INVITED ARTICLE

MANAGEMENT OF UNEXPLAINED INFERTILITY

C L K Chan, S S Ratnam

ABSTRACT

Unexplained or idiopathic infertility means no cause can be found to account for the infertility. This depends on the enthusiasm to look for the subtle causes like luteal phase defect (LPD), luteinizing unruptured follicle syndrome (LUFS), abnormal prolactin secretion, psychogenic, environmental, nutritional and immunological factors. Sometimes, these subclinical conditions can be corrected. Failing to identify these treatable conditions, various empirical treatments, laboratory manipulation or assisted reproductive techniques (ART) can be attempted to achieve conception.

Keywords: Management, unexplained infertility.

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INTRODUCTION

Unexplained (Stauber 1979) (1) or idiopathic (Keller 1978) (2) infertility are terms meaning no cause can be found to account for the difficulty to conceive in a couple. The problerh was recognised even in 1956 while Stone and Ward called it psychological factor. Other synonymous terms include normal infertile couple (Jones and Pourmand 1962) (3), dyspareunia (Wyper 1962) (4) and apparently normal couple (Cox 1975) (5). The reported incidence ranged from 1.4% (Insler 1981) (6) to 50% (Stone and Ward 1956) (7). This big discrepancy probably reflects a difference in definition and how hard one tries to look for a cause through clinical history, examination and investigations. Although nowadays the basic examination and investigation of the infertile couple are similar in most infertility centres, there still exists some minor differences, depending on the availability of tests and costs.

This subject is therefore discussed in the following sequences:

a) the usual investigations of infertility;
b) diagnosis of the more subtle causes;
c) treatments for the "unexplained" infertility.

I. THE USUAL INVESTIGATIONS

The basic or routine investigations of an infertile couple may vary slightly among different centres. But on the whole, these usually include the following investigations:

1). Semen Analysis

This is widely accepted as a basic and screening test of male infertility. Repeatedly abnormal results should alarm the physician to look for causes for azoospermia, oligo- or astheno- or terato-spermia, hypospermia and abnormal agglutination.

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2). Endocrine Profiles

The hormonal profiles in the female usually include the measurement of plasma FSH, LH, oestradiol, progesterone, prolactin and testosterone. Progesterone in the luteal phase indirectly reflects ovulatory status. Persistently raised gonadotrophins with very low oestradiol in an anovulatory woman suggests ovarian failure. Low gonadotrophins may indicate hypothalamo-pituitary dysfunction. LH to FSH ratio of over 2 together with raised androgen suggest polycystic ovarian syndrome. Persistently raised prolactin should warrant further investigations into the causes for the hyperprolactinaemia.

The male hormonal profiles are not routinely carried out at the first visit. Most physicians would include the measurements of serum FSH, LH, prolactin and testosterine in the male if there is any sexual dysfunction, or when the serum analysis repeatedly showed azoospermia, severe oligo- or astheno- or teratospermia. Again, markedly raised FSH suggests testicular failure. Low gonadotrophins or testosterone may indicate specific replacement thereapy after excluding other organic lesions in the hypothalamo-pituitary-testicular axis. Again after exclusion of reversible or organic causes for hyperprolactinaemia, suppression therapy may sometimes help the patients' sexual problems.

3). Investigations of Utero-Tubo-Peritoneal Causes

Nowadays, the use of laparoscopy and chromopertubation become the prime investigations for the tubo-peritoneal status. These, supplemented with the hysteroscopy or hysterosalpingogram, will probably reveal most utero-tubo-peritoneal lesions like uterine malformation, intrauterine synechiae, tubal occlusion, intraperitoneal adhesions and endometriosis which may jeopardise a woman's fertility.

4). Endometrial Biopsy and Basal Body Temperature (BBT)

These two still remain part of the routine investigations of the ovulation status. Endometrial biopsy can be obtained by dilatation and curettage performed concurrently with the laparoscopy. Therefore, laparoscopy should ideally be carried out around the third week of the cycle. Occasionally, the woman can incidentally conceive just prior to the operation. Although there is no well documented proof that such pregnancy should be terminated, yet it is fairly difficult for both the physician or the couple to decide whether or not to carry on the pregnancy. The psychological burden will be enormous and last until a healthy baby is born.

