A Therapeutic Scheme For Oligospermia Based On Serum Levels Of FSH And Estradiol

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Citation

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Abstract

Oligospermia is a major cause of infertility in couples. It is usually managed by assisted reproductive techniques. In these techniques the female partners are treated, while the male partners having this medical problem are left untreated! 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. These empirical therapies put emphasis on the stimulatory role of testosterone in the process of spermatogenesis while estrogens are considered inhibitory in this respect. In the last decade, however, positive role of estrogens in male reproduction has been reported by some authors. In view of this evidence, a therapeutic scheme for oligospermia based on serum levels of FSH and estradiol, is presented. Its aim is to develop a system by which a clinician may possibly identify a suitable therapy before starting the treatment of an infertile man. Thus it may reduce unnecessary trial of treatments and save on costs and time, and it may save some women from being treated for a problem of male infertility.

INTRODUCTION

Oligospermia is a major cause of infertility in large number of couples. It is usually managed by assisted reproductive techniques. In these techniques the female partners are treated, while the male partners having this medical problem are left untreated! 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.

The empirical therapies to treat oligospermia include gonadotropins, androgens and antiestrogens [1]. Most of these therapies put emphasis on the stimulatory role of testosterone in the process of spermatogenesis while estrogens are considered inhibitory to this process. In the last few years, however, some reports including [2, 3] have mentioned the positive role of estrogens in male reproduction. The author of this article too has reported the beneficial effects of low dose estrogen and testosterone combination therapy (ETCT) on the sperm count in men having oligospermia [4, 5, 6]. In this article a therapeutic scheme for oligospermia, based on serum levels of FSH and estradiol, is presented. Its aim is to develop a system by which a clinician may possibly identify a suitable therapy before starting the treatment of an oligospermic man.

Usually serum levels of FSH, LH and testosterone are measured in men having oligospermia. However, it is extremely uncommon to find clinically significant abnormalities in LH and testosterone levels in the presence of normal FSH levels [1] and FSH is also the most suitable hormone for diagnostic classification of oligospermia [7]. Hence, LH and testosterone are not included in the proposed scheme and only FSH and estradiol are included.

DISCUSSION

Theoretically the maximum number of possible combinations of FSH and estradiol, depending on whether their serum levels are normal, elevated or depressed, is nine. But in practice all the possible combinations may not exist, six groups are identified remaining combinations are clubbed with other groups.

These groups are as follows:

1. Idiopathic: serum levels of FSH and estradiol are normal as may be found in most of the oligospermic men.

2. Spermatogenic deficiency or seminiferous tubular failure: these men have elevated (may be normal) serum levels of FSH [7] and normal serum levels of estradiol.

3. Estrogen resistance: elevated serum levels of FSH and of estradiol are found in these men [8].

4. Estrogen excess: these men have elevated serum levels of estradiol and normal (or depressed) serum levels of FSH [1].

5. Hypogonadotropism: these men have depressed serum levels of FSH and of testosterone, and consequently they may have depressed (or normal) levels of estradiol, because FSH causes aromatisation of testosterone to estrogen [9].

6. Aromatase deficiency: these men may have undetectable (depressed) serum levels of estradiol and elevated serum levels of FSH [10, 11, 12].

Furthermore, in all these aromatase deficient men serum FSH levels were elevated and serum estradiol levels were undetectable, but serum levels of testosterone and LH were variable [$_{10}$, $_{11}$, $_{12}$]. These evidences further emphasize the appropriateness of FSH and estradiol measurement in making a diagnostic and therapeutic scheme for oligospermia.

The proposed treatments for the different groups are as follows:

1. Idiopathic: ETCT is suggested for this group. In a clinical study of ETCT on 14 men with oligospermia, 64% of the men showed definite improvement in sperm counts with a resultant pregnancy rate of 21% [4].

2. Spermatogenic deficiency: this group also may be treated with ETCT. In one case report a man having very severe oligospermia (mean sperm count less than 0.1 x106 per mL) due to partial maturation arrest, showed enormous increase in his sperm count (35 x106 per mL) after receiving ETCT, though he had not responded to earlier treatments with clomiphene citrate and mesterolone .This resulted in his wife giving a live birth [5].

3. Estrogen resistance: this group has elevated serum levels of FSH and estradiol [8] and may be treated with aromatase inhibitors or may be with ETCT. In another case report a man having moderately severe oligospermia (mean sperm count 3.8 x106 per mL) together with elevated serum levels of FSH and estradiol, showed increase in his sperm count (25 x106 per mL) after receiving ETCT. His serum levels of FSH and estradiol became normal after therapy and his wife conceived spontaneously and gave birth to a live baby [6].

4. Estrogen excess: this group may be treated with antiestrogens, however the cause of estrogen excess has to be determined and treated.

5. Hypogonadotropism: this group requires treatment with HCG/ HMG, [1] it may be treated with ETCT also because the serum levels of testosterone and consequently that of estradiol shall be depressed.

6. Aromatase deficiency: this group has undetectable serum levels of estradiol [10, 11, 12] and may be treated with ETCT.

