Clomiphene citrate in the management of oligoasthenospermia.

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الملخص

بالرغم من كون الكلومفين ستراىت(كلوميد) يستخدم لعلاج العقم عند النساء،لكن هناك العديد من الدراسات المتنوعه لاستخدامه في علاج عقم الرجال.الهدف من هذه الدراسه هو معرفة دور الكلوميد في علاج حالات قلة عدد و سرعة حركة الحيوانات المنويه المسببه لعقم الرجال.طريقة البحث دراسه مستقبليه اكلينيكيه تضمنت اربعون رجل مشخصين حسب طريقة منظمة الصحه العالميه كحالات قلة عددوحركة الحيوانات المنويه في محافظة واسط العراق وذلك للفتره من تموز 2007و لغاية تموز 2008. حيث ان الكلوميد اعطي للمرضى بمعدل حبه واحده (50) ملغم يوميا ولمدة اربعة اشهر.تم خلالها ملاحظةوتسجيل التغيرات التي حصلت في عدد ونسبة نشاط حركة الحيوانات المنويه ونسبة الحمل التي حدثت خلال فتر ة الدراسه.كانت نتائج الدراسة ان هناك زياده في معدل العدد من 11 مليون لكل واحد مل الى 35 مليون لكل مل (ثلاثة مرات) وزيادة نسبة نشاط الحيامن من 15% الى 30% (مرتين) كما تم تسجيل ثمانية حالات حمل.
الكلوميد من الممكن ان يزيد عدد و نشاط الحيوانت المنوية عند الرجال والتالي فأنه من الممكن ان يزيد نسبة الحمل اويسهم في تغيير طريقة العلاج من الاخصاب الخارجي واطفال الانابيب الى الاخصاب الداخلي الاقل كلفه كما انه يقلل من الافراط في علاج الاناث.

Abstract

Background: Although clomiphene citrate (clomid) is, anti-estrogen, typically used for women with fertility problems, there have been a variety studies as to the use of clomiphene citrate in treating male subfertility.
Objective: To evaluate the role of clomid in treating male with oligoasthenospermia.
Methods: A prospective clinical study of 40 men with preliminary diagnosis of oligoasthenospermia according to WHO protocols in Wassit Government Iraq from July 2007 through July 2008.Clomid 50 mg oral daily dose was given for 4 months. The changes in sperm counts, the percentage of active sperms, pregnancy rate and side effects were recorded and analyzed.
Results: The mean sperm count before treatment was 11millions per ml, while the mean percentages of sperm motility were 15%. After treatment the mean sperm count increased to 35 millions per ml (3 times) and the mean percentage of motile sperm to 30 % (2 times).8 patients (20%) reported their wives became pregnant.4 patients (10%) failed to respond.

Conclusions and recommendations:
In patients with normogonadotrophic oligoasthenospermia, clomiphene citrate improves sperm counts and motility and probably increase pregnancy rate.This can possibly convert the choice of treatment from IVF/ICSI to less costly IUI.Also it may save some women from being treated for a problem of male infertility.However, controlled trails with larger number of patients are needed to confirm the findings of this study.

Keywords: clomiphene citrate, oligoasthenospermia, male infertility

Introduction

Male infertility factors are present in about 20 percent of infertile couples and contributory in about 30 to 40 percent.It Male infertility can result from a variety of conditions. Of these conditions that are identifiable, some are reversible and some are not.The purpose of the evaluation of the male is to identify conditions contributing to infertility ,and these are:
(a) Potentially reversible
(b) Irreversible, but suited to assisted reproductive technique using the man's sperms. (c) Irreversible and not suited to assisted reproductive techniques.
(d) Potentially life-or health-threatening and that may underlie the infertility. Also detecting genetic causes of male infertility can allow couples to become informed about the possibility for transmitting genetic abnormalities to their offspring and obtain genetic counseling (1).
Infertility evaluation should be performed if a couple has not achieved conception after one year of unprotected intercourse. An evaluation should be performed earlier if male infertility risk factors exist (e.g., a history of bilateral cryptorchidism).The initial screening of the male should include a reproductive history and two semen analyses. The reproductive history should include the frequency and timing of intercourse; prior fertility and the duration of current infertility; childhood illnesses and developmental history; systemic illnesses and previous surgeries; sexual history and sexual transmitted diseases; and gonadal toxins exposure including heat and history of prescription and nonprescription drug use.During the general physical examination, particular attention should be given to the genitalia ,so the evaluation should include examination of the penis,including the location of external meatus; measurement and palpation of the testes; checking the presence and consistency of the vas and the epididymides; checking for the presence of varicocele and secondary sexual characteristics(1).
The first and most important test for the male remains the semen analysis, however, a poor semen analysis, does not rule out natural

conception, and a normal sperm count does not necessarily mean that the husband's sperm can fertilize the wife's eggs (2).