Recently, there was also a preliminary report suggesting methylene blue which is used in chromopertubation may be embryotoxic in vitro. Basing on these, I personally always warn the couple of this and advise the use of condom or contraception for that particular cycle.

5). Cervical Mucus and Post Coital Test

Both tests can be performed in the same cycle. The cervical mucus reflects the oestrogen status and change of physical characteristics indirectly supports other investigations that ovulation has occurred. It is an inexpensive, non-invasive and well accepted method to the couple as a method of monitoring of ovulation to time coitus. Repeatedly abnormal postcoital tests, which is an in vivo sperm – cervical mucus test, when done at the periovulatory period, may hint the possibility of cervical hostility or immunological infertility. A satisfactory semen analysis or a good postcoital test are enough for the investigations of the male. Otherwise, further investigations may be indicated.

SUMMARY

With the basic investigations listed, in over 80% of the couples, a cause like endometriosis, utero-tubo-peritoneal, ovulatory or male factor, or combine male and female problems can be found. For the rest, some physician may give the diagnosis of "unexplained infertility". But with further effort and a few more investigations to be discussed in the following section, some subclinical or subtle causes can be further revealed.

II. DIAGNOSIS OF THE MORE SUBTLE CAUSES

1) Luteal Phase Defect (LPD)

This is not an uncommon condition with an incidence of 0.4 to 13%. This can be diagnosed if:

a) the BBT shows rise of temperature of less than 10 days, or
b) serial daily progesterone study in the luteal phase shows the peak progesterone level of less than 15ng/ml or
c) endometrial biopsy around the third week of the cycle shows histological dating (Noyes, Hertig and Rock 1950) (8) lag behind by 2 or more days.

There is some suggestion it may be associated with a lower follicular phase FSH, midcycle estradiol peak and absence of luteal rise of estradiol. Other reported associated abnormalities include higher baseline LH and testosterone, exaggerated response of LH to LHRH. All these suggest this may not only be a corpus luteal dysfunction but a sequence of events arising from an abnormal folliculogenesis.

2) Luteinizing Unruptured Follicle Syndrome (LUFS)

Stein and Levental (9) first proposed in 1935 the possibility of having the ovarian stroma and follicle luteinised as one of the explanation for the discrepancy between the "apparent ovulation" and pregnancy rate with the clomiphene citrate treatment. This LUFS has been demonstrated to cause infertility [Marik and Hulka 1978 (10); Brosens et al 1978 (11); Koninckx et al 1978 (12)].

It has also been proposed to be a cause of endometriosis. Its diagnosis is based on the laparoscopic findings of the absence of ostium during the first week of luteal phase, the lower peritoneal fluid 17 β-oestradiol and progesterone concentration, or the serial ultrasound follicular scanning.

3) Prolactin

It is well accepted that hyperprolactinaemia can be a cause of subfertility. The hypothalmo-pituitary-ovarian axis is affected in such condition. There are evidences that the LHRH secretion pattern is altered, gonadotrophin response to LHRH is disturbed, and luteal phases defect may be present.

But one normal reading of serum prolactin is not enough to preclude the prolactin effect on fertility. There were reports that nocturnal (Board et al 1981) (13) or transient (Fleming et al 1980) (15) hyperprolactinaemia exists. It was also found that in the non-conceptual cycle, the serum prolactin is higher though within normal range when compared with the conceptual cycle. Also, the discovery of prolactins which had different biological potency may also be the reason for subfertility.

If there is a suspicion that hyperprolactinaemia is the cause, the primary cause should be sought. Pituitary tumour should be excluded by either x-ray pituitary fossa or preferably CT scan. Visual field should be checked. Drug history like neuroleptics, oestrogens, metochlopramide should be sought. Renal and thyroid dysfunction should be excluded.

Hyperprolactinaemia in male has also been shown to decrease testicular androgen production. On top, it may also affect the libido.

