

Examining the Efficacy of Clomiphene Citrate as a Treatment for Male Infertility

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Abstract

The infertility rates in adult males have been rising at an alarming rate in recent years. Studies have shown that sperm counts have declined more than 59% in the past 50 years among men throughout North America, Europe, and Australia. The recent emergence of COVID-19 has further increased male fertility concerns, with studies evidencing potential damage the virus could inflict upon the testes. While it is not clear yet whether these developments have any major implications on the future of the human race as a whole, couples around the world struggle to come to terms with the fact that a biological child is not an option for them. The majority of these cases are a result of functional hypogonadism, a condition where infertility is caused by a secondary factor such as hormone abnormalities, obesity, and chronic illnesses, rather than an impaired hypothalamic-pituitary-testicular axis. Clomiphene citrate is a treatment for functional hypogonadism that has yet to be approved by the FDA for men, but has shown promising results in clinical trials and is used off-label. This project analyzes the recently emerging drug of as a gonadotropin-inducer in men by corroborating existing research to find causations and interviewing a user of the drug for his experiences. An educated claim (with limitations considered) is then made to identify whether the treatment is safe and effective and an ideal patient target and dosage is stated.

Keywords: COVID-19; Infertility; FDA

Introduction

Male infertility continues to be a developing crisis, as studies have suggested factors like microplastics and diet have lowered sperm counts globally. In addition, the COVID-19 virus has been linked to male infertility, with various studies showing that patients who had contracted COVID-19 have a considerably higher number of inflammation and oxidative stress markers in sperm cells [14]. Many treatments come to mind when addressing male infertility such as varicocele surgery and *in-vitro* fertilization, but one intriguing prospect has begun to emerge as an off-label treatment. Clomiphene Citrate, a drug which is often used in women as an ovulation inducer, has potential to treat male infertility by blocking estrogen from affecting the pituitary gland. Several studies have been conducted testing its safety and efficacy both short and long term, with most providing desirable results. However, it

is yet to be approved for men by the FDA, who state that "There are no adequate or well-controlled studies that demonstrate the effectiveness of CLOMID in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using clomiphene" [7]. The goal of this research is to determine whether Clomiphene Citrate is a viable option in treating the crisis of male infertility.

Literature Review

Male infertility is a condition with a variety of causes, including but not limited to genetic mutations, illnesses, or structural issues. Consequently, there are also a wide selection of treatments, invasive and noninvasive. When mentioning infertility, the mind often wanders to testosterone replacement therapy. However, while TRT has shown to give favorable results towards increasing testoster-

one levels, it is shown to have adverse effects on fertility, due to its indirect suppression of gonadotropin-releasing hormones [23]. This suppression of GnRH halts the production of follicle-stimulating hormones and luteinizing hormones, which signal sperm and testosterone production in the testes, respectively. A recently emerging treatment that encourages the increase of both testosterone levels and sperm quality is clomiphene citrate. One of the most intriguing characteristics of clomiphene therapy (clomid) is that it does not suppress gonadotropin hormones due to its identification as a selective estrogen receptor modulator (antagonistic). Because it blocks estrogen receptors, it also blocks the handicaps of estrogen on FSH and LH, which consequently improves spermatogenesis and testosterone production.

Figure 1: This is a visual of clomiphene's obstruction of estrogen receptors to produce LH (FSH prod. not displayed) [16].

Considering these circumstances, clomiphene is most effective in the setting of men with low testosterone, low sperm counts, and low gonadotropin levels. Another important detail to note is that the use of clomiphene can only be administered in men with an operative hypothalamic-pituitary-gonadal axis, and will not be effective in men with organic hypogonadism [12]. Furthermore, patients with already sufficient FSH and LH levels will not experience significant results from CC, owing to the fact that CC relies on improved gonadotropin production to stimulate fertility and hormone production.

