

INTRODUCTION

The problem of infertility is not a new one. Much of the improvement that has taken place in the investigation and diagnosis of patients has not been paralleled by improvements in pregnancy rates. The management of infertility therefore remains a time-consuming, often costly exercise which can end in further frustration.

Infertility is best defined as the inability to conceive after one year of unprotected intercourse. Changes in life-style, family structure and particularly in the female role have led to a greater proportion of women postponing childbearing to the later reproductive years.

As a rule one would avoid an aggressive approach to infertility before 3 years (e.g. IVF) but if the woman is 35 years or older, this may be considered earlier.

About 10-15% of couples have been estimated to be infertile (Pepperell RJ 1984)

The increased incidence of infertility with age is shown in Table 1.

Infertility is commoner in negro populations when compared to white; 18.1 % vs 9.4 % the difference being mainly due to an increased incidence of tubal disease in blacks.

TABLE 2 – INFERTILITY vs PARITY

Para 0	10.1 %
Para 1	12.4 %
Para 2	6.0 %
Para >3	7.9 %

It also decreases with increasing parity up to para 3 and over when it increases slightly.

Infertility is more common in patients who do not reach high school education (14.0 %) compared to those who do (9.4 %) and those who go further (8.7 %).

After the first year of unprotected intercourse, only 75% of perfectly normal couples would have achieved a pregnancy, and only 90% after 2 years.

With these figures in mind, it is unusual to investigate infertility before a year of unprotected intercourse has elapsed.

female patient will be considered first.

The first factor to consider is the age of the patient: at 35 years, the chances of conception are half those at age 25 while at 40 they diminish further to one-fifth (20%).

The duration of infertility and the age of the patient will indicate the pace with which investigation and what therapeutic approach is to be offered.

Menstrual history: nobody has a 28 day cycle, the regularity being as important as the cycle length. It is more worrying if the cycle is short rather than if it is long (N.B. Oligomenorrhoea is defined as a cycle longer than 42 days).

SCHEME OF MANAGEMENT OF INFERTILITY

It is an essential aspect of infertility that the couple be seen together, at least for the first visit.

Initial assessment begins with the interview at the first visit. The

The presence of dysmenorrhoea must be classified. Primary dysmenorrhoea is defined as pain beginning on the first day of menstruation and as menstruation proceeds, the pain improves. It is associated with ovulation. Secondary dysmenorrhoea is pain beginning 1 - 5 days prior to the onset of menstruation and is relieved by menstruation. The latter is considered to be related to pelvic disease e.g. endometriosis, fibroids, PID, Mid-cycle pain and vaginal discharge are biological markers of ovulation. Only 30% of patients will admit to recognising ovulation at the initial visit.

The method of contraception previously adopted by the patient may be associated with infertility. This is especially so for IUCD's.

TABLE 1 – INFERTILITY WITH AGE

Age (in yrs)	% incidence of infertility
15 - 19	2.1 %
20 - 24	6.4 %
36 - 39	12.5 %
40 - 44	15.9 %

Galactorrhoea is uncommon. Though hyperprolactinaemia is a frequent cause of infertility (about 5%), only 30% of patients with high prolactin levels will also have galactorrhoea.

The occupation of the patient and other aspects of her lifestyle will provide information regarding risk factors for infertility (e.g. PID).

Since conceptions occur through a 3 day window a frequency of four times a week does not bind conception strictly to day 14. The presence of dyspareunia may indicate the presence of pelvic disease or it may simply be positional (Hawton K., 1982). It may also be a complaint used to mask deeper sexual problems. While on the subject, the male partner should be asked whether there is any difficulty maintaining an erection whether there is any premature ejaculation and whether penetration occurs properly.



Any past endocrine abnormality or pelvic surgery of any type must be recorded in detail. Vaginal surgery is also important as for example, with a cone biopsy; when too large a cone is excised. This restricts the production of cervical mucus and sperm transport cannot occur appropriately. This may also follow laser ablation.

As previously stated, the social and occupational history of the patient is important. Smoking >10 cigarettes a day will interfere with tubal function. Nicotine interferes with ciliary action in the tube as it does with those in the chest.

A basic general examination with particular attention to height and weight, body hair, thyroid and breasts is performed. The presence of galactorrhoea should be demonstrated. A thorough gynaecological examination is mandatory with due care being given to the appearance of the external genitalia. A cervical smear, if indicated, is taken.

The male partner should also be examined. Intersex e.g.

The presence of spermatozoa in an urinalysis specimen should alert the physician to the possibility of retrograde ejaculation.

It is estimated that in approximately 30% of infertile couples the cause lies partly or wholly with the male. (Hull Mr. et al, 1985)

Long stressful hours may suggest a low frequency of intercourse. A past history of inguinal hernia repairs, testicular tumours or orchido-pxy and any chemotherapy must be sought.

