Male Infertility and the Present Status of its Management by Drugs

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SUMMARY

Infertility is a common problem and in about 40% of childless couples the husband may also need treatment, alone or along with the wife. In India, however, not much attention has been paid to problems of male fertility and traditionally it is the wife who is primarily held at fault. A proper evaluation of every individual patient and exclusion of surgical conditions like varicocele or obstruction are necessary before starting any drug treatment. No stereotyped regime can succeed for each and every case. Androgens, gonadotropins, vitamins A & E, antibiotics and anti-inflammatory agents are well established modes of therapy, but the dose-schedule has to be carefully determined. Some newer androgens (mesterolone and fluoxymesterone) can be given orally and are very effective in directly stimulating spermatogenesis. Indigenous drugs (Speman) can be of considerable help in properly selected cases. The hypothalamic releasing factors (GH-RH), Bromocriptine etc., are still on trial but hold promise for the future. Thyroid, anti-estrogens (Clomiphon), corticosteroids, arginine and vitamin B_{12} are of doubtful value only. Excessive smoking and alcohol ought to be discouraged.

Since the beneficial effect of treatment could be only short lived, it is essential that the wife's fertility is simultaneously assured.

INTRODUCTION

The predominant concern with population control in recent years has tended to over-shadow the importance of involuntary sterility as a medical problem. On an average, about 10% of all couples face difficulty in starting a family and this creates a feeling of great personal failure, particularly in India where religious and socio-economic traditions have made it almost imperative for everyone to have children. A recent W.H.O. Report suggests that the incidence of sterility may reach as high a figure as 30% in some parts of the World, but everywhere there is at least a 5% core of irreversible sterility due to complex and obscure reasons. Unfortunately, little effort seems to have been made in our country, so far, to put the management of this common problem on a proper scientific basis and one often comes across couples who have been unscrupulously exposed to everything from powerful synthetic hormones to shocking "tantric" practices.

Another important aspect of this problem in India is that it is the wife alone who has been traditionally blamed for sterility. But Buxton & Southam have emphasized that the husband alone is at fault in 20% cases, while in another 20% the abnormality lies in both husband and wife. Thus, in 40% childless couples the husband may need specific treatment himself, while the gynaecologist takes care of the wife.

It is beyond the scope of this brief presentation to describe the various investigative procedures for the infertile male. Very often such simple things as a careful physical examination or semen culture may prove more rewarding than highly sophisticated tests like hormone-assay. Although a precise etiological diagnosis may still not be possible, a proper evaluation is always necessary before putting the infertile patient on any line of medical treatment. It is, of course, presumed that any indications for surgery (as in the case of varicocele or obstruction) have been excluded.
DRUG TREATMENT OF MALE INFERTILITY:

Androgens: Testosterone is perhaps the most widely used drug in male infertility. The long-acting compounds like testosterone enanthate (Testoviron depot, Schering), or combinations of different esters (Sustanon, Organon) are now generally preferred. But each physician seems to have his own dose schedule and the results can be highly variable. It is now well recognised that a high local concentration of testosterone (about 80 times the blood concentration), aided by a specific Androgen-Binding-Protein in the seminiferous tubules, is the most important stimulus for spermatogenesis. Small doses of exogenous testosterone (e.g. 50 mg fortnightly) which are carried to the testes after dilution in the bloodstream may, therefore, produce little improvement in sperm count. On the other hand, large doses (e.g. 250 mg weekly) tend to depress the pituitary, thereby inhibiting spermatogenesis. To choose the correct dose has, therefore, been a problem.

In this connection one can make use of the "rebound phenomenon" which often occurs when testosterone administration is stopped. Testosterone propionate or enanthate, 100-200 mg/week for 10-12 weeks (the normal duration of one spermatogenetic cycle being about 80 days) will promptly bring down the sperm count to almost zero. It is better if counts are made at intervals of 3-4 weeks and the treatment stopped if azoospermia is obtained earlier. After nearly 5-6 months of stopping the testosterone, the sperm count shows a marked improvement over the initial level through a reactive hyperfunction of the pituitary. Considerable patience is, however, required both on the part of the patient as well as the doctor since this "rebound" may sometimes take almost an year to develop. The possibility of a prolonged or even permanent suppression of spermatogenesis in a small percentage of cases (2%), particularly with excessive dosage, must always be borne in mind.

Testosterone therapy should be given a trial in patients with oligospermia or poor motility and those in which biopsy shows maturation arrest and suppressed sperm formation but not atrophy. As is well known, testosterone is not effective orally.

