Clomiphene citrate in the management of oligoasthenospermia.

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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.

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.

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-Zahraa 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

<table>
<thead>
<tr>
<th>Infertility (years)</th>
<th>Age (years)</th>
<th>&lt;5</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>20-29</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>&gt;40</td>
<td>-</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Indices</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermatozoa (million/ml)</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

Discussion
World wide, male infertility contributes to more than half of all cases of childhood; 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 clomid 100 mg three times weekly for 15 months. table (3).

Table -3: previous studies of different regimens

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

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 trials with larger number of patients are needed to confirm the findings of this study.

References

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