4) Psychogenic, Environmental and Nutritional Factors

Stress in many forms may affect the fertility in both male and female. Marathon runners and women under strenous training may suffer menstrual and ovulation disturbance. Anorexia nervosa also have similar effect. Stress in male may also decrease libido and androgen production. Similar to anorexia nervosa, fasting in male causes decrease in testosterine production. In artificial insemination treatment cycles, it is not unusual to find women who were ovulating before become anovulatory. Men who are required to perform coitus at the perovulatory period or produce semen for insemination at a particular time may fail to do so.

5) Immunological Factor

A persistently negative postcoital test despite accurate timing and cervical mucus may indicate the possibility of the presence of antisperm antibody both in male and female. This can be confirmed with the in-vitro sperm – cervical mucus tests like immunobead test (Clarke 1985) (16) or Mix Antiglobulin test (MAR) (Jager et al 1978) (17).

III. TREATMENTS OF "UNEXPLAINED" INFERTILITY

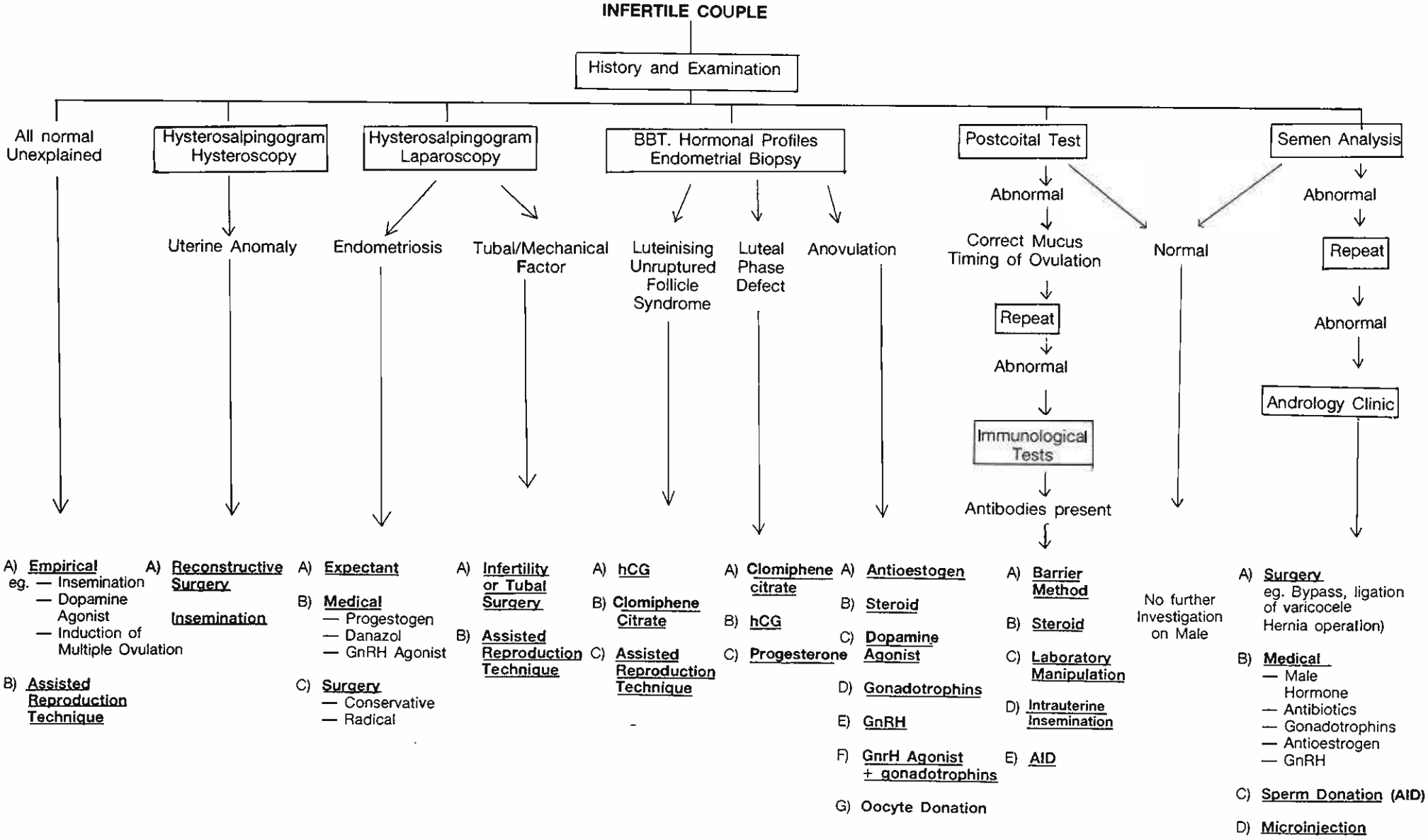
Having diagnosed the cause of the infertility, the treatment should be directed towards its correction. Fig 1 summarizes how the infertility problem may be managed.

