

Empirical Therapy of the Male with Clomiphene in Couples with Unexplained Infertility

Jerome H. Check, M.D.

Jeffrey S. Chase, M.D.

Khosrow Nowroozi, M.D.

Chung H. Wu, M.D.

Harriet G. Adelson, B.S.

Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
The Jefferson Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania

ABSTRACT: Unexplained infertility may be secondary to a cryptic male or female factor. Although most often empirical therapy of the female partner may be attempted, clomiphene has been claimed, after uncontrolled studies, to improve fertility in men with subnormal spermograms. We chose to determine if clomiphene therapy of the male would improve fertility in couples with unexplained infertility despite normal-appearing semen parameters. One hundred husbands were randomized to treatment with clomiphene citrate, 25 mg daily for 25 days with 5 days' rest each month, if their social security numbers ended in an even number or ascorbic acid, 500 mg daily, if ending in an odd number. All female infertility factors had to be meticulously corrected for at least eight cycles for inclusion in the study, along with a minimum of 1½ years' duration of infertility. Within 8 months, 29 of 50 couples (58%) with clomiphene therapy of the male achieved a pregnancy, but only 8 of 50 (16%) with ascorbic acid treatment of the male. There were no appreciable changes in sperm counts, motility, or morphology after either treatment, nor were there any significant differences in semen parameters in those conceiving versus those who did not. Further, improved fertility could not be accounted for by improvement in the hamster ova penetration test. Possibly, clomiphene improves some quality of the sperm that is defective but not measurable by standard androgenologic methods, or it improves some aspect of the seminal plasma. Perhaps, though, the results might be better explained on a psychogenic basis, i.e., clomiphene is a "better" placebo than ascorbic acid. A further study should be carried out using inert tablets as the placebo instead of ascorbic acid.

INTRODUCTION

UNEXPLAINED INFERTILITY MAY BE secondary to a cryptic male or female factor. Empirically, many wives have been offered ovulation-inducing drugs in the hope that there was a subtle ovulation problem not being detected by

modern tests of ovulation. However, the problem is equally likely to be in the male. The most likely reason women are offered therapy is that ovulation-inducing drugs do improve fertility rates in anovulatory women, but there is no definite medical therapy of the male even when oligospermia exists. Nevertheless, since there have been reports from

uncontrolled studies of the efficacy of clomiphene citrate in improving fertility in the treatment of oligospermia and asthenospermia,¹⁻³ the possibility exists that the drug might improve some unknown adverse factor in the seminal plasma or in some way enhance the fertilizing capacity of the sperm. A study was designed to determine if the empirical use of clomiphene citrate would provide any benefit as compared with placebo controls.

PATIENTS AND METHODS

One hundred patients with unexplained infertility were enlisted in the study. Inclusion in the study required all known factors connected with infertility to be normal or corrected for at least eight cycles: (1) normal semen analysis (count of $40 \times 10^6/\text{mL}$ or more, motility 60% or greater with linear progressive motion; morphology 60% or more normal; volume—minimum of 2 mL); (2) normal postcoital test with progressive forward motion (greater than 5 sperm/high-power field 8 to 16 hours after intercourse); (3) normal ovulation (formation of a mature follicle of 18 mm or more associated with an estradiol level of 200 pg/mL; release of ovum demonstrated by sonography; normal endometrial biopsy); (4) fairly normal laparoscopy (bilateral tubal patency; minimal endometriosis or adhesions at best seemingly adequately corrected through the laparoscope). Hamster ova penetration tests⁴ were performed on all husbands. The couples were required to have a minimum of 1½ years of infertility.

The patients were randomized into treatment group versus controls in which the first 50 men whose social security number ended with an odd digit were started on clomiphene citrate, 25 mg daily for 25 days each month with a 5-day abstinence; the first 50 men in this unexplained infertility group with an even ending digit were treated with ascorbic acid, 500 mg daily. The number of pregnancies achieved during the next 8 months of male therapy was then evaluated and compared between groups. Repeat semen analyses were performed every 2 months. A repeat hamster ova penetration test was done once, 3 months after therapy, even in those who already had fertilized their wives (they were asked to continue therapy until this repeat test).

RESULTS

The incidence of pregnancies after 8 months was as

follows: 29 of 50 women (58%) whose husbands were treated with clomiphene achieved a pregnancy versus only 8 of 50 (16%) whose husbands received ascorbic acid (chi-square analysis: $P < .001$).

