

TREATMENT OF OLIGOSPERMIC SUBFERTILE MEN

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Male reproductive dysfunction has always remained a neglected field, and it is only recently that there has been full recognition and acceptance of the fact that husband is frequently the cause for couple's infertility. The contribution of male hypofertility to barren union may range from 30 to 50 per cent (Murphy and Torrano, 1965), has stimulated interest in various diagnostic approaches and has resulted in the development of successful therapeutic modalities. While successful management of all types of male reproductive disorders is not possible; the present day evidence shows that a definitive diagnosis can be made in most of these men. Following a proper diagnosis, at least a limited group can be treated successfully and made to father a child.

Since 1974 we have followed the current approach to infertility which calls for the evaluation of the couple as a unit and management of the problem which is 'couple-directed' rather than 'partner-directed'. Both male and female evaluations, including semen analysis, were done by the senior author in all the infertile couple. A decision to treat the male partner is made only after excluding any dysfunction in the female. In this article

an attempt is made to summarise the various therapeutic approaches tried on subfertile oligospermic men.

Material and Methods

Since 1974, over a period of 6 years, 158 subfertile men were treated for various reproductive dysfunctions. The therapeutic modalities employed included varicocelelectomy, hormone therapy with human Chorionic Gonadotropin (H.C.G.), and clomiphene Citrate (Fertyl). The details of the patient groups are given in Table I. Since the clinical trial with clomiphene citrate has been initiated only recently, results related to this study will not be included in this article.

Human Chorionic Gonadotropin (H.C.G.):

We have employed HCG therapy empirically in patients with idiopathic oligospermia, and post-varicocelelectomy subjects who did not improve following the surgery. All these patients, 36 of them, had a sperm count of 20 million/ml or less, poor sperm motility and morphology. Female fertility status in these couples were evaluated by the basic investigation such as endometrial biopsy, hysterosalpingography and cervical mucus study. Only after excluding any fertility problems in the female that the hormone injections were advised for the male.

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TABLE I
Treatment of Male Hypofertility

Treatment Modality and Period of Study	Men recruited	Men Followed	Age (years)		Infertility duration (years)	
			Mean	Range	Mean	Range
Hormone Therapy with Human Chorionic Gonadotropin (HCG) February, 1976 to April, 1979 (3 years)	36	30	31.70	(23-42)	4.30	(1-26)
Varicolectomy September, 1974 to June, 1979 (5 years)	72	57	31.92	(23-45)	4.32	(1-14)
Clomiphene Citrate (Fertyl) From January, 1979 (1 year)	49	—	32.10	(23-45)	4.85	(1-13)

The HCG dosage used by us was 3000 units given intramuscularly twice a week for 10 weeks (20 injections). Semen analysis was repeated every two months after the completion of the therapy, and frequently a post-coital test was also performed. The couple were advised to have intercourse at least on alternate days and to report any alteration in the menstrual pattern.

Varicolectomy

Since 1974, over a period of 6 years, 72 men underwent varicolectomy (majority unilateral) as a treatment for subfertility. Among them, 55 had left sided varicocele, and the remaining 17 had bilateral varicosity. Size of the varicocele was small in 13, moderate in 16 and big in 43 subjects. The duration of infertility ranged from 1 to 14 years, and the female factor was ruled out in all these couples by the basic investigations.

Except the 5 azoospermic men, all the patients included in this study had vary-

ing amounts of oligospermia, severely impaired sperm motility and stress pattern of sperm morphology. Seminal study was repeated every 2 months following the surgery, anticipating any improvement in the quality of semen. Five oligospermic men who did not improve following surgery were given HCG therapy after 6 months of varicolectomy.

The operation performed was the Ivanissevich procedure which consisted of the internal spermatic vein ligation high at the internal inguinal ring in the extraperitoneal space. Earlier we were obtaining bilateral testis biopsy simultaneously, for assessment of prognosis. (Rajan *et al.*, 1978).

Clomiphene Citrate (Fertyl)

Of late, from January 1979, we have recruited 49 men with idiopathic oligospermia for treatment with clomiphene citrate. The duration of infertility ranged from 1 to 13 years, and the female partners had no infertility problems. Similar to the HCG-treated group, these men had

a sperm count of less than 20 million with poor sperm motility and morphology. No azoospermic men were included in this particular study.

The treatment regime followed was that advocated by Paulson and Wacksman in 1976. Clomiphene citrate (Fertyl) was administered in a dose of 2 mgms daily for 25 days, with five days' rest, for 6 to 9 months or till pregnancy resulted in the wife. Semen study was repeated every 2 months, and frequently a post-coital test was also performed.