Sperm agglutinating or immobilising antibodies have been estimated to occur 3 - 13% of infertile men. Corticosteroids decrease the antibody titres but do not increase the pregnancy rates.

All of the treatment options for male infertility including anti-

oestrogens, gonadotrophins and androgens have proved disappointing. (Schill W.B. 1986)

Artificial insemination with husband's semen (A.I.H.) is largely unsuccessful when applied to the oligoasthenospermic male (pregnancy rate 2% per cycle). AIH may be particularly successful in patients with relative oligospermia due to a high semen volume and patients with retrograde ejaculation; while IVF can be expected to have good results (pregnancy rate 60%/cycle) in patients with asthenospermia only.

B. AIH using especially prepared 'washed sperm' and intrauterine insemination is more successful especially if the woman has had some form of ovulation induction or even superovulation. This latter procedure does however carry the risk of multiple pregnancy and ultrasound monitoring of the number of follicles needs to be carried out before insemination.

The ultimate solution the Male Factor problems is Artificial Insemination by Donor. Great care in counselling the couple needs to be taken before embarking on this course of therapy. AID should only be carried out in centres where established sperm banks exist. Donors need to be carefully screened and in accordance with current recommendations frozen sperm only used. The advent of the HIV risk has made the use of fresh sperm not recommended. Unfortunately this has led to a lower pregnancy rate since frozen

sperm results have consistently failed to be as good as results with fresh ones.

DISORDERS OF OVULATION

1. Ovarian Failure

This may be either primary, presenting with primary amenorrhoea or secondary causing oligomenorrhoea or secondary amenorrhoea.

The Resistant Ovary Syndrome presents with secondary amenorrhoea and very high gonadotrophin levels. Primordial follicles are present on ovarian biopsy, but also FSH and LH receptors are absent. The condition is associated with universally unsuccessful treatment - the only option remaining is oocyte donation (Bromwick P., 1990)

Other types of ovarian failure may be treated with oral contraceptives for 3 months in order to down-regulate the hypothalamic-pituitary and ovarian axis; on withdrawing a rebound phenomenon may stimulate ovulation.

2. Polycystic Ovary Syndrome

This condition previously known as Stein-Leventhal is characterised by oligomenorrhoea (cycles longer than 42 days), obesity and hirsutism.

Hormone analysis will reveal a raised LH/FSH ratio in the order of 3:1 (Baird C.T. et al 1977). The sample should be repeated during menstruation when a raise in FSH is expected in order to provoke subsequent follicular menstruation. In PCO the FSH/LH will again be found to be elevated.

The pulsatile secretion of FSH and LH is abnormal in PCO. The high level of LH can interfere with chromosome division from Metaphase I to Metaphase II at the time of ovulation. If the ovum is not released in Metaphase II then the ova are not suitable for ovulation. This accounts for the high percentage of spontaneous abortion in PCO patients.

3. Anovulatory cycles: abnormal follicular growth and corpus luteum function.

The ovary as an endocrine organ is responsible for the production of oestrogens for which 17 β oestradiol is specific for the follicular growth. A single sample is not enough to confirm normal follicular growth and 2 or 3 samples in the first half (follicular phase) of the cycle may be necessary. Ovulation is confirmed by a progesterone assay-evidence of corpus luteum formation. This needs to be done 7 days prior to menstruation in day 21 in a 28 day cycle.

UTERINE CAUSES OF INFERTILITY

Disease of the endometrium will prevent implantation and establishment of a pregnancy and the commonest causes are endometrial atrophy eg as a result of pelvic Tb and Asherman's Syndrome (intra-uterine synechiae).

The diagnosis may be suggested by a hystero salpingogram but is best made by hysteroecopy.

For patients with mullerian tube abnormalities, metroplasty can

CAUSES OF FEMALE INFERTILITY (Hull M.R. et al 1985)

1. Disorders of ovulation (20%)
2. Tubal factors (15%)
3. Cervical factors (3%)
4. Endometriosis (6%)
5. Unexplained infertility (30%)

render someone infertile. The incidence of infertility after metroplasty is in the region of 20-30%. This is because it may be associated with the development of Asherman's syndrome.

Cervical stenosis may cause infertility from a lack of mucous. Fibroids only cause infertility if they occlude the tubes; they are a cause of recurrent abortion rather than infertility.

Mymectomies are associated with very high rates of tubal disease.

ASSESSMENTS OF OVARIAN ACTIVITY

1. Changes in cervical mucous

Pre-ovulatory cervical mucous is plentiful, clear, acellular and with a low viscosity. Spirbarkeit can be demonstrated and it ferns on drying.

On the day of ovulation threads as long as 15-20cms long can be formed without breaking.

The cervix opens slightly at the time of ovulation.