There were no definite discernible differences in the various semen parameters, i.e., count, motility, or morphology, before or after therapy or in those conceiving versus those not conceiving, as seen in Table I. There were three first-trimester abortions in the 37 pregnancies (8%).

DISCUSSION

The exact mechanism for the higher number of pregnancies in the couples whose husbands were

TABLE I

	<i>Clomiphene</i>	<i>Ascorbic Acid</i>
Baseline sperm count	$49.4 \times 10^6/\text{mL}$	$55.3 \times 10^6/\text{mL}$
Avg. count following treatment	$51.8 \times 10^6/\text{mL}$	$50.2 \times 10^6/\text{mL}$
Last count before conception	$57.1 \times 10^6/\text{mL}$	$52.8 \times 10^6/\text{mL}$
Last count in those not conceiving	$49.1 \times 10^6/\text{mL}$	$49.6 \times 10^6/\text{mL}$
Baseline motility* before treatment	62.4%	58.5%
Avg. motility following treatment	66.0%	68.3%
Avg. motility in those conceiving	64.6%	70.2%
Avg. motility in those not conceiving	67.5%	66.3%
% normal forms, baseline	68.4%	61.2%
% normal forms, following treatment	64.5%	66.0%
% normal forms, before conception	65.5%	78.1%
% normal forms in those not conceiving	63.6%	65.0%
No. with normal baseline hamster tests	19	29
No. with normal hamster test 3 months after treatment	24	33
No. with normal hamster test who conceived	12	5

*Percentage with at least grade 3 – out of 4 quality.

treated with clomiphene is unknown. Chi-square analysis suggests that chance alone was not responsible. In contrast to other reports of improvement of count and motility in men with oligospermia and asthenospermia by clomiphene, in this group of "normal" men there was no such improvement in those treated with the drug. Similarly, there was no improvement in the hamster ova penetration test. Possibly, improved fertility would have been associated with some other parameter of sperm function, e.g., velocity or lateral head displacement,⁵ osmotic sensitivity,⁶ or acrosin reaction.⁷ Improvement in some factor in the seminal plasma without improvement of the sperm itself is also possible.

Even though we attempted to organize a controlled study, it is possible that clomiphene represented a "better" placebo than ascorbic acid, despite our presentation of both drugs in a positive way to the patients. The best controlled study would use inert clomiphene tablets and would be both randomized and double-blinded. Perhaps our results will stimulate interest in organizing a more definitive study.

Nevertheless, even if the drug is working by a placebo mechanism, so might GIFT⁸ or in vitro fertilization^{9,10} when used for unexplained infertility. It would obviously be far cheaper and less risky to try clomiphene in the husband than to attempt GIFT or IVF in the wife.

REFERENCES

1. Paulson D, Wacksman J: Clomiphene citrate in the management of male infertility. *J Urol* 115:73, 1976.

2. Check JH, Rakoff AE: Improved fertility in oligospermic males treated with clomiphene citrate. *Fertil Steril* 28:746, 1977.
3. Check JH: Improved semen quality in subfertile males with varicocele-associated oligospermia following treatment with clomiphene citrate. *Fertil Steril* 33:423, 1980.
4. Yanagimachi R, Yanagimachi H, Rogers BJ: The use of zona-free animal ova as a test-system for the assessment of the fertilizing capacity of human spermatozoa. *Biol Reprod* 15:471, 1976.
5. Mathur S, Carlton M, Ziegler J, et al: A computerized sperm motion analysis. *Fertil Steril* 46:484, 1986.
6. Jeyendran RS, Van der Ven HH, Perez-Pelaez M, et al: Development of an assay to assess the functional integrity of the human sperm membrane and its relationship to other semen characteristics. *J Reprod Fertil* 70:219, 1984.
7. Mohsenian M, Snyder FN, Moghissi KS: A study of sperm acrosin in patients with unexplained infertility. *Fertil Steril* 37:223, 1982.
8. Asch RH, Balmaceda JP, Ellsworth CR: Gamete intrafallopian transfer (GIFT): A new treatment for infertility. *Int J Fertil* 30(1):41, 1985.
9. Edwards RG, Steptoe PC: Current status of in vitro fertilization and implantation of human embryos. *Lancet* 2:1265, 1983.
10. Jones HW, Acosta AA, Andrews MC, et al: Three years of in vitro fertilization at Norfolk. *Fertil Steril* 42:826, 1984.

Address reprint requests to:
Jerome H. Check, M.D.
1015 Chestnut Street
Suite 1020
Philadelphia, PA 19107