Results of Treatment

H.C.G. Therapy

Among the 36 men treated with HCG, 29 were oligospermic and 8 were azoospermic. The age group of these patients ranged from 23 to 42 years with a mean, of 31.7 years, and the duration of infertility ranged from 1 to 26 years with a mean of 4.3 years. Treatment results analysed in the 30 treated men, who had regular follow-up, is given in Table II. Before treatment 52.78 per cent of the patients had a sperm count of less than 10 million, whereas after HCG therapy only 26.67 per cent were in that range. Similarly, in the post-treatment group 23.33 per cent had a sperm count of 20 million and more against none in this range prior to treatment. However, apparently the

azoospermic group did not show any response to therapy.

Breakdown of the figures of 30 men who were regularly followed after the hormone therapy is as follows: Among those 19 men who had an initial count of less than 10 million sperms/ml, 6 had shown definite improvement in count as well as sperm motility after the treatment. In this group 4 men could impregnate their wives. Of the 9 men with the initial sperm count ranging from 10 to 19 million/ml, 3 had shown improvement in semen quality post-treatment and all could impregnate their wives. Nevertheless, there were no conceptions following HCG therapy of azoospermic men.

As indicated in this date, among the 26 oligospermic men treated and followed, 9 could improve their semen quality (34.61%), and 7 could achieve a pregnancy (26.92%). Seminal improvement and pregnancy rate were certainly better in those men treated with an initial sperm count of 10 million/ml or more than those who had an initial count of less than 10 million. In all the 7 couples conception had occurred within one year of treatment, earliest was in 3 couples after 2 months of therapy.

Varicocelectomy

A comparison of the sperm count before and after varicocelectomy is

TABLE II
Semen Quality Before and After Treatment with Gonadotropin (H.C.G.)

	No. of men	Azoospermia		Less than 10 million		10 to 19 million		20 million and above	
		No.	%	No.	%	No.	%	No.	%
Before Treatment	36	8	22.22	19	52.78	9	25.00		nil
After Treatment	30	7	23.33	8	26.67	8	26.67	7	23.33

shown in Table iii. None of the 5 azoospermic men showed any improvement following varicocelectomy. Excluding the azoospermic men, of the 67 oligospermic men who underwent the surgery, 57 men could be regularly followed. Hence the results presented relate only to the 57 oligospermic men, who were divided into three groups as shown in Table III.

in achieving conception in their wives (55.6 per cent). There were 16 men who were operated with an initial sperm count of 20 million/ml or more. In this group the significant observation was improvement in sperm motility in 10 subjects (62.50%), with a conception rate of 43.75 per cent (7 couple).

TABLE III
Effect of Varicocelectomy on Semen Quality and Pregnancy Rate

Initial sperm count	Men followed	No. of men showing improvement in				Pregnancy in the wife
		count	motility	count & motility	none	
Below 10 million/ml	32	4 (12.50%)	3 (9.40%)	17 (53.10%)	8 (25.00%)	11 (34.40)
Between 10 and 19 million/ml	9	—	3 (33.30%)	5 (55.60%)	1 (11.10%)	5 (55.60%)
20 million/ml and above	16	1 (6.30%)	10 (62.50%)	—	5 (31.30%)	7 (43.75%)
Total	57	5 (8.80%)	16 (28.10%)	22 (38.60%)	14 (24.57%)	23 (40.36%)

Among the 32 subjects with an initial count of less than 10 million sperms/ml, 24 (75%) improved the quality of semen after ligation, and in this group 11 men (34.40 per cent) succeeded in impregnating their wives. Post-ligation results were more gratifying in the 9 men who had an initial sperm count ranging between 10 to 19 million/ml. Eight of them (88.88%) showed significant improvement in the quality of semen, and 5 men succeeded

When one considers the overall results of varicocelectomy in oligospermic men with poor sperm motility and 'stress pattern' of sperm morphology, for the 57 men followed-up, 43 (75.43 per cent) had improved the quality of their ejaculate and 23 (40.36 per cent) succeeded in impregnating their wives. The nature of semen quality at the time of conception in the 23 successful subjects is given in Table IV.

TABLE IV
Seminal Status at the Time of Conception Following Varicocelectomy

Initial Sperm count	Pregnancy in wife	Improvement in count	Improvement in motility	Improvement in count and motility	No improvement
Below 10 million/ml	11	2	1	7	nil
10 to 19 million/ml	5	nil	2	3	nil
20 million/ml and above	7	1	4	nil	2
Total:	23	3	7	10	2

Interval between varicocelectomy and conception has ranged from 2 months to 3 years, with a mean of 8.6 months. Twelve of the 23 pregnancies (52.2%) were conceived within 6 months of surgery, and 20 (87.00%) within 1 year.