1). Luteal Phase Defect and Poor Cervical Mucus

Patients with luteal phase defect can be treated with clomiphene citrate, progesterone or hCG injection. Clomiphene citrate can be given as 50 to 150 mg daily dose for 5 days starting day 2 of the cycle. The disadvantages include inadequate cervical mucus in the follicular phase for which 1 mg estradiol benzoate can be injected 7 days after the last dose of clomiphene citrate. Not only may it improve the quality of cervical mucus, it may also induce LH surge after 72 hours. Another sequential preparation which some have used includes 2 mg estradiol valerate from day 5 to 15 and 50 mg levonorgestrel is added from day 16 to 25.

Other than clomiphene citrate which can be given in early follicular phase 25 mg progesterone in oil can be injected daily starting 3 days after ovulation. Another

FIG 1. MANAGEMENT OF INFERTILITY OVERVIEW



reproduction technique.

Only if AIH fails and all resorts are exhausted that the couple should be counselled for the possible use of AID.

5) Assisted Reproduction Technique

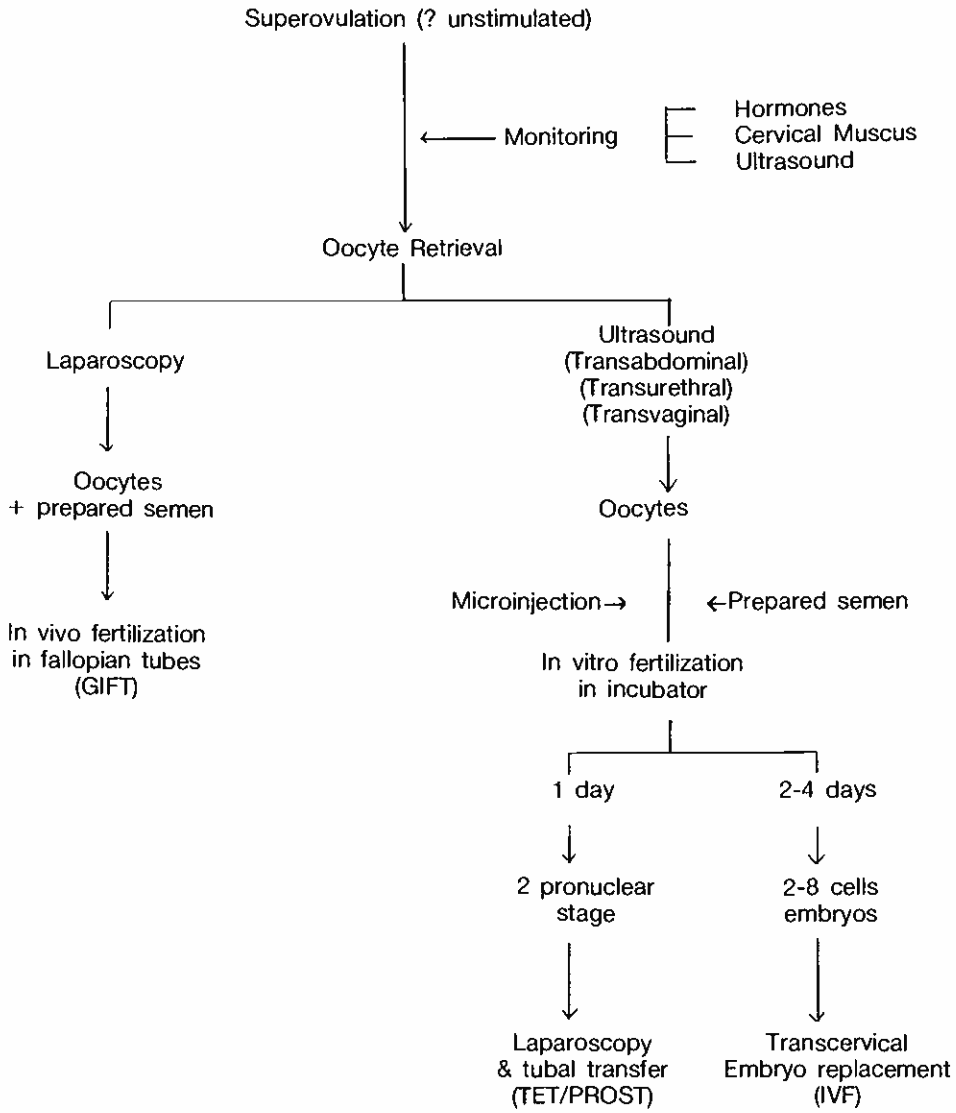
Fig 2 shows the various procedures involved in the 3 types of assisted reproduction techniques, namely, In-Vitro Fertilisation (IVF), Gamete Intra-Fallopian Transfer (GIFT) and Pronuclear Stage Transfer (PROST) (or in our department, called Tubal Embryo Transfer, TET). Basically it involves 3 stages. The first stage is the superovulation whereby multiple follicles are stimulated with various ovulation induction agents. The follicular development is monitored by serial ultrasound follicular scanning, plasma hormonal profiles (eg. estradiol, progesterone or luteinizing hormones) or cervical mucus until the follicles are mature enough. Then the second stage involves the aspiration of all the follicles to recover the oocytes either via laparoscopy or under ultrasound guidance. The third stage refers to the replacement of the gametes (ie. sperms and eggs immediately after oocyte recovery in GIFT) or