similar reasons we thought that it would not be helpful to go back to our records of the women aged 50 to establish how many of these had delayed their first live birth until the age of 35 and over, as they formed such a different group from our current 35 year olds.

The difficulty in classifying voluntarily childless women has been considered elsewhere.⁸ A woman's perception of her childless state may well alter during her reproductive life. She may be "infertile" during one liaison but "childless by choice" in another; she may leave conception to chance without pursuing the option of treatment; or she may declare her childlessness, in retrospect, to be voluntary in order to avoid the stigma of infertility.

We were intrigued by the group of childless women who were not using prescribed contraception but had never sought help for infertility. Possible reasons include (a) no established sexual relationship (including non-consummation of marriage); (b) voluntarily childlessness, using non-prescription methods successfully; (c) a partner who had already had a vasectomy in a previous relationship; (d) sexual problems, including impotence of a partner; (e) too ashamed or embarrassed to seek help for infertility. It was noticeable that this group contained many patients who did not often consult their doctors.

The presence of this unclassified group means that our estimates of infertility and voluntary childlessness are necessarily imprecise; even if we had more information women in some of the above categories would be difficult to classify. Our method of dividing this group (in the same proportions as those for whom the reason for childlessness was known) is open to question, but it produced figures for the two age groups which could conveniently be compared.

A recent paper concluded that infertility is becoming more prevalent.¹² Despite the large increase which we found in the proportion of women aged 35 who were childless compared with those aged 50, and the increase in the number of women requesting specialist consultations for infertility, we found no evidence of an increase in involuntary childlessness—that is, due to infertility. Our range of 3.3% to 4.5% is much lower than the 8-10% predicted by previous statistical projections.

The number of women who chose to remain childless greatly increased during the study period; we estimate that they accounted for one in nine of all 35 year olds. This figure has not been measured

in any previous British report, though there are some American data.¹⁷ Another recent paper states: "It is estimated that 12% of couples are childless. In the great majority of cases they consult their gynecologist for advice and therapy."⁴ Our finding that only one in five of our childless 35 year old women had ever consulted a specialist about infertility disputes this. We submit that the significant increase in voluntary childlessness which we have documented is a factor of considerable importance in examining fertility statistics.

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SHORT REPORTS

Pressor effects of thyrotrophin releasing hormone during thyroid function testing

Thyrotrophin releasing hormone is often given intravenously to stimulate release of thyrotrophin during tests of thyroid and pituitary function. Pressor and chronotropic responses are well recognised in pharmacological doses,¹ and recently 500 µg doses were found to have similar effects.^{2,3} We measured the haemodynamic effects of 200 µg thyrotrophin releasing hormone in 20 patients with suspected coronary artery disease.

Patients, methods, and results

We studied 20 consecutive adults (mean age 57 (range 36-73); 17 men, three women) during routine cardiac catheterisation. They continued taking their usual drugs, and premedication comprised oral diazepam with 5-10 mg diazepam and 12.5 mg prochlorperazine given intravenously five minutes before the procedure. After arterial cannulation the systemic arterial pressure tracing and electrocardiogram were recorded continuously. The baseline reading was taken as that over 30-60 seconds, and then 200 µg thyrotrophin releasing hormone was given intravenously over 15 seconds. We then continued recording for at least two minutes. Subsequent haemodynamic and angiographic recordings were made according to our standard practice.

Systolic and diastolic blood pressure, heart rate, and rate-pressure product were taken as the average over 10 consecutive beats during the baseline period and at peak response (figure). Mean systolic pressure rose by 17% from 121.8 (SD 19.1) to 142.6 (24.0) mm Hg (range 9-43) and diastolic pressure by 20% from 64.2 (7.3) to 76.9 (9.5) mm Hg (range 3-25). Mean heart rate rose by 12% from 63.5

(15.0) to 70.6 (15.0) beats/min (range 1-17) and the mean rate-pressure product by 31% from 7.6 (1.6) × 10³ to 10.0 (2.3) × 10³ beats.mm Hg/min (range 0.3-5.3 × 10³). All changes were significant (p < 0.001, paired t test). The rate-pressure product was maximum at a mean of 56 seconds (range 21-98) after administration of thyrotrophin releasing hormone and returned to baseline values within two to five minutes. There were no electrocardiographic changes or ischaemic symptoms.

Nine patients were taking β blockers, eight calcium antagonists, seven nitrates, four diuretics, two digoxin, one methyl dopa, and one amiodarone; three were not taking any drugs. Angiography showed coronary artery disease in 16 patients (triple vessel disease in six, double vessel disease in eight, and single vessel disease in two) and aortic valve disease in two. Baseline thyroid function was normal in all, including one patient taking thyroxine 50 µg daily. Pressor changes were similar in all patients irrespective of drugs taken or degree of coronary artery disease.