Discussion

Administration of human chorionic gonadotropin (HCG), perhaps, is a physiologic approach to therapy for oligospermic men with poor sperm motility (Misurale *et al.*, 1969). The theory that Leydig cell failure leads to poor sperm motility has been supported by MacLeod *et al.*, (1964). Similarly, a significant correlation between testosterone synthesis and sperm motility has been observed (Weiss *et al.*, 1978). Chorionic Gonadotropin has been observed to restore Leydig cell function and normal testosterone synthesis, thus improving the sperm motility.

Our regime of 3000 units of HCG twice a week for 10 weeks, has resulted in improvement in semen quality and motility in 34.61 per cent and a conception rate of 26.92 per cent. Effectiveness of HCG therapy in idiopathic oligospermic men was more spectacular in the group with an initial sperm count of 10 million or more than in the group with the initial count of less than 10 million sperms/ml.

While the commercially obtainable preparations of HCG have mostly LH activity, they may also have a small amount of FSH activity (Northcutt and Albert, 1970), and this may be responsible for success noted in the treatment of idiopathic oligospermia with HCG injections (Glass and Holland, 1963). Eventhough gonadotropin therapy is a simple procedure, unfortunately, neither entirely ade-

quate gonadotropic preparations are available nor is the knowledge concerning the form of therapy or the dosage advanced to a sufficient degree to permit formulation of precise recommendations concerning details of therapy for the various types and degrees of oligospermia. Because of this deficiency, a great discrepancy exists in recommended schedules of treatment. Nevertheless, according to Steinberger (1979), the most affective form of therapy involves administration of 4000 unit of HCG twice a week for 6 to 8 weeks, followed by a combination of 2000 units of HCG, and Human Menopausal gonadotropin (HMG) (75 units FSH and 75 units LH) three times a week for a minimum of 6 months.

The deleterious effect of varicocele on male fertility is well documented (Charny, 1962, Brown, *et al* 1967, K. Johnson *et al* 1970, and Dubin and Amelar, 1971). Seminal cytology in subfertile men with varicocele was described in 1965 by MacLeod. Oligospermia of varying degrees with marked impairment of sperm motility and a definite increase of immature and tapering sperm forms were the abnormalities noticed in the ejaculate. Dubin and Hotchkiss in 1969 studied the testicular morphology in men with varicocele, and found germinal cell hypoplasia and premature sloughing of immature sperm forms within the lumina of the seminiferous tubules. While Leydig cell hyperplasia has been recognised as one of the prominent features in biopsy, in the recent work of Weiss and others (1978), on quantitation of Leydig cells in testes biopsies of men with varicocele, this observation could not be confirmed.

Recent findings (Weiss *et al* 1978) support the hypothesis that Leydig cell dysfunction, resulting in decreased intratesti-

cular testosterone concentrations, could be the mechanism responsible for the poor sperm quality, especially the motility, in subfertile men with varicocele. The fact that varicocelectomy does not significantly improve sperm count in oligospermic men further supports this assumption. Moreover, in an attempt to overcome the poor results of varicocelectomy, in patients with poor sperm quality, Dubin and Amelar (1975) employed postoperative therapy with HCG, which resulted in improved testosterone synthesis and thus marked improvement of semen quality and pregnancy rate.

In our study, the improvement of semen quality as well as the pregnancy rate were consistently poor in those men with initial sperm count of less than 10 million sperms/ml. These men, we feel, would have been better served with postoperative HCG therapy in a dose of 4000 units twice a week for 20 injections, as suggested by Dubin and Amelar (1975).

Yet another treatment modality of recent interest for idiopathic oligospermia is by stimulating endogenous gonadotropin release with clomiphene citrate (Fertyl) (Palti, 1970, Paulson and Wacksman, 1976 and Epstein, 1977). Encouraging results in improvement of semen quality and pregnancy rate have been documented by Check and Rakoff (1977) with clomiphene citrate in a dose schedule of 25 mgms daily for 25 days, with 5 days' rest, for upto 7 months. To select the clomiphene responders, Paulson (1977) segregated the patient population into 'pregerminal hypofertility', 'primary germinal hypofertility', and 'postgerminal hypofertility', based on testicular biopsy with simultaneous gonadotropin and serum testosterone determinations. Men with 'pregerminal hypofertility', charac-

terised by oligospermia of varying degree, serum FSH levels within the normal range and normal levels of serum LH and testosterone, with testicular biopsy revealing spermatogenic hypoplasia, could be expected to respond to clomiphene citrate with an improved ejaculate and an enhanced chance of pregnancy.

We have instituted empirical therapy with clomiphene citrate (Fertyl) in 49 subfertile men with idiopathic oligospermia, and the treatment schedule followed was as described by Check and Rakoff (1977). However, since the study has been initiated recently, the results have not yet been analysed.

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