawa Eye Institute's Ophthalmology Clinic stated, "The effect of clomiphene citrate on vision was minimal, and the visual disturbances were reversible in all patients (78)"

An evaluation of over 900 Millennium patients, who have been on clomiphene citrate 50mg every 72 hours for 1-60 months, did not support the occurrence of visual disturbances as a common encounter. In fact, in those patients who perceived to have new on-set of "floaters", upon ophthalmologic evaluation they were not present, or they were deemed to be pre-existing from a prior causation (79).

A study published in the journal "Fertility and Sterility" reported a case of a 35-year-old woman who developed bilateral visual disturbances while undergoing treatment with clomiphene citrate for infertility. The patient experienced blurred vision and photopsia (perceived flashes of light) shortly after starting clomiphene therapy. Ophthalmologic evaluation revealed no abnormalities in the anterior or posterior segments of the eye. However, electroretinography (ERG) testing showed reduced retinal function, suggesting a potential toxic effect of clomiphene on the retina (80).

Another study published in "Archives of Gynecology and Obstetrics" described a case of central serous chorioretinopathy (CSCR) associated with clomiphene citrate use. CSCR is a retinal disorder characterized by the accumulation of fluid under the retina, leading to visual disturbances such as blurred or distorted vision. The case involved a 29-year-old woman who developed CSCR after three cycles of clomiphene therapy for ovulation induction. Ophthalmologic examination confirmed the diagnosis of CSCR, and the patient's symptoms improved after discontinuation of clomiphene citrate (81).

A study published in the "Journal of Urology" reported a case of a 40-year-old man who developed bilateral visual disturbances while undergoing clomiphene citrate therapy for low testosterone levels. The patient experienced blurred vision and photopsia shortly after starting clomiphene treatment. Ophthalmologic evaluation revealed no abnormalities in the anterior or posterior segments of the eye. However, electroretinography (ERG) testing showed reduced retinal function, suggesting a potential toxic effect of clomiphene on the retina in men as well (82).

The medical literature, relative to the actual and perceived ophthalmologic complications of clomiphene citrate, does not take into consideration the vast difference in dosing between males and females. In a female going through ovulatory induction with clomiphene, they usually start with 50mg a day for 5 consecutive days. If this dose fails to produce a response the dose is increased in each subsequent cycle up to 250mg a day (83). Millennium patients, mostly males, receive a starting dose of 50mg every 72 hours which might be decrease to 25mg every 72 hours based upon the LH-Testosterone response. Others might take the clomiphene every 48 hours if their initial response is less than optimal after the initial dosing regimen. We believe that this protocol accounts for the general lack of any complications directed towards clomiphene's use.

2c – The Liver, Clomiphene, and Suppression of Hepatic IGF-1 Production

Since transitioning to the use of SERMs as the initial treatment for veterans with hypogonadism, clinically we noted that there was a proportionate decrease in IGF-1 production (84) without a reduction in growth hormone or IGF1-BP3 levels. In fact, woman who were on bio-identical estradiol had an increase in GH

and IGF-1 as long as they were not on a SERM (85). Looking into the medical literature it became clear how important estradiol is for the production of growth hormone by the anterior pituitary gland and how both estradiol and GH are needed for the optimal production of IGF-1 in the liver (86).

Clomiphene citrate is known to influence the hepatic production of insulin-like growth factor-1 (IGF-1) through its action on estrogen receptors. Normally, estradiol plays a crucial role in enhancing the liver's sensitivity to growth hormone (GH), which in turn stimulates IGF-1 production (87). Clomiphene citrate, as a selective estrogen receptor modulator (SERM), can block estradiol's action at its receptors. This antagonistic effect can potentially reduce the liver's response to GH, thereby decreasing the production of IGF-1 (88).

When clomiphene citrate is administered, it competes with estradiol for estrogen receptors, inhibiting estradiol's physiological effects. Since estradiol enhances GH receptor sensitivity and the downstream signaling necessary for IGF-1 synthesis, blocking its action can attenuate these processes. This reduced sensitivity can lead to lower levels of IGF-1 production despite normal or elevated levels of GH.

Research has shown that estradiol significantly enhances GH-stimulated IGF-1 production by upregulating GH receptor expression and facilitating the post-receptor signaling pathways essential for IGF-1 synthesis in hepatocytes. Thus, clomiphene citrate's antagonism of estrogen receptors can disrupt these processes, leading to a decrease in hepatic IGF-1 production. This mechanism highlights the complex interplay between sex hormones and growth factors in regulating metabolic functions (89).

2d. Benefits of Clomiphene with Atypical Cluster Headaches

Clomiphene citrate, traditionally utilized for its role in inducing ovulation, exerts significant influence on the endocrine system, particularly in modulating estrogen levels. Emerging evidence suggests that the pathophysiology of both atypical migraines and cluster headaches may be intricately linked to hormonal fluctuations and serotonin dysregulation (90). By acting as a selective estrogen receptor modulator, clomiphene citrate can stabilize these hormonal imbalances, potentially reducing the frequency and severity of headache episodes (91). Moreover, its influence on serotonin pathways aligns with the neurochemical targets common to migraine and cluster headache treatments. The unique pharmacological profile of clomiphene citrate offers a dual mechanism of action: hormonal stabilization and serotonin modulation, which could provide substantial therapeutic benefits for patients unresponsive to conventional therapies. Ongoing research and clinical trials are crucial to validate these findings and establish clomiphene citrate as a groundbreaking treatment option in headache management, promising a new horizon for patients suffering from these debilitating conditions (**92**).

