

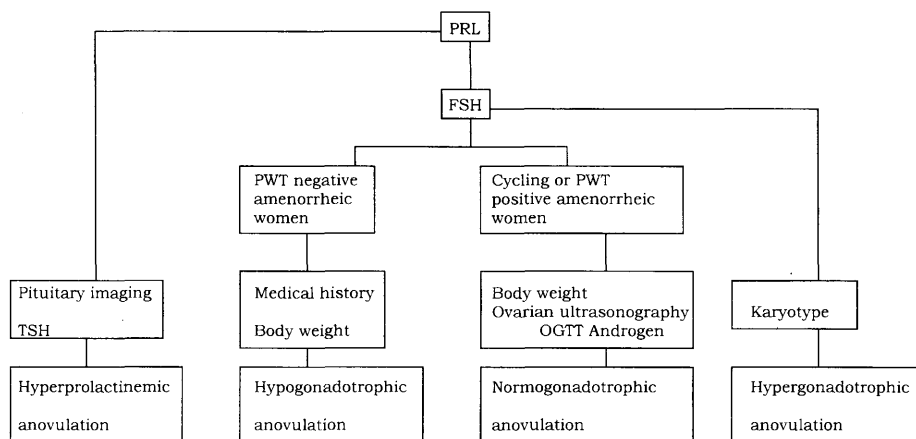
## Management of anovulatory infertility

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Chronic anovulation is probably the major cause of human infertility and is essentially associated with four distinct endocrine conditions; hyperprolactinemic anovulation, hypogonadotrophic anovulation, normogonadotrophic anovulation and hypergonadotrophic anovulation. Hyperprolactinaemia and microprolactinoma are frequent findings in young women and excessive prolactin secretion impairs ovarian function causing anovulatory subfertility. Dopaminergic treatment restores ovarian function and shrinks prolactinoma. In these patients restoration of fertility with prolactin lowering drugs does not increase the incidence of multiple pregnancies or early pregnancy loss. In the vast majority of hyperprolactinemic women pregnancy is safe and could be beneficial. Cabergoline is the most effective and tolerated of the antiprolactinemic drugs. Hypogonadotrophic anovulation is frequently associated with acute or chronic emotional stress and in this case the patient should be counselled. Explanation and reassurance are the first important management steps. The use of pulsatile gonadotrophin-releasing hormone is the best strategy to induce fertility. Patients with normogonadotrophic anovulation are likely to have polycystic ovary. The most cost effective pro-fertility treatment is the administration of an anti-oestrogen such as clomiphene or tamoxifen. The second choice therapy for patients with normogonadotrophic anovulation is ovarian stimulation with human gonadotrophin preparations. Low dose modifications give pregnancy rates lower than that with the traditional high-dose step-up protocol and intensive monitoring is required, but multiple pregnancies are less frequent. No treatment is available to enable women with hypergonadotrophic anovulation to conceive. Fertility in these patients can be promoted only by an egg donation programme. *Key words:* chronic anovulation/hyperprolactaemia/hypergonadotrophic anovulation/hypogonadotrophic anovulation/normogonadotrophic anovulation



FSH = follicle-stimulating hormone; PRL = prolactin; PWT = progestogen withdrawal test; TSH = thyroid-stimulating hormone. OGTT = Glucose Challenge Test.

Figure 1. Anovulatory infertility: diagnostic steps (Crosignani and Vegetti, 1996)

### Introduction

Chronic anovulation is probably the major cause of human infertility. Fundamental knowledge necessary to understand the problem has been gained in the last 90 years. The cornerstone was laid by Crowe *et al.* (1909) who showed that the male and the female reproductive systems are under the control of the pituitary gland. Gonadotrophic hormones were identified 18 years later (Smith and Engel, 1927; Zondek and Ascherim, 1927). The key role of the hypothalamus was then demonstrated and the gonadotrophin-releasing hormone (GnRH) was characterized, synthesized and its pulsatile secretion clearly shown (Guillemin, 1978; Schally, 1978; Knobil, 1980).

In 1961 Robert Greenblatt *et al.* reported the first successful induction of ovulation and pregnancies with clomiphene (Greenblatt *et al.*, 1961). Gemzell *et al.* (1958) and Borth *et al.* (1961) described the potent ovarian stimulation exerted by gonadotrophin hormones extracted from human pituitaries or from urine of post-menopausal women.