early embryos (ie. pronuclear or 2 cells stage embryos about 24 hours after the oocyte recover in PROST or TET) into the fallopian tubes, usually via laparoscopy or mini-laparotomy; or later stage embryos (eg. 2 to 8 cells embryos about 2-3 days after oocyte recovery in IVF) into the uterus via a catheter passed transcervically.

Assisted reproduction techniques now becomes the last resort for the treatment of unexplained infertility when all above- mentioned treatments fail. Before the establishment of GIFT and PROST/TET, IVF is the only choice. Now with reported slightly better pregnancies rates for GIFT and PROST/TET, most cases of unexplained infertility are treated with GIFT or PROST/TET rather than IVF (although strictly speaking, the results are not comparable because of the different selection criteria).

CONCLUSION

The term Unexplained Infertility probably reflects the inadequacy of the present medical knowledge to diagnose the etiology. However, with the ultrastructural study of the endometrium, persistent study of the reproductive endorinology, immunological or biochemical study of the cervical mucus, hopefully our understanding of the subject will improve with time.

FIG. 2 TYPES OF ASSISTED CONCEPTIONS



way is to use 25-50 mg progesterone suppositories intravaginally daily instead of injection. Synthetic progestogens like the nortestosterone derivative should not be used because of the possible musculinisation of the female fetus. Dydrogesterone can be given because it does not cause the musculinisation, elevation of the BBT or suppresion of progesterone production by corpus luteum. It can be given as 10mg three times a day starting 3 days after ovulation. 17 α-hydroxy progesterone caproate 250mg can be given on day 17 or 18 as another alternative. However, it does not give a steady blood level and may cause menstrual irregularities.

An alternative of luteal support is the use of hCG injection 1000 to 2500 IU once every 2 to 3 days starting 3 to 5 days after ovulation.

