Today's Treatment

Endocrine and metabolic diseases

Treatment of infertility and menopausal symptoms

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Treatment of infertility associated with anovulation

The development of effective treatment has a marvellously encouraging effect on the incidence of a disease. When, as has happened with the occasional spectacular overkill of gonadotrophin treatment of infertility, the media takes an intense interest in the treatment, the number of patients seeking it rises still more steeply. There are, however, more worthy reasons for the rising pressure. The large number of abortions has greatly reduced the availability of babies for adoption and forced would-be parents to exhaust every possibility of having a child of their own. Oral contraceptives have contributed a new cause of infertility by way of post-pill amenorrhoea, and failure of ovulation can now be simply and securely diagnosed by a single, judiciously timed plasma progesterone assay.

Good infertility clinics practise a strict investigative routine, and the existence of simple, effective treatment for one form of infertility is no good reason for short-circuiting such a routine. At the least it must be established by seminal analysis that the husband is fertile and by tubal insufflation that the wife has patent Fallopian tubes. In addition, anovulation needs to be proved. In the case of women with secondary amenorrhoea this may be taken for granted but primary amenorrhoea warrants much more extensive investigation of its own accord. Even with secondary amenorrhoea overt disease should be excluded. Occasionally the cause of anovulation is untreatable—such as menopause praecox. This condition is a likely cause of infertility when amenorrhoea is accompanied by high levels of follicle-stimulating hormone (FSH) in the blood or urine. Few doctors have not fallen into the trap of an unsuspected pregnancy. Investigation of the infertile couple needs in the first instance to go no further than establishing that the husband is fertile and that the wife has patent tubes and is not menopausal or pregnant. Then amenorrhoea or oligomenorrhoea is sufficient evidence of anovulation or infrequent ovulation to warrant an attempt to induce ovulation with antioestrogens.

ANTIOESTROGENS

The most commonly used antioestrogen is clomiphene citrate, although others (notably tamoxifen in Britain) are coming into use. These compounds lead to the increased secretion of pituitary gonadotrophin by stimulating the release of the hypothalamic

gonadotrophin-releasing factor. As ovulation is produced by the same endogenous endocrine events as in the normal cycle, the use of antioestrogens seldom results in overstimulation or multiple pregnancy. Indeed, there is no strong reason why their use should be confined to specialist infertility clinics. Although tamoxifen is used in smaller doses than clomiphene, the toxicity of both is so low that this is of no consequence. The standard regimen is to give clomiphene citrate 50 mg twice a day or tamoxifen 10 mg twice a day by mouth for four days. In successful cases this starts the growth of a Graafian follicle, which releases an ovum about 10 days after the start of treatment. Intercourse should therefore take place around this time. If ovulation but not conception occurs the patient will have a menstrual period three to four weeks after the start of treatment.

It is necessary to try to ascertain whether ovulation has taken place. The simplest way is by recording the basal temperature before getting up in the morning. The progesterone produced by the corpus luteum causes a sustained rise in the second half of the cycle, often as much as 0.2-0.3°C. Now that the assay of plasma progesterone is widely available a single blood specimen some three weeks after starting the antioestrogen will tell with certainty whether ovulation has taken place. Because chorionic gonadotrophin will cause a mature follicle to ovulate and will stimulate progesterone production by the corpus luteum the treatment with an antioestrogen is sometimes combined with an intramuscular injection of 5000 IU of chorionic gonadotrophin 10 days after starting the tablets. There is little evidence that such adjuvant treatment substantially improves the chance of a pregnancy.

If the first two or three courses of clomiphene or tamoxifen do not induce ovulation it is worth doubling the dose. If this also fails gonadotrophin treatment might be contemplated. This is quite a different kettle of fish and should not be embarked on lightly. A second round of investigation—FSH assay, prolactin assay, dynamic tests of ovarian function, and laparoscopy—should be considered. It is not appropriate here to consider in any depth the investigation and treatment of secondary amenorrhoea, which really arises at this stage. For the treatment of infertility it must be established that the woman has ovaries capable of responding to direct stimulation and a genital tract sufficiently developed to permit the meeting of the gametes and the full growth of the conceptus. This treatment is too dangerous and requires too many resources for it to be undertaken on an empirical basis.