Newer oral androgens – Recently, mesterolone (Proviron, Schering) has been introduced as a highly effective oral androgen which can stimulate spermatogenesis without suppressing the pituitary. Although not marketed in India so far, our limited experience with 25-50 mg mesterolone daily for 2-3 months has given very encouraging results. The sperm count went up from 6 to 90 million in one patient. Another oral androgen, fluoxymesterone, has also been used in the dose of 5-20 mg daily with good results. In particular, sperm motility seems to improve well with oral androgen therapy, perhaps through action on the epididymis where sperm maturation occurs.

Gonadotropins: It has long been known that spermatogenesis is under control of the pituitary gonadotropins. However, it has only been realised in recent years that the two gonadotropins may stimulate spermatogenesis through a common mechanism of providing a high local concentration of testosterone: LH directly stimulates the Leydig cells which produce testosterone and FSH promotes the synthesis of a specific Androgen-Binding-Protein in the tubules. It is because of this that LH, available as Human Chronic Gonadotropin (Antuitrin-S, Parke-Davis) is much more effective in human infertility than FSH available as Post-Menopausal Gonadotropin or Pregnant Mare's Serum (Anteron, Schering). HCG in the dose of 1000-2000 IU twice a week for 10-12 weeks will often improve depressed spermatogenesis and could be followed by a course of testosterone, if needed. A proper selection of cases is, however, necessary because both when spermatogenesis is entirely absent or entirely normal, no benefit can be expected.

Anti-estrogenic Drugs: Clomiphene citrate (Clomid), a weak anti-estrogen, has proved highly effective in inducing ovulation in women and has fully established its value in gynaecological practice. It increase the gonadotropin secretion, provided the pituitary is normally functioning, through competitive inhibition of the hypothalamic receptor sites which are responsible for the
normal androgen/estrogen feed-back mechanism. The use of clomiphene in the male to promote spermatogenesis has, however, been disappointing. A dose of 50-200 mg per day orally for 1-3 months of this costly drug could raise the sperm count only marginally and that too in a few of the patients only. Its better use is for a diagnostic test of pituitary gonadotrophic function in the male.

**Vitamins:** The role of vitamins in maintaining spermatogenesis in man is still a matter of controversy.

Vitamin A deficiency damages the epithelium in general, and vitamin A deficient rats have shown atrophy of the germinal epithelium in the testis. Because of this known epitheliotrophic action, large doses of vitamin A have been used for the treatment of male infertility. The effect seems to be entirely pharmacological, quite unrelated to any deficiency. The dose of vitamin A (Arovit, Roche; Aquasol-A, U.S. Vit. Pharm.) to be used is rather high: 50,000-150,000 IU for 1 to 3 months in idiopathic oligospermia or azoospermia. A paradoxical depression of spermatogenesis occurs at first but a significant improvement in the ejaculate often follows. This is almost similar to the rebound action with testosterone. The simultaneous administration of vitamin E and restricting the therapy to less than 6 months protects against any danger of hypervitaminosis.

The anti-sterility function of Vitamin E has been demonstrated only in laboratory animals, particularly the rat. It has, however, been used extensively in male infertility, although the deficiency of vitamin E has never been shown to be the cause of infertility in man. Vitamin E (Ephynal, Roche; E-toplex, U.S. Vit. Pharm.), 100 mg daily, can be given alone or along with vitamin A for 1-3 months to improve the number and motility of the sperms. But the use still remains largely empirical.

Although there is no specific indication for the use of vitamin C in male infertility, 0.5-1.0 gm daily can sometimes be helpful in improving liquification of the semen and combating any infection.

Vitamin B₁₂ has often been used in combination with testosterone in male infertility. Some workers have postulated its role in spermatogenesis and Pardanani et al. found low serum and seminal B₁₂ levels in infertile patients. But there is little to suggest that a combination of small doses of testosterone with massive doses of B₁₂, as often employed (Aquaviron-B₁₂, Schering), has any advantage over testosterone therapy alone. Except, therefore, when B₁₂ deficiency is clinically suspected, there is little to be gained from B₁₂ administration in human infertility.

**Indigenous drugs:** Many indigenous drugs are reputed to cure all types of sterility, but they do not seem to have been critically examined. One preparation which is particularly popular and handy is Speman (The Himalaya Drug Co.). Besides many reports about its beneficial effects towards raising the sperm count, some recent experimental studies have yielded more concrete support. Thus, Jaya Tilak et al. have shown that Speman increased testicular weight as well as secretory activity of the accessory sex glands. It produced an anabolic-cum-androgenic effect, with rise in maltase and fructose content of the semen, in castrated mice. Formulated from herbal ingredients without any synthetic steroids, it is entirely safe and without any adverse effects. In properly selected cases of oligospermia in whom no other complicating factors like infection or obstruction are present, we have found Speman to be of definite value in improving the sperm count. Speman plain is to be preferred to Speman forte, which has some tranquillising action also and might be more useful in patients with premature ejaculation or associated emotional problems.