Comment

This study is the first to report pressor effects after the administration of 200 µg thyrotrophin releasing hormone.⁴ The short duration of the response may account for the previous failure to show such effects by non-invasive methods. Nausea often occurs during testing with thyrotrophin releasing hormone and may offset some of the pressor effects. None of our patients experienced nausea, presumably because of the amount of premedication, though this itself may have affected the degree of the response. The premedication allowed stable baseline readings, and the absence of nausea and retching allowed clean pressure traces.

The mechanism of the pressor effects is uncertain: raised catecholamine

Effect of giving 200 µg thyrotrophin releasing hormone intravenously on blood pressure, heart rate, and rate-pressure product in 20 patients. Vertical lines indicate means (SD).

* $p < 0.001$.

concentrations are not found consistently,^{3,5} and increases in vascular resistance have been noted both before and after β blockade.³ Nine of the patients were taking β blockers, but their responses were similar to those of the other patients. Our study did not address the mechanism of the response, which did not seem to be affected by the vasoactive drugs being taken. Although useful in animals,⁶ thyrotrophin releasing hormone has yet to be used therapeutically.

Though the thyrotrophin releasing hormone did not cause adverse effects in this study, it should be used cautiously in patients with uncontrolled angina or hypertension. The side effect of chest tightness reported previously⁴ may be due to myocardial ischaemia resulting from the rise in the rate-pressure product.

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Chlorpromazine induced fluid retention masquerading as idiopathic oedema

An abnormality in dopaminergic tone has been implicated in the pathogenesis of idiopathic oedema. Chlorpromazine has antidopaminergic activity, and we describe a patient in whom chlorpromazine was reproducibly associated with severe fluid retention.

Case report

A 45 year old woman was investigated for severe, persistent oedema of two years' duration. She had a 25 year history of schizophrenia, and two years

previously she had begun treatment with chlorpromazine hydrochloride 400 mg daily. There was no history of organic disease.

Examination showed a woman 156 cm tall and weighing 70 kg. Blood pressure was 120/80 mm Hg and pulse 80/min. Swelling of the face, breasts, and abdomen and pitting oedema of the ankles were evident. There was no other physical abnormality. Serum urea concentration was 3.8 mmol/l, creatinine 102 mmol/l, sodium 143 mmol/l, total protein 70 g/l, and albumin 48 g/l. Results of urine analysis and an electrocardiogram and chest radiograph were all normal. Endocrine evaluation showed a free thyroxine concentration of 16.3 pmol/l and a thyroid stimulating hormone concentration of 2.0 mU/l. Resting plasma renin activity was 1.6 µg/h/l and aldosterone concentration 4.58 nmol/l (mean control values (SD) 1.66 (0.99) and 2.25 (0.04), respectively). After the patient had been standing for two hours her plasma renin activity rose to 5.6 µg/h/l and aldosterone concentration to 10.45 nmol/l (mean control values 5.81 (3.30) and 6.11 (0.09), respectively). Prolactin concentration was raised (56 µg/l).

She was treated with spironolactone 200 mg daily but with no response. There was also no diuresis with kaluril (hydrochlorothiazide 50 mg with amiloride 5 mg) and ethacrynic acid 50 mg daily. The possibility of chlorpromazine induced alterations in dopaminergic tone was considered and she received bromocriptine 7.5 mg daily for three months. No change was noted in body weight with this regimen. Chlorpromazine was then stopped. This was followed by a weight loss of 12 kg and the swelling resolved completely for the first time in two years. Six months later chlorpromazine was reintroduced because of an exacerbation of schizophrenia. She again gained weight (15 kg), accompanied by generalised swelling and facial bloating. The oedema dramatically resolved on withdrawal of the drug.

Comment

Peripheral oedema occurs in 1-3% of patients taking phenothiazines and other psychotropic agents associated with prominent antidopaminergic activity.¹ Dopaminergic neurones enhance renal sodium excretion by a direct effect on the renal tubule and by modulating renin and aldosterone secretion.² Evidence exists that diminished dopaminergic tone may have a pathophysiological role in the fluid retention of idiopathic oedema. Kuchel *et al* found diminished urinary dopamine secretion in patients with idiopathic oedema.² Norbiato *et al* reported an exaggerated rise in aldosterone concentrations in response to the dopamine antagonist metoclopramide in patients with idiopathic oedema.³ Sowers *et al* reported that patients with idiopathic oedema responded to the dopamine agonist bromocriptine with a diuresis.⁴

By virtue of its antidopaminergic effects chlorpromazine may lead to fluid retention in patients so predisposed. The lack of response to bromocriptine in our patient while taking chlorpromazine may be accounted for by the antagonistic antidopaminergic effect of the phenothiazines.⁵

From all this evidence it is tempting to speculate that idiopathic oedema represents a range of varying degrees of fluid retention from overt oedema to a latent tendency for fluid retention (subclinical idiopathic oedema). Cryptic diminution of endogenous dopaminergic tone, further compromised by administration of antidopaminergic agents, might precipitate the appearance of clinically important oedema. Other undetermined factors working in concert with decreased dopaminergic tone may also play a part.