It is obvious from the above observations that men having depressed or normal serum levels of estradiol may be treated with ETCT. Those having elevated serum levels of estradiol together with normal or depressed serum level of FSH shall benefit by treatment with antiestrogens (Tamoxifen, Clomiphene), because antiestrogens are known to stimulate FSH secretion. Others having elevated serum levels of estradiol together with elevated serum levels of FSH shall benefit by treatment with aromatase inhibitors (Testolactone, Anastrozole), because FSH causes aromatisation of testosterone to estrogen [$_{9}$].

Thus it may be inferred that ‘Men having oligospermia can be divided in two clinical groups based on their serum levels of estradiol. The first group having normal or depressed serum levels of estradiol may benefit with low-dose estrogen-testosterone combination therapy, the second group having elevated serum levels of estradiol may benefit by treatment with antiestrogens or aromatase inhibitors depending on whether their serum levels of FSH are normal/ depressed or are elevated respectively'.

In the above scheme antiestrogens and/ or aromatase inhibitors may be substituted with a combination of antiestrogen and androgen. In a prospective, randomized, placebo-controlled trial of 212 men with idiopathic oligozoospermia with a combination of tamoxifen citrate and testosterone undecanoate, the authors reported significant increase in the sperm counts of men in the active treatment group, but not in the placebo group [$_{13}$]. The doses used were tamoxifen citrate, 20 mg/d, and testosterone undecanoate,

120 mg/d for 6 months. In the active treatment group total sperm count , median [25th, 75th percentile] 27.1 x 10(6) cells/mL [9.4, 54.0 x 10(6) cells/mL] at baseline and 61.5 x 10(6) cells/mL [28.2, 119.6 x 10(6) cells/mL] at 6 months, were noted. The two combination therapies for oligospermia, mentioned above, are opposite in nature one contains estrogen and the other contains antiestrogen, together with testosterone. This interesting paradoxical observation further emphasizes the importance of serum estradiol estimation in making a therapeutic scheme.

In the search for Cochrane reviews of therapies for idiopathic male factor subfertility, the only available review was that regarding the use of gonadotrophins in this condition. Here the authors could not reach a final conclusion about the efficacy of this treatment because the number of trials and participants was insufficient [$_{14}$]. Therefore it implies that an effective empirical therapy of oligospermia is yet to be determined. Our proposed scheme hopes to do so.

Large multicentre controlled studies will be required to decide the utility of this therapeutic scheme in the management of oligospermia. Hopefully, this approach can evolve to more effective management of men having oligospermia and reduce unnecessary trial of treatments and save on costs and time. In some infertile couples this approach can possibly convert the choice of treatment from IVF/ICSI to less costly IUI, after the sperm count is suitably increased with treatment. Also it may save some women from being treated for a problem of male infertility.

Figure 1

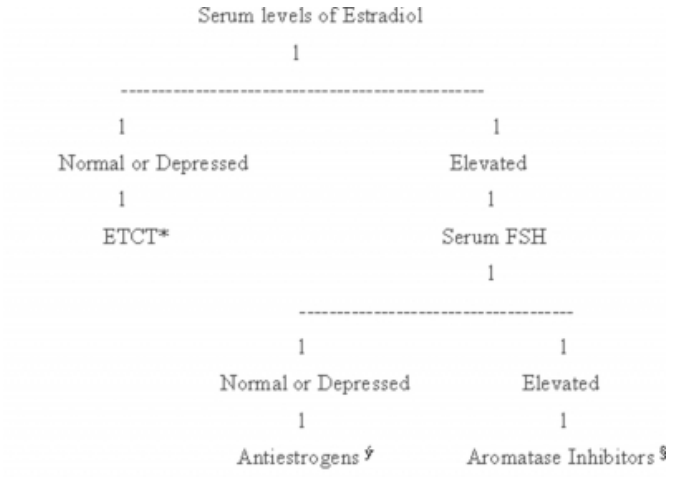
Table 1:Therapeutic groups of oligospermia based on serum levels of FSH and estradiol.

HORMONE	GROUP	TREATMENT
En, FSHn	IDIOPATHIC	ETCT
En, FSHe	SPERMATOGENIC DEFICIENCY	ETCT
Ee, FSHe	ESTROGEN RESISTANCE	AROMATASE INHIBITORS
Ee, FSHn (Ee, FSHd)	ESTROGEN EXCESS	ANTIESTROGENS
Ed, FSHd (En, FSHd)	HYPOGONADOTROPISM	HCG/ HMG (ETCT)
Ed, FSHe (Ed, FSHn)	AROMATASE DEFICIENCY	ETCT

E: Estradiol, n : Normal, e: Elevated, d: Depressed or undetectable.
ETCT: Low-dose estrogen-testosterone combination therapy.

Figure 2

Figure 1: Scheme for treatment of oligospermia based on serum levels of FSH and estradiol.



* Low-dose estrogen-testosterone combination therapy
ý Tamoxifen, Clomiphene
§ Testolactone, Anastrozole

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