**Antibiotics:** Chronic inflammation of the seminal tract is a common problem. Every patient with oligospermia, pus cells in the semen, epididymal tenderness, occasional pain in the scrotum or history of urinary tract infection should, therefore, have a semen culture done. A wide variety of
pathogenic bacteria may be isolated and depending on the sensitivity tests, appropriate therapy should be instituted. Although the patient may not be bothered by such seminal infection, it can affect fertility in many ways—by producing inflammatory blockage of the passage, by directly damaging the sperms (particularly with *E. coli*), or by producing congestion which raises the temperature of the testis and hampers the secretion of the epididymis.

Antibiotic therapy has to be in full dosage and over a sufficient time to be of any use in such cases. The more useful antibiotics are Ampicillin, Erythromycin and Chloramphenicol; a repeat course may be given if the first one has been of some benefit. Sulpha-Trimethoprim combinations (Bactrim; Sepran) are being extensively used and are very effective, but sometimes we have observed marked drop in the sperm count after these. This may probably be related to trimethoprim and needs further documentation and study. We now keep this possibility in mind before deciding on sulphathiazole-trimethoprim combination vis-à-vis other antibiotics.

In the Western countries considerable attention has been paid to the role of 'Mycoplasma' in human sterility (Horne, *et al*), but to isolate these smallest of the bacteria is a difficult job and has not received much attention in our country so far.

When specific infections like tuberculosis, sexually transmitted diseases, filariasis, leprosy etc., involve the male reproductive tract and lead to infertility, specific treatment is called for. Chronic prostatitis is a problem by itself, associated with all sorts of vague complaints, and requires prolonged care, which is outside the scope of the present discussion.

*Anti-inflammatory drugs*: Homonnai *et al* have suggested that antibiotics can usefully be combined with anti-inflammatory agents and have recommended the use of phenylbutazone, 300 mg a day for 3 weeks, in such patients. If necessary, the antibiotics plus phenylbutazone regime can be repeated after a month's gap. Alternatively, oxyphenbutazone (Suganril, Geigy) or ibuprofen (Brufen) can be used.

Non-specific anti-inflammatory, fibrinolytic agents like chymotrypsin (Chymoral, Armour Pharmaceutical) and Placentrex injections (Albert David), although frequently used in women with blocked tubes, have yet to establish their value in inflammation of the seminal tract. Corticosteroids have also been tried sometimes (as Deltabutazolidin or separately) but without any special advantage. The prolonged use of these anti-inflammatory drugs is not without danger and requires all the usual care. An antacid may be given along with.

*Miscellaneous*: Thyroxine, as a general metabolic stimulant, has long been tried in the treatment of oligospermia. Horax reported improved sperm counts and motility with 5-25 µg of Lio-thyronine daily for 4-6 months. Subsequent workers, however, could not substantiate these results. There now seems to be little justification for using thyroid hormones in the management of male infertility, unless there is some definite reason to suspect a deficiency.

The hypothalamic releasing factors (GH-RH) act as powerful physiological stimulants for the secretion of pituitary gonadotropins and are being put to limited trials, particularly in female patients. As yet they are not available commercially but hold great promise for the future.

An interesting suggestion had been made that the simple non-essential aminoacid, arginine, could stimulate spermatogenesis. But 18 infertile patients treated with 4 gm arginine daily for two months failed to show any improvement and the idea has been abandoned recently*. Another recent innovation is the use of Bromocriptine in both male and female patients. It is likely to be effective in infertility associated with hyper prolactinemia but is still to gain general acceptance.
**General measures:** It is often overlooked how some simple measures might be able to help the infertile couple. There is no clear cut sperm count below which a person is totally sterile. Van Zyl et al\(^6\) have emphasized this and we have had two pregnancies recently with counts of less than 10 million. Patients with such low counts should not, therefore, be discouraged outright. Tight fitting woollen or synthetic fibre under-garments, so popular today, can adversely affect spermatogenesis in our hot climate and ought to be replaced by loose cotton ones. Excessive alcohol and smoking can also lower fertility and ought to be discouraged. Finally, reassuring the patient and restoring his self-confidence can help a lot towards improving his libido and performance.

**CONCLUSIONS**

1. No "blanket" treatment can work for one and all sterility patients. Each has to be carefully evaluated and appropriately treated.

2. Since spermatogenesis takes roughly three months in man, treatment has generally to be a long one. Results cannot be expected in days and no regime ought to be undertaken halfheartedly or abandoned prematurely.

3. The overall success rate in treating male infertility is still disappointing everywhere. But if the patients are correctly chosen for any particular surgical or medical mode of treatment, the results can be much more rewarding.

4. The improvement in the male, under treatment, may only be short-lived. It is important, therefore, that the wife's fertility is simultaneously assured during this period.

**REFERENCES**