2). Luteinising Unruptured Follicle Syndrome (LUFS)

Study on LUFS is difficult because the diagnosis depends on laparoscopy and peritoneal steroid concentration. The use of clomiphene citrate or hCG have been proposed. If everything fails, oocyte retrieval and assisted reproduction technique may be the treatment of choice.

3). Hyperprolactinaemia

Hyperprolactinaemia may also be present in cases of polycystic ovarian disease, luteal phase defect or amenorrhoea – galactorrhoea syndrome. These can be treated medically with dopamine agonists like bromocriptine, lisuride, metergoline or pergolide. Bromocriptine has been the mainstay of treatment for many years. Studies suggest probably the different preparations are probably equal in effectiveness. Bromocriptine can be given as 1.25 or 2.5 mg at the evening with meals to minimise the side effects like nausea and dizziness. Its optimal dose can be titrated until the serum prolactin level is normalised. Experience showed its use even during pregnancy do not give rise to significant teratogenecity. The use of bromocriptine in normoprolactinaemic patient with unexplained infertility, luteal phase defect, anovulation have been reported but is still controversial. These may not be related to the lowering of prolactin level but probably represent the dopominergic action of the drug on the hypothalamic output of LHRH. Not only in hyperprolactinaemic patient, it can also be used in conjunction with clomiphene citrate in normoprolactinaemic patients who have previously failed to ovulate with clomiphene citrate alone. It was suggested that the bromocriptine increases the oestrogens to enhance the action of the antioestrogen on the hypothalamus. Bromocriptine can also be used in cases of decreased libido due to hyperprolactinaemia in both male and female.

4). Immunological Factor

a) Occlusion Therapy

By the use of condom for 6 to 9 months, it is hoped the antibody level in the women will be decreased. The first unprotected coitus has to be well timed. However, review by Jones (1976) (18) and Kremer et al (1978)(19) did not show promising results.

b) Immunosuppression

Prednisolone 40 mg daily for 3 to 4 weeks (Bandhauer 1966) (20) or 2 weeks to be followed by reduced dose up to 9 weeks (Bassilli and el-Alfi 1970) (21) decreased the antibody titre in the men with pregnancies. Shulman et al (1978) (22) proposed the use of Prednisolone 96 mg daily for 7 days starting on the 21st day of the wife's menstrual cycle. The treatment can be repeated if necessary after 4 weeks.

Similarly dexamethasone acetate 2 or 3 mg daily may be given for 3 or 9 weeks respectively (De Ameida and Jouannet 1981) (23). Testosterone 250 mg when given over 2 weeks was also shown to decrease antibody titre and result in some pregnancies (Schoysman 1970) (24).

On the whole, the use of immunosuppression is not encouraging.

c) Artificial Insemination Using Husband's (AIH) or Donor's (AID) Semen

AIH can be done using unprepared fresh semen for intracervical, pericervical or intravaginal deposition. Split ejaculate after centrifugation can be used to achieve 33% pregnancy rate (David 1975) (25). Washed and prepared semen can also be deposited as intrauterine insemination. Table I shows how the semen is prepared for intrauterine insemination or assisted

Table I
PROCEDURES OF SEMEN PREPARATION FOR ASSISTED CONCEPTION/INTRAUTERINE INSEMINATION

1. Husband abstains from ejaculation 3-5 days before
2. Void urine and wash hands
3. Collect semen by masturbation in sterile 100 ml plastic screw top jar (tested for cytotoxicity)
4. Liquefy 20-30 minutes for 37°C
5. A sample for semen analysis
6. 1 — 1.5 ml used (depending on sperm counts)
7. Dilute with culture medium (1-3 fold)
8. Centrifuged (300g for 5 minutes)
9. Discard the supernatant
10. Add 1 — 1.5 ml of culture medium to the sperm pellet
11. Incubate at 37°C for 20 minutes
    (NB: In male infertility, in step 10, only 0.5 ml of culture medium is added and incubated for 45-60 minutes)
12. Alliquot for semen analysis
13. The supernatant for insemination (100,000 to 150,000 motile sperm to each egg)

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