PITUITARY GONADOTROPHINS

Human gonadotrophins are species-specific proteins and no adequate synthetic or animal substitutes are available. The FSH component may be extracted directly from human pituitaries or from menopausal urine, where it is present in relatively high concentration. Some countries, notably Australia, have organised

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national programmes for preparing FSH from necropsy material, and one or two large clinics in Britain also work up human pituitaries for their own use, but the only preparations commercially available are the urinary extracts Pergonal and Humegon. Although these are used primarily to induce follicular growth, the extracts contain a good deal of luteinising hormone as well as FSH, and the ovarian response is monitored by measuring the rising output of oestrogen in blood or urine. The dose required to evoke the desired response is critical and varies from patient to patient, so that monitoring by hormone assay is mandatory, both to avoid overstimulation and to determine when a follicle mature enough to ovulate is present.

In the normal menstrual cycle ovulation is precipitated by a surge of luteinising hormone. Fortunately human chorionic gonadotrophin has a similar action and is widely available. A single injection of 5000 IU of chorionic gonadotrophin will cause the follicle, stimulated to the right stage of development by the FSH injections, to ovulate some 36 hours after the human chorionic gonadotrophin injection. Unfortunately even a slight overdose of FSH will cause numerous follicles to develop and all will be ovulated by the human chorionic gonadotrophin. The litters that may result from such an unhappy therapeutic accident have been one of medicine's less fortunate contributions to the lay press.

ERGOT ALKALOIDS

A third therapeutic agent has lately joined antioestrogens and pituitary gonadotrophins. In some anovulatory, generally amenorrhoeic women the menstrual irregularity is accompanied by excess prolactin production from the anterior pituitary. Such hyperprolactinaemia can be suppressed by various ergot alkaloids, notably bromocriptine. Even in the absence of demonstrable prolactin excess this compound may induce ovulation. At present it is still basking in a rising sun, but, although its eventual role may be smaller than is presently assigned to it by enthusiasts, it is undoubtedly an important addition to the therapeutic armamentarium against failure of ovulation.

LUTEINISING HORMONE-RELEASING HORMONE

Many ovulation-inducing agents act by liberating luteinising hormone-releasing hormone (LH-RH) from the hypothalamus. The constitution of this decapeptide is now known. It has been synthesised and is commercially available. At first glance this appears to be the logical way to treat anovulation so long as the pituitary is intact and able to respond. As an agent for inducing ovulation LH-RH has proved disappointing for physiological reasons that were obvious from the start. LH-RH has a short half life in the circulation and is destroyed within a few minutes. Under normal physiological conditions it has only a few centimetres to travel from the hypothalamus to the target organ, the pituitary. It does so dissolved in a few millilitres of blood. Once past the pituitary it is greatly diluted and rapidly removed. Treatment necessarily starts by administering the polypeptide into the general circulation, and very little reaches the pituitary. To achieve sufficient gonadotrophin release to cause ovulation LH-RH has to be administered often and in high doses over a long time. Although the use of the natural material is thus impracticable, many experiments with analogues, less easily metabolised, are under way, and it may be that one of these will give us mastery over releasing gonadotrophins from the pituitary.

ETHINYLOESTRADIOL

Other attempts to imitate the physiological signals causing gonadotrophin release have met with modest and unpredictable

success. The growing Graafian follicle secretes increasing amounts of oestradiol. The rising oestrogen concentration is the physiological feedback control of the hypothalamus. When the oestrogen reaches a critical level LH-RH is liberated and causes a surge of luteinising hormone, which immediately precedes ovulation. It is sometimes possible in an amenorrhoeic woman producing little oestrogen to imitate this positive oestrogen feedback by giving small doses of ethinyloestradiol or oestradiol-17 β . This treatment, although it has the attraction of simplicity and safety, is so much less predictable than other means of inducing ovulation that it is seldom used.

Hormonal treatment of menopausal symptoms

Although effective endocrine agents for suppressing the unpleasant manifestations of the climacteric have been known for nearly 50 years, they have been used on a large scale only in the past decade. Even today their widespread use is more a matter of social pressure than medical enterprise. As is often the case, the wave of therapeutic enthusiasm started in the United States. Some of the more extravagant claims—"no woman need have a menopause"—may be discounted, but it is proper that we should respond to the needs of our patients even when these are voiced in the lay press with more force than wisdom. The question is not whether general practitioners should prescribe endocrine preparations and hospitals create hormone-replacement clinics. We are already too far down that path to turn back. The problem is how to control the traffic: how to select patients, what preparations to give, and when to stop.