Twenty-five years ago it was thought that a sperm count of <40 million spermatozoa per ml means that the husband was infertile with a poor prognosis for pregnancy. The World Health Organization, in 1992, issued a list of normal values for semen analysis which included a sperm concentration of >20 million per cc, total sperm count of >40 million per ejaculate, >50% of sperm exhibiting forward progressive motility and >30% with normal morphology (3).

In the past pharmacological treatment has been used empirically for infertile patients, today attempts are made to specifically identify causes of male infertility in order to prescribe a specific treatment.

although male factors contribute to over half of all cases of infertility ,in most infertile men no specific cause can be found and are described as idiopathic oligo/asthenospermic rather than diagnosed precisely;hence,specific medical treatment is not possible and empirical treatments are still used(4).

Many treatments have been strongly advocated over the past four decades, such as clomiphene citrate, testosterone, human menopausal gonadotropin, human chorionic gonadotropin, corticosteroids, cold wet athletic supporters and vitamins without any documented evidence of effectiveness(5)(6).

This is true for all attempts at hormone replacement except for testosterone. The patient who is given any form of testosterone replacement will suffer a progressive decline in the function of the testicles, as exogenous testosterone is a powerful

inhibitor of the feedback loop that governs spermatogenesis and testicular testosterone production.Administration of anti-estrogens is a common treatment because anti-estrogens interfere with the normal negative feedback of sex steroids at hypothalamic and pituitary levels in order to increase endogenous gonadotropin–releasing hormone secretion from the hypothalamus and LH and FSH secretion directly from the pituitary. In turn, FSH and LH stimulate Leydig cells in the testes, and this has been claimed to increase local testosterone production, thereby boosting spermatogenesis with a possible improvement in fertility (7).

There have been a variety of uncontrolled studies as to the effectiveness of clomiphene citrate (clomid) in treating male subfertility. To boost testosterone levels in the subfertile men, clomiphene citrate, and a synthetic nonsteroidal antiestrogen is given daily; it blocks feedback inhibition and so increases FSH and LH thus increasing testosterone and sperm production (8).

The development of intracytoplasmic sperm injection as an effective therapy for all cases of male infertility which have failed to respond to conventional treatment has caused a major reassessment and critical analysis of the diagnostic and therapeutic approaches to male infertility (9).

Materials and Methods

Patients

Male patients who had been unable to initiate pregnancy during a period of at least one year of unprotected sexual intercourse ,had through clinical workups that included a clinical history, clinical examinations, endocrine studies and laboratory testing of the ejaculates.

The inclusion criteria were:

(1) Male partner with at least one year infertility with availability of the female partner's clinical fertility data.

(2) A minimum of two semen analysis at an interval of 6 weeks showing oligasthenospermia (sperm count <20 million per ml, total sperm count of <40 million per ejaculate and rapid+ slow motility> 50%) according to WHO criteria (10).

(3) Normal values in a baseline endocrine evaluation that measured FSH, LH, prolactine and testosterone.

(4) No history of receiving andrologically effective treatment for a minimum of 6 months.

Study design

This study was conducted as a prospective clinical study over 1 year period from July 2007 through July 2008. Patients referred from private clinics or seen in outpatients in Al-Zahra,a and al-Karama hospitals in Kut Government-Iraq.

40 patients who fulfilled the inclusion criteria were selected for the study and each patient give his written informed consent after explaining the nature of the study, before the start of treatment. Each patient received oral clomid tablet 50 mg daily for 4 months .Patients were followed monthly and the results reported regarding the positive response rate and pregnancy rate after the end of treatment.

Semen collection and analysis

Semen samples were collected by masturbation after a period of sexual abstinence of 3-5 days. The samples were analyzed by the same technician following standard protocols of WHO laboratory manual. Semen samples were liquefied at 37c and then the sperm count and the different motility grades were assessed and reported.

Results

Forty patients (mean age: 30 years, range: 19 to 45), affected by primary infertility (mean duration 4 years, range1-15) with oligoasthenospermia diagnosed according to WHO criteria enrolled in this study. Table (1).