2. Endometrical Biopsy

The presence of secretory endometrium simply confirms the presence of progesterone but is not confirmatory for ovulation e.g. luteiniseal unruptured follicle (LUF cycle) (Mudge T.J., 1982).

3. Basal Body Temperature

On average a patient gets bored of keeping a BBT chart after 2 months. Mistakes in the charting are common. This method identifies a shift in temperature which points out when progesterone is produced rather than when ovulation occurs. It does however give an idea of the length of the luteal phase and it is therefore advisable to keep a BBT for a short while.

4. Laparoscopy

* This needs to be done in the luteal phase in order to confirm ovulation but if performed in the follicular phase, the developing follicle should be identified.

5. Ultrasound

Sequential ultrasound examination will demonstrate growth of the dominant follicle and in addition to oestradiol levels will confirm whether growth is appropriate.

A rising LH level is a sensitive indication of ovulation but in the case of the LUTEINISED UNRUPTURED FOLLICLE ovulation will still occur.

6. Hormone Levels

Assessment of reproductive hormones, FSH/LH, prolactin, oestrogen and day 21 (18-25) progesterone are an essential part of the diagnostic work up of infertility.

Testosterone levels are useful in the diagnosis of PCO's though only 20% of the PCO's will have raised levels.

TREATMENT OF ANOVULATORY INFERTILITY

1. Clomiphene citrate

This compound is oestrogenic and anti-oestrogenic at the same

time. It should not be given to patients who are ovulating because it will interfere with estradiol receptors in the endometrium and with the production of cervical mucus

Clomiphene can be started in a dose of 450mgs only for five days from D3 to D7 of the cycle. the serum progesterone should be assessed and if no ovulation occurs the dose is raised to 100mgs and then to 150mgs. There is however no benefit in going above that level.

Treatment should continue for at least 9 - 12 months unless the patient conceives.

If this does not occur at a dose of 150mgs, follicular growth should be monitored in the next cycle and oestradiol checked on days 10 and 13 and progesterone on day 21.

If the oestradiol rise is consistent with the presence of a follicle but a low level of progesterone, then the patient is not releasing an ovum. In the absence of an LH surge, HCG can be given along with clomiphene. If both oestradiol and progesterone are flat, then gonadotrophins should be used. Pergonal therapy must however have good monitoring facilities.

2. Gonadotrophins

Pergonal is a mixture of FSH/LH having mainly an action of FSH i.e. follicular growth. Ovulation induction can be achieved by HCG.

TABLE 3 - RELATIONSHIP OF OVULATION TO CONCEPTION IN PATIENTS WITH OVULATORY DISORDERS AFTER TREATMENT.

	% ovulation	% conceived
1. Primary Amenorrhoea	0	0
2. Secondary Amenorrhoea	56	34
3. Oligomenorrhoea	74	51
4. Anovulatory cycles	85	62

The regimen for Pergonal is to give on days 1,3,5,... to stimulate follicular growth, in a dose of 150i.v. by i.m. injection. A pure FSH preparation (Metrodin) may also be used.

On days 10 or 12, if the follicular response is adequate, HCG may be given and the couple advised to have sexual intercourse.

If the response is not adequate the dose is increased to 300 and to 450 subsequently.

Monitoring with oestradiol levels only will not indicate the degree of follicular development i.e. two small follicles will produce as much oestradiol as of one large one.

It is best to monitor with a combination of oestradiol levels and ultrasound examination on alternate stages. The main complication to be avoided with this treatment is Hyperstimulation Syndrome.

3. LHRH pumps

LHRH pumps secrete LHRH in a particular manner, simulating the natural process. It may be administered subcutaneously or intra-venously. The pump stimulates normal pituitary function, by substituting the hypothalamus and the thereby stimulating normal follicular growth.

In theory there is no need to monitor follicular response but hyperstimulation does occur and therefore the need to monitor as with gonadotrophin therapy is necessary.

Pregnancy rates in hypothalamic, hypopituitary syndrome are good but no better than with pergonal. LHRH pumps are better physiologically but there are no data to confirm that pregnancy rates are superior.

LHRH has been applied successfully for cases of hypergonadotrophic hypogonadism

(e.g. Kellman's Syndrome), multicystic and polycystic ovaries. (Arner M.A. et al, 1968)

4. Bromocryptine - Dopamine agonists

Anovulation due to hyperprolactinaemia is associated with very favourable results after treatment: 90% will get pregnant within 3 months. Bromocryptine, a dopamine agonist, reduces the level of prolactin and reduces the size and growth of prolactin-secreting adenomas. It is considered the treatment of choice with recourse to surgery being rarely necessary.

Bromocryptine is usually started in a dose of 2.5mgs b.d. and continued in a maintenance dose of 1.25mgs bd.

In cases of borderline levels of prolactin, bromocryptine will not work.

*(to be continued
in the next issue)*