Clomiphene citrate and Testicular Cancer

A comprehensive review of the literature, including data from the American Cancer Society and multiple meta-analyses of worldwide medical studies, indicates that the relationship between clomiphene citrate use and testicular cancer risk is complex and not definitively established. Some studies suggest that clomiphene may increase the risk of testicular cancer due to its stimulating effects on the gonads. The hypothesis is that

increased gonadotropic stimulation could potentially lead to cellular changes or proliferation that might predispose to malignancy (93).

However, the evidence remains inconclusive. For instance, a large meta-analysis of patient data showed no significant increase in testicular cancer incidence among men treated with clomiphene citrate compared to the general population. This suggests that while the drug does stimulate testicular activity, it does not necessarily translate into an elevated cancer risk (94). Moreover, the American Cancer Society emphasizes that known risk factors for testicular cancer include a family history of the disease, undescended testes (cryptorchidism), and certain genetic conditions, rather than medication use per se.

In a 2012 study with 650 infertile men, two young patients developed a testis tumor, one of them even 21 months after discontinuing CC (95). According to the American Cancer Society, one out of 250 men develop testicular cancer during their life, at an average age of 33 years (96). Thus, the possibility of developing testis tumor during CC treatment seems comparable with the normal population. Furthermore, infertile males seem to have a double or triple life-time risk of developing testicular cancer in comparison with the fertile population (97) Taking this in account, two of 650 infertile patients are actually a low prevalence of developing a testis tumor in this patient group.

Therefore, while theoretical concerns exist about the possible link between clomiphene citrate and testicular cancer, current evidence does not strongly support a significant increase in risk. Patients using clomiphene citrate should be monitored regularly, and any new or unusual symptoms should be evaluated promptly. More research, particularly long-term, prospective studies, are needed to fully elucidate the safety profile of clomiphene citrate concerning testicular cancer risk (98).

Discussion

Clomiphene citrate, originally developed and approved for female infertility in the 1960s, began to be explored for the treatment of male hypogonadism in the late 1970s and early 1980s. This off-label use leverages clomiphene's ability to block estrogen receptors in the hypothalamus, leading to an increase in gonadotropin-releasing hormone secretion. Consequently, this stimulates the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland, which in turn promotes testosterone production in the testes.

The benefits of using clomiphene citrate or enclomiphene citrate for male hypogonadism include its ability to improve testosterone levels without the negative feedback suppression of spermatogenesis often seen with exogenous testosterone therapy. Studies have shown significant improvements in serum testosterone levels, sperm count, and motility, which are crucial for men with hypogonadotropic hypogonadism who are seeking fertility treatments.

Although the majority of articles published on clomiphene and enclomiphene citrate show its low or rare occurrence of side-effects, it is important to know that they do exist. These potential side-effects include visual disturbances, gynecomastia, mood swings, and an increased risk of venous thromboembolism (testosterone related) (99). Additionally, concerns about the long-term safety of clomiphene, particularly regarding its impact on testicular function and the potential risk of cancer, necessitate regular monitoring and further research.

Overall, while clomiphene citrate and enclomiphene citrate present beneficial alternatives for managing male hypogonadism and preserving fertility, careful consideration of the risks and close medical supervision are essential for optimizing treatment outcomes.

The Millennium Health Centers has studied the safety and efficacy of clomiphene citrate for more than 15 years. To date, the Millennium has introduced over 900 patients to a pulsatile use of 25mg to 50mg of clomiphene citrate at bedtime for months to 9 years of use.

At present, we have 5 patients that are using enclomiphene due to initial side-effects from clomiphene citrate that included emotional volatility and fatigue. These individuals were started on 12.5mg of enclomiphene every 48 to 72 hours and monitored for efficacy as well as side effects.

Overall, once a patient is started on clomiphene citrate 50mg every 72 hours, we perform a follow-up blood test at about 90 days after initiation of treatment. This includes free (fT) and total testosterone (tT), DHT, SHBG, DHEA-s, estradiol (E2), and luteinizing hormone (LH). What we are looking for is an elevation in LH that drives an increase in fT. If LH does not rise significantly we will increase the dosing frequency of clomiphene to every 48 hours. If there is a rise in LH with a corresponding elevation in fT, we continue on this protocol. In the event that the LH rises, and fT does not then based upon the patient's history the issue might be an NSAID (ibuprofen/ Naproxen) for which we will increase the dosing frequency to every night for 30 days. If there is a response with production of free testosterone then the dosing is reduced to every 48 hours. If not, then another protocol for testosterone replenishment is initiated.

Laboratory Patterns of Hypogonadism

Condition	Testosterone	GnRH	LH	FSH
Normal HAP-Gonadal Axis	Normal	Normal	Normal	Normal
Primary Hypogonadism	Low	Normal	High	High/normal
Secondary Hypogonadism	Low	Low/normal	Low	Low/normal
Tertiary Hypogonadism	Low	Low	Low/normal	Low/normal
Compensatory Hypogonadism	Low	Normal/high	High/normal	High/normal

Table 1: Primary hypogonadism is attributed to a dysfunction in the Leydig cells of the testes, impairing their ability to produce testosterone. Secondary hypogonadism arises from a dysfunction in the pituitary gonadotrophs, which are responsible for the secretion of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Tertiary hypogonadism is due to a failure in the hypothalamic arcuate nuclei to produce gonadotropin-releasing hormone (GnRH). This failure can result from traumatic damage to the GnRH-producing nuclei or from inflammation that inhibits the production of astrocytic prostaglandin E2 (PGE2). Compensatory hypogonadism occurs when Leydig cells do not respond adequately to LH stimulation, prompting the hypothalamus and anterior pituitary gland to increase LH production in an attempt to compensate for the low testosterone levels. This condition can be considered a subtype of primary hypogonadism, potentially induced by the use of nonsteroidal anti-inflammatory drugs such as ibuprofen.

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