The mean sperm count before treatment was 11millions per ml, while the mean percentages of sperm motility were 15%.

After treatment the mean sperm count increased to 35 millions per ml (3 times) to and the mean percentage of motile sperm was 30 %(2 times).Table (2).
8 patients (20%) reported their wives became pregnant.
4 patients (10%) failed to respond.
No significant side effects were reported during the period of the study apart from gynaecomastia in one patient.

Table -1:40 patients distributed according to their ages and period of infertility

Infertility (years) Age (years)	<5	5-9	10-14	15-19	Total
<20	2	-	-	-	2
20-29	16	-	-	-	16
30-39	4	10	-	-	14
>40	-	2	5	1	8
Total	22	12	5	1	40

Table -2: The results of forty patients treated with clomid (represented in mean values)

Indices	Before treatment	After treatment
Spermatozoa (million/ml)	11	35
Motility (%)	15	30

Discussion

World wide, male infertility contributes to more than half of all cases of childness; yet it is a reproductive health problem that is poorly studied and understood.In 40% to 50% of males with infertility, the etiology is unknown (11, 12).
Oligospermia is a major cause of infertility .It usually managed nowadays by assisted reproductive techniques. In these techniques the female partners are treated, while the male partners having this medical problem are left untreated (13).
In a study of men attending a specialist male subfertility clinic they found them experiencing high levels of anxiety feeling" less of a man" and blaming themselves for the subfertility (14). The cost of treating reversible causes of male infertility is less than the cost of advanced reproductive techniques, furthermore, if treatment succeeds subsequent pregnancies does not demand repeated interventions.
The treatment of male-factor subfertility does not preclude the subsequent use of advanced reproductive techniques when the response to therapy is suboptimal (15).

Though several empirical therapies are available to treat oligospermia, it is difficult to identify a therapy that is most likely to benefit a man having oligospermia. This leads to trial of different therapies resulting in varied success rates.Although clomid is typically used for women with fertility problems, there have been a variety of controlled studies as to the effectiveness of clomiphene citrate in treating male subfertility (7, 8, 13, 16, 17, and 18).

This study examines the problem of male infertility in Iraq –Kut, where men may be at increased risk of male infertility because of environmental factors, it is argued that that male infertility may be particularly problematic for men in the society where both virility and fertility are typically tied to manhood and thus male infertility is a potentially condition, surrounded by a secrecy and stigma. In our study there were 3 times increase in sperm count and 2 times increase in the percentage of motile sperms. 8 patients (20%) reported their wives became pregnant, which is close to the result of Singh L *et al* (19) who reported 19% pregnancy rate over one year follow up period.Our results were higher than the result of Ronnberg L who reported 10% pregnancy rate when used clomid 50 mg for 3 months (20).

Our result lower than the pregnancy rate reported by Paulson *et al* (21) in Germany (22.8%)when they used clomid 25 mg daily for 9 months, and lower than the results of Rross LS *et al* (22) were they reported 26% pregnancy rate after the use of clomid100mg three times weekly for 15 months. table(3).

Table -3: previous studies of different regimens

Author	year	Regimens	Pregnancyrate
Paulson *et al*.	1976	clomid 25 mg daily for 9 months	22.8%
Ronnberg L.	1980	clomid 50 mg daily for 3 months	10 %
Rross LS *et al*	1980	100 mg clomid 3 times weekly for 15 months	26%
Singh L *et al*	2001	Clomid 50 mg daily for 6 months	19%
Our study	2008	Clomid 50 mg daily for 4 months	20%

The duration of observation period was a major factor in the discrepancies, and sperm counts were dose related where low doses caused an increase, intermediate doses caused an increase, decrease or no changes, and high dosages caused precipitous decrease (23).

The results are widely divergent because of the fact that the selection of the patients, the dosage, and the length of therapy are not always appropriate, however, the experience with clomid appears to show sufficient effectiveness in oligospermic men (24).

Conclusions and Recommendations

In patients with normogonadotrophic oligoasthenospermia, clomiphene citrate improves sperm counts and motility and probably increase pregnancy rate.This can possibly convert the choice of treatment from IVF/ICSI to less costly IUI.Also it may save some women from being treated for a problem of male infertility.However, controlled trails with larger number of patients are needed to confirm the findings of this study.

