clinic compared with controls, though they were found in a minority subgroup of patients seen in a referral rheumatology clinic.[25] The fibromyalgia syndrome shares the features of other well recognised functional disorders, such as the irritable bowel syndrome, tension headache, and primary dysmenorrhoea. All of these syndromes are significantly more common in primary fibromyalgia than in rheumatoid arthritis and normal controls.[26] Common to fibromyalgia and these other functional syndromes are muscle pain and tenderness, female preponderance or exclusiveness, psychological abnormalities in a minority subgroup of patients, and lack of a specific laboratory test.[6 7] The common physiological mechanism in these conditions may well be non-restorative sleep, as has been suggested,[27] and the important abnormalities are probably neuroendocrine or biochemical rather than anatomical.

The primary fibromyalgia syndrome should be diagnosed on the basis of its own characteristic features and not by exclusion alone. Chronic widespread and diffuse aching at many sites and multiple tender points at characteristic locations in an otherwise healthy patient are important diagnostic considerations. Most patients will have five or more tender points, although as few as two to four among 14 discriminating sites[28] may be sufficient for the diagnosis if they are very tender. The management includes firm diagnosis and assurance regarding its benign nature, explanation of the probable mechanisms of pain,[6] gradually increasing physical activity,[29] use of simple analgesics, prescribing tricyclic agents in small doses,[30 31] and occasional injections of a limited number of tender points with a local anaesthetic and a corticosteroid preparation.[6] Successful management is facilitated by a caring and understanding doctor who gently but firmly guides the patient to assume responsibility for her own well being. Much can be achieved by doctors who recognise the fibromyalgia syndrome as a characteristic clinical entity and treat their patients with understanding.

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Gonadotrophin releasing hormone analogues for gynaecological disorders and infertility

A real advance

Repeated administration of gonadotrophin releasing hormone agonists initially stimulate but then desensitise the pituitary cells responsible for producing the gonadotrophins. This specific deprivation of gonadotrophin support to the gonads has been used for treating disorders dependent on the sex hormones and, paradoxically, also infertility. Pilot studies for the treatment of endometriosis, uterine fibroids, menorrhagia, the premenstrual syndrome, the polycystic ovary syndrome, and timed induction of ovulation have proved promising. We now have the results of large scale clinical trials and have begun to evaluate the consequences of long term suppression of oestrogen concentrations so that the place of these agents in clinical practice can be objectively assessed.

In the two largest multicentre randomised studies of these agonists in treating endometriosis 213 women were treated for six months with either danazol or the agonist nafarelin[1] and 172 women with danazol or buserelin.[2] Both treatments were equally effective in reducing American Fertility Society scores and symptoms and over four fifths of patients benefited from treatment. The patients found the side effects of danazol less acceptable, however, than those of the agonists, though danazol may have advantages over agonists because of its immunosuppressive effects—which may be important if autoimmunity has a role in the disease, as has recently been postulated.[3] Many patients with endometriosis present with infertility. Conception rates are 30-50% during the six mon ; after treatment with either gonadotrophin releasing hormo. agonist or danazol, but we need large scale double blind controlled trials before we know whether there is any real advantage of treatment with either of these drugs over

expectant management. Stopping medical treatment of endometriosis is often followed by a recurrence of the disease, indicating the need for additional treatment. Treatment with gonadotrophin releasing agonists to reduce pelvic vascularity as an adjunct to definitive laser surgery is a promising approach, but the long term gain remains to be determined.[4]

Uterine fibroids are the commonest indication for hysterectomy, and many trials have described the relief of symptoms and an appreciable reduction of uterine volume in over four fifths of patients treated with gonadotrophin releasing agonists for four to six months.[5,6] Again, however, when treatment is stopped the fibroids regrow, but measuring the uterine size by ultrasonography may overestimate these changes.[7] One proposal is that treatment with a gonadotrophin releasing agonist should be used preoperatively to alleviate symptoms, reduce blood loss, and make subsequent surgery technically easier.[8] The suggestion that younger women show a better response to treatment may be because more recently formed fibroids are possibly more responsive to withdrawal of oestrogen.[6]

Women with menorrhagia or the premenstrual syndrome may also benefit from treatment with gondatrophin releasing hormone agonists,[9,10] but the ratio of risk to benefit may be less favourable than that in more serious disorders. Infertility is common in the polycystic ovary syndrome, partly from the increased concentrations of luteinising hormone, which may lead to impaired follicular development and ovulation. Improved pregnancy rates have followed treatment with gonadotrophin releasing hormone agonists to reduce circulating luteinising hormone concentrations and ovarian stimulation with purified follicle stimulating hormone or human menopausal gonadotrophin.[11,12]

The side effects of gonadotrophin releasing hormone agonists given for prolonged periods require careful evaluation. The hypo-oestrogenism induced by therapeutic dosages is associated with hot flushes in almost all patients, and a few women also report vaginal dryness, decreased libido, and headaches. These side effects are generally well tolerated and are more acceptable than the androgenic side effects of danazol, which include myalgia, oedema, and weight gain, as well as decreased concentrations of high density lipoproteins and increased concentrations of low density lipoproteins.[1,2] One problem with the prolonged use of these agonists is the association of hypo-oestrogenism with bone loss. Quantitative computed tomography of the distal radius showed unchanged bone density after six to 12 months after treatment with gonadotrophin releasing hormone agonists,[13] but the vertebral bone showed a small but significant decrease.[14] Probably, however, this decrease is reversible on discontinuing treatment of this duration.[15]

Gonadotrophin releasing hormone agonists have increased the efficacy of in vitro fertilisation programmes. They are applied to suppress the endogenous luteinising hormone concentrations.[16] Given with gonadotrophin they permit timed follicular recruitment and harvesting of oocytes. Particularly encouraging results have been obtained with patients who have responded poorly to clomiphene and human menopausal gonadotrophin. In the initial description of the induction of ovulation with this technique 87 oocytes were harvested in 11 treatment cycles in 11 women, who with the conventional approach had had only 21 oocytes collected in 20 previous attempts.[17] In a randomised study oocyte collection was compared in 20 patients treated either with follicle stimulating hormone alone or buserelin and follicle stimulating hormone. Follicle stimulating hormone alone resulted in an average of 4·8 oocytes collected per cycle, with a fertility rate of 49% and one successful pregnancy, and follicle stimulating hormone and buserelin in 8·2 oocytes, with a fertility rate of 78% and six pregnancies.[18] Gonadotrophin releasing hormone agonists are inactivated when taken by mouth, and nasal spray delivery systems are now widely used. Depot preparations lead to more effective suppression of oestradiol concentrations at smaller doses and are more convenient for long term treatment; by varying the dose or composition the duration of action can be adjusted to one or three months.[5,19,20] Antagonist analogues are theoretically ideal agents for ovulation induction programmes because they are not stimulatory. Their development has been delayed because of associated local histaminic effects, but with the resolution of this problem these compounds are starting to be used clinically.[21]

Within the past five years, the role of gonadotrophin releasing hormone analogues in gynaecological disorders and infertility has become defined. Their use for prolonged periods outside limited clinical trials should await the assessment of their long term effects on bone.

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