One lingering concern with clomiphene are the side effects, which include gynecomastia, visual abnormalities, irritability, and

headaches [9]. Reports of deep vein thrombosis and other thromboembolic complications have emerged in women that underwent CC therapy, possibly due to hypercoagulation from the abnormal hormone activity [2]. However, it is unclear if these same complications can arise in men. Nevertheless, it is safe to assume that patients with a history of thromboembolic conditions should stay wary of SERMs like CC. The largest study yet on the efficacy of the drug features the study mentioned earlier, in which 400 hypogonadal patients went through CC treatment with 280 taking it for less than 3 years, and 120 taking it for more. The vast majority experienced eugonadism and improved testosterone levels, and a slightly smaller majority experienced improved sexual symptoms. The side effects reported in this drug were minimal, and included impairments such as blurred vision, changes in mood, and breast tenderness. There were no significant adverse effects in any patients that warranted a cessation of the treatment/dosage [10]. Moreover, all these details proved to be consistent in both the long and short-term patients. While 3 years is a relatively short period to be considered long term, the project was a relative success in solidifying CC as a remedy for low testosterone levels from hypogonadism, and in the context of this paper, it provided valuable data on the side effects clomiphene can induce. However, it failed to give definitive data on its effects on sperm counts, although patients reported larger testes size.

Many other studies proved a consistent improvement in testosterone production as well as gonadotropin production. In one, 32 prospective fathers were treated with CC for 6-12 months for idiopathic oligospermia, and 13 pregnancies occurred [17]. Another study involving 76 men proved that an average pretreatment testicular volume of less than 14 mL and an LH level of less than 6 IU/mL are adequate forecasters of a desirable response to CC [13]. For reference, the average testicular volume in men is around 20 mL, and average LH levels range from 1.24 to 7.8 IU/mL [3]. Another case involving a 34-year-old man treated with clomid for low sperm counts presented some helpful insight on CC's side effects, as the man experienced extreme mood changes and anxiety while on the drug [15]. Following termination of the treatment, he experienced a resolution of the effects just one week later. This kind of account regarding extreme side effects is not uncommon. Another considerable detail regarding the effects clomid has on various bioprocesses includes the rise in sex hormone-binding globulin (SHBG) that clomiphene can induce, which was proved by a study

involving 10 oligozoospermic men and 6 normospermic men [11]. High SBGH levels can actually be detrimental to the amount of testosterone actually used by the body (bioavailable T), because, in men, 45-65% of testosterone in the blood is bound to SHBG [3]. This would explain why many men on clomiphene see a large spike in their testosterone levels on paper, but fail to experience significantly improved sexual symptoms.

Limitations

Concerns with this treatment's existing data start with the fact that there are no standards for the optimal dosage due to the FDA's reluctance. Studies show that a dosage between 12.5 and 400 milligrams a day would be sufficient, but that is a relatively large range [21]. This forces doctors to use their best judgment on the matter. Existing research, while showing some positive results, has lacked a clear description of the research participants. The description of the population is often broad, and the studies have failed to distinguish members with functional hypogonadism, organic hypogonadism, abnormal sperm counts, and other hormonal conditions. This is a significant limitation, as patients with organic hypogonadism often have a severely hampered hypothalamic-pituitary-testicular axis, and generally suffer from permanent hypogonadism and infertility [6]. The majority of studies also often fixate on the hypogonadism and testosterone production aspect of the drug and rarely discuss its efficacy on sperm production and fertility, and the few studies that do report on spermatogenesis are often decades old. Clomid therapy has potential as a treatment for male infertility, but more research needs to be done regarding its safety. Additionally, medical professionals owe to patients to formulate an efficient and formal treatment that would guarantee patients that they are getting the most out of clomiphene that they possibly can, especially considering that doctors are already prescribing their patients the drug off label.

Methodology

To gain a better understanding of how clomiphene can treat male infertility, a 38-year-old man suffering from oligospermia was interviewed. He and his wife are trying for a 3rd baby, and in midst of this he was prescribed clomiphene citrate. The interview was conducted utilizing direct messages for anonymity purposes, and the participant was informed on the risks and benefits of the study. The expectation is that lab testosterone results will come back generally positive, but its effects on male infertility and sexual symptoms will be mixed.