In the seventies it was found that prolactin-lowering drugs restore ovulation and fertility in patients with hyperprolactinaemic anovulation (Thorner *et al.*, 1975). Leyendecker *et al.* (1980) then showed that ovulation and pregnancy could be induced in patients suffering from hypothalamic anovulation by pulsatile administration of synthetic GnRH. Pure gonadotrophin preparations have now been obtained by recombinant techniques. The routine use of radioimmunoassay for steroid and protein hormones has permitted better definitions of the various ovarian dysfunctions (WHO Scientific Group, 1975).

Chronic anovulation today is essentially associated with four distinct endocrine conditions with different natural history, prognosis and treatment involving high or low prolactin, high or normal gonadotrophin concentrations (Figure 1).

## Hyperprolactinaemic anovulation

The upper limit of prolactin concentrations usual in plasma for a hypo-oestrogenic woman is 400–500 mIU/ml (20–25 ng/ml). When normal oestrogen concentrations are restored, the maximal usual prolactin concentration is 600–800 mIU/ml (30–40 ng/ml) (Lenton *et al.*, 1982). If the result seems elevated, the measurement should be repeated. Causes of hyperprolactinaemia include: the growth of a prolactin-producing adenoma (40–50% frequency); other tumours of the pituitary region which block the inhibitory influence of the hypothalamus; certain endocrine diseases: primary hypothyroidism (due to the prolactin-stimulating action of thyrotrophin-releasing hormone (TRH)); polycystic ovary syndrome (20% frequency); and certain drugs: neuroleptics (phenothiazines, butyrophenones); antidepressants (dibenzazepines); antihypertensives (reserpine, methyldopa); oestrogen (high dose).

Excessive prolactin secretion frequently impairs ovarian function causing cycle disturbances or anovulatory subfertility (Blackwell, 1992). Hyperprolactinaemia can disturb ovarian physiology at several levels, including follicular maturation and steroidogenesis, ovulation, the process of luteinization, and the corpus luteum function (Jacobs *et al.*, 1976; Kauppila *et al.*, 1982). The mechanism by which prolactin inhibits ovulation could occur either at the hypothalamic-pituitary level or directly in the ovary (Smith and Neil, 1977; Hamada *et al.*, 1980). Nevertheless, since pulsatile administration of GnRH in patients with hyperprolactinaemia results in normal fertility, the hypothalamus seems to be the most sensitive target in the reproductive axis. Ovulation and pregnancy may otherwise occur spontaneously even in a woman with mild to moderate hyperprolactinaemia (Crosignani *et al.*, 1985).

Some type of pituitary imaging should be done in hyperprolactinaemic patients (radiography, computerized tomography, magnetic resonance imaging) to detect an empty sella or a prolactin-producing adenoma (Keye *et al.*, 1980). A pituitary microadenoma is very frequent, and is found in up to 27% of healthy asymptomatic young women (Burrow *et al.*, 1981). Thyroid-stimulating hormone (TSH) should be measured to exclude hypothyroidism (Blackwell, 1992), though subclinical hypothyroidism does not impair fertility (Bals-Pratsch *et al.*, 1997). In addition, the medical history must be taken to rule out recent use of prolactin-stimulating drugs such as phenothiazine derivatives, reserpine or ganglia-blocking agents.

### *Treatment*

There are three treatment options to increase fertility in anovulatory hyperprolactinemic women: surgery, dopamine agonists and ovarian stimulation. Transphenoidal pituitary adenomectomy used to be an established treatment for prolactinomas (Molitch, 1989). Normalization of prolactin concentrations was reported in ~ 75% of patients with preoperative prolactin values of <200 µg/l. However, recurrence rates 5 years after surgery are high, usually about 20% in patients with microprolactinomas. Furthermore, surgery results in hypopituitarism

in many cases and has an important morbidity rate (0.4%) in patients with microprolactinomas rising to 6.5% in those with macroprolactinomas (Laws, 1987). For these reasons and because of the efficacy of medical treatment, surgery is now an infrequent choice (Spark *et al.*, 1982).

Ergoline dopaminergic drugs are the treatment of choice for idiopathic disease and prolactinoma. Bromocriptine is by far the most widely used drug. A daily dosage of 2.5 to 20 mg divided into two or three doses (Crosignani *et al.*, 1982) restores normal serum prolactin concentrations in about 80% of patients with microprolactinoma or idiopathic disease, leading to restoration of ovarian function in ~ 85% (Vance *et al.*, 1984). Prolactin concentrations become normal in about 65% of patients with macroprolactinoma, with restored gonadal function in over 50%. A decrease in tumour size is reported in ~ 70% of patients with a prolactinoma (Murphy *et al.*, 1987).