HOT FLUSHES

The menopause presents a whole constellation of symptoms—loss of libido, insomnia, headaches, hot flushes, atrophic vaginitis, and a lot more besides. It is therapeutic nonsense to attack them all with a barrage of medicines. By and large the commonest and most troublesome manifestation is hot flushes, and treatment should be directed at it. Fortunately the effect of treatment may be evaluated objectively by a flush count. Because of insomnia, restlessness, and depression, hypnotics or sedatives are sometimes combined with hormones in proprietary preparations. This approach should be eschewed. In the few cases when such symptoms altogether outweigh the flushes they should be treated in their own right. Androgens such as testosterone are protein anabolics. They may give a feeling of wellbeing, increase appetite, increase weight, and improve libido. They are not a specific treatment for the ill effects of the menopause. Menopausal women are naturally prone to hirsuties. When the growth of a moustache coincides with taking androgens the doctor may be unjustly blamed. On the whole, androgens are best avoided.

OESTROGEN REPLACEMENT

The principal endocrine change of the menopause is that the ovaries cease to secrete oestradiol. The postmenopausal woman is not altogether deprived of oestrogen. Some oestrone is made by the peripheral conversion of androstenedione but not enough to prevent the consequences of oestrogen deprivation—namely, bone and skin changes and vascular instability. Treatment in the menopause should replace the missing oestrogen. To this end many compounds are available, mostly synthetic, and different from the 22 oestrogens that have been isolated from the biological fluids of pregnant women. A third category are oestrogens such as equilin and equilenin, which, although isolated from other mammals, do not occur in man. The most commonly used artificial oestrogens are ethinyloestradiol, mestranol, and stilboestrol. The liver and other tissues have an array of enzymes that metabolise and inactivate oestrogens in various ways, so

that any natural oestrogen not taken up by target organs is rapidly disposed of. The synthetic oestrogens are metabolised much more slowly and owe their potency and perhaps their toxicity to the physiological mechanisms for their inactivation being much less efficient.

Many untoward effects have been ascribed to synthetic oestrogens. Their tendency to cause thrombosis and to affect carbohydrate tolerance deleteriously has been well documented. The problem of whether synthetic oestrogens can cause cancer is unresolved. In a few particular instances the evidence is strong—for instance, cancer of the vagina in girls resulting from the antenatal treatment of their mothers with artificial oestrogens. In the context of menopausal treatment much disquiet has been aroused by the apparent association between endometrial carcinoma and the use of so-called “natural” oestrogens from equine sources.

The evidence against the natural oestrogens—oestrone, oestradiol, and oestriol—is less strong. Therapeutically they have the disadvantage that when taken by mouth they are rapidly inactivated before they reach the target organs. This has been overcome by preparing combinations, generally fatty-acid esters, that hydrolyse slowly in the body, yielding the free oestrogen. Oestrone and oestradiol benzoate are old familiars. To these, more advanced preparations, such as oestradiol valerate and

oestrone piperazine sulphate, have lately been added. Oestriol, an impeded oestrogen, is worth special consideration. It binds to the oestrogen receptor in the cytoplasm of the cells of oestrogen-responsive tissues and is conveyed to the nucleus, where it sets in train the cascade of events leading to fresh protein synthesis and cell replication. It is, however, less strongly bound than oestradiol and tends to escape from the cell before the whole sequence is completed. Although it will cause vaginal cornification and suppress hot flushes (both desirable effects in menopausal women), it is not a strong stimulus to endometrial proliferation and seldom causes postmenopausal bleeding. In so far as menopausal treatment is aimed at replacing lost ovarian secretion, it is logical to use oestradiol—the very material produced by the ovary. In summary, oestriol 0.5–1.0 mg daily or oestradiol valerate or oestrone sulphate up to 2 mg daily is the first choice.

Whether to give hormone replacement therapy to menopausal women and when to stop are matters of nice judgment. To some degree, as earlier with pain-killers in labour, our attitudes are socially not medically conditioned. In face of the strength of public demand our apparent choice is to some extent deceptive. A reasonable course between Scylla and Charybdis is to treat those who ask for it but not to push it and to use such agents as will relieve our patients without exposing them to undue risk.