Interview

The first question asked was the amount of dosage the patient was prescribed of the drug. It turned out to be 50 mg taken Mondays, Wednesdays, and Fridays, which seems to be the agreed upon dosage for most patients, give or take 15-25 milligrams. The patient began treatment on April 1st, 2021. On March 15th, around 2 weeks before beginning treatment, sperm concentration was measured at 3.4 million, and volume measured at 3.9 milliliters. Just around 4 months after beginning treatment, on a July 15th test, concentration shot up to 27.5 million, which is a significant improvement. In addition, during this time testosterone levels rose from around 150 to 450. Sexual symptoms such as libido improved, however any improvements of low testosterone symptoms are unclear due to the lack of data prior to treatment. In addition, motility had improved 34% since treatment as discovered from the July 15th SA. Another notable improvement in sperm quality was the decrease in DNA fragmentation, which is a term for the abnormalities and "breaks" in a sperm's genetic material, which can delineate the difference between fertile and infertile men. Recent fragmentation rates read at 13 percent, which is a considerable drop from 38 percent in previous SAs. The patient also described side effects as "minimal," stating high libido and sexual frustration as a minor detriment. In the patient's own words, "While it doesn't help every man (no single fertility treatment has been shown to), there are a group of men who benefit significantly from it. So you throw [mud] at the wall and hope some sticks".

Findings

Regarding the improved DNA fragmentation, it could be a result of decreased caspase activity (apoptosis/cell death) brought on by the increase in gonadotropin production. For more context, a study was conducted in which 53 men suffering from heightened DFI values went through FSH therapy, with the average fragmentation rate reduced by a significant six percent [19]. In addition, sperm production takes around 2 months, and consequently, this is the amount of time that it takes for results to show up in men undergoing fertility treatment. This lines up with the timeframe for the patient above in regards to sperm improvement, which is a positive sign. Another detail to note is the patient's increased testicular volume. There have not been any decisive studies conducted proving supplements can increase testicular volume, barring one study detecting a link between fish oils and volume (patient stated his diet was low in omega 3s) [22]. Therefore, this improvement can be

attributed to CC, which is a noteworthy piece of evidence verifying clomid's effect on the patient's spermatogenesis. The 200 percent increase in testosterone levels can also be accredited to clomid, as an improvement of that magnitude is unlikely to be caused by dietary improvements. To summarize, the patient's results mostly agreed with the initial hypothesis, which is that clomid is a suitable drug for patients with both SECONDARY fertility issues and low testosterone, with minimal side effects for the majority of patients.

Discussion and Conclusion

Before making any assertions, the limitations and additional factors must be considered. While the participant's fertility and testosterone levels improved significantly, many changes to his diet and lifestyle were made concurrently with his treatment, which include vitamin supplements and better care of his body. The patient also suffered from Covid in November of 2020, which can potentially affect sperm quality. The most evident limitation was the limited sample size of just one interviewee. While the data of this person did not provide adequate data to make a convincing claim, it provided a valuable experience to add on to other clinical data on the topic to further advance research on the complex topic of infertility. Existing research coupled with various case studies including this one leads to the conclusion that clomid is generally a safe treatment for men that should be in contention for FDA approval. Its testosterone benefits have been proven by numerous clinical studies due to its assistance with the production of luteinizing hormone, and while its sperm benefits vary between men, the cheap and simple administration of the drug combined with its largely minimal drawbacks make for a promising treatment. One factor that can greatly influence the drug's efficacy on fertility is the patient's initial gonadotropin levels, as a patient with already improved FSH levels will not experience CC's main benefit. Patients with congenital/acquired testicular damage will not be helped by CC. A dosage of 25-50 mgs should be taken a few days a week by men, depending on the severity of their condition. Clomiphene can and should (in some cases) be taken alongside other treatments to maximize improvements, such as anastrozole to combat the high estradiol counts that come with CC treatment. For these reasons, a patient trying for a child with functional hypogonadism/idiopathic oligoasthenoteratozoospermia with low testosterone levels should be a candidate for clomiphene.

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Author

Rohan Rai is a junior at Clements High School in Sugar Land, Texas. He has an interest in the field of medicine, endocrinology, and epidemiology. He hopes to explore all areas of the field in hopes of one day becoming a physician and helping those around him.

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