References

1. **Elaine Kierl Gange. AUA and ASRM. produce recommendation for male infertility. American Family physician vol.65/no.12 (June 15, 2002).**
2. **Sokol RZ and Sparkes R. demonstrated paternity inspite of oligospermia. Fertil Steril.1987, 47 (2):356-358.**
3. **World Health Organization. WHO laboratory manual for the examination of human semen and sperm cervical mucous interaction. 3rd Edition Cambridge University Press, Cambridge, 1992, pp44-45.**
4. **Peter Y. Liu and J. Handelsman. The present and future state of hormonal treatment for male ifertility.Hum Reprod. 2003, 9(1):9-23.**
5. **Devory P, Vandervorst M, Nagy P, Van Steirteghem A. Do we treat the male or his gamete? Hum Reprod. 1998, 13(suppl 1):178-185.**
6. **Sigman M, Howards SS: Male infertility. In: Walsh PC, Retik A, Vaughan ED Jr., Wein A, eds. Campbell's Urology, 7th ed. Philadelphia, Saunders,1998, pp1287-1330.**
7. **Vandekerckhove P, Lilford R, Vail A, Hughes E. Clomiphene or tamoxifen for oligoasthenospermia. Cochrane database system rev. 1996; CD000151.**
8. **Sokol, R.Z., Steiner, B.S., Bustillo, M., Petersen, G., Swerdloff, R.S.. A controlled comparison of the efficacy of clomiphene citrate in male infertility, Fertility and Sterility. (1988) 45(5), 865-870.**
9. **Van Steirteghem AC, Nagy Z, Joris H, Liu J, Staessen C, Smitz J, Wisanto A, Devroey P. High fertilization and implantation rates after intracytoplasmic sperm injection. Hum Reprod. 1993, 8:1061-1066.**
10. **World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and sperm-cervical Mucus Interaction (4thed). Cambridge University Press, 1999.**
11. **Marcia C. Inhorn. Middle easten masculinities in the age of new reproductive technologies: male infertility and stigma in Egypt and Lebanon. Medical Anthropology Quarterly.2002, 18 (2), 162-182.**
12. **Jian Pei, Erwin Strehler, Ulrich Noss, Markus Abt., Paola Piomboni, Baccetti and Karl Sterzik. Quantitative evaluation of**

spermatozoa ultrastructure after acupuncture treatment for idiopathic male infertility. Fertile.Streil. 2005 July, 84(1).

13. **Purushottam Sah: A therapeutic scheme for oligospermia based on serum level of FSH and estradiol. The internet Journal of Gynecology and Obstetrics. 2007. Volume 8 number 1.**
14. **Glover L, Gannon K, Sherr L, Abel P. Distress in sub-fertile men: a longitudinal study. J reproductive Infant psychology. 1996; 14: 23-36.**
15. **Jay I.Sandlow, James F.Donovan. The infertile couple.N Eng J Med 1994; 330(16): 1154-1155.**
16. **Xinyun H. Acupuncture plus medication for male idiopathic oligospermatic sterility.Shanghai J Acupunct Moxibustion 1998; 2:35-7.**
17. **Adashi EY, Hsueh AJ, Bambino Th, Yen SS. Disparate effect of clomiphene and tamoxifen on pituitary gonadotropin release in vitro. Am J Physiol 1981 Feb; 240(2): E125-30.**
18. **-Adamopoulos, Kapollea *et al*. The effect of clomiphene citrate on sex hormone binding globulin in normospermic and oligozoospermic men. Int J Androl 1981(4):639-45.**
19. **Singh l, Kumar A, Bhandari p. comparison of the efficacy of Addyzoa and clomiphene in male factor subfertility. Int J Gyn Obs Ind 2001; 4(6).**
20. **Ronnberg L.The effect of clomiphene citrate on different sperm parameters and**
21. **serum hormone levels in preselected infertile men: a controlled double-blind cross-over study.Int J Androl. 1980 Oct; 3(5):479-86.**
22. **Paulson DF, Wacksman J. Clomiphene citrate in the management of male infertility. J Urol.1976 Jan; 115(1): 73-6.**
23. **Ross LS, Kandel GL, Prinz LM, Auletta F. Clomiphene treatment of the idiopathic hypofertile male: high-dose, alternate-day therapy. Fertil Steril.1980 Jun; 33(6):618-23.**
24. **Heller GV, Heller CG. The effect of clomiphene citrate on the normal human male reproductive system. Clinical Research, 1969; 17: 143.**
25. **Schellen TM.Clomiphene treatment in male infertility. Int J Fert.1982; 27(3):136- 45.**