MALE SUBFERTILITY

Therapeutic Approaches

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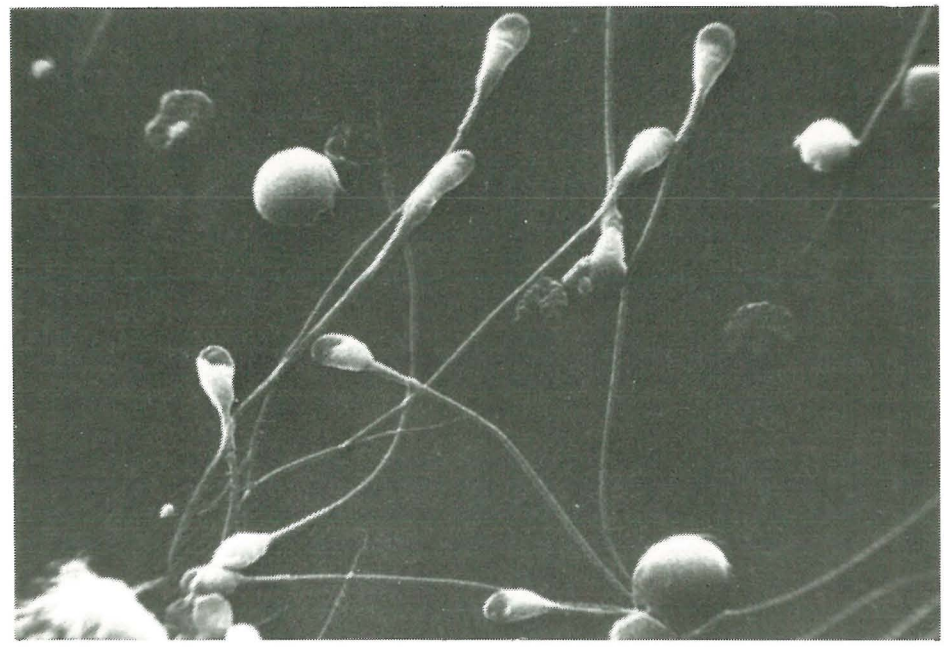
Extensive clinical studies have been reported for the management of male subfertility. The results of such therapy have often proved to be inconclusive and controversial mainly because of variation in diagnostic criteria. Therapy can only be successfully initiated after establishing the correct diagnosis, and treatment must be planned according to the findings of the semen analysis (Table 3.1). There are at present only a few standardized therapeutic measures available for the management of male subfertility including medical and hormonal therapy, surgical measures, and therapeutic insemination. Non-specific measures may also help improve the semen analysis.



Non-specific measures

Spermatogenesis is affected by a number of physical factors which can influence fertility. Several experimental studies have shown that scrotal hyperthermia has a rapid detrimental effect on testicular function through arrest of sperm maturation. Removal of the hyperthermia results in a return to normal levels. Tight underclothes could have the same effect and in men with oligospermia, a change to looser fitting undercloths may improve fertility. Personal habits such as smoking, alcohol or drug use should be discussed with the patient since these may influence the semen analysis.

Medical therapy

A number of hormones, vitamins and pharmacological drugs have been used for the treatment of male subfertility. The use of these agents has often been empirical and of controversial value in the management of male subfertility. Extensive long-term research and clinical trials utilizing common protocol and standardized diagnostic techniques have to be conducted. Some causes of an abnormal semen analysis may be amenable to specific therapy.

Male subfertility secondary to infectious disease may improve after specific therapy of the primary condition. The course of therapy must be long enough if pregnancy is to occur. The appropriate antibiotic against *Chlamydia* or *U. urelyticum* in non-specific urethritis is tetracycline. Penicillin and tetracycline are the appropriate treatment for *Neisseria gonorrhoea*. If the patient has a pathogenic organism such as *E. coli*, trimethoprim — sulphamethoxazole should be used. The patient's partner would also require therapy to prevent possible re-infection.

Medical therapy also appears to be promising in the management of semen analysis abnormalities associated with immunological disorders. Early reports of the use of ACTH or prednisone as immunosuppressive therapy for antisperm antibodies were disappointing. However recent studies have shown that prednisone therapy may be helpful. In men with immunological hypospermatogenesis causing azospermia or oligospermia where cellular immunity is operative and where irreversible testicular changes have not occurred, relative long-term prednisone therapy may be helpful. Prednisone 15mg daily for 3 to 12 months appears to be effective. The most consistently successful therapy for normospermic men with antisperm antibodies involves a regimen of cyclical very high dose corticosteroid administration. In this approach, methylprednisolone is given to the male in a dosage of up to 96mg daily for seven days on either days 1 to 7 or days 22 to 28 of the female's menstrual cycle.