Bromocriptine can be administered intravaginally. Because absorption is slower, effective blood concentrations persist longer and the drug can therefore be given less frequently and at a lower dose (Vermesh *et al.*, 1988). Long-term treatment with bromocriptine has yielded pregnancy rates of 34 to 70% in large-scale outcome studies (Tang *et al.*, 1983; Al-Suleiman *et al.*, 1989). This compound, however, gives rise to a high incidence of adverse effects (nausea, headache, dizziness) though they are usually mild and transient, and only 5% of patients discontinue the treatment for this reason. Alternative drugs are lisuride, pergolide, quinagolide (Ferrari and Crosignani, 1986) and the most effective recent dopaminergic drug is cabergoline (Webster *et al.*, 1994; Ferrari *et al.*, 1995).

With cabergoline, a prolactin-lowering drug with long-lasting effect, most patients require doses as low as 0.5 to 1.0 mg per week. The cumulative proportion of patients in whom prolactin concentrations become normal with weekly cabergoline doses of 1.0 mg or less is 78%. Thus it may be advisable to use the once-weekly regimen for doses of up to 0.5–1.0 mg weekly, and the twice-weekly regimen for doses over 1.0 mg in order to minimize adverse events related to high single doses.

In a large controlled trial involving 459 hyperprolactinemic women, serum prolactin concentrations returned to normal in 83.4% of patients treated with cabergoline compared with 58% given bromocriptine, and ovulatory cycles or pregnancy occurred in 72 and 52% respectively. Although the overall incidence of adverse events was relatively high in both groups, severe adverse events were less frequent in the cabergoline-treated patients (14 versus 20%) (Webster *et al.*, 1994).

In patients who do not ovulate even when prolactin concentrations are normal, bromocriptine can be combined with cyclic administration of anti-oestrogens (Diamant *et al.*, 1980). If, despite the addition of anti-oestrogens, ovulation still does not occur, attempts can be made to induce it either using pulsatile GnRH or cyclic administration of gonadotrophin. In these patients, restoration of fertility with prolactin-lowering drugs does not increase the incidence of multiple pregnancies or early pregnancy loss, as occurs with gonadotrophin therapy (Weil, 1986).

## Hypogonadotrophic anovulation

Congenital forms are caused by an irreversible defect in gonadotrophin synthesis, sometimes associated with an olfactory sensory defect (Kallmann's syndrome; Kallmann *et al.*, 1944). Acquired forms of hypogonadotrophic amenorrhoea have several potential causes. It is frequently associated with acute or chronic emotional stress. Hypothalamic suppression in patients with classic anorexia nervosa, or who are simply too thin, leads to chronic anovulation and amenorrhoea. Similarly, women who maintain a borderline body weight but who practise strenuous physical activity may develop secondary amenorrhoea.

Reproduction has a very high caloric cost for women; a single pregnancy and lactation requires 130–150 000 kilocalories (Emerson *et al.*, 1972). This caloric expenditure corresponds to approximately the amount of energy stored in 15–16 kg of adipose tissue. A certain amount of fat tissue is therefore a real requisite for reproduction. This is why a girl has 9–10 kg more fat tissue in her body composition than a boy, even though they may be comparable in terms of weight, height and age (Frisch, 1981). This is also why a woman needs a critical proportion of fat tissue to start menarche (27% of body weight) and to maintain ovulatory cycles and regular ovarian cyclicity (22%). A simple nomogram can be used to check the minimal body weight needed to start and maintain normal ovarian activity in each individual (Frisch and McArthur, 1974).

Diseases of the hypothalamus and pituitary can also impair gonadotrophin secretion. Craniopharyngiomas or non-functioning pituitary adenomas may be accompanied by neurological symptoms (blindness) and signs of other trophic hormone deficiencies, and ischaemia and necrosis of the pituitary gland secondary to obstetric shock are associated with various degrees of insufficiency of all the pituitary hormones.

The best indirect way to demonstrate a hypogonadotrophic state is to check oestrogen status. Serum oestradiol concentrations should be <40 ng/l (<110 pmol/l) (Rowe *et al.*, 1993), and there should be no withdrawal bleeding after a progestogen withdrawal test (Steinkampf, 1994).

### *Management*

Surgery is recommended for central nervous system (CNS) tumours.