Could a doctor ever be held to be negligent if he fails to perform amniocentesis in early pregnancy despite the parents' wish for this procedure and the baby subsequently turns out to be a mongol?

A doctor could be held negligent for having failed to perform amniocentesis when there were clinical indications to do so. The Law Commission¹ said that, while the Abortion Act, 1967, had no direct bearing on questions of civil liability, a doctor would probably be negligent if he failed to warn a pregnant woman that there was a risk of the child being disabled and that therefore she was legally entitled to an abortion. The Commission took the view that if the child was subsequently born disabled he should not have a right of action against the doctor because he never had a chance of being born other than disabled. In short, it was considered that “wrongful life” should not form the basis of a claim. The likely plaintiffs would, therefore, be the parents.

¹ *Report on Injuries to Unborn Children*, Cmnd 5709. London, HMSO, 1974.

What are the medical hazards of the common insects, particularly the earwig, to children playing with them?

The common earwig *Forficula auricularia* has fearsome pincers and forcifera means little scissors. In German the insect is called ohrwurm and in French perceoreille, so there would appear to be some justification, at least linguistically, in the belief that they are attracted to the human ear. Most entomologists would disagree with this notion, but there have been reports in medical journals of insects, including earwigs, entering human ears and patients complaining of a “noise of thunder” in the ear. It is doubtful, however, if earwigs or other insects have any special predilection for human ears. They are probably exploring odd cracks or crannies. Campers or those sleeping rough should plug the ears with cotton wool. Once an insect is entrapped float it out with olive oil. There seems to be no great hazard to children who play with insects such as earwigs. Wasps, bees, and hornets, on the other hand, are not to be encouraged.

Are there any dangers or disadvantages from using microwave ovens?

The construction of microwave ovens is now governed by British Standard Specifications intended to minimise the possibility of irradiation of an operator or bystander. Interlocks turn off the power supply if the door begins to open, and constructional details prevent radiation leaking through the crack at the door opening. The mechanism by which microwave radiation harms is quite different from ionising

radiation. Absorption of microwave energy produces local heating, and safety standards (limit 5 mW/cm²) are based on the efficacy of the blood circulation in removing excess heat. The lens of the eye is the most vulnerable tissue because it lacks this method of cooling. The culinary disadvantages of microwave ovens are broadly twofold. Plates do not always warm up as fast as, say, meat, so that hot dishes may come out on cold plates. Microwaves heat tissue remarkably uniformly so that part of the attraction of traditional cooking methods is missing, such as the variation in taste from surface to middle associated, for example, with roasting. On the other hand, the advantages of complete cooking of deep frozen food in a few seconds may be considerable: the system should minimise waste and “food poisoning” arising from maintaining bacterially contaminated food at room temperatures for longish periods before cooking.

Co-trimoxazole has been recommended for the prophylaxis of infections in patients with severe neutropenia during the treatment of leukaemia. Since this drug has been reported to cause neutropenia and even agranulocytosis in a small minority of patients treated for other conditions^{1 2} is it safe?

Neutropenia during treatment with co-trimoxazole occurs only in patients previously sensitised to the sulphonamide component of the drug. This sensitisation is rare. There is no reason whatever for supposing that either sulphamethoxazole or trimethoprim would accentuate the effect on granulopoiesis of drugs used in treating leukaemia, which act in an entirely different way. The treatment is thus theoretically safe, and practical experience has confirmed this. Its advocates, whose experience now extends to over five years, have seen no deleterious effects on the marrow and continue to maintain that in preventing infections it is of great benefit.

¹ Havas, L, *et al*, *Clinical Trials Journal*, 1973, 10, 81.

² De Gruchy, G C, *Drug-induced Blood Disorders*. Oxford, Blackwell Scientific, 1975.

A patient with menopausal hot flushes has been blind in one eye for 20 years as a result of Eales's disease. Is there any contraindication to using hormonal replacement for these symptoms?

Thromboembolic disease of the retina has been reported in association with oestrogen treatment. In treating menopausal symptoms it would be wise to avoid giving an oestrogen preparation that increased the general risk of thromboembolism to a patient who had only one useful eye. There is, however, no evidence that thromboembolism is associated with Eales's disease itself.