Immunological infertility associated with antisperm antibodies may also occur in the female. The use of immunosuppression before ovulation (5-12 days) has also been advocated and there are anecdotal reports of lowered antibody levels and the occurrence of pregnancies. There have also been enthusiastic claims for the success of occlusion therapy where the male partner uses a condom for six to nine months. Great care must be exercised in the selection of patients for high dose steroid therapy and they

should be monitored closely for untoward effects and immunological efficacy.

Secondary hypogonadism resulting from hyper or hypothyrodism may also improve following control to the thyroid status. Retrograde ejaculation may be corrected by administering sympathicomimetic medication such as phenylpropanolamine. In uncurable cases, the fertility problem can be dealt with by homologous insemmination of semen obtained after bladder washings. The empirical use of Vitamin E and C, caffeine and kallikrein to improve spermatogenesis lacks scientific confirmation.

Hormonal therapy

Sex hormones in the management of male subfertility are generally misused. The wide use of synthetic steroids and other hormones might eventually create a variety of hitherto unknown problems because all reproductive phenomena are hormone-dependent and, therefore, sensitive to disturbances by exogenous compounds. The selection of the method of hormonal therapy for hypogonadism should be based on the levels of gonadotrophin and testosterone of the patient (Figure 3.1).

The administration of androgenic substances such as testosterone or mesterolone is indicated for the maintainance or development of secondary sexual characteristics. They have little effect on spermatogenesis and testosterone by interfering with gonadotrophin secretion probably has an inhibitory effect. Mesterolone has been reported to have little effect on the hypogonadal — pituitary function. By influencing the secondary sexual organ function, this drug may thus improve an abnormal semen analysis resulting from disease of the secondary sexual organs. Testosterone rebound therapy seems to be beneficial in certain types of patients. If spermatogenesis is depressed by testosterone administration, subsequent months show a "rebound" of the sperm count to levels higher than those before treatment. The length of time needed for an oligospermic male to achieve the maximum effect of the rebound phenomenon is about 2 years.

Hypogonadism due to hyperprolactinaemia can be successfully managed by treatment which lowers serum prolactin levels. Bromocriptine, a long-acting dopamine agonist, will reduce prolactin levels to normal even in men with pituitary tumours, resulting in a

TABLE 3.1
Management of Male Infertility
All parameters abnormal or predominance of single parameter.

SEMEN ANALYSIS	AETIOLOGY	TREATMENT
1. Abnormality of concentration — azospermia or oligospermia	a. Ductal obstruction	Surgical; AID
	b. Varicocoele	Surgical; AIH
	c. Endocrine	Hormonal; split AIH
2. Abnormality of motility and/or viability	a. Infection	appropriate Rx
	b. Immunological	condom, sperm washing, corticosteroids
	c. Early varicocoele	Surgical
	d. epididymal dysfunction	AID
3. Abnormality of volume	Disease of accessory glands	
	a. low volume 1. retrograde ejaculation	AIH after bladder washouts; sympathicomimetics
	2. hypoandrogenic	Hormonal
	b. high volume	split AIH
4. Abnormality of viscosity	c. hyperviscosity	amylase; mucolytics; mechanical disruption AIH
5. Abnormality of morphology	Usually transient and non-specific: Drugs, stress, heat etc.	Manage primary cause

TABLE 3.2
Indications for Artificial Insemination

TYPE OF INSEMINATION	INDICATIONS
A.I.H.	*small semen volume with normal sperm density *oligospermia with normal motility and morphology *impotence or refractory premature ejaculation *congenital or acquired anatomic anomalies preventing adequate cervical insemination: procidentia, hypospadias, retrograde ejaculation, vaginal anomalies *cervical hostility
AID.	*irreversible male infertility *husband with proven gene errors *Rh incompatibility: husband homozygous Rhesus positive with one or more hydropic fetuses.

rise in serum testosterone and improvement in sexual function. This treatment can also reduce the size of the tumour.

Spermatogenesis can only be induced by stimulating the testes with gonadotrophins. Clomiphene citrate has been used in the release of LH and to a lesser degree FSH in patients with a responsive pituitary gland and hypothalamus. Its effects appear to be dose related: higher doses reduce spermatogenesis while lower doses may improve sperm numbers and motility. The drug is usually given in doses of 25-50mg daily for 3 months. Although clomiphene appears to increase both LH and testosterone levels in most men, its effects on semen analysis are not predictable.