When anovulation is linked to known behavioural conditions such as underweight and excessive exercise the patient should be counselled. Explanation and reassurance are the first and very important steps in treatment.

Pulsatile GnRH (5 µg i.v. every 60 to 90 min for several days) is the best way to induce fertility in patients in whom anovulation persists after weight gain. Alternatives are human menopausal gonadotrophin (HMG) and human chorionic gonadotrophin (HCG). The advantages of pulsatile GnRH over menotrophins are that it is associated with a high pregnancy rate per cycle, there is little risk of hyperstimulation and the need for monitoring is minimal (Filicori *et al.*, 1991); however not all patients like to wear the pump necessary for intermittent GnRH

delivery. Nevertheless, when a severely underweight woman becomes pregnant, she has a greater chance of delivering an underweight baby which in turn has a higher risk of perinatal morbidity and mortality (van der Spuy *et al.*, 1988).

If, however, the cause of anovulation is pituitary failure, ovulation must be induced with gonadotrophins. The normal starting dose of menotrophins is 75–150 IU/day, which is usually increased until there is a response. The patient should be monitored by ultrasonography and/or plasma oestradiol concentrations, and the expected pregnancy rate per cycle is 20–25%.

Ovarian hyperstimulation is a recognized complication of the treatment and can have serious consequences. Even with the closest monitoring, it is difficult to reduce the incidence of multiple pregnancies, which is at least 20%. Pure follicle-stimulating hormone preparations (FSH) are not indicated for this group of patients because some luteinizing hormone (LH) is required to stimulate adequate oestrogen production (Couzinet *et al.*, 1988).

### Normogonadotrophic anovulation

These women have some disturbance in the pattern of pulsatile GnRH secretion (The ESHRE Capri Workshop Group, 1995). Diagnosing the condition requires frequent blood sampling, which is impractical and expensive in routine clinical practice. As these women have some ovarian activity, they are not hypo-oestrogenic and will bleed in response to the progestogen withdrawal test.

Most of these patients are likely to have polycystic ovary (PCO) (Adams *et al.*, 1985). PCO is a heterogeneous group of disorders characterized by increased free androgen, glucose intolerance (Legro *et al.*, 1999), low sex hormone binding globulin (SHBG), menstrual alterations, acne, hirsutism and often subfertility. Androgen excess associated with PCO must be distinguished from hyperandrogenism due to ovarian and adrenal tumours and from congenital adrenal hyperplasia.

A higher incidence of primary anovulation is frequently associated with simple excess in body weight (Grodstein *et al.*, 1994). Similarly, high waist to hip ratio is negatively associated with the probability of conception (Zaadstra *et al.*, 1993). Moderate weight loss can restore fertility in overweight anovulatory women (Clark *et al.*, 1998).

As in PCO patients, many obese women have high LH and androgen secretion together with a relative insulin insensitivity. Caloric restriction in overweight subjects lowers insulin concentrations and raises SHBG concentrations (Kiddy *et al.*, 1992), and in severely obese patients, post-gastroplasty recovery of ideal weight restores normal glucose and insulin metabolism (Letiexhe *et al.*, 1995).

In women with PCO, obesity exacerbates the syndrome and insulin insensitivity in particular appears to be directly related to the body mass index (Pasquali *et al.*, 1986); weight reduction in these patients lowers LH secretion and reverses insulin insensitivity (Kiddy *et al.*, 1990).

Normogonadotrophic anovulation is sometimes associated with thyroid and adrenal dysfunctions (Yen, 1986).

### *Treatment*

Women with normogonadotrophic anovulation show a reduced response to ovulation induction and when they do respond they have a greater risk of ovarian hyperstimulation. The most effective and easiest treatment is an anti-oestrogen such as clomiphene or tamoxifen. The usual starting dosage of clomiphene is 50 mg/day for 5 days, beginning 2–6 days after spontaneous or induced bleeding. Patients with normogonadotrophic anovulation have very sensitive ovaries. Even a dose of 75 IU FSH is often too high. In the case of multifollicular growth, supernumerary follicles can be reduced by selective follicular aspiration before ovulation. Thus the risk of multiple pregnancies can be reduced (De Geyter *et al.*, 1996). The treatment can be monitored by ultrasound and plasma progesterone measurement at the mid luteal phase of the induced cycles. Ultrasound monitoring is advisable because twins and triplets are often reported after uncontrolled ovarian stimulation with clomiphene. If no ovulation occurs, the dose can be increased by 50 mg each cycle up to 250 mg/day for 5 days (Hammond *et al.*, 1983). If adrenal androgens are high [dehydroepiandrosterone (DHEAS) sulphate >30 ng/l] the addition of dexamethasone to clomiphene may be helpful (Daly *et al.*, 1984). With clomiphene there is a 5.5-fold increase in the pregnancy rate (Connaughton *et al.*, 1974) with a slightly elevated incidence of twin pregnancies (5–10%) (Gysler *et al.*, 1982).