Induction of spermatogenesis may be achieved in about 85 percent of cases of hypogonadotrophic hypogonadism by using a combined regimen of HCG and HMG. HCG is given intramuscularly 2000 units once or twice weekly, the dose dependent on reaching a normal testosterone level checked initially after 3 and 5 days and then monthly. Semen analysis is doen every three months and if spermatogenesis is not fully restored in 6 months HMG is added, 75 units intramuscularly 2-5 times weekly. If gonadotrophin deficiency is due to impaired synthesis or secretion of GnRH, it seems logical to suggest the use of GnRH or its agonist analogues for treatment. This thereapy is still at the experimental stage and exact doses remain to be established.

Surgical procedures

Surgical procedures for male subfertility are limited in scope. They include the repair of penile and urethral disorders, orchidopexy, and varicocelectomy. Ductal obstruction may be corrected using microsurgical techniques performing vasovasostomy and epididymovasostomy.

Therapeutic insemination

Before considering the different aspects of artificial insemination, it is important to differentiate its two types - homologous or husband insemination (AIH) and donor insemination (AID). Somewhat less than 10% of couples with male infertility will be candidates for AIH (Table 3.2). This procedure is artificial in that all or part of the husband's ejaculate is placed in or around the wife's cervix without coitus. The goal is the concentration of what little the husband has to offer at the wife's cervical os. The subfertile ejeaculate is protected from further insults by the vaginal acidity and can exert its full potential in the reproductive process. Some subfertile males can improve their semen quality by collecting the firs portion (1-2cc) of a masturbation ejaculate. In this first half of the ejaculate both the motility and concentration are better then in the

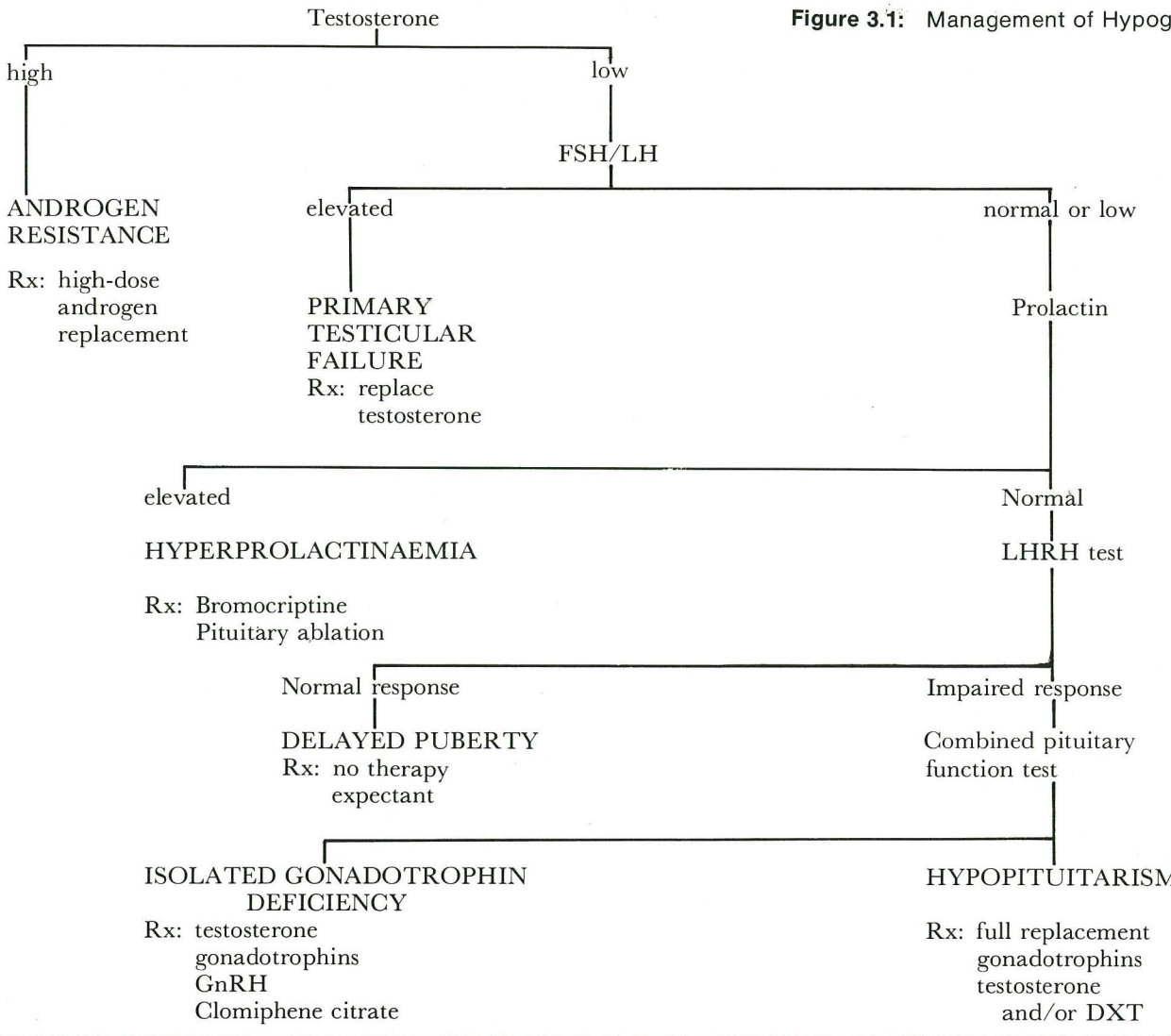


Figure 3.1: Management of Hypogonadism.

unsplit ejaculate. Several attempts have been made to improve sperm motility in cases of asthenozoospermia, or to separate motile from immotile spermatozoa. Kallikrein, albumin or arginine have been used to improve sperm motility in the split ejaculate with variable reported success.

Unfortunately the vast majority of couples with male infertility cannot resort to AIH. In this situation of irreversible male infertility donor insemination is indicated. Other indications for AID include proven gene errors and Rhesus incompatibility. AID can provoke more anxieties than AIH because of the extra marital element. Careful conselling of the couple if essential. Potential donors need to be carefully screened particularly for venereally transmitted disease.

The biggest single factor in unsuccessful inseminations is the timing of ovulation. Because of the variable nature of a woman's day of ovulation even when using a basal body temperature chart, it is illogical to offer the patient only one insemination per cycle. It is beter to plan for a minimum of two inseminations per cycle: the second being scheduled for the predicted day of ovulation and the first two days earlier. In women with irregular cycles and inconsistent ovulation times, it may be necessary to induce ovulation medically. Insemination may be:

(1) intrauterine for those situations where there is cervical hostility;
(2) cervico-vaginal; or
(3) cervical cup technique.

The latter overcomes many of the deficiences of the other methods and gives better conception rates.

Another method of artificial insemination by husband sperm is in vitro fertilization. Snce less than one million spermatozoa are required for IVF, the technique has been offered to men with very low sperm counts for whom there is often no other form of effective treatment. IVF has also been used to overcome infertility resulting from cervical mucus hostility from antisperm antibodies.

AIDS, CRABS AND BANANAS

For decades now we've had electronic transducers that will convert most physical quantities into their electrical analogues. Temperature, pressure, light intensity, mass and nuclear radiation are just a few examples of quantities that are easily measurable with cheap and readily available transducers.

More recently, this list has begun to include detectors for chemical entities such as hydrocarbons, smoke particles, alcohol etc. But imagine the range of uses for a transducer that could generate an electrical output directly proportional to the concentration of AIDS virus....

So far, the development of entity-specific sensors has proceeded very slow indeed for a number of reasons, some practical and some to do with the chemical reactions on which they depend. The most obvious approach of coating a chemical reagent directly on to a silicon circuit element has proved disappointing because of corrosion or other interactions between the two.

Two interesting new approaches are, however, proving more successful. George Guilbault, a chemistry professor at New Orleans University is one of a number of researchers who are experimenting with monoclonal antibodies coated on piezo-electric transducers. Monoclonal antibodies, developed originally in Cambridge, are highly specific reagents that will bind chemically to individual complex chemicals. Thus it is possible to create a monoclonal antibody that will react only with one particular protein. When such an antibody is coated on a piezo-electric crystal the resonant frequency is critically determinbed by its mass. So if a protein comes along that binds to the antibody the mass will increase and the resonant frequency will decrease. Guilbault has so far employed such a system to make electronic detectors that are specific for cocaine and for various agricultural pesticides.

Another intriguing approach to biochemical sensing goes one stage beyond the use of biologically active substances. Garry Rechnitz of the University of Delaware is using bits of living creatures built into electrodes. In particular he's fitted lead-out wires to the antennae of blue crabs. When immersed in water the crab antennae act more-or-less as ready-made transducers, producing electrical nerve impulses in direct proportion to the concentration of certain toxic pollutants.

Plants, too, can be pressed into service as chemical sensors. Rechnitz has used oxygen-sensing electrode in conjunction with a slice of banana to detect an important brain chemical called dopamine. This 'bananatrode', as he calls it, produces an electrical signal that could, in theory at least, measure susceptibility to Parkinson's disease (due essentially to lack of dopamine).

Some of these experimental devices may seem somewhat whimsical, but there's a huge range of important applications awaiting biochemical sensors that are stable, reliable and resistant to the corrosive environment of the human body. Imagine, for example, a cure for diabetes in which an insulin pump were directly controlled by a feedback loop attached to a continuous-reading glucose sensor inside an artery.

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