The adverse effects of clomiphene may include persistent ovarian enlargement, vasomotor and visual disturbances, urticaria and alopecia. These require discontinuation of treatment in only a small percentage of patients.

The second choice for patients with normogonadotrophic anovulation is ovarian stimulation with human gonadotrophin preparations. This is associated with a 10% pregnancy rate per cycle but the risk of ovarian hyperstimulation and multiple pregnancies is high (Salat-Baroux and Antoine, 1990).

Low dose modifications to the traditional regimen of gonadotrophin treatment have been suggested for these patients (Hamilton-Fairley *et al.*, 1992; Fauser *et al.*, 1993; Schoemaker *et al.*, 1993). With these new schedules the FSH threshold is exceeded only marginally in order to recruit as few follicles as possible and to allow selection and dominance to occur (Lobo, 1991). With the low-dose treatment, pregnancy rates are lower than with the traditional high-dose step-up protocol and intensive, expensive monitoring is required but multiple pregnancies are less frequent and the abortion rate may also be lower.

If anti-oestrogen and gonadotrophin treatment both fail, then ovarian electrocautery (Li *et al.*, 1998) or focused ultrasound (Moussatov *et al.*, 1998) may be considered. This procedure increases the sensitivity of the ovary to endogenous and exogenous gonadotrophins through still unknown mechanisms leading to the resumption of spontaneous ovulatory cycles or improving the ovarian response to stimulatory drugs.

After surgical treatment of PCO, the risk of adhesions varies between 30 and 90% (Campo, 1998) and this complication must be carefully weighed against the consistent success rate associated with the technique.

**Table I.** Specific treatment options for patients with chronic anovulation.

Diagnosis- type of anovulation	Treatment
Hyperprolactinemic	Prolactin-lowering drugs; pulsatile GnRH; HMG
Hypogonadotrophic	Counselling; pulsatile GnRH; HMG
Normogonadotrophic	Diet when necessary; anti-oestrogen; HMG-FSH
Hypergonadotrophic	None

GnRH = gonadotrophin-releasing hormone

HMG = human menopausal gonadotrophin

FSH = follicle-stimulating hormone

### Hypergonadotrophic anovulation

For all practical purposes, no treatment is available to enable women with hypergonadotrophic anovulation to conceive although FSH concentrations may fluctuate for months and there have even been cases of women who became pregnant after the diagnosis was confirmed by biopsy (Rebar and Connolly, 1990). Fertility in these patients can be promoted only by an egg donation programme.

Table I summarizes the treatment options for inducing fertility in patients with chronic anovulation.

### Future developments

The vast majority of anovulatory patients can already be successfully treated, through precise diagnostic procedures and thanks to the availability of effective treatments but the scenario is still far from ideal. The very high twinning rate associated with treatment is no longer accepted, and in most instances induction of ovulation is complicated and expensive therapy. Therefore on a global scale the rate of use is limited. In addition quite a large proportion of women respond poorly to specific stimulation. This is why work is proceeding to develop simpler and milder forms of personalized ovarian stimulation programmes. As these are developed new strategies will be adopted to improve the patient's response. The recent use of GnRH antagonists both in induced and non-stimulated cycles seems promising (Felberbaum and Diedrich, 1998).

The powerful profertility action resulting from normalization of body weight in obese (Clark *et al.*, 1998) and underweight patients (Frisch, 1981) is very interesting as is the activity of new drugs able to influence the ovarian response by acting on the woman's metabolism. This is the case of metformin which can increase 8-fold the rate of ovulation achieved with clomiphene in patients with polycystic ovaries (Nestler *et al.*, 1998). Similar results have been reported in these patients with the combined use of FSH and a somatostatin analogue (Lidor *et al.*, 1998).

In conclusion, better ovarian stimulation will rely on more careful use of the



available drugs in order to avoid multiple pregnancies and on strategies to improve ovarian response in women who